M A T R I X

To,
The Controller of Patents
Delhi Patent Office,
Intellectual Property Office Building, Plot
No. 32, Sector 14, Dwarka,
New Delhi-110075.

From
Mr. Sandeep K. Rathod,
Matrix Laboratories Limited,
1-1-151/1, IV Floor, Sairam Towers,
Alexander Road, Secunderabad-500003
Tel:+91 800 800 1482

Dear Sir,

Sub: Filing of pre-grant Opposition to Application # 2474/DELNP/2009 on behalf of Matrix Laboratories Limited

I, Sandeep K. Rathod, on behalf of my employer- Matrix Laboratories Limited, am filing a pre-grant opposition u/s 25(1) against the afore mentioned application.

The relevant statement and accompanying evidence are attached in duplicate.

Please take our opposition on record and give us an acknowledgment of the same.

Please grant us a personal hearing in this matter.

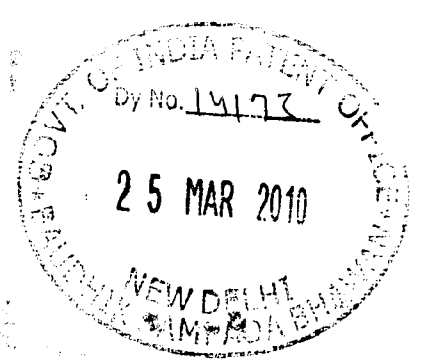
Thank you,

With best regards,

23/Nov/2010

Sandeep K. Rathod
Head - IP
Matrix Laboratories Limited

Attachments:
a) Statement of Opposition [duplicate] and
b) Exhibits 1 to 9 [duplicate]



The Patents Act, 1970

IN THE MATTER OF:

A representation under section 25(1) of The Patents Act, 1970 as amended by the Patents (Amendment) Act 2005 ("the Act") and Rule 55 of The Patents Rules, 2003 as amended by the Patents Rules, 2006 ("the Rules")

by
M/s Matrix Laboratories Limited
(the "Opponent")

And

IN THE MATTER OF:

Indian Patent Application No. 2474/DELNP/2009, filed on 15/April/2009 by Abbott Laboratories (the "Applicant")

STATEMENT OF OPPOSITION

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1. ***The Opposition in brief:***

The Opponent hereby files a pre-grant opposition under Section 25(1) of the Patent Act 1970, as amended by the Patents (Amendment) Act, 2005 against the application entitled:

"Solid pharmaceutical dosage form", filed by Abbott Laboratories,

on 15/April/2009, bearing No. 2474/DELNP/2009 (the "Application").

A copy of the electronic publication showing the Application's bibliographic detail is attached as **Exhibit 1**.

2. ***Maintainability of the present Opposition:***

2.1 The Act states:

> "25. Opposition to the patent:
> (1) Where an application for a patent has been published but a patent has not been granted, any person may, in writing, represent by way of opposition to the Controller against the grant of patent on the ground --..."

Thus, the Act clearly allows any person to file a written opposition to a published application for patent that has not matured into a patent.

2.2 Matrix Laboratories Limited ("Matrix"), the Opponent herein, is a key player in the pharmaceutical market and has significant commercial interests on a global level in the business of anti-retro viral drugs ("ARV's"), including HIV protease inhibitor compositions, (the field to which the present Application pertains). It is a leading supplier of generic anti-retro viral drug compositions in the global market such as the US President's Emergency Plan for AIDS Relief (PEPFAR) as well as other National tenders issued by governments and as such Matrix has considerable interests in ARVs, and in particular, protease inhibitors. Therefore Matrix is directly impacted by the present Application.

2.3 The Opponent believes that the Application has not been abandoned, is currently under examination and has not matured into a patent. The Opponent further states that in its search of the Patent Office Gazette [for Gazette published until 19/March/2010], no patent was advertised as granted for this Application. Hence the present pre-grant opposition is covered within the framework envisaged in the Act and the Rules made there-under.

3 ***Maintainability of the Patent Application***

(a) ***The above application filing does not qualify as a divisional application under the Act.***

3.1.1 The Application has been filed as a divisional application out of parent application No. 339/MUMNP/2006. The Opponent submits that the claims within the Application are not maintainable in the light of the claims of said parent application under section 16(3) of the Patents Act, 1970. A comparison of the claims of parent application and the present Application demonstrates that the claims of the Application are exactly the same as those of the parent .

As has been noted by the Patent Office in the matter of application No. 237/DEL/2001, the concept of divisional applications, in most statutes across the

world is basically to protect multiple inventions disclosed in one patent application, if such multiple inventions do not constitute a single invention concept. A similar provision to protect multiple inventions is available in the Patents Act 1970, in the form of section 16.

3.1.2 A divisional application cannot be allowed to subsist along with the parent application where the divisional application contains effectively the same claims as the parent application. The Patent Office has held, in the matter of application No. 748/DEL/2002, that, in the case of a divisional application filed out of a parent application, the divisional application cannot include any claim already claimed in the parent application. Any situation where the divisional application contains substantially the same claims as the parent application may be considered an abuse of the patent application process by the applicant for the sole purpose of resurrecting claims lapsed/ rejected in an earlier patent, or for allowing substantially similar claims to remain pending, indefinitely, with the Patent Office.

A divisional application is meant to be filed when the parent application, in contravention of section 10(5) of the Patents Act, 1970, relates to more than one invention or inventive concept, and therefore contains more than one invention. In the present case, the parent application does not contain more than one invention or inventive concept, as an examination of the prosecution history of the parent application will show. The fact that the parent application contains only a single inventive concept is amply demonstrated by an examination of the contents of the present divisional application filed by the Applicant, which shows that the claims of the present divisional application relate to exactly the same invention as that claimed by the parent application.

3.1.3 The Patent Office has held, in a number of cases, including in the matter of patent application No. 832/DEL/2001, that, in order to become eligible as a divisional application under section 16, it is essential that the parent application out of which the divisional application is filed, should disclose more than one invention and not just the same invention.

It is clear, therefore, that in the present situation, the Applicant has merely filed the present divisional application not as a way to divide the subject matter of the parent application, but to keep open the prospect of re-agitating the claims covered in the parent at the Delhi Patent Office in the event the parent application/ 1st divisional application is refused by the Mumbai Patent Office. Such an abuse of the patent application process is prohibited under section 16 of the Patents Act, 1970. This prohibition has already been enforced by the Patent Office in a number of cases, one example of which is the matter of patent application No. 1427/DEL/1999. In this case, the Deputy Controller of Patents and Designs refused a divisional application which had been filed in order to revive an earlier parent application which had been refused under section 5(1) of the Patents Act, 1970 at the time. In refusing the divisional application, the Deputy Controller noted that:

> "The attempt of the agent for the applicants in filing the instant application as divisional application is not to divide the subject matter of the invention on the basis of plurality of distinct invention but to revive the abandoned invention which was not protectable at that time which is also not the objective of the provisions of section 16 of the Act."

***(b) Filing parallel divisional applications is an abuse of the process*:**

3.2.1 It is a matter of fact that, on the same date on which the Applicant filed the present Application (i.e. on April 15, 2009), the Applicant also filed divisional application No. 726/MUMNP/2009 out of parent application No. 339/MUMNP/2006. The Applicant, in addition to filing two divisional applications simultaneously, out of the same parent application, has filed the first divisional application No. 726/MUMNP/2009 in the Patent Office at Mumbai, where the parent application was filed, and has filed the second divisional application (i.e., the present Application) in the Patent Office at New Delhi. Moreover, the divisional application No. 726/MUMNP/2009 filed by the Applicant, contains the exact same claims as the parent application No. 339/MUMNP/2006. The Opponent submits that the presence of an additional divisional application filed on the exact same day as the date of filing of the present Application, and containing the exact same claims as the present Application and the parent application, demonstrates beyond reasonable doubt that the Applicant has merely filed said divisional applications as an abuse of the patent application process, and in order to keep open the prospect of

re-agitating the claims of parent application No. 339/MUMNP/2006 at a different branch of the Patent Office.

It is worth pointing that these two divisional applications were filed on the day when the Patent Office held a pre-grant opposition hearing for the parent application – the '339. The multiple divisional filings, and that too at different patent offices, only highlight the vexatious attempts of an Applicant who has huge resources at his disposal, towards patent office forum shopping so as to have an application to perpetuate within the patent system and increase uncertainty for generic drug companies- an unwarranted luxury which impacts the generic pharmaceuticals sector and availability of generic drugs.

3.2.2 This Hon'ble Office should strictly condemn any attempt to game the system by misusing the resources and time of the Patent Office. Thus, the Applicant's present Application warrants a rejection *in limine*. For these reasons, the Opponent submits that the present Application is liable to be refused on the grounds of failing to qualify under section 16(3) of the Patents Act, 1970.

(c) ***Impermissibility of Changing the Appropriate Office***

3.3.1 Additionally, the Opponent submits that the present divisional Application in not maintainable for violation of rule 4 of the Patents Rules, 2003. The parent application No. 339/MUMNP/2006 was filed in Mumbai on March 24, 2006. By this, the Applicant had elected the Patent Office at Mumbai as the appropriate office in respect of any proceedings related to its application No. 339/MUMNP/2006. However, on April 15, 2009, the Applicant filed two divisional applications out of the parent application.

Divisional application No. 726/MUMNP/2009 was filed in Mumbai.

The present divisional Application ['2474], however, was filed in New Delhi.

3.3.2 Rule 4(2) of the Patents Act, 1970, expressly states that the appropriate office, once decided in respect of any proceedings under the Act, shall not ordinarily be changed. By their act of filing a divisional application before the Patent Office at New Delhi

out of the parent application which was originally filed in Mumbai, the Applicant has acted in contravention of rule 4 of the Patents Rules, 2003. Moreover, there can be no justification for changing the appropriate office when the Applicant has exercised this option in Mumbai by filing first divisional, i.e., Application No. 726/MUMNP/2009.

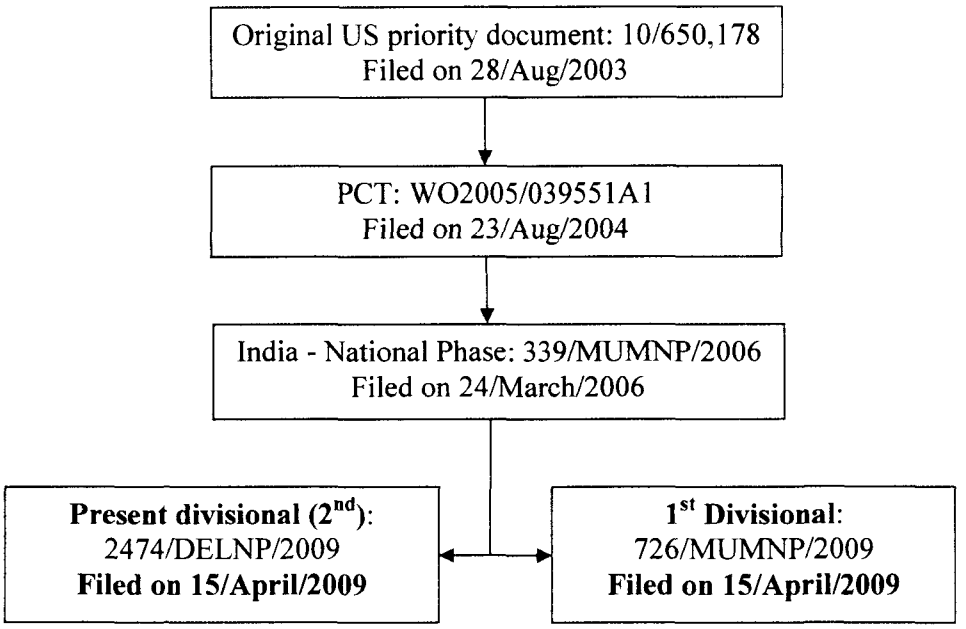
Accordingly, the present Application is liable to be rejected as the same is not maintainable before this Hon'ble Office under the Patents Act and Rules. In other words, this Hon'ble Office does not have the jurisdiction to examine the Application.

4. Jurisdiction of the Patent Office:

This Hon'ble Office does not have the jurisdiction to substantively examine the Application or grant any patent thereto, as the same is not filed before the appropriate office for reasons mentioned under para 3.3. The Parent Application and another divisional were filed at the Patent Office in Mumbai. Therefore only the Mumbai Patent Office has the jurisdiction to substantively hear and deliberate upon this Application.

5. The Application – Filing details:

5.1 The Application principally claims a solid dispersion of at least one HIV protease inhibitor in a polymer and a surfactant. The Application was filed as a divisional filing from an earlier Indian application. Its genesis is represented below:



5.2 In view of the above, it is clear that publications or public use prior to 28/Aug/2003 will be considered as prior art against the Application and the invention claimed therein.

5.3 At this juncture, the Opponent states the following:

a) That the parent '339 filing currently faces multiple pre-grant oppositions by various entities/ companies [including this Opponent].

b) As per the information in public domain[1], an opposition hearing on the parent '339 was conducted on 15/April/2009. This is the same date as the filing of the present divisional Application.

c) Interestingly, the present '2474 was filed at the Delhi Patent Office, while the original filing (339/MumNP/2006) was filed at the Mumbai Patent Office.

d) Applicant has filed the current '2474 Application with the exact same set of claims as the parent '339, already opposed and the simultaneously filed '726 at Mumbai. That means that there are three filings at two different patent offices which have the exact same set of claims.

e) The Opponent would like to point out that it is in contradiction to Indian

[1] http://www.i-mak.org/i-mak-blog-updates/2009/5/9/new-look-website-and-updates.html

patent practise detailed in section 16(3) of the Patents Act, 1970, where a divisional is filed with different/ lesser number of claims than the original, so as to divide the originally filed claims in 2 distinct parts- for instance – division into product and process claims – usually to overcome a 'unity of invention' objection. The Opponent believes that the present divisional filing, using the same set of claims as the 339 parent, is against the practise of Indian patent office.

f) As of the date of filing of the present opposition, the present Opponent is not aware of any decision by the Patent Office on the parent '339 or its first divisional – '726, nor is the Opponent aware of any instruction issued by the Patent Controller seeking a divisional filing from the parent '339.

6. ***The Application – in brief:***

6.1 The invention claimed in the Application principally relates to a solid dispersion of at least one HIV protease inhibitor in at least one water soluble polymer in the presence of at least one surfactant. The Specification defines the term "solid dispersion" as follows:

> '"solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed evenly throughout the other component or components. For example, the active ingredient or combination of active ingredients is dispersed in a matrix comprised of the pharmaceutically acceptable water-soluble polymer (s) and pharmaceutically acceptable surfactant (s). The term "solid dispersion" encompasses systems having small particles, typically of less than 1 pm in diameter, of one phase dispersed in another phase. When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase (as defined in thermodynamics), such a solid dispersion will be called a "solid solution" or a "glassy solution". A glassy solution is a homogeneous, glassy system in which a solute is dissolved in a glassy solvent. Glassy solutions and solid solutions of HIV protease inhibitors are preferred physical systems. These systems do not contain any significant amounts of active ingredients in their crystalline or microcrystalline state, as evidenced by thermal analysis (DSC) or X-ray diffraction analysis (WAXS).'

6.2 The Specification and claims cover ritonavir and ritonavir in combination with another protease inhibitor or protease inhibitors. However, the Specification only provides working examples for ritonavir and the combination of ritonavir and lopinavir. No other combination of protease inhibitors is exemplified in the Specification, nor is any data/ working example/ guidance provided for making a

composition comprising HIV protease inhibitors.

7. The Application contains the following thirty seven claims:

1. A solid pharmaceutical dosage form which comprises a solid dispersion of at least one HIV protease inhibitor and at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant, said pharmaceutically acceptable water-soluble polymer having a Tg of at least about 50 °C.

2. The dosage form of claim 1 comprising a glassy solution or solid solution of said HIV protease inhibitor.

3. The dosage form of claim 1, wherein said pharmaceutically acceptable surfactant has an HLB value of from about 4 to about 10.

4. The dosage form of claim 1, wherein said pharmaceutically acceptable surfactant is a combination of at least one pharmaceutically acceptable surfactant having an HLB value of from about 4 to about 10 and at least one further pharmaceutically acceptable surfactant.

5. The dosage form of Claim 1 wherein said pharmaceutically acceptable surfactant is a sorbitan fatty acid ester.

6. The dosage form of Claim 1 which comprises, relative to the weight of the dosage form, from about 5 to about 30 % by weight of said HIV protease inhibitor, from about 50 to about 85 % by weight of said water-soluble polymer, from about 2 to about 20 % by weight of said surfactant, and from about 0 to about 15 % by weight of additives.

7. The dosage form of claim 1, wherein said HIV protease. inhibitor is selected from the group consisting of : (2S, 3S, 5S)-5- (N- (N- ((N-methyl-N- ((2-isopropyl -4- thiazolyl) methyl) amino) carbonyl)-L-valinyl) amino-2- (N- ((5-thiazolyl) methoxy- carbonyl) -amino) -amino-1, 6-diphenyl-3-hydroxyhexane (ritonavir); (2S, 3S, 5S)-2- (2, 6-Dimethylphenoxyacetyl) amino-3- hydroxy-5- [2S-(l-tetrahydro -pyrimid-2-onyl) -3-methylbutanoyl] amino, 1, 6-diphenylhexane (lopinavir); N- (2 (R)-hydroxy-l (S) -indanyl) -2 (R)-phenylmethyl-4 (S)-hydroxy-5- (1- (4- (3-pyridylmethyl) -2 (S)-N'- (t-butylcarboxamido)-piperazinyl)) -pentaneamide (indinavir); N-tert-butyl- decahydro-2- [2 (R) –hydroxy -4-phenyl-3 (S)- [[N- (2-quinolylcarbonyl)-Lasparaginyl] amino] butyl]- (4aS, 8aS) -isoquinoline-3 (S) -carboxamide (saquinavir); 5 (S) -Boc-amino-4 (S) -hydroxy-6-phenyl-2 (R) phenylmethylhexanoyl- (L)-Val- (L)-Phemorpholin -4-ylamide; 1-Naphthoxyacetyl-beta-methylthio -Ala- (2S, 3S) 3-amino-2-hydroxy-4-butanoyl 1,3- thiazolidine-4t-butylamide; 5-isoquinolinoxyacetyl-beta-methylthio-Ala- (2S, 3S) -3-amino-2-hydroxy-4-butanoyl- 1,3-thiazolidine-4-t-butylamide; [1 S-[lR-(R-), 2S*])-N'-[3-[[[(1, 1-dimethylethyl) amino] carbonyl] (2- methylpropyl) amino]-2hydroxy-1- (phenylmethyl) propyl] -2- [(2quinolinylcarbonyl) amino] -butanediamide; amprenavir (VX-478); DMP-323; DMP-450; AG1343 (nelfinavir); atazanavir (BMS 232,632) tipranavir palinavir TMC-114 R0033-4649 fosamprenavir (GW433908) P-1946, BMS 186,318; SC-55389a; BILA 1096 BS; U-140690, or combinations thereof.

8. The dosage form of Claim 1 wherein said HIV protease inhibitor is (2S, 3S, 5S)-5- (N- (N- ((N-methyl-N- ((2-isopropyl-4-thiazolyl) methyl) amino) carbonyl) -L-valinyl) amino- 2- (N- ((5-thiazolyl) methoxy-carbonyl) -amino) amino-1, 6-diphenyl-3-hydroxyhexane (ritonavir).

9. The dosage form of Claim 8 which shows a dose-adjusted AUC, in dogs under non- fasting conditions, of ritonavir plasma concentration of at least about 9 μg. h/ml/100 mg.

10. The dosage form of Claim 1 wherein said HIV protease inhibitor is (2S, 3S, 5S)-2- (2, 6- Dimethylphenoxyacetyl)-amino-3-hydroxy-5-[2S-(l-tetrahydropyrimid-2-onyl)-3- methyl-butanoyl] amino-1, 6-diphenylhexane (lopinavir).

11. The dosage form of claim 10 which shows a dose-adjusted AUC, in dogs under non- fasting conditions, of lopinavir plasma concentration of at least about 20 μg. h/ml/100 mg.

12. The dosage form of claim 1 wherein said HIV protease inhibitor is a combination of (2S, 3S, 5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl) methyl) amino) carbonyl)- L-valinyl) amino-2- (N- ((5-thiazolyl) methoxy-carbonyl)-amino)-amino-1, 6-diphenyl-3-hydroxyhexane (ritonavir) and (2S. 3S, 5S)-2-(2, 6-Dimethylphenoxyacetyl) amino-3- hydroxy-5- [2S- (1-tetrahydropyrimid-2-onyl)-3-methylbutanoyl] amino-1,6-diphenylhexane (lopinavir).

13. The dosage form of claim 12 which shows a dose-adjusted AUC, in dogs under non- fasting conditions, of ritonavir plasma concentration of at least 9 about μ.g.h/ml/100 mg and a dose-adjusted AUC of lopinavir plasma concentration of at least about 20 μg. h/ml/l00mg.

14. The solid dosage form of Claim 1 wherein said water-soluble polymer has a Tg of from about 80 to about 180 °C.

15. The solid dosage form of Claim 1 wherein said water-soluble polymer is a homopolymer or copolymer of N-vinyl pyrrolidone.

16. The solid dosage form of Claim 1 wherein said water-soluble polymer is a copolymer of N-vinyl pyrrolidone and vinyl acetate.

17. The solid dosage form of Claim 1 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

18. The solid dosage form of Claim 1 which contains, upon storage for about 6 weeks at about 40 C and about 75% humidity, at least about 98 % of the initial content of HIV protease inhibitor.

19. A method of preparing a solid-dosage-form of claim 1 which comprises:
    i. preparing a homogeneous melt of said HIV protease inhibitor (s), said water- soluble polymer (s) and said surfactant (s), and
    ii. allowing the melt to solidify to obtain a solid dispersion product.

20. The method of claim 19 additionally comprising grinding said solid dispersion product and compressing said solid dispersion product into a tablet.

21. A method of treating an HIV infection comprising administering the solid dosage form of claim 1 to a mammal in need of such treatment.

22. A solid pharmaceutical dosage form comprising, (2S, 3S, 5 S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl) methyl) amino) carbonyl) -L- valinyl) amino-2- (N- ((5-thiazolyl) methoxy-carbonyl)-amino)-amino-1, 6-diphenyl-3- hydroxyhexane (ritonavir); a homopolymer of N-vinyl pyrrolidone; and a sorbitan fatty acid ester.

23. The solid dosage form of Claim 22 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

24. A solid pharmaceutical dosage form comprising, (2S, 3S, 5S)-2-(2, 6-Dimethylphenoxyacetyl) amino-3-hydroxy-5- [2S- (l-tetrahydro-pyrimid-2- onyl) -3-methylbutanoyl] amino-1, 6-diphenylhexane (lopinavir); a copolymer of N-vinyl pyrrolidone; and a sorbitan fatty acid ester.

25. The solid dosage form of Claim 24 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

26. A solid pharmaceutical dosage form comprising, (2S, 3 S, 5 S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl) methyl) amino) carbonyl)-L- valinyl) amino-2-(N-((5-thiazolyl) methoxy-carbonyl)-amino)-amino-1, 6-diphenyl-3- hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2- (2, 6-Dimethylphenoxyacetyl) amino-3-hydroxy- 5-[2S-(l-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl] amino-1, 6-diphenylhexane (lopinavir):
a copolymer of N-vinyl pyrrolidone and vinyl acetate; and
a sorbitan fatty acid ester.

27. The solid dosage form of Claim 26 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

28. A solid pharmaceutical dosage form comprising, (2S, 3S, 5 S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl) methyl) amino) carbonyl) -L- valinyl) amino-2-(N-((5-thiazolyl) methoxy-carbonyl)-amino)-amino-1, 6-diphenyl-3- hydroxyhexane (ritonavir) from about 5 % to about 30 % by weight of the dosage form; a homopolymer of N-vinyl pyrrolidone from about 50 % to about 85 % by weight of the dosage form; and a sorbitan fatty acid ester from about 2 % to about 20 % by weight of the dosage form.

29. The solid dosage form of Claim 28 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

30. The solid dosage form of claim 29 wherein the at least one additive is present in an amount from about 0 % to about 15 % by weight.

31. A solid pharmaceutical dosage form comprising, (2S, 3S, 5S)-2- (2, 6-Dimethylphenoxyacetyl) amino-3-hydroxy-5- [2S-(l-tetrahydro-pyrimid-2- onyl) -3-methylbutanoyl] amino-1, 6-diphenylhexane (lopinavir) from about 5 % to about 30 % by weight of the dosage form; a copolymer of N-vinyl pyrrolidone from about 50 % to about 85 % by weight of the dosage form; and a sorbitan fatty acid ester from about 2 % to about 20 % by weight of the dosage form.

32. The solid dosage form of Claim 31 containing at least one additive selected from flow regulators. disintegrants, bulking agents and lubricants.

33. The solid dosage form of claim 32 wherein the at least one additive is present in an amount from about 0 % to about 15 % by weight.

34. A solid pharmaceutical dosage form comprising, (2S, 3 S, 5 S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl) methyl) amino) carbonyl) -L- valinyl) amino-2- (N- ((5-thiazolyl) methoxy-carbonyl)-amino)-amino-1, 6-diphenyl-3- hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2, 6-Dimethylphenoxyacetyl) amino-3-hydroxy- 5-[2S-(l-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl] amino-1, 6-diphenylhexane (lopinavir) present in an amount from about 5 % to about 30 % by weight of the dosage form; a copolymer of N-vinyl pyrrolidone and vinyl acetate from about 50 % to about 85 % by weight of the dosage form; and a sorbitan fatty acid ester from about 2 % to about 20 % by weight of the dosage form.

35. The solid dosage form of Claim 34 containing at least one additive selected from flow regulators. disintegrants. bulking agents and lubricants.

36. The solid dosage form of claim 35 wherein the at least one additive is present in an amount from about 0 % to about 15 % by weight of the dosage form.

37. A method of treating an HIV infection comprising administering the solid dosage form of any one of claims 22-36 to a mammal in need of such treatment.

8. The Opponent opposes the present application on the following grounds allowed under section 25(1):

25. Opposition to the patent:. –
(1) Where an application for a patent has been published but a patent has not been granted, any person may, in writing, represent by way of opposition to the Controller against the grant of patent on the ground –

(b) that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim –
... (ii) in India or elsewhere, in any document:...
(e) that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step,
having regard to the matter published as mentioned in clause (b)
or
having regard to what was used in India before the priority date of the applicant's claim;
(f) that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act;
(g) that the complete application does not sufficiently and clearly describe the invention or the method by which it is to be performed;
(h) that the applicant failed to disclose to the Controller the information required by section 8 or has furnished the information which in any material particular was false to his knowledge;

...

9. *Discussion of above grounds for opposition:*

The Opponent opposes the Application, in its entirety. The grounds stated above are distinct and independent of each other. Each ground provides sufficient reason to bar the issuance of a patent from the Application.

10. S. 25(1)(b) Prior publication [Anticipation]

10.1 S. 25(1)(b) states:

(b) that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim –
(i) in any specification filed in pursuance of an application for a patent made in India on or after the 1st day of January 1912; or
(ii) in India or elsewhere, in any document:
Provided that the ground specified in sub-clause (ii) shall not be available where such publication does not constitute an anticipation of the invention by virtue of sub-section (2) or sub-section (3) of section 29; (emphasis supplied)

10.2 As can be seen from the claims, Applicant's alleged invention is a composition with the following main components:

a) HIV protease inhibitor in a solid dispersion;

b) with a water soluble polymer having a Tg of at least about 50 °C;

c) with a surfactant.

i.e. a dispersion composition of a HIV protease inhibitor drug in a water soluble

polymer + surfactant.

Solid dispersions can be made by multiple processes and solvent evaporation is one process while melt extrusion is another alternative process. The Applicant has himself stated:

> 'Various techniques exist for preparing solid solutions including melt-extrusion, spray drying and solution-evaporation...'
> Page 10, lines 5/6 of the Specification.

10.3 The Applicant has, over the years, published a number of papers/ articles on the development of HIV protease inhibitors and their formulations. L. Dias *et al.* (1996) *Pharmaceutical Research Supplement* 13(9): page S-351 PDD 7475 published in September, 1996 [**Exhibit 2**] is one such publication. In view of this date of publication, this article is clearly prior art to the Application.

Dias discloses the following:

> 'Poly vinyl pyrrolidone (PVP) has been used to form coprecipitates of an insoluble antiviral compound, ABT-538, in an effort to increase bioavailability of this drug. PVP:drug coprecipitates were prepared using solvent evaporation method.
> ...
> The drug:PVP co-precipitates also showed further improvement in bioavailabilties when combined with surfactants and acidifying agents.'

10.4 Solid dispersions have also been conventionally known as co-precipitates. For e.g. refer the seminal paper on solid dispersions- Win Loung Chiou, *Journal of Pharmaceutical Sciences,* Vol. 60; page 1283 [1971] [**Exhibit 3**]. Additionally, processes to make solid dispersions of drugs in polymer by melting and subsequent solidification have been known for many decades. The above Chiou reference itself gives a description of dispersion by melt method at page 1283 [column 1, 2nd full paragraph]. The present dispersion formulation was exemplified in the Applications' examples by using a process conventionally known as melt extrusion [e.g. 1 at page 16]. Patents disclosing melt-extrusion processes to make pharmaceutical compositions also anticipate the present process claims; for instance refer US 5073379 [**Exhibit 4**; published on 17/Dec/1991, which belongs to BASF- the company from which the Applicant has licensed the dispersion technology] which discloses processes to make extrusion based compositions using polymers –

specifically PVP as well as N-Vinyl Pyrrolidone.

10.5 ABT 538 was the lab code for Ritonavir [Merck Index, **Exhibit 5**]. Thus, the PDD 7475 document **[Exhibit 2]** clearly discloses all aspects of the present claims:

- solid dispersion of
- Ritonavir [HIV protease inhibitor]
- in PVP [a water soluble polymer] and
- a surfactant.

Hence, it is the Opponent's position that the alleged invention of the Application is anticipated by the Dias disclosure; hence the entire set of claims is liable for rejection, in *toto*. Additionally, the process claims 19-20 are also anticipated independently by the Chiou reference as well as US 5073379.

11. S. 25(1)(e) Lack of inventive step/ Obviousness:

11.1 S. 25(1)(e) states:

> (e) that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in clause (b)
> or
> having regard to what was used in India before the priority date of the applicant's claim;

The following definitions from the Act, are important for the present argument:

> 'S. 2(j) "invention" means a new product or process involving an inventive step and capable of industrial application;
> S. 2(ja) "inventive step" means a feature of an invention that involves technical advance as compared to existing knowledge or having economic significance or both and makes the invention not obvious to a person skilled in the art; '
> S. 2(l) "new invention" means any invention or technology which has not been anticipated by publication in any document or used in the country or elsewhere in the world before the date of filing of patent application with complete specification, i.e. the subject matter has not fallen in public domain or that it does not form part of the state of the art;'

11.2 The critical components of the alleged invention in claim 1 are:

a) HIV protease inhibitor in a solid dispersion;

b) in a water soluble polymer having a Tg of at least about 50 °C;

c) with a surfactant.

Claim 12 brings in an additional HIV protease inhibitor – lopinavir and ritonavir in a

single dosage form. Claim 34 is for a dosage and is a narrower version of claim 12 – it has the 2 drugs, polymer and surfactant in ranges. Claim 21 is a method of use claim for treating HIV by using the dosage form of claim 1. Claim 37 takes the dosage of claim 34 and employs this to treat HIV infection. In all the claims – the core theme remains constant– a dispersion of HIV protease inhibitor drug in a water soluble polymer and a surfactant. Without prejudice to the arguments made under section 25(1)(b); **Exhibit 2**, without doubt, makes it obvious to use PVP and surfactants to form solid dispersions of Ritonavir that have suitable bioavailability.

11.3 **Alternatively**:

WO 01/034119 [**Exhibit 6**; published on 17/May/2001] is a PCT application from the Applicant. It discloses a solid dispersion of a HIV protease inhibitor in a water soluble carrier, wherein the carrier includes PVP. Additionally, the Applicant himself refers to an old US patent [US 4769236; **Exhibit 7**] that categorically discloses a process for preparation of a stable pharmaceutical composition containing PVP with high dissolution rate in the gastrointestinal tract. Lines 54-65 of the '236 patent disclose use of PVP alone to give stability and solubility by maintaining the drug in an amorphous state. The role of surfactants in pharmaceutical industry has been well documented. For instance, 'Surfactants in pharmaceutical products and systems, published within the *Encyclopaedia of Pharmaceutical Technology* [2002]' clearly states the following at page 2649 [**Exhibit 8**]:

> '**Solid Dispersion Systems**:
> The bioavailability of hydrophobic drugs can be increased by strategies designed to enhance the dissolution rate of the drug. This has been achieved in many cases by forming a solid dispersion of the drug in a suitable carrier, often a hydrophilic polymer such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP). The drug is dispersed in the carrier by coprecipitation from a suitable solution containing both the drug and carrier, by melting both components together ....'

Hence, keeping in view the prior art, it would be obvious to use PVP to make a dispersion of a poorly water soluble drug like Ritonavir, while adding surfactants to the composition.

11.4 Keeping in view the above state of prior art, it is the Opponent's contention that the present Application does not involve any technical breakthrough/ advantage nor

does it involve any aspect which was not known to the person skilled in the art on the priority date. On a related note, the European Patent Office too believes that the corresponding EP application is not inventive over the same prior art document referred above - WO 01/034119. Refer to the EPO's rejection for EP1663183 dated 17/Apr/2009 [**Exhibit 9**].

12. S. 25(1)(f) Not an invention

12.1 S. 25(1)(f) states:

> (f) that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act;

Chapter II of the Act is titled 'Inventions not patentable' and specifically enumerates categories of developments that are, by statute, not considered to be patentable inventions. The relevant section is set forth:

> 'The following inventions are not inventions within the meaning of this Act, -
> ....
> (d) the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance
> or the mere discovery of any new property
> or new use of a known substance
> or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.
>
> Explanation: For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same'
>
> (e) a substance obtained by mere admixture resulting only in aggregation of the properties of the components thereof or a process for producing such substance;
> ....
> (i) any process for the medicinal, surgical, curative, prophylactic, diagnostic, therapeutic or other treatment of human beings or any process for a similar treatment to animals to render them free of disease or to increase their economic value or that of their products;(emphasis supplied)

12.2 At the outset, claims 21 and 37 of the Application are for a method of treating human beings. That said, claims 21/ 37 are not patentable under the Act in view of S. 25(1)(f) in conjunction with S. 3(i).

12.3 As has been noted, the product claims are for a combination of known substances- a HIV protease inhibitor drug dispersed in a polymer and having a surfactant. All of

these constituents were known in the prior art. In fact, Applicant's earlier marketed product – Kaletra™ capsule disclosed in WO 00/74677, published on 14/Dec/2000, had Ritonavir & Lopinavir dispersed in a solvent. The only benefit of the present dispersion composition is 'enhanced stability' / 'shelf life' versus the earlier capsule.

12.4 It is the Opponent's contention that a combination of known substances is not patentable per section 3(d) if enhanced efficacy is not shown. It is worthwhile to note that enhanced stability is NOT the same as enhanced efficacy and this position has been upheld by the Patent Office on multiple occasions, for instance the Controller has held:

> '...a mere enhancement in stability by way of lesser degradabilty by 1 to 2% only, does not entitle an applicant to a grant of patent. Moreover this amounts to improvement in the quality of the product rather than the therapeutic efficacy.'
>
> Refer: 1577/DEL/1996

Importantly, in a case very similar to the present Application – a new composition claimed in view of a prior art composition, the Controller squarely rejected the argument that greater stability resulting in extended shelf life should be equated as enhanced efficacy [refer decision IN/PCT/2000/00119]. This is the exact situation as the present case, wherein the 'new' dispersion tablet has arguably enhanced shelf life but the same efficacy as the earlier capsule.

12.5 The earlier capsule dosage [having 133.3 mg lopinavir /33.3 mg ritonavir in each capsule] for Lopinavir/ Ritonavir was three capsules twice daily, providing an aggregate of 800 mg Lopinavir and 200 mg Ritonavir [over the course of entire day]. The present dispersion composition – known as Kaletra heat stable tablet [having 200 mg lopinavir /50 mg ritonavir in each tablet] – also has exactly same gross dosage -- 2 tablets (400 mg/100 mg) twice daily. The new dispersion tablet does not result in the patient taking lesser amount of drug, but merely results in lesser number of tablets. The final amount of drug that the patient ingests in the present dispersion tablet is the same as the earlier capsule [i.e. 800 mg Lopinavir and 200 mg Ritonavir]. The applicant has failed to prove enhanced '*in vivo*' efficacy for the said formulation. The efficacy of the drug, as per the Madras High Court's interpretation of section 3(d), in the case of pharmaceuticals will mean

Exhibit 6: WO 01/034119
Exhibit 7: US 4769236
Exhibit 8: *Encyclopaedia of Pharmaceutical Technology* [2002]
Exhibit 9: EPO's rejection for EP1663183

Ex. 1

(12) PATENT APPLICATION PUBLICATION

(19) INDIA

(22) Date of filing of Application :15/04/2009

(21) Application No. : 2474/DELNP/2009

(43) Publication Date : 31/07/2009
Journal No. - 31/2009

(54) Title of the invention : Solid Pharmaceutical Dosage Form

(51) International classification	:A61K 9/14
(31) Priority Document No	:10/650,178
(32) Priority Date	:28/08/2003
(33) Name of priority country	:U.S.A.
(86) International Application No Filing Date	:PCT/US2004/027401 :23/08/2004
(87) International Publication No	: NA
(61) Patent of Addition to Application Number Filing Date	:NA :NA
(62) Divisional to Application Number Filed on	:339/MumNP/2006 :24/03/2006

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(57) Abstract :
A solid pharmaceutical dosage form providing improved oral bioavailability is disclosed for inhibitors of HIV protease. In particular, the dosage form comprises a solid dispersion of at least one HIV protease inhibitor and at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant, said pharmaceutically acceptable water-soluble polymer having a Tg of at least about 50 °C. Preferably, the pharmaceutically acceptable surfactant has an HLB value of from about 4 to about 10.

Number of Pages = 27

Ex. 2

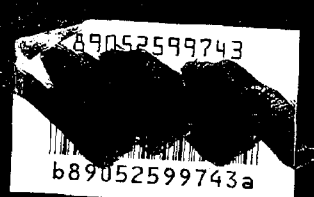
September 1996 (Supplement)
Volume 13, Number
PHREEB 13(9) S1–S604 (199
ISSN 0724-874

PHARMACEUTICAL RESEARCH

An Official Journal of the American Association of Pharmaceutical Scientists

aaps

Encompassing Research in the Physical, Chemical, Biological, Clinical, Socioeconomic, and Pharmacoeconomic Aspects of the Pharmaceutical Sciences



LENUM PRESS • NEW YORK AND LONDON

PHARMACEUTICAL RESEARCH

An Official Journal of the American Association of Pharmaceutical Scientists

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Pharmaceutical Research is published monthly by Plenum Publishing Corporation, 233 Spring Street, New York, N.Y. 10013. *Pharmaceutical Research* is abstracted or indexed in Bioscience Abstracts, Chemical Abstracts, Excerpta Medica, Gazette de l'APGI, Index Medicus/MEDLARS, and International Pharmaceutical Abstracts.

Subscription inquiries and subscription orders should be addressed to the publisher at Subscription Department, Plenum Publishing Corporation, 233 Spring Street, New York, N.Y. 10013 or faxed to the Subscription Department at its number (212) 807-1047, or may be telephoned to the Subscription Department's Journal Customer Service at (212)620-8468, -8470, -8472, or -8082. Subscription rates:

Volume 13, 1996 (12 issues) $575.00 (outside the U.S., $675.00). Prices for individual subscribers certifying that the journal is for their personal use, $129.00 (outside the U.S., $151.00).

Periodicals postage paid at New York, N.Y., and at additional mailing offices. Postmaster: Send address changes to *Pharmaceutical Research*, Plenum Publishing Corporation, 233 Spring Street, New York, N.Y. 10013.

Printed in the USA.

PDD 7473

ORAL ABSORPTION OF XR543, A NEUROTRANSMITTER RELEASE ENHANCER, IN DOGS FROM VARIOUS FORMULATIONS - IN VITRO AND IN VIVO CORRELATION. Shiew-Mei Huang*, Lei-Shu Wu, Maria D. Ribadeneira, Cecilia L. Chi, Philip L. Saxton, Benjamin M. Chien, and Check Y. Quon. The *DuPont Merck Pharmaceutical Company, Newark, DE* 19714

XR543 is a drug candidate for improvement of cognitive performance in patients with Alzheimer's-type dementia. The purpose of this study was to determine the oral bioavailability of XR543 in dogs from various formulations. *In vitro* dissolution (in 0.1% Na dodecyl sulfate [SDS] aqueous solution, at 100 rpm, for 60 min) and Caco-2 permeation (passage 32, non-stagnant conditions) were also determined. XR543 (0.3 mg/kg) in 0.25% MC suspension or capsule formulations were administered to groups of male beagle dogs (n=4/group) under fasting conditions. XR543 levels in plasma were determined by LC/MS/MS (QL=0.1 ng/mL). The results indicate that the dry mix of XR543 and lactose was ~60% as bioavailable as the suspension formulation. The formulations prepared by dissolving XR543 in ethanol or Tween 80/ethanol solution prior to spraying on lactose showed comparably good bioavailability (absolute % F: 25-40%) to the suspension formulations. In vitro studies showed the dissolution and Caco-2 flux rates of the suspension ≥ Tween 80/ethanol = ethanol > dry lactose. Formulations containing dry blending or wet granulation with SDS, which did not improve the dissolution rate, also showed the lowest Caco-2 flux rates *in vitro*. Results of the study indicate that XR543 has a good membrane permeability and its bioavailability *in vivo* appears to be dissolution-limited.

PDD 7474

METHOD OF PREPARING AN ORALLY BIOAVAILABLE SOLID FORMULATION OF AN INSOLUBLE PROTEASE INHIBITOR AS A COPRECIPITATE WITH PVP AND OTHER EXCIPIENTS. D. Martin*, L. Al-Razzak, L. Dias, E. Eiden, R. Gao, D. Kaul, D. Lechuga-Ballesteros, K. Marsh and R. Poska. Pharmaceutical and Analytical R&D, Abbott Laboratories, 1401 Sheridan Road, North Chicago, Illinois, 60064.

In order to enhance the oral bioavailability of a poorly soluble antiviral compound, a coprecipitate with polyvinylpyrrolidone (PVP) was deposited onto a solid substrate. Granulations containing a variety of excipients were prepared using a prototype high shear granulator. A granulating solution (ABT-538, PVP and ethanol), was slowly applied onto a solid substrate followed by drying. The oral dog bioavailability of ABT-538 in the resulting formulations was improved, however, it was highly variable. The *in vivo* variability observed was thought to be related to either poor formation of the coprecipitate due to the lack of process control during drying or enhanced wettability due to the presence of residual solvent. A fluidized bed coating technique (using a STREA-1 fluidized bed coater) was found to be an effective means of controlling the formation and drying of the coprecipitate in the formulation. Spherical particles containing sugar spheres NF and granules consisting of either lactose or microcrystalline cellulose were coated with a *ca.* 10-50 μm film of ABT-538 & PVP coprecipitate. The coprecipitate formulation were qualitatively studied using X-ray powder diffraction and differential scanning calorimetry. ABT-538 was shown to exist in the amorphous state and remained as such for up to 6 months at uncontrolled ambient conditions, and for up to four weeks in a dry oven at 40 °C. Liquid surfactants and solid additives were incorporated into the films to improve wetting and ABT-538 solubility. The oral dog bioavailability was improved at least 10 fold as compared to the unformulated ABT-538.

PDD 7475

PHYSICAL AND ORAL DOG BIOAVAILABILITY EVALUATION OF ABT-538:PVP CO-PRECIPITATES. L. Dias*, L. Al-Razzak, E. Eiden, R. Gao, D. Kaul, D. Lechuga-Ballesteros, K. Marsh and R. Poska, Pharmaceutical and Analytical R&D, Abbott Laboratories, North Chicago, IL 60064.

Polyvinylpyrillodone (PVP) has been used to form co-precipitates of an insoluble antiviral compound, ABT-538, in an effort to increase bioavailability of this drug. PVP:drug co-precipitates were prepared using a solvent evaporation method. Two techniques were used to prepare the PVP:drug co-precipitates namely spray drying and layering onto suitable substrates. Several ratios of drug to PVP and various molecular weight grades of PVP were evaluated in this study using differential scanning calorimetry and X-ray powder diffraction. Preliminary studies indicate that the co-precipitates maintained the drug in an amorphous form which were stable at 80°C and at ambient room temperature/75% RH conditions for two weeks. Evaluation of the encapsulated spray dried material revealed a non-disintegrating mass during dissolution testing and this was reflected in the formulation having no bioavailability. In order to prevent the formation of this non-disintegrating mass and to increase the dissolution rate, the PVP:drug co-precipitate was layered onto substrates like microcrystalline cellulose (MCC) and silicon dioxide since they provided a large layering surface area. Dissolution of the layered substrate showed that all the drug was released in about one hour. However, the increase in dissolution rate was not consistently reflected in increased bioavailability indicating no *in vitro/in-vivo* correlation for this dosage form. The drug:PVP co-precipitates also showed further improvement in bioavailabilities when combined with surfactants and acidifying agents. Preliminary results indicate that a dramatic increase in the bioavailability of ABT-538 could be obtained using formulation modification techniques.

PDD 7476

CYCLODEXTRINS AS POTENTIAL EXCIPIENTS IN TABLET DOSAGE FORMS

Priyashri Nayak* and Sunil Jambhekar,
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The purpose of this study was to evaluate cyclodextrins (CYDs) as excipients with potential for enhancing the dissolution of poorly soluble drugs. Ketoprofen (KPF), a poorly water soluble drug, was selected as a model. Tablets were prepared by wet granulation using β-CYD, hydroxypropyl β-CYD, conventional diluents like lactose and M.C.C., and several combinations of conventional diluents with CYDs. The particle size, bulk and tap density, and the angle of repose of the granules were determined. Tablets were evaluated for the in-vitro dissolution of KPF using a modified reverse phase HPLC method and other parameters such as weight variation, content uniformity, friability, hardness, and disintegration. The dissolution results indicated that the rate and cumulative amount of KPF dissolved from all formulations containing CYDs was greater than those containing lactose and/or M.C.C. alone. It is postulated that the presence of CYDs may improve the wettability of KPF which increases the effective surface area available for dissolution. Alternatively, faster dissolution may be attributed to the formation of a complex between KPF and CYD. [Supported by Zeneca Pharmaceuticals, Inc.]

Ex. 3

Journal of Pharmaceutical Sciences

SEPTEMBER 1971
VOLUME 60 NUMBER 9

REVIEW ARTICLE

Pharmaceutical Applications of Solid Dispersion Systems

WIN LOUNG CHIOU*‡ and SIDNEY RIEGELMAN†

Keyphrases ☐ Solid dispersion systems—review ☐ Dispersions, solid systems—review ☐ Absorption kinetics—solid dispersion systems, review ☐ Dosage forms, fast-release—solid dispersion systems, review

CONTENTS

HISTORICAL BACKGROUND

The effect of the particle size of drugs on their dissolution rates and biological availability was reviewed comprehensively by Fincher (1). For drugs whose GI absorption is rate limited by dissolution, reduction of the particle size generally increases the rate of absorption and/or total bioavailability. This commonly occurs for drugs with poor water solubility. For example, the therapeutic dose of griseofulvin was reduced to 50% by micronization (2), and it also produced a more constant and reliable blood level. The commercial dose of spironolactone was also decreased to half by just a slight reduction of particle size (3). Such enhancement of drug absorption could further be increased several fold if a micronized product was used (3, 4).

Particle-size reduction is usually achieved by: (*a*) conventional trituration and grinding; (*b*) ball milling; (*c*) fluid energy micronization; (*d*) controlled precipitation by change of solvents or temperature, application of ultrasonic waves (5–7), and spray drying (8); (*e*)

administration of liquid solutions from which, upon dilution with gastric fluids, the dissolved drug may precipitate in very fine particles (9); and (*f*) administration of water-soluble salts of poorly soluble compounds from which the parent, neutral forms may precipitate in ultrafine form in GI fluids. Although the reduction of particle size can be easily and directly accomplished by the first four methods (*a–d*), the resultant fine particles may not produce the expected faster dissolution and absorption. This primarily results from the possible aggregation and agglomeration of the fine particles due to their increased surface energy and the subsequent stronger van der Waals' attraction between nonpolar molecules. This was demonstrated by Lin *et al.* (10), who showed that the *in vitro* dissolution rates of micronized griseofulvin and glutethimide were slower than those of their coarser particles. However, the opposite finding for griseofulvin was reported by Chiou and Riegelman (11, 12). Another inherent disadvantage of these pure fine powders of poorly soluble drugs is their poor wettability in water. The wetting of powders is the first step for them to dissolve and sometimes disperse in fluids (13). Furthermore, drugs with plastic properties are difficult to subdivide by methods *a–c*. They have more tendency to stick together, even if fine powders can be produced by controlled precipitation.

Theoretically, the solvent method (*c*) seems to be an ideal approach in achieving particle-size reduction. However, it is not frequently employed in the commercial market due to such reasons as selection of a nontoxic solvent, limitation to drugs with a low dose, and high costs of production. The water-soluble salts of many poorly soluble acidic or basic drugs have been widely used clinically as solid dosage forms. Indeed, they have been shown frequently to produce better absorption than their parent forms. It has been shown that the potassium or sodium salts may react with atmospheric carbon dioxide and water to precipitate out poorly soluble parent compounds. This occurs especially on the outer layer of a dosage form and thereby retards rates of dissolution and absorption. This precipitation effect is believed to be responsible for the slower *in vitro* dissolution rates and the lower novobiocin plasma levels in dogs following the oral administration of its soluble sodium salt rather than the less soluble amorphous form of the parent compound (14). The reported failure of the clinical response from three commercial capsule dosage forms containing sodium diphenylhydantoin may be caused by the same reason (15). In addition, the alkalinity of some salts may cause epigastric distress following administration (16).

In 1961, a unique approach of solid dispersion to reduce the particle size and increase rates of dissolution and absorption was first demonstrated by Sekiguchi and Obi (17). They proposed the formation of a eutectic mixture of a poorly soluble drug such as sulfathiazole with a physiologically inert, easily soluble carrier such as urea. The eutectic mixture was prepared by melting the physical mixture of the drug and the carrier, followed by a rapid solidification process. Upon exposure to aqueous fluids, the active drug was expected to be released into the fluids as fine, dispersed particles because of the fine dispersion of the drug in the solid eutectic mixture and the rapid dissolution of the soluble matrix. Levy (9) and Kanig (18) subsequently noted the possibility of using a solid solution approach in which a drug is dispersed molecularly in a soluble carrier. In a series of reports in 1965–1966, Goldberg *et al.* (19–22) presented a detailed experimental and theoretical discussion of advantages of the solid solution over the eutectic mixture.

In 1965, Tachibana and Nakamura (23) reported a novel method for preparing aqueous colloidal dispersions of β-carotene by using water-soluble polymers such as polyvinylpyrrolidone. They dissolved the drug and the polymer carrier in a common solvent and then evaporated the solvent completely. A colloidal dispersion was obtained when the coprecipitate was exposed to water. In 1966, Mayersohn and Gibaldi (24) demonstrated that the dissolution rate of griseofulvin could be markedly enhanced when dispersed in polyvinylpyrrolidone by the same solvent method. The mechanisms of increased dissolution rates of drugs, solid dispersed in polyvinylpyrrolidone carriers, were thoroughly discussed by Simonelli *et al.* (25, 26). Chiou and Riegelman (11) recently advocated the application of glass solutions to increase dissolution rates. The significance of the solid dispersion technique was strengthened by the demonstration of Chiou and Riegelman (27–29) of the fast and almost complete absorption of the insoluble griseofulvin in man and dogs while the commercial micronized griseofulvin was incompletely absorbed (30–60%). They used polyethylene glycol 6000 as a dispersion carrier. The main advantages of using water-soluble polymers as carriers are their nontoxicity and general applicability to most drugs.

It is believed that this relatively new field of pharmaceutical technique and principles will play an important role in increasing dissolution, absorption, and therapeutic efficacy of drugs in future dosage forms. Therefore, a thorough understanding of its fast-release principles, methods of preparation, selection of suitable carriers, determination of physical properties, limitations, and disadvantages will be essential in the practical and effective application of this approach. The main purpose of this article is to review critically the hitherto limited pharmaceutical literature pertinent to this area. Since a great amount of excellent work on solid dispersion systems has been accumulated in the sciences of metallurgy, geology, and chemistry, a brief summary of some of these findings would be extremely helpful in the future study and understanding of pharmaceutical applications of solid dispersion systems. One major objective of this review article is to introduce and correlate these works to possible pharmaceutical applications.

In addition to absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications which remain to be further explored. It is possible that such a technique can be used to obtain a homogeneous distribution of a small amount of drugs at solid state, to stabilize unstable drugs, to dispense liquid or gaseous compounds, to formulate a fast-release priming dose in a sustained-release dosage form, and to formulate sustained-

release or prolonged-release regimens of soluble drugs by using poorly soluble or insoluble carriers. It is hoped that this review paper will stimulate interest and research in these unexplored areas.

DEFINITION AND METHODS OF PREPARATION OF SOLID DISPERSIONS

Definition—It seems suitable here to define the term "solid dispersions" as used in this paper. The term refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting–solvent method. The dispersion of a drug or drugs in a solid diluent or diluents by traditional mechanical mixing is not included in this category. The solid dispersions may also be called solid-state dispersions, as first used by Mayersohn and Gibaldi (24). The term "coprecipitates" has also been frequently used to refer to those preparations obtained by the solvent methods such as coprecipitates of sulfathiazole–polyvinylpyrrolidone (25) and reserpine–polyvinylpyrrolidone (30). Since the dissolution rate of a component from a surface is affected by the second component in a multiple-component mixture (31), the selection of the carrier has an ultimate influence on the dissolution characteristics of the dispersed drug. Therefore, a water-soluble carrier results in a fast release of the drug from the matrix, and a poorly soluble or insoluble carrier leads to a slower release of the drug from the matrix. This review paper primarily deals with fast-release solid dispersions, although some principles discussed later may also be applied to slow-release solid dispersion systems. To achieve a faster release of a drug from the matrix, it is generally necessary that the active drug be a minor component in the dispersion system in terms of the percent weight (not on molar basis).

Methods of Preparation—*Melting Method*—The melting or fusion method was first proposed by Sekiguchi and Obi (17) to prepare fast-release solid dispersion dosage forms. The physical mixture of a drug and a water-soluble carrier was heated directly until it melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved. Such a technique was subsequently employed with some modification by Goldberg *et al.* (20–22) and Chiou and Riegelman (11). To facilitate faster solidification, the homogeneous melt was poured in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. The solidified masses of drug–polyethylene glycol polymer systems were often found to require storage of 1 or more days in a desiccator at ambient temperatures for hardening and ease of powdering (11). Some systems, such as griseofulvin and citric acid, were found to harden more rapidly if kept at 37° or higher temperatures (11, 32).

The main advantages of this direct melting method are its simplicity and economy. In addition, a supersaturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature (34). Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. Similarly, a much finer dispersion of crystallites was obtained for systems of simple eutectic mixtures if such quenching techniques were used (34, 35). The disadvantage is that many substances, either drugs or carriers, may decompose or evaporate during the fusion process at high temperatures. For example, succinic acid, used as a carrier for griseofulvin (21), is quite volatile and may also partially decompose by dehydration near its melting point (36). However, this evaporation problem can be avoided if the physical mixture is heated in a sealed container. Melting under vacuum or a blanket of an inert gas such as nitrogen may be employed to prevent oxidation of the drug or carrier (37).

The melting point of a binary system is dependent upon its composition, *i.e.*, the selection of the carrier and the weight fraction of the drug in the system (33). By proper control, the melting point (the temperature at which the mixture completely melts) of a binary system may be much lower than the melting points of its two components. Under such a condition, this simple melting method can still be used to prepare solid dispersions, even if the pure drug may undergo decomposition at or near its melting point. This principle was used to prepare solid dispersions of steroids and a cardiac glycoside in polyethylene glycol 6000 (38) and that of griseofulvin in pentaerythritol (11).

Solvent Method—This method has been used for a long time in the preparation of solid solutions or mixed crystals of organic or inorganic compounds (33). They are prepared by dissolving a physical mixture of two solid components in a common solvent, followed by evaporation of the solvent. This method was used to prepare solid dispersions of β-carotene–polyvinylpyrrolidone (23), griseofulvin–polyvinylpyrrolidone (24), sulfathiazole–polyvinylpyrrolidone (25), steroid–polyvinylpyrrolidone (26), reserpine–polyvinylpyrrolidone (30), and reserpine–deoxycholic acid (39).

The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents. However, some disadvantages associated with this method are the higher cost of preparation, the difficulty in completely removing liquid solvent, the possible adverse effect of the supposedly negligible amount of the solvent on the chemical stability of the drug, the selection of a common volatile solvent, and the difficulty of reproducing crystal forms. In addition, a supersaturation of the solute in the solid system cannot be attained except in a system showing highly viscous properties, as is discussed later. It must be emphasized that the suitability of the solvent method to prepare simple eutectics or partial solid solutions remains to be studied further because their final physical properties may be quite different from those obtained by the melting method.

Melting–Solvent Method—It was shown recently that 5–10% (w/w) of liquid compounds could be incorporated into polyethylene glycol 6000 without significant loss of its solid property (40). Hence, it is

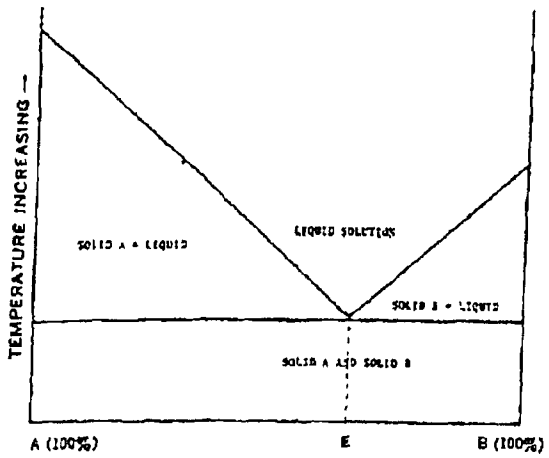


Figure 1—*Phase diagram of a simple eutectic mixture with negligible solid solubility.*

possible to prepare solid dispersions by first dissolving a drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, obtainable below 70°, without removing the liquid solvent. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of polyethylene glycol. The polymorphic form of the drug precipitated in the solid dispersion may be affected by the liquid solvent used. Such a unique method possesses the advantages of both the melting and solvent methods. Unfortunately, from a practical standpoint, it is only limited to drugs with a low therapeutic dose, *e.g.*, below 50 mg. The feasibility of this method was demonstrated on spironolactone–polyethylene glycol 6000 and griseofulvin–polyethylene glycol 6000 systems (41). Its application to other drugs and carriers, however, remains to be explored.

CLASSIFICATION AND FAST-RELEASE MECHANISMS

Although solid dispersion systems may include more than two components, for the sake of simplicity and practicality, this article is primarily limited to binary systems. As a measure of the interaction between the two components, 30 different phase diagrams were proposed for binary alloy systems (42). Vasil'ev (43) further classified phase diagrams according to: (*a*) the relative strength of interaction between similar and different atoms, and (*b*) the limiting permissible degree of deformation of the energy field of the liquid solvent or its crystal lattice in the solid state. While it is believed that these classifications can also be applied to most organic drugs, in this article it is felt more appropriate to classify various systems of solid dispersions on the basis of their major fast-release mechanisms. Accordingly, they are discussed in the following six groups: Group 1, simple eutectic mixtures; Group 2, solid solutions; Group 3, glass solutions and glass suspensions; Group 4, amorphous precipitations of a drug in a crystalline carrier; Group 5, compound or complex formations between the drug and the carrier; and Group 6, any combinations among Groups 1–5. The methods used to identify these systems are reviewed in the next section.

Simple Eutectic Mixtures—The simple eutectic mixture is usually prepared from the rapid solidification of the fused liquid of two components which show complete liquid miscibility and negligible solid–solid solubility (33). These properties can be illustrated in a phase diagram (Fig. 1). Thermodynamically, such a system is regarded as an intimately blended physical mixture of its two crystalline components (19, 33, 34).

When a eutectic (Composition E in Fig. 1) composed of a poorly soluble drug is exposed to water or GI fluids, the carrier may be released into aqueous medium in fine crystalline form (17). This is based on the assumption that both components may simultaneously crystallize out in very small particulate sizes (33). The increase of the specific area due to this reduction of particle size generally increases rates of dissolution and oral absorption of poorly soluble drugs. Ultrafine or colloidal crystallites of eutectics can be found in such examples as tin–lead (34) and naphthalene–phenanthrene (44) systems. In addition to the reduction of the crystallite size, the following factors may contribute to the faster dissolution rate of a drug dispersed in the eutectic:

1. An increase in drug solubility may occur if the majority of its solid crystallites are extremely small (45).

2. A possible solubilization effect by the carrier may operate in the microenvironment (diffusion layer) immediately surrounding the drug particle in the early stage of dissolution since the carrier completely dissolves in a short time. This was demonstrated by the faster dissolution rate of acetaminophen from its physical mixture with urea than that of the pure compound with comparable particle size (22). This hypothesis was further supported by a marked increase of acetaminophen solubility in the presence of urea in water (22). A similar rationale was also given to the enhancement of dissolution rates of reserpine from a physical mixture of reserpine and polyvinylpyrrolidone (30).

3. The absence of aggregation and agglomeration between fine crystallites of the pure hydrophobic drug may play a far more important role in increasing rates of dissolution and absorption than is presently recognized by research workers in this field. An aggregate is defined as a particle or an assembly of particles held together by strong inter- or intramolecular or atomic cohesive forces (46). Usually the aggregate is stable to high-speed mixing or ultrasonic forces. An agglomerate is defined as a gathering of two or more particles and/or aggregates held together by relatively weak cohesive forces. In many cases, these forces are due to an electrostatic surface charge generated during handling or processing operations (46). It is also likely that these electrostatic forces may be involved only in bringing particles together, but they are not responsible for holding them together. Such agglomeration is more severe for very finely divided particles (about 0.1 μ) due to the greater specific surface charge. Although the agglomerates may be broken, their dispersion in the mildly stirred GI fluids may not be very efficient. As mentioned previously, these problems of aggregation and agglomeration are most

detrimental to the application and efficacy of pure fine particles because their effective specific surface area is markedly reduced[1]. Serious drawbacks of aggregation and agglomeration and lumping in the dissolution medium between pure drug particles are, however, rarely present in most solid dispersion systems because the individually dispersed particles are surrounded in the matrix by carrier particles. It must be emphasized that the aggregation and agglomeration of the solid dispersion powders may not significantly affect the dissolution of the drug, which can still disintegrate quickly due to the more rapid dissolution of the soluble carrier. Such a unique advantage of solid dispersion systems was demonstrated in the *in vivo* absorption (28, 29) of griseofulvin when dispersed in polyethylene glycol 6000 (10% w/w) and compressed into a hard tablet. As discussed later, the 10% griseofulvin dispersion in polyethylene glycol 6000 contains at least half of the griseofulvin in the finely dispersed crystalline form. The dissolution rates of the pure and dispersed griseofulvin are shown in Fig. 2.

4. Excellent wettability and dispersibility of a drug from a eutectic or other solid dispersion system prepared with a water-soluble matrix result in an increased dissolution rate of the drug in aqueous media. This is due to the fact that each single crystallite of the drug is very intimately encircled by the soluble carrier which can readily dissolve and cause the water to contact and wet the drug particle. As a consequence, a fine homogeneous suspension of a drug can be easily obtained with minimum stirring (17). These striking advantages were observed by the authors with various drug–polyethylene glycol solid dispersions. In contrast, the aggregates and agglomerates of poorly soluble pure powders are surrounded by the nonpolar air, which is hard to penetrate or displace by water.

5. An increased rate of dissolution and absorption may also occur if a drug crystallizes in a metastable form after solidification from the fused solution. A metastable, crystalline form has a higher solubility which, in turn, leads to a faster dissolution rate according to the well-known Noyes–Whitney equation. Interested readers should consult an excellent review paper by Haleblian and McCrone (47) on the pharmaceutical applications of polymorphism. The high possibility of the polymorphic crystallization during the preparation of solid dispersions can be seen from the facts that many compounds can exhibit polymorphism. For example, 67% of steroids, 43% of sulfonamides, and 63% of barbiturates were shown to exhibit polymorphism in an extensive survey by Kuhnert-Brandstätter (48). It must be noted that the existence of a different polymorphic form or forms results in a phase diagram differing from that shown in Fig. 1 (47).

[1] Peculiar examples were encountered by the authors when 125 mg. of the pure micronized griseofulvin and 100–200-mesh griseofulvin, loosely packed in a No. 3 gelatin capsule, were studied for dissolution rates in 18 l. of water at 37° under a fairly vigorous stirring condition (*Reference 11*; the capsule kept in a cylindrical container, 5 × 3 cm., made of No. 8 mesh stainless steel screen and moved by a standard USP disintegration apparatus). The griseofulvin lumped together as a single mass even after 4–6 hr. of study, and dissolution only took place at the surface of the mass. This phenomenon was also noted in a commercial capsule product of griseofulvin.

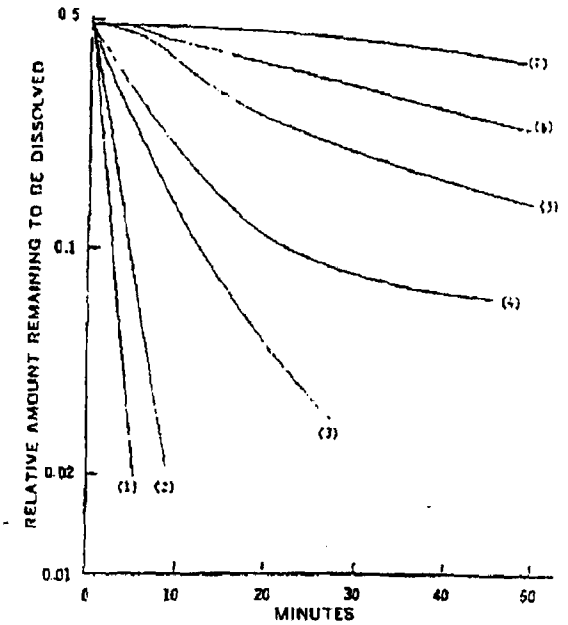


Figure 2—Griseofulvin dissolution-rate data (amount remaining to be dissolved) from 125 mg. in 18 l. of water at 36.7°. Key: (1), 10% griseofulvin–polyethylene glycol 6000 powder; (2), 20% griseofulvin–polyethylene glycol 6000 powder; (3), 40% griseofulvin–polyethylene glycol 6000 powder; (4), wetted, micronized griseofulvin powder; (5), nonwetted, micronized griseofulvin powder; (6), micronized griseofulvin in capsule; and (7), 100–200-mesh griseofulvin powder in capsule.

In addition to the possible aforementioned differences between the eutectics and the physical or mechanical mixtures, the rapidly crystallized (quenched) eutectics are characterized by increased hardness (49). This was explained on the basis of a high degree of strain resulting from the action of mechanical forces. The effect of such increased hardness on the dissolution rate, however, remains to be explored. Savchenko (49) advocated that a eutectic is formed by some sort of loose molecular or atomic interaction which does not involve the formation of a chemical bond. This is thought to relate to some of the changes in physical properties of eutectic alloys such as a reduction in electrical conductivity, vapor pressure, and thermal effects. It must be emphasized that a slow process of cooling and solidification from the melt may not result in fine dispersion of the phases (49), which is primarily responsible for the higher dissolution rate of the drug.

The composition of a eutectic may have a significant effect on the particle size of the crystallite. If it is made up of a high weight fraction of drug, an ultrafine crystallization of the drug may not be obtained. This is logical if one expects that the higher the dilution, the finer the crystalline size of its precipitate. This probably accounts for the failure to find an increased dissolution rate of acetaminophen from the eutectic with urea which contains 52% of the acetaminophen (20). It is believed that the hardening effect of the eutectic may also play a role in retarding its dissolution.

Recently, Chiou (50) contended that the system of chloramphenicol–urea should be described as a simple eutectic mixture with negligible solid–solid solubility

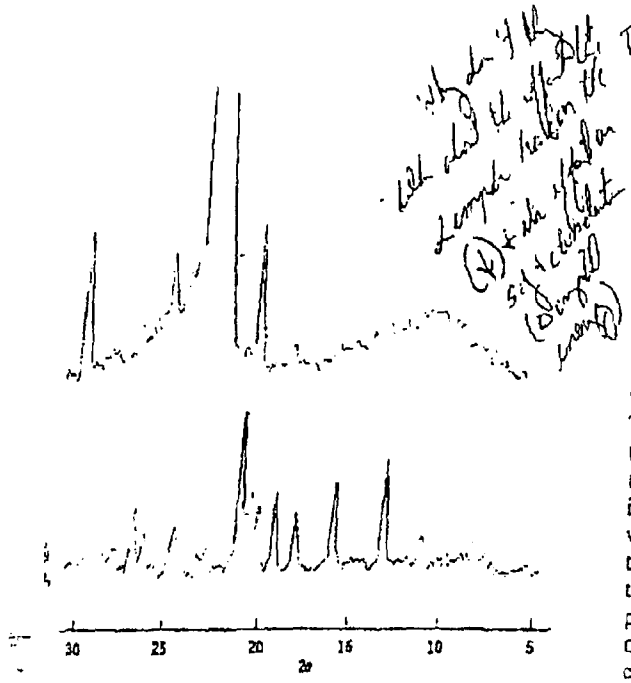


Figure 3—*X-ray diffraction spectra of pure chloramphenicol (bottom) and pure urea (top).*

rather than an extensive, partial solid solution as previously proposed by Sekiguchi *et al.* (51) and Goldberg *et al.* (22). This appears to be supported by differential thermal analysis (DTA) and X-ray diffraction data. The endothermic peaks of 2.5 and 97% chloramphenicol resolidified samples at the eutectic temperature (51) indicate that the samples started to thaw at that temperature. If their compositions did not belong to a simple eutectic system, then the thaw points should begin at a higher temperature (52).

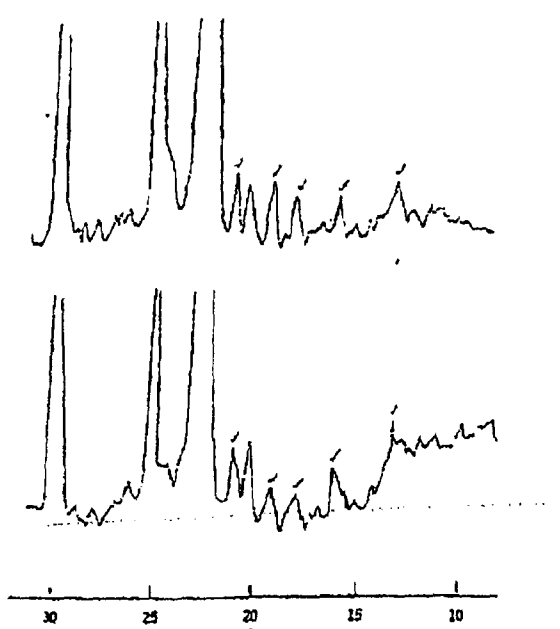


Figure 4—*X-ray diffraction spectra of a physical mixture of 10% chloramphenicol–90% urea (bottom) and resolidified fused mixture of 10% chloramphenicol–90% urea (top). Arrows indicate diffraction peaks due to the presence of chloramphenicol crystallites.*

In the previously proposed phase diagram, chloramphenicol was shown to dissolve in the solid urea at a concentration of 25% (w/w). To investigate this system further, diffraction spectra were obtained from a Norelco X-ray diffractometer using CuKα radiation. The spectra of pure chloramphenicol, pure urea, and the physical mixture and resolidified mixture of 10% chloramphenicol are shown in Figs. 3 and 4. The presence of the typical X-ray diffraction peaks of chloramphenicol in the freshly prepared, quenched sample of 10% chloramphenicol unmistakably indicates that the sample is not a solid solution but a eutectic mixture. The height of these peaks, which are comparable with those obtained from the physical mixture, also indicates the negligibility of solid solubility. The slight increase in dissolution rate of the eutectic (75% chloramphenicol w/w) over the pure chloramphenicol (22) may be due to a coarser particle size of chloramphenicol crystallization and the hardening effect of the eutectic. The small particle size of the precipitate at the lower concentration of the chloramphenicol, however, may be primarily contributory to the reported attainment of supersaturation and marked enhancement of dissolution rate from 25% solid dispersion (22, 51). It is further expected that a much faster dissolution rate may be obtained from the lower concentrations of the chloramphenicol in such a eutectic mixture.

From their microthermal microscope studies, Goldberg *et al.* (21) reported that griseofulvin, a water-insoluble antibiotic, forms a solid solution with succinic acid at a concentration of 25% w/w. The dissolution rate from such dispersions was found to be several times higher than that of the micronized griseofulvin. Furthermore, a supersaturation of about 250% of the solubility was also observed. Chiou and Niazi (53) recently concluded from their DTA and X-ray diffraction studies that such a binary system is a simple eutectic mixture with negligible solid solubility. The dissolution rates of griseofulvin were found to increase as the concentration of griseofulvin in the solid dispersion decreased.

Solid Solutions—A solid solution, compared to a liquid solution, is made up of a solid solute dissolved in a solid solvent. It is often called a mixed crystal because the two components crystallize together in a homogeneous one-phase system (33). In their theoretical paper, Goldberg *et al.* (19) suggested that a solid solution of a poorly soluble drug in a rapidly soluble carrier achieves a faster dissolution rate than a eutectic mixture because the particle size of the drug in the solid solution is reduced to a minimum state, i.e., its molecular size. In other words, the dissolution of the drug takes place in the solid state prior to its exposure to the liquid medium. In addition to such maximum size reduction, other factors such as Factors 1–4 discussed under *Simple Eutectic Mixtures* may contribute to increased rates of dissolution and absorption of drugs dispersed in solid solutions. It must be emphasized that the advantage of a solid solution may not be so significant if the solid solution is exposed to a medium with a volume much less capable to dissolve all the drug. Under these conditions, a drug may precipitate. However, due to the maximum particle-size reduction

in the solid solution and to the possible solubilization effect of the carrier in the microenvironmental diffusion layer of bulk fluids, the drug may temporarily result in a high supersaturation of the bulk fluid. Obviously, this is temporary and would lead to precipitation if the drug is not being absorbed or removed by other processes.

Solid solutions can generally be classified according to the extent of miscibility between the two components or the crystalline structure of the solid solution (33, 34, 54). Based on the former criterion, they can be divided into two groups: continuous (or isomorphous, unlimited, complete) solid solutions and discontinuous (or limited, restricted, partial, incomplete) solid solutions. According to the latter criterion, they can also be classified into two groups: substitutional solid solutions and interstitial solid solutions. The important physical properties of each group are reviewed briefly.

Continuous Solid Solution—In this system, the two components are miscible or soluble at solid state in all proportions (Fig. 5). No established solid solution of this kind has been shown to exhibit fast-release dissolution properties, although it is theoretically possible. It is obvious that a faster dissolution rate would be obtained if the drug is present as a minor component. However, the presence of a small amount of the soluble carrier in the crystalline lattice of the poorly soluble drug may also produce a dissolution rate faster than the pure compound with similar particle size. This may be due to a small number of the neighboring drug molecules holding the dissolving drug molecule after the rapid dissolution of the neighboring water-soluble carrier. The total lattice energy of the continuous solid solution at various compositions theoretically should be greater than that of either pure component, because the strength of bond between the two different components at the solid state, U_{AB}, should be greater than that between the same species of molecules, U_{AA} and U_{BB}, in order to form a continuous solid solution (33). The solid solution above the temperature of the miscibility gap, as shown in Fig. 5, is also thermodynamically stable, with a free energy lower than that anticipated from the mixture law (54, 55). The miscibility gap noted in Fig. 5 may occur as a result of limited solid-state solubility at lower temperatures. The implication of this phenomenon is discussed later in this article.

Discontinuous Solid Solution—In contrast to the continuous solid solution, there is only a limited solubility of a solute in a solid solvent in this group of solid solutions. This can be best depicted in a standard phase diagram (Fig. 6). The regions of solid solutions in this diagram are shown as the α and β regions. Each component shown is capable of dissolving the other component to a certain degree above the eutectic temperature. However, as the temperature is lowered, the solid solution regions become narrower. The implication of the decreasing solubility with declining temperature is discussed later. The free energy of a stable, limited solid solution is also lower than that of the pure solvent (55).

In reality, some solid-state solubility can be expected for all two-component systems (19, 34). However, the degree of solubility is usually small enough to be considered negligible. Goldberg *et al.* (19) suggested that, for practical purposes, solubility of greater than 5% of one component in the other could be considered to be a solid solution. It is felt that such a criterion is not adequate. Sensitive instruments now allow the detection of solid solution formation below a 5% level. Furthermore, many drugs with low therapeutic doses (*e.g.*, below 25 mg.) can be practically incorporated into solid solutions at concentrations of less than 5%.

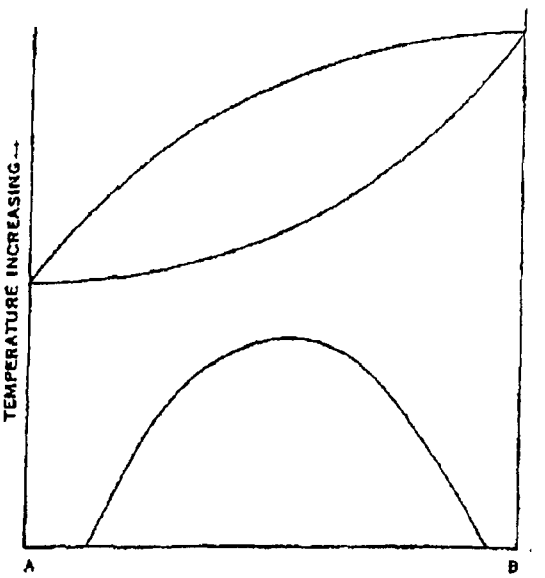


Figure 5—*A typical phase diagram of continuous solid solution of a binary system, A and B. The lowest curve indicates a solubility gap at lower temperatures.*

The phase diagram of a sulfathiazole–urea binary system was studied by thermal analysis (17). It was interpreted as a system of limited solid solution, in which the maximum solubility of sulfathiazole is about 10% w/w and that of urea is about 8% w/w (19). The eutectic composition is located at 52% of sulfathiazole. Therefore, the eutectic of this system is

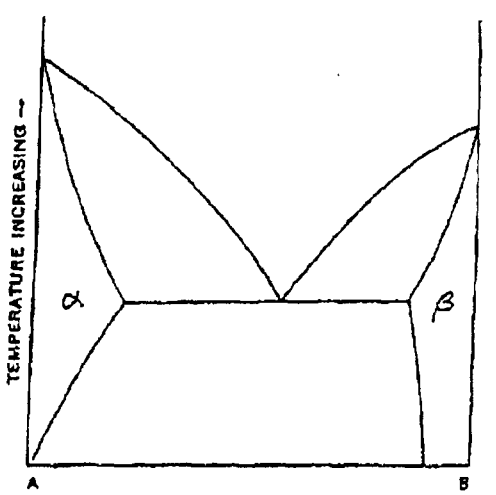


Figure 6—*A typical phase diagram of a discontinuous solid solution of a binary system, A and B. α and β are regions of solid solution formation*

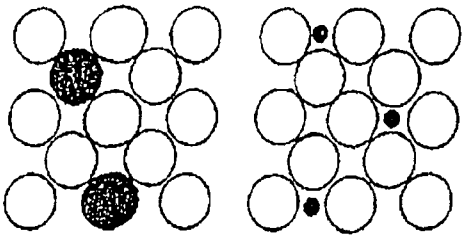


Figure 7—*Right diagram shows the formation of an interstitial solid solution, and left diagram shows the formation of a substitutional solid solution. Dark circles indicate solute atoms or molecules, while open circles indicate solvent atoms or molecules (from* Reference 54, *reprinted with permission).*

theoretically a physical mixture of two solid solutions, α and β. The faster absorption rates found in man with this eutectic mixture were claimed to be primarily due to these solid solutions. However, it was also recently noted by Chiou and Niazi (56), from their X-ray diffraction studies, that sulfathiazole is mainly present as an amorphous form (more correctly a glass solution) in the freshly prepared eutectic. No significant amount of sulfathiazole was found to crystallize when kept at 27° for 2 weeks. It was proposed that such an amorphous form, with a solubility much greater than the crystalline form (25), was an important contributing factor to the increased rate of dissolution and absorption.

Substitutional Solid Solution—In this type of solid solution, the solute molecule substitutes for the solvent molecule in the crystal lattice of the solid solvent. A schematic diagram is shown in Fig. 7. It can form a continuous or discontinuous solid solution. The size and steric factors of the solute molecule were shown to play a decisive role in the formation of solid solutions (33, 34, 43, 54). The size of the solute and the solvent molecule should be as close as possible. According to the Hume-Ruthery rule (54, 57), an extensive solid solution can be formed only when the effective diameter of the solute differs less than 15% from that of the solvent. This has been experimentally proven in a variety of solid solutions of metals and inorganic compounds.

Timmermans (60) proposed a term called the degree of molecular isomorphism to express the degree of similarity of the shape of the two components. He superimposed the two molecules and calculated the overlapping volume, r, and the nonoverlapping volume, Δ. The degree of molecular isomorphism, e, is then equal to $1 - \Delta/r$. From his extensive studies of phase diagrams of organic compounds, he found that wide or complete solubility required the value of e to be around 0.9. Examples of continuous solid solutions of systems include mixtures of *p*-dibromobenzene–*p*-chlorobromobenzene (61) and anthracene–acenaphthene (62).

The distortion of the crystal lattice of the solvent by the steric effect or chemical interaction (63) is also important. The solubility of the solute increases until the distortion of the lattice field of the solvent by the solute molecule can no longer be tolerated. For example, naphthalene (59) can form solid solutions with its β-derivatives substituted with halogens, hydroxyl, or amino groups but it only forms eutectic mixtures with its α-substituted derivatives. However, e values are the same for the pairs of α- and β-derivatives with naphthalene.

Frequently, water-insoluble drugs contain halogens, hydroxyl, methyl, methoxy, or other small functional groups. It might be possible to synthesize relatively inert soluble congeners by substituting a specific functional group which will change the physical properties with minimal changes in the degree of molecular isomorphism. It is expected that the insoluble drugs and the congeners can possibly form wide ranges of solid solutions due to their similarity in size and shape. Under such conditions, the relatively inactive soluble derivatives can serve as carriers for the active drugs. Such a combination may result in more rapid dissolution and absorption.

It is well known that globular or plastic compounds form a wide range of solid solutions above their plastic points. For example, pairs of cyclopentane–2,2-dimethylbutane (64) and chemically unrelated methane and argon (65) form continuous solid solutions at appropriate temperatures. Typical properties of globular or plastic compounds are (64): (*a*) low entropy of fusion, usually less than 5 e.u.; (*b*) high triple-point temperature and pressure; (*c*) crystals, usually of cubic or hexagonal symmetry, which are clear (almost glasslike), tacky, and easily deformed; and (*d*) one or more energetic transitions in the solid state. The reasons for their mutual solubility are the similarity in their symmetry and almost free rotation (hence, low lattice energy) above their plastic points. Since plastic compounds have the lowest lattice energy and strain, it is reasonable to expect that they will more easily accommodate all kinds of molecules in their crystal lattice.

Pentaerythritol, a typical plastic compound (64) with an entropy of fusion of 3.2 e.u., was selected as a carrier to disperse griseofulvin (11). The 10% griseofulvin dispersion was found to dissolve much faster than micronized griseofulvin. In addition, a supersaturation was rapidly obtained when an excess amount was studied. Its potential usage as a carrier for other drugs, however, remains to be further explored. A similar carrier, pentaerythritol tetraacetate, was also shown to enhance the dissolution rate of griseofulvin (11). The phase diagrams of both systems have not been established. A comprehensive listing of globular molecules and some skeleton structures with low entropies of fusion was compiled by Ubbelohde (66). Interested readers should consult it for their possible applications.

Interstitial Solid Solution—In this type of solid solution, the solute (guest) molecule occupies the interstitial space of the solvent (host) lattice. A schematic diagram is shown in Fig. 7. It usually forms only a discontinuous (limited) solid solution. The size of the solute is critical in order to fit into the interstices (34, 54). It was found that the apparent diameter of the solute atom should be less than 0.59 that of the solvent (54) in order to obtain an extensive interstitial solid solution of metals. From this, one may calculate that the volume of the solute should be less than 20% of

the solvent. It is likely that the principle can also be applied to organic compounds. Water-soluble crystalline polymers of high molecular weight appear to be logical choices for this type of solid solution of insoluble drugs, since the molecular weight of most organic drugs is usually less than 1000. Low toxicity and lack of absorption from the GI tract are the advantages of polymer carriers.

Polyethylene glycols of 4000, 6000, and 20,000 molecular weights are crystalline, water-soluble polymers with two parallel helixes in a unit cell (67). It is predicted that significant amounts of drug can be trapped in the helical interstitial space when polyethylene glycol–drug melts are solidified. Such systems were prepared using griseofulvin, digitoxin, methyltestosterone, prednisolone acetate, and hydrocortisone acetate in the matrix of polyethylene glycol 6000. They all possess a fast rate of dissolution (11, 38). The results of these dissolution studies, except for griseofulvin, are summarized in Table I. The griseofulvin dispersed in polyethylene glycol 4000 and 20,000 was also shown to have a marked increase in dissolution rate (11). Indomethacin dispersed in polyethylene glycol 6000 was also shown to produce a faster dissolution rate (68).

In addition to the large molecular size of the polymers favoring the formation of thermodynamically stable interstitial solid solutions, other factors such as high viscosity, supercooling, and physical–chemical interaction between the drugs and the polymers may contribute to the formation of metastable solid solutions if the drug–polyethylene glycol melt is solidified rapidly. The melt of polyethylene glycol polymers is highly viscous, even at a temperature of 200° (67). Furthermore, the viscosity increases rapidly with the decrease in temperature. Therefore, as drug–polyethylene glycol melt is allowed to solidify quickly, the crystallization of the drug is retarded due to reduced solute migration and the difficulty in nucleation of the drug in the viscous medium (11, 64, 69).

Although the melting points of some polyethylene glycol polymers are higher than 50°, they can often be supercooled to below 40° (11). Such supercooling phenomena were also observed with the drug–polyethylene glycol mixture. For example, it was found feasible to supercool 10, 20, and even 40% of griseofulvin in polyethylene glycol 4000 or 6000 to about 40° before solidification started, although their upper melting points (when mixtures completely melt) ranged from about 150 to 200°. The possible physical or chemical interaction between drugs and polyethylene glycol polymers has been well documented, as demonstrated by their solubilization effect in the aqueous medium (45, 72). It is believed that such interaction may also exist in the drug–polyethylene glycol melt and may contribute to the retardation of crystallization of the pure drugs. In the case of griseofulvin, its solubility was found to increase onefold in the 7% (w/w) polyethylene glycol 6000 aqueous solution (41).

The possibility of the existence of a metastable solid solution of a drug in polyethylene glycol was investigated in quenched 5% griseofulvin–95% polyethylene glycol 4000 and 5% griseofulvin–95% polyethylene glycol 6000 (41). The freshly quenched samples of both systems showed no noticeable X-ray diffraction peaks of the crystalline griseofulvin, while their powdered samples exhibited such peaks. It was suggested that the powdering process might cause some of the supersaturated griseofulvin in the metastable solid solution to precipitate out. Therefore, the solid solubility of griseofulvin in polyethylene glycol 4000 or 6000 is much less than 5%. The X-ray diffraction spectra of the griseofulvin–polyethylene glycol 6000 system are shown in Figs. 8 and 9. Similar findings were also reported for the 10% indomethacin–90% polyethylene glycol 6000 solid dispersion (68). In 10 and 20% griseofulvin dispersed in polyethylene glycol 6000, both the pulverized and nonpulverized quenched samples showed the diffraction spectra of crystalline griseofulvin. This is because the concentrations of griseofulvin now exceeded its maximum solid solubility in the polyethylene glycol.

In addition to working as a universal solvent for the formation of stable or metastable limited solid solutions of most drugs, the polyethylene glycol can also be expected to produce an ultrafine or colloidal crystallization of the pure drug if its concentration is much greater than its solid solubility and the drug–polyethylene glycol melt is solidified rapidly (11). This is mainly due to the difficulty of growth of the crystallite in a highly viscous medium and the short time interval for the completion of solidification. This is often referred to by some surface chemists as the transition from primary to secondary nucleation. The phenomenon is well known and is taken advantage of in the preparation of single crystals in microelectronics. It is also the method by which doped crystals are prepared to render specific physical properties in a system in which a material is crystallized in a retarded manner due to solute depletion in the immediate environment affecting crystal growth. The highly possible physical–chemical interaction between the drug and polyethylene glycol may also play a role in preventing the crystalline growth. Such a contention is indirectly supported by a recent study of the ability of polyvinylpyrrolidone to inhibit the crystalline growth of sulfathiazole and methylprednisolone in

Table I—Twenty, Fifty, and Seventy Percent Dissolution Times for Selected Drugs in Various Physical Forms in Half-Saturation Dissolution Test

Preparations	T_{20}, min.	T_{50}, min.	T_{70}, min.
Pure prednisolone acetate*	8.0	45.0	—
Fused mixture of prednisolone* acetate–polyethylene glycol 6000 (5:95 w/w)	≪1.0	≪1.0	~0.6
Pure 17-methyltestosterone	2.0	12.0	28.0
Fused mixtures of 17-methyltestosterone–polyethylene glycol 6000 (5:95 w/w)	≪1.0	≪1.0	~0.6
Pure hydrocortisone acetate	20.0	—	—
Fused mixture of hydrocortisone acetate–polyethylene glycol 6000 (5:95 w/w)	≪1.0	≪1.0	1.5
Pure microcrystalline digitoxin	15.0	80.0	—
Fused mixture of digitoxin–polyethylene glycol 6000 (2:98 w/w)	≪1.0	≪1.0	0.3–0.5

* This test system utilized only 30% saturation.

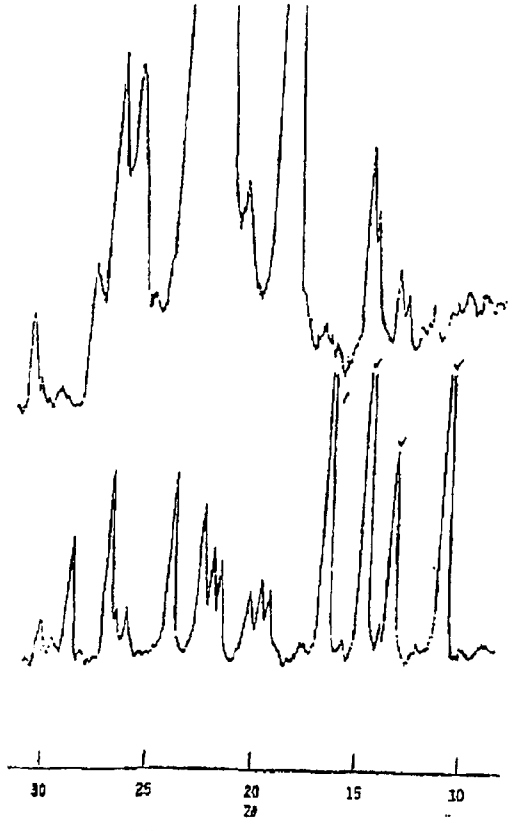


Figure 8—X-ray diffraction spectra of pure griseofulvin (bottom) and pure polyethylene glycol 6000 powders (top).

water, even at a very low concentration (73). The adsorption of the polyvinylpyrrolidone on the crystalline surface was used to explain such a phenomenon. It seems logical to assume that the polyethylene glycol polymer may also act as a protective colloid in retarding the coagulation, aggregation, or coarsening of the fine crystallites before solidification. The possibility of an ultrafine or colloidal dispersion of drugs in polyethylene glycol polymers is demonstrated by the fact that even the solid dispersion of 40% griseofulvin–60% polyethylene glycol 6000 showed a faster dissolution rate than the wetted micronized griseofulvin (11). It is believed that this rationale for employing polyethylene glycol polymers as ideal solid-dispersing carriers may also be applied to other soluble polymers. As mentioned, the short interval of solidification is critical in the formation of metastable solid solutions from the viscous melt of drug–polyethylene glycol systems. Therefore, in the solvent method of preparation, the control of temperature and time of evaporation are very important to the final physical properties of the solid dispersions (11). It was found that big crystals of griseofulvin were formed if the griseofulvin–polyethylene glycol 6000–ethanol mixture was kept at high temperatures (*e.g.*, 120°) for a relatively long period (0.5–2 hr.).

A patent was obtained for the use of water-soluble polymers such as polyethylene glycol, polyoxyethylene esters or ethers, polyoxyethylene sorbitan esters, or their mixtures that form solid solutions of insoluble estrogens for preparation of pessary dosage forms (74). The estrogen was claimed to be precipitated in an extremely fine state of subdivision when the preparation was placed in water. The concentration of the drug preferred was below 20%. This patent may not be known to many research workers in this area, and no experimental data in the pharmaceutical literature could be found to support the claim. One interesting suggestion in the patent is that the inclusion of effervescent materials, such as combinations of sodium bicarbonate and citric or tartaric acid, would increase the distribution (or dispersion) of the drug upon exposure to an aqueous medium. No oral application of such dosage forms was advocated.

Glass Solutions and Glass Suspensions—The concept of formation of a glass solution (75) was first introduced by Chiou and Riegelman (11) as another potential modification of dosage forms in increasing drug dissolution and absorption. Since physical-chemical properties of glass solutions have not been adequately discussed in the pharmaceutical literature, they are briefly reviewed in this article. A glass solution is a homogeneous, glassy system in which a solute dissolves in a glassy solvent. The familiar term "glass," however, can be used to describe either a pure chemical or a mixture of chemicals (window glass is a mixture of inorganic oxides) in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt (76, 77). It is characterized by transparency and brittleness below the glass-transforming temperature, T_g. On heating, it softens progressively and continuously without a sharp melting point. This is primarily due to the facts that the chemical bonds in the glass differ considerably in length and, therefore, in strength and that there is no one temperature at which all the bonds become loosened simultaneously (34). The glassy form of pure compounds can often be transformed to a crystalline state upon heating. It is likely that such transformation may also

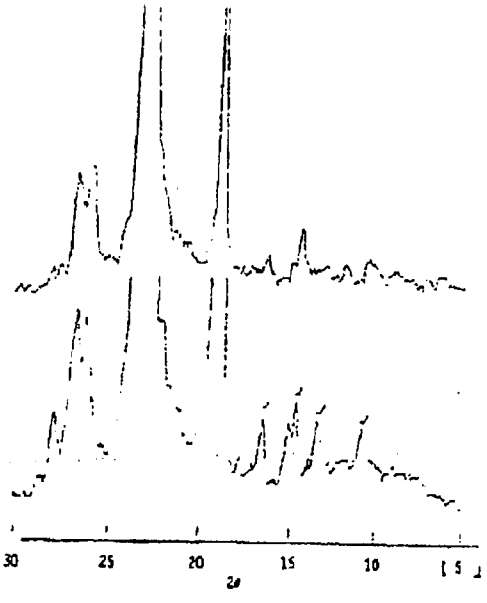


Figure 9—X-ray diffraction spectra of solid dispersion of 5% griseofulvin–95% polyethylene glycol 6000. The top spectrum was obtained from a nonpowdered sample, and the bottom spectrum was obtained from a powdered sample.

occur in some glassy solutions. Usually the thermodynamic properties of a glass, such as specific volume, specific heat, viscosity, refractive index, compressibility, and thermal conductivity, all show critical change around the temperature T_g.

The relation of the volume between the glassy, liquid, and solid states is shown in Fig. 10 (76). As the liquid is cooled through the freezing point, T_f, it may either freeze into a crystalline solid, with a discontinuous change in volume, or it may continue as a supercooled liquid below this temperature. Many substances may behave in either way, according to circumstances. For example, supercooling is increasingly likely to occur if the presence of any nuclei is carefully avoided. The viscosity of a supercooled liquid may be so great that the behavior of the material starts to appear indistinguishable from that of an ordinary solid. If the liquid is further cooled rapidly, a change in slope of the volume–temperature curve occurs and the new slope is often nearly the same as that of the corresponding curve for the crystal. The temperature at which the curve changes slope is called the glass-transforming temperature, T_g. Below T_g, the curve is no longer an equilibrium curve. Therefore, a glass or glass solution is metastable. It is also interesting to note that any liquid or supercooled liquid whose viscosity is greater than 10^{13} poises is generally called a glass (75).

A crystalline solid possesses both long-range and short-range orders of structure, whereas a glass or liquid has a structure only with a short-range order (76, 78). This can be differentiated easily by X-ray diffraction methods. A glass or liquid can only produce weak and diffuse diffraction effects, while crystallites can give strong and sharp diffraction effects (76, 79). In this sense, a glass is also amorphous to X-ray diffraction.

Many compounds have been shown to be able to form glasses readily upon cooling from the liquid state. These compounds include sucrose, glucose, ethanol, and 3-methylhexane (66). Glass formation is common in many polyhydroxyl molecules such as sugars, presumably due to their strong hydrogen bonding which may prevent their crystallization (64). Polymers possessing linear, flexible chains can freeze into a glassy state of transparency and brittleness (66). Glass formation can occur for the pure substance itself or when in the presence of other components. If a water-insoluble drug forms a glass solution with a water-soluble, glass-forming carrier, then the *in situ* dissolved drug is released into the aqueous medium rapidly because the carrier quickly dissolves upon exposure to the aqueous medium (11).

There is usually a relatively strong chemical binding between the solute and the solvent in the solid solution (4), while the lattice energy in the glass solution is expected to be much less because of its similarity with the liquid solution. Similarly, the dissolution rate from a crystal is usually faster than from an amorphous or glassy solid of the same chemical identity. Therefore, if everything is equal, the dissolution rate of drugs in the glass solution should be theoretically faster than that in the solid solution. There is another important advantage of glass solutions over solid solutions. When

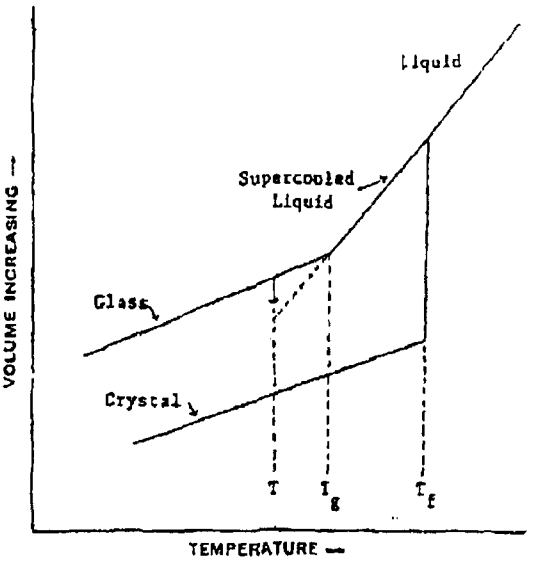


Figure 10—*Relation between the glassy, liquid, and solid states (from* Reference 76, *reprinted with permission).*

the content of the solute exceeds the solubility in both solutions at ambient temperatures, the particle size of crystallization of the solute is much smaller in the glass solution due to the difficult growth of the crystal in its viscous medium. A higher supersaturation of the drug in the glass solution is also more likely to take place if the extremely viscous melt is cooled rapidly.

Citric acid, a normal constituent of animals, was found capable of glass formation (11). The melt is highly viscous and can be drawn into a thread or sheet[1]. After standing at 37° for a few days, a hard, brittle, and transparent glass can be obtained. However, this glassy state was transformed into a crystalline state after months of standing at room temperature. Glassy solutions were obtained after the cooling of melts of 5 and 20% griseofulvin (11), 10% phenobarbital, and 10% hexobarbital (12). A marked increase in the dissolution rate of griseofulvin in the citric acid glass solution was reported (11). The potential usage of citric acid and the previously mentioned glass-forming polyhydroxyl compounds as water-soluble carriers remains to be investigated.

The properties of a glass may be related to the method of solidification or cooling (79). The particle-size distribution in the crystallization of benzophenone in hydrocarbon glass was shown to be a function of the cooling rate, ranging from being invisible to opaque in appearance as the rate of cooling was prolonged (80). A term of "glass suspension" is proposed here to refer to a mixture in which precipitated particles are suspended in a glassy solvent.

Pure polyvinylpyrrolidone and some other polymers dissolved in the organic solvents may become glassy after the evaporation of the solvents. It is possible that the precipitation of drugs introduced into the system is inhibited due to the increase in viscosity as the solvents evaporate. Such inhibition may also be

[1] It is entirely possible that the formation of the citric acid glass is partially due to decomposition of some molecules by dehydration into aconitic acid.

Table II—Dissolution Studies of Griseofulvin[a]

Sample	Relative Dissolution Rate 1 min.	4 min.
Micronized griseofulvin	1 0	1 0
Griseofulvin–chloroform solvate	0 5	0 4
Griseofulvin–polyvinylpyrrolidone (1:5)	6 1	5 1
Griseofulvin–polyvinylpyrrolidone (1:10)	7 2	6 1
Griseofulvin–polyvinylpyrrolidone (1:20)	11 0	7.3

[a] Obtained from *Reference 24*.

facilitated by the possible complexation between the drug and the polymer. Thereby, a transparent, brittle, glassy solution is formed. This principle of glass formation probably best explains the rationale behind the polymer approach suggested by Tachibana and Nakamura (23) and Mayersohn and Gibaldi (24). The amorphous and glassy property of polyvinylpyrrolidone is also evidenced by its diffuse, broädening, X-ray diffraction spectra (25, 41). Evidence for molecular dispersion of drugs in polyvinylpyrrolidone (*i.e.*, glass solution) is provided by use of the UV method for β-carotene (23), high-resolution electron microscope method for iopanoic acid (41), and X-ray diffraction method for sulfathiazole (25) and iopanoic acid (41). By the same reasoning as was discussed for the polyethylene glycol carrier, the crystallite size of the drug may also be very fine if the drug concentration greatly exceeds its solubility in polyvinylpyrrolidone. The crystallization was found to occur at the higher concentration of sulfathiazole by the X-ray diffraction method (25). Amorphous precipitation of iopanoic acid was also found in the 50% iopanoic acid–50% polyvinylpyrrolidone 10,000 coprecipitate by the electron microscope technique (41). These systems also appear to be metastable since crystallization has been initiated in fissures or cracks in the glass on standing.

Due to the chemical stability of polyvinylpyrrolidone to heat (81) and its high melting point (probably decomposing before melting at a temperature beyond 250°), the drug–polyvinylpyrrolidone solid dispersions can only be prepared by the solvent method. Polyvinylpyrrolidone is also soluble in a variety of organic solvents (81), an advantage in accommodating various drugs which possess limited solubility properties. The marked enhancement of griseofulvin dissolution from the coprecipitate is shown in Table II (24). Almost 100% supersaturation was also obtained in 1 min. Such a striking effect is also reported for reserpine (30). For a 1:6 reserpine–polyvinylpyrrolidone coprecipitate, a 200-fold increase in dissolution was found in comparison with the equal particle size of the pure drug. The dissolution rates of the drugs decreased as the concentrations of the drugs in the coprecipitates increased in both systems. Probably this is mainly due to the increase of particle size of the drugs in the higher concentration compositions (30).

Table III—Experimental Relative Release Rates of Sulfathiazole as a Function of Polyvinylpyrrolidone Weight Fraction[a]

Polyvinylpyrrolidone Weight Fraction	Absolute Sulfathiazole Release Rate		Relative[b] Sulfathiazole Release Rate	
	Initial	Limiting	Initial	Limiting
0.25 (3:1)	0 135	—	—	—
0.40 (1 5:1)	0.510	0 140	3.78	1 02
0 50 (1:1)	0 520	0.140	3 85	1.04
0 60 (1:1.5)	0 520	—	3 85	—
0 67 (1:2)	0 680	—	5 04	—
0.75 (1:3)	1.155	—	8 90	—
0 83 (1:5)	1 100	—	8 15	—
0 91 (1:10)	0 934	—	6 91	—
0.95 (1:20)	0 450	—	3 33	—

[a] Obtained from *Reference 25*. [b] Relative to a pure sulfathiazole crystalline Form I tablet

Simonelli *et al.* (25) presented thorough experimental studies to elucidate the dissolution mechanisms from a constant surface for compressed tablets of polyvinylpyrrolidone–sulfathiazole coprecipitates. The enhancement of dissolution rate was found to be a function of the molecular weight of polyvinylpyrrolidone, the concentration of sulfathiazole in the coprecipitates, and, in some instances, the dissolution medium and time. A model was presented to describe dissolution mechanisms of the coprecipitates and physical mixtures over a wide range of composition. For the coprecipitates, it was concluded that the sulfathiazole was the controlling external layer at lower polyvinylpyrrolidone weight fractions and the polyvinylpyrrolidone at higher weight fractions. For details, interested readers are urged to consult this detailed original paper. The relative release rates of sulfathiazole as a function of the polyvinylpyrrolidone weight fraction are shown in Table III. In 40 and 50% polyvinylpyrrolidone samples, the release rates were not linear but changed with time.

Several points arising from the Simonelli *et al.* (25) paper seem to warrant further discussion. The possible effect of molecular dispersion (in this case, glass solution) and colloidal dispersion of sulfathiazole in the polyvinylpyrrolidone on the dissolution rate of sulfathiazole was ignored by the authors. The necessity of taking the molecular dispersion into account for the enhancement of dissolution rate from tablet forms with a constant surface was clearly demonstrated by an approximately 10-fold increase in dissolution rate from a solid solution of 10% indomethacin–90% polyethylene glycol 6000 and also a threefold increase from a solid solution of 5% sulfathiazole–95% urea over the physical mixtures with the same chemical composition (68). A tablet made of 10% griseofulvin–90% succinic acid eutectic mixture was also found to dissolve about threefold faster than the mechanical mixture of 10% micronized griseofulvin–90% succinic acid (53). Such effects are more likely to take place at the higher weight fractions of a carrier.

In their dissolution model, Simonelli *et al.* (25) proposed polyvinylpyrrolidone as the controlling external layer at higher polyvinylpyrrolidone fractions. The identity of the controlling layer can easily be determined by comparing the relative movement of the solid–liquid boundary of each component (25, 31). On the basis of the dissolution data shown in the original article, in the first 20 min. the ratios of the movement of polyvinylpyrrolidone over sulfathiazole at compositions of 1:20, 1:10, and 1:5 (sulfathiazole–polyvinylpyrrolidone) were found to be all close to 1. These ratios indicate that both components were released

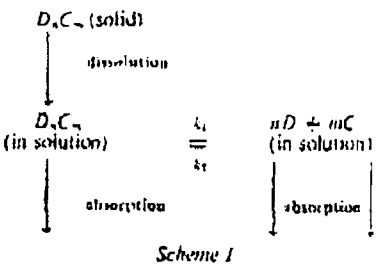
almost simultaneously from the tablets. This finding is contradictory to the dissolution model proposed by Higuchi (31), which defines a congruent dissolution from a binary mixture tablet only taking place at a single, fixed composition. This is valid only when the solubilities of the two components remain constant. It is well known that the magnitude of solubility increases as the particle size reduces to submicron or colloidal range (45). In the solid solution or glass solution of a drug in the soluble carrier, the maximum concentration of a drug at the dissolution interface is undoubtedly much higher than the regular solubility. Furthermore, colloidal or molecular particulates probably cannot aggregate or agglomerate into bigger particles in the short time that they exist at the dissolution surface. If this is true, it is difficult to define the solubility value at different weight fractions of solid dispersions.

The theoretical dissolution rates of sulfathiazole in the higher polyvinylpyrrolidone fractions, calculated according to the model proposed by Simonelli *et al.* (25), imply that similar dissolution rates also can be obtained from the physical mixtures. Although this has not been proved experimentally, it is regarded as unlikely in light of the striking increase of dissolution rates of the drugs dispersed in polyvinylpyrrolidone in powdered forms (24, 30). Group 4

Amorphous Precipitations in a Crystalline Carrier—Instead of forming a simple eutectic mixture in which both the drug and the carrier crystallize simultaneously from a melting or a solvent method of preparation, the drug may also precipitate out in an amorphous form in the crystalline carrier. Since the amorphous form is the highest energy form of a pure drug, it should, under almost all conditions[1], produce faster dissolution and absorption rates than the crystalline form whether the crystals are or are not dispersed in a carrier. Amorphous novobiocin has 10-fold higher solubility than its crystalline form (82). A much faster dissolution rate and higher blood levels were also found for the amorphous form of novobiocin (82). As discussed previously, the amorphous sulfathiazole dispersed in the crystalline urea was believed to be a primary contributing factor in increasing its oral absorption in man (17). It is postulated that a drug with a high supercooling property has more tendency to solidify as an amorphous form in the presence of a carrier. Group 5

Compound or Complex Formations—In a strict sense, the modification of a dosage form by a compound or complex formation (D_nC_m) between a drug (D) and an inert soluble carrier (C) should not be classified under the applications of solid dispersion systems. Nevertheless, due to their frequent occurrence during preparation of solid dispersions by the standard methods, it seems worthwhile to review them here briefly.

The dissolution and absorption of a drug into the body from a complex or a compound are schematically shown in Scheme I. It is clear from Scheme I that the availability of a drug depends on the solubility, the dissociation constant, and the intrinsic absorption rate



Scheme I

of the complex. Although the water-soluble polymers have been considered as ideal carriers for the solid dispersion of poorly soluble drugs, the implication of the possible complexation should not be overlooked. Polyvinylpyrrolidone was shown to retard the pharmacological action of numerous compounds such as penicillin, novocaine, prostigmine, hexobarbital, quinine (83), and hexylresorcinol (84). The formation of an insoluble complex between phenobarbital and polyethylene glycol 4000 or 6000 was shown to reduce rates of dissolution and permeation of phenobarbital through everted guts of rats (85). The complexation between griseofulvin and polyethylene glycol 6000 may be thought to occur on the basis of the traditional solubility study. (The solubility is increased onefold by the presence of 7% polyethylene glycol 6000 in water.) Such a water-soluble weak complex apparently did not retard the oral absorption of griseofulvin in man and dogs (27–29). It is believed that in comparison with pure, insoluble, solid drugs, the rates of dissolution and GI absorption can be increased by the formation of a soluble complex with a low association constant.

The compound formation among simple organic chemicals seems more common than expected. Among 12 phase diagrams, Sekiguchi *et al.* (51) found 11 cases of compound formations. Guillory *et al.* (86) reported four compound formations out of nine phase diagrams studied. However, the occurrence of these compound formations, which previously took place at melt state, does not necessarily mean that they will also take place in a liquid medium. On the other hand, the existence of compound or complex formation in a liquid medium does not predicate its occurrence in the solid state. This is shown in the griseofulvin–succinic acid system. Although the solubility of griseofulvin was increased markedly by the succinic acid in water (approximately onefold per 1.5% succinic acid), their interaction could not be detected by the phase diagram study (53). Group 6

Combinations and Miscellaneous Mechanisms—Quite often a solid dispersion does not entirely belong to any of the four groups discussed but is made up of combinations of different groups. Therefore, the observed increase in dissolution and absorption rates may be the contribution of different mechanisms. The griseofulvin dispersed at high concentrations in polyethylene glycol may exist as individual molecules and as microcrystalline particles. The sulfathiazole dispersed at high concentrations in polyvinylpyrrolidone may be present as individual sulfathiazole and sulfathiazole–polyvinylpyrrolidone complex molecules, amorphous and polymorphic sulfathiazole, and possibly an amorphous sulfathiazole–polyvinylpyrrolidone complex.

[1] A large amorphous mass with entrapped air probably will not dissolve faster than microcrystals dispersed in a water-soluble carrier

The coprecipitates of reserpine with bile steroids such as deoxycholic acid (39), cholic acid, lithocholic acid, and 3,12,24-trihydroxycholane (87) were shown to increase blepharoptotic activity of reserpine in mice. The exact physical properties of such systems have not been elucidated. A decrease in the particle size of reserpine in the coprecipitates was proposed from the *in vitro* dissolution studies (88, 89). The ability of these carriers to reduce the surface tension of aqueous fluids led Stoll *et al.* (89) to propose that the carriers may also facilitate the wetting and, hence, the dissolution rate of reserpine. Since these bile steroids can form clathrate compounds (inclusion compounds) with a variety of organic molecules (90), it is possible that this may also occur with reserpine and thus cause molecular or ultrafine dispersion of reserpine in the hollow channels of the clathrates.

METHODS OF DETERMINATION OF TYPES OF SOLID DISPERSION SYSTEMS

Many methods are available that can contribute information regarding the physical nature of a solid dispersion system. In many instances, a combination of two or more methods is required to study its complete picture. The advantages and disadvantages of each method are briefly expounded here.

Thermal Analysis—This is the most common approach used to study the physicochemical interactions of two or more component systems. Several modified techniques utilizing the principle of change of thermal energy as a function of temperature are discussed separately.

Cooling-Curve Method—In this method, the physical mixtures of various compositions are heated until a homogeneous melt is obtained. The temperature of the mixture is then recorded as a function of time. From a series of temperature–time curves, the phase diagram can be established (33, 34). The method suffers from many inherent disadvantages. It is time consuming, it requires a relatively large amount of sample, and changes in slopes can be missed, especially if cooling takes place rapidly (86). In addition, the method cannot be applied to samples that decompose after melting. It is also difficult to detect samples with small solid–solid solubility. This method was recently used to determine phase diagrams of deoxycholic acid–menadione and caffeine–phenobarbital (86).

Thaw-Melt Method—In this method, a sample of a solidified mixture in a capillary melting-point tube is heated gradually. The thaw point is referred to a temperature on crossing a solidus line (33). This simple method was used extensively by Rheinboldt (91), Rheinboldt and Kircheisen (92, 93), and Guillory *et al.* (86). A stirring device in the capillary tube was employed for more accurate results by Sekiguchi *et al.* (94). The stirring facilitates the attainment of a homogeneous system; however, such stirring only affects the melting point and not the thaw point. In differentiating between a simple eutectic system and a limited solid solution, the diagnostic point lies at the thaw point. Therefore, the usage of this more complicated device is not necessary for such a purpose. The principal drawback of this thaw-melt method is that it depends on a subjective observation and, thereby, is not highly reproducible (86). This is especially serious for the determination of thaw points. A range of six degrees of variation was reported in the study of thaw points of a chloramphenicol–urea system (51). Furthermore, a suitable, upper range of melting points is only limited to about 300° due to the problem associated with capability of visualization (86, 94). The sample used for study may also be prepared from merely the physical mixture or the evaporated mixture obtained after removing the liquid solvent from the solution (94). Thaw points are often found at lower temperatures from the samples of physical mixtures, while the melting points are not affected (94). A special quenching method is proposed for samples exhibiting supercooling properties (33). A mixture that has not completely solidified results in lower thaw and melting points upon reheating. This was observed in the eutectic composition of a sulfathiazole–urea system (56).

Thermomicroscopic Method—Goldberg *et al.* (20) used polarized microscopy with a hot stage to study phase diagrams of binary systems. The physical mixture is placed on a slide covered with a cover slip and sealed with silicone grease to prevent sublimation. The mixture is heated until it completely liquifies. After cooling, the mixture is heated at the rate of 4°/min. The thaw and melting points are then determined by visual observation. The advantages of this method are that it is simple and it requires only a small amount of sample. However, it suffers some disadvantages by often being subjective, limited to thermally stable compounds, and potentially inhomogeneous in distribution after resolidification. Furthermore, the melting of isotropic crystals often cannot be detected accurately under a polarizing microscope (95). The existence of a limited solid solution of griseofulvin in succinic acid determined by this method (21) appears to have been disproved by the DTA and X-ray diffraction method (53). The Köfler contact method, also utilizing polarizing microscopes, was proposed to establish various forms of phase diagrams (95). However, the usage of such a technique seems to require a good knowledge of crystallography.

DTA—DTA is an effective thermal method for studying phase equilibria of either a pure compound or a mixture. Differential effects, associated with physical or chemical changes, are automatically recorded as a function of temperature or time as the substance is heated at a uniform rate (96). In addition to thawing and melting, polymorphic transitions, evaporation, sublimation, desolvation, and other types of decomposition can be detected. Apparatus permitting direct observation of samples during heating were used to facilitate the observation of any physical–chemical changes (97).

The greatest advantage of using this technique is in constructing phase diagrams of high reproducibility; a higher temperature range is permitted, and greater resolution results (52). A sample size of less than 1 mg. can be used for measurement with some commercial instruments. Although the sensitivity and accuracy of the DTA thermograms can be influenced by many

factors such as sample size, heating rate, sample geometry, thermal conductivity of the sample container, and method of measurement of the sample temperature, these variables can be adjusted to optimize the desired characteristics of the DTA apparatus (52).

The DTA method was used extensively to construct phase diagrams of a number of binary systems (51, 52, 86, 98–110). The correlation of DTA data with most frequently encountered phase diagrams is shown in Figs. 11 and 12. This technique is especially valuable in detecting the presence of a small amount of eutectic in the mixture, because its melting at the eutectic temperature can be sensitively detected (98). The observation of such small fractions of melting at eutectic temperature can often be missed when employing thaw-melt or thermomicroscopic methods.

Zone Melting Method—This technique was first introduced in 1952 (111). It has been primarily used for ultrapurification of metals and inorganic and organic compounds. The phase diagram can be constructed for metals and inorganic and organic compounds. A molten zone effected by a heater traverses a cylindrical ingot or solidified melt at a rate of about 0.5–0.001 cm./hr. A mechanical stirring device is also required for the mixing of the liquid in the molten zone. After zone melting is finished, the bar is sectioned and analyzed for its chemical composition. From their chemical compositions and freezing temperatures of the corresponding sections, a phase diagram of a binary or multicomponent system can be constructed. This method is limited to compounds with high thermal stability and low volatility (111, 112). It is especially valuable in determining the exact chemical composition of a eutectic and the minute solid–solid solubility at the eutectic temperature by merely a single pass. The solubility of InSe in InSb was found to be less than 1%; that of InSb in InSe was also found to be less than 1% by this method (113). Many phase diagrams of metal systems have been determined by this method (114–118).

X-Ray Diffraction Method—In this method, the intensity of the X-ray diffraction (or reflection) from a sample is measured as a function of diffraction angles. Counter and film methods detect the diffraction intensity. The advantages and disadvantages of these two methods were well discussed (119, 120). In the former method, a better resolution of diffraction peaks can be obtained, and it is also easier to compare their relative diffraction intensity. However, it requires more sample and has less reliability and more sensitivity to sample preparation and position. The latter method is more sensitive for the detection of weak lines.

The diffraction method is a very important and efficient tool in studying the physical nature of solid dispersions. Recently, it was used to study binary eutectic systems of chloramphenicol–urea (50) and griseofulvin–succinic acid (53). Many phase diagrams of inorganic and metal compounds were also determined by this method (121–125).

In simple eutectic systems, diffraction peaks of each crystalline component can be found in the diffraction spectra. In a substitutional solid solution, the lattice parameter of the solvent crystal is either increased, unchanged, or decreased, depending on the relative

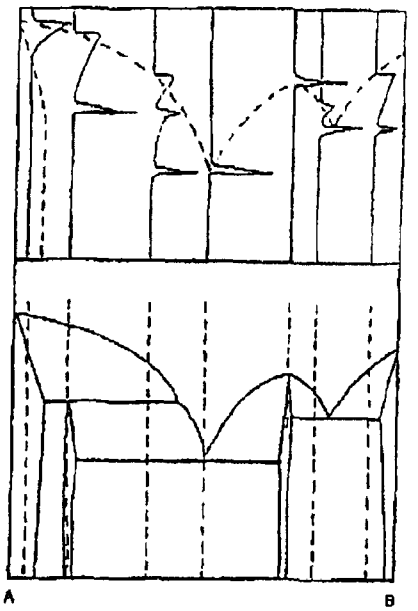


Figure 11—*Typical DTA thermograms corresponding to a hypothetical binary system (from* Reference 52, *reprinted with permission).*

size of the solute atom or molecule (55). However, a gradual shift in the positions of the diffraction lines with changes in composition, which reflects the resulting change in the lattice parameter, is accepted generally as sufficient evidence for the existence of solid solutions. In a system of a continuous solid solution, there will be a shift from the position in one pure component to those in the other (126). The interruption of this smooth change is indicative of immiscibility in the system. The change of lattice parameter, unit cell volume, and density in a continuous solid solution of ammonium chloride–ammonium bromide is shown in Fig. 13. In an interstitial solid solution, the diffraction spectra of the solvent component may or may not

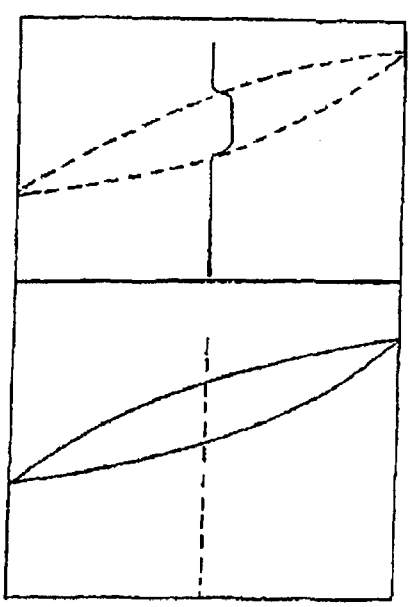


Figure 12—*A DTA thermogram of a continuous solid solution system (from* Reference 52, *reprinted with permission).*

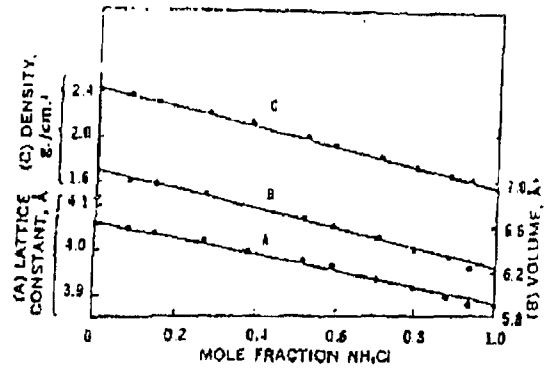


Figure 13—*Variation of composition of continuous solid solution of NH_4Cl–NH_4Br system with (A) lattice constant, Å; (B) unit cell volume, Å³; and (C) density, g./cm.³; low temperature, high-angle data only (from* Reference 125, *Fig. 3, reprinted with permission).*

be changed, while those of the solute component disappear.

The diffraction method is also particularly valuable in detecting compound or complex formation since its spectra or lattice parameters are markedly different from those of pure components. It has been used to disprove the existence of a patented salt formation between *penicillin V* and *tetracycline* (126). The biggest drawback of using the diffraction method to study dispersion systems is its frequent inability to differentiate amorphous precipitation from molecular dispersion if the lattice parameter of the solvent component is not changed. This is because of the disappearance of the diffraction peaks or lines of the crystalline solute compound in both systems. This problem is encountered in the lower concentrations of drugs dispersed in polyethylene glycol (41) or polyvinylpyrrolidone (25) polymers. The solidified eutectic of sulfathiazole–urea has a broad (instead of sharp melting point as found for its physical mixture) and lower melting range. This is attributed to the presence of amorphous sulfathiazole. The amorphous form is transformed into a crystalline form after annealing at high temperature, as shown by the appearance of its sharp diffraction peaks (56).

The diffraction method has been used to study quantitatively the concentration of a crystalline component in the mixture (126–128). The ability of this method to quantitate the crystalline component in solid dispersion systems may be limited by its low concentration or weak intrinsic intensity of diffraction. The height of diffraction peaks may be attenuated by a reduction of crystallite size, usually below 0.2 μ. This is also accompanied by a broadening of the peaks (126). An extremely fine crystalline dispersion of sulfathiazole in polyvinylpyrrolidone has also been considered one reason leading to the disappearance of sulfathiazole diffraction peaks (25). Integrated diffraction peak areas were used to study particle-size distribution between 0.002 and 0.2 μ (125).

Microscopic Method—Microscopy has been used quite often to study the polymorphism (47) and morphology of solid dispersions (34, 44, 51, 54, 55, 124, 129). The fine particles of crystallization in the glassy polyvinylpyrrolidone matrix can be readily detected by the polarizing microscope (41). The high resolution of an electron microscope was used to study the dispersed particle size of iopanoic acid in polyvinylpyrrolidone (41). The application of the electron microscope technique is, however, usually limited to chemicals with high atomic numbers (130).

Spectroscopic Method—Visible absorption spectroscopy was used to study the low concentration dispersion of β-carotene in polyvinylpyrrolidone (23). The spectrum of the dispersed β-carotene resembles that of β-carotene dissolved in organic solvents but not that of β-carotene particles. These results indicated that β-carotene is dispersed molecularly in the polymer. The undetected shift of IR bands of the dispersed β-carotene was thought to indicate the absence of the marked interaction between β-carotene and polyvinylpyrrolidone. IR spectroscopy was also used to study the solid solutions of nitrite ion in many inorganic halides such as KBr, NaCl, and KI (131, 132).

Dissolution-Rate Method—The dissolution-rate method was recently proposed by Allen and Kwan (68) to study the degree of crystallinity in solid–solid equilibria, especially in temperature regions below solid–liquid equilibria. The method involves comparing the *in vitro* dissolution rates of the solute component from a constant-surface tablet made from molecular dispersion (*i.e.*, solid or glass solution) with a physical mixture of the same chemical composition. The technique is simple to perform, except that in some binary systems the tablet surface may not remain constant due to the leaching of particles into the dissolution medium. Such difficulty was encountered in the mechanical mixture of the high sulfathiazole to polyvinylpyrrolidone ratio tablets (25), solid dispersion of barbital–polyethylene glycol 6000 system (41), and physical mixture of 10% griseofulvin–90% polyethylene glycol 6000 (41). Tablets made up of 10% sulfathiazole–90% urea physical mixture under various pressures were also found to disintegrate almost immediately in the aqueous medium (56). This was primarily due to the almost instantaneous dissolution of urea into water because the solubility of this small molecule compound in water is very high, approximately 1 g. in 1 ml. The dissolution of 10% sulfathiazole–90% urea solid solution from 10–20-mesh granules was also found to be complete almost immediately upon their exposure to water (56). The almost instantaneous dissolution from such dispersion systems will make them difficult to compare quantitatively with the dissolution from physical mixtures.

The application of this method also requires: (*a*) the observed dissolution rate to be proportional to the surface area, (*b*) a reasonably large difference between the dissolution rate of the physical mixture and the corresponding solid solution, and (*c*) the use of the same polymorphic form of a drug in the tablet of the physical mixture as that precipitated out from the solid dispersion (68). Most commercially available sulfathiazole, which was often used to prepare solid dispersions, is polymorphic Form *I*, while the precipitated sulfathiazole in the sulfathiazole–urea system is polymorphic Form *II* (56). The dissolution rate of Form *II* was found to be 1.6 times higher than that of Form *I* (56).

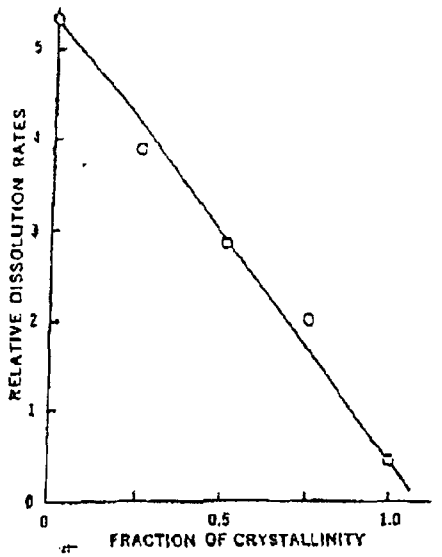


Figure 14—*Dissolution rate versus degree of crystallinity of indomethacin in indomethacin–polyethylene glycol 6000 system (from* Reference 68, *reprinted with permission).*

Furthermore, one must assume in this dissolution method that the distribution of particle size (maybe as small as in the subcolloidal range) precipitated from the solid solution or glass solution does not affect the dissolution rate. Such assumption needs to be proved experimentally.

The dissolution-rate method has been shown to be applicable to simulated systems of indomethacin–polyethylene glycol 6000 and sulfathiazole–urea. The data on 10% indomethacin–90% polyethylene glycol 6000 are shown in Fig. 14. The validity of this principle, however, needs further confirmation by other methods.

Thermodynamic Method—The phase diagrams of eutectic and solid solution systems can be constructed on the basis of some thermodynamic parameters (34, 54, 62, 121, 133, 134). A knowledge of heats of fusion, entropies, and partial pressures at various compositions enables one to determine the solubility gap below the solid–liquid equilibrium temperature (133). A solubility gap in the continuous solid solution of the AgBr–NaBr system was also found from thermodynamic data obtained from an electromotive force study by galvanic cells (121). The detailed mathematical discussion of such an approach is beyond the scope of this article.

AGING OF SOLID DISPERSIONS

The solid dispersion appears to be a potential dosage form modification for increasing dissolution and absorption rates of poorly soluble drugs. However, the result of aging or storage under various conditions and the effects on the fast-release characteristics and chemical stabilities have not been reported extensively. Undoubtedly, this will be an interesting and important research subject for pharmaceutical scientists before the wide and long-range practical applications of this unique approach are feasible. The effects of aging in many nonpharmaceutical systems such as alloys and inorganic compounds have been well studied. The purpose of this section is to review these studies with a hope that similar principles and methodologies can be utilized to apply to our systems.

Aging Effects of Eutectic Mixture—It is well known that the dispersed-phase particles tend to coarsen on aging because the interfacial energy of the system is reduced by the concomitant reduction in interface area (129). The phenomenon of particle coarsening was extensively studied both theoretically (135, 136) and experimentally (137–140). This phenomenon occurs in eutectic systems with or without solid solution formation. The extent of coarsening increases with time and aging temperature. The morphology and transparency of a freshly prepared eutectic mixture of naphthalene–phenanthrene were found to change after standing primarily due to recrystallization of fine grains (44).

The increased hardness of freshly prepared eutectics of Pb–Sn systems was found to decrease considerably after annealing (49). Eutectic alloys are more sensitive to corrosion, because in the eutectics the metals are in a somewhat activated or reactivated state (49). It is thought that the displacement of the electrons into higher orbitals facilitate their transfer to a third component, such as oxygen, which is an active agent in corrosion. One should also bear in mind that different polymorphic forms in the solid dispersion may also have different chemical stabilities (47).

Aging Effects of Solid Solution—The most important aging effect from solid solutions is the precipitation from supersaturated solid solutions along with the subsequent changes of physical–chemical properties (33, 34, 54, 55, 63).

The precipitation (also called decomposition or demixing) from a solid solution occurs when the concentration of the solute exceeds its equilibrium solubility. As shown in Figs. 5 and 6, the solubility in the continuous or discontinuous solid solution may decrease with decreasing temperature. When a mixture within the solid solution range at high temperature is quenched from the melt to ambient temperature, a

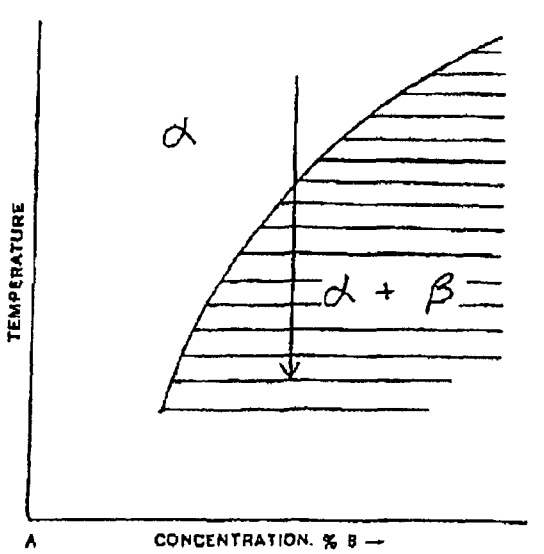


Figure 15—*Phase relation for precipitation. The solid phase, β, precipitates from the solid solution, α, on cooling (arrow) (from* Reference 55, *p. 392, reprinted with permission).*

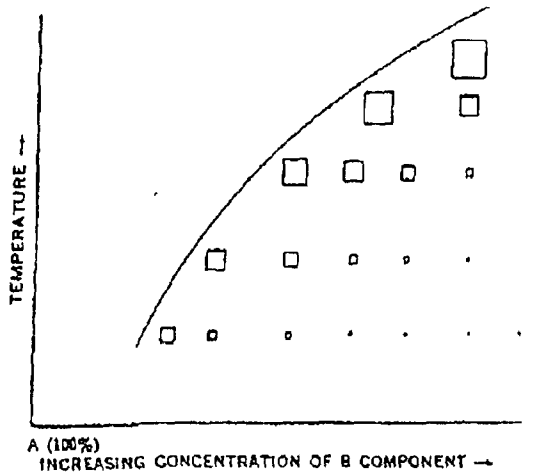


Figure 16—*Diagram illustrating relative nuclei and particle size of precipitation from supersaturated solid solutions at various temperatures and compositions (from* Reference *55, p. 398, reprinted with permission).*

metastable solid solution is usually obtained. Such excess solute is bound to precipitate out in order to reduce the total free energy of the mixture to a minimum. The phase relations for precipitation are schematically shown in Fig. 15, in which the supersaturated α-phase is transformed into the saturated α-phase and β-solid phase. The β-phase may be a pure crystalline solute, *B*, or a saturated solid solution of the other component, *A*, in the *B* component. The percentage of precipitation can be calculated according to the tieline or lever rule (34, 54, 55).

The particle size and the rate of precipitation certainly have a critical influence upon the dissolution behavior of the dispersed drug. Based on nucleation and growth theory, the relative size of stable nuclei and subsequent precipitation are expected to vary with the composition and storage temperature (Fig. 16). The rate of precipitation is a function of time. After an initial delay of nucleation, it usually proceeds rapidly and finishes slowly (54, 124). A typical example

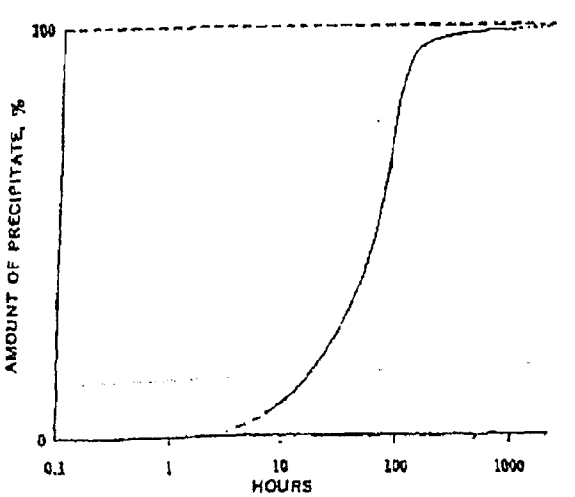


Figure 17—*Amount of precipitate as a function of time in an iron-carbon alloy (0.018% carbon) allowed to precipitate from a supersaturated solution at 76° (from* Reference *54, p. 239, reprinted with permission).*

of the precipitation of carbon from an iron–carbon alloy annealed at 76° is shown in Fig. 17. The rate of precipitation also varies with temperature (Fig. 18). The rate is slow at very low temperatures because the diffusion rate of molecules is very low. The precipitation rate is also very low at temperatures just below the solvus line. In this case, the solution is only slightly supersaturated, and the free energy decrease resulting from the precipitation is very small. The nucleation rate is accordingly slow, although the diffusion rate at these high temperatures is high. The maximum precipitation rate, therefore, lies at an intermediate temperature as a compensated result of moderate diffusion and nucleation rates.

The presence of precipitation is usually detected by X-ray diffraction (54, 55, 122, 124, 129, 141–143), X-ray small-angle scattering (141), and electron microscopy (54, 55, 124, 129, 141, 143, 144). A change of lattice parameter of the solvent component after aging is considered as definite evidence of precipitation (55). As discussed previously, the capability of X-ray diffractometry may be handicapped by small particle-size effects. Diffraction from particle sizes well below 0.01 μ may not be detected (145). The appearance of second-phase particles in electron microscopy is also indicative of the occurrence of precipitation. The dissolution-rate method was also recently proposed to study precipitation (68).

The effect of precipitation from supersaturated solid solutions on the age-hardening of alloys is well known (34, 54, 55). The extent of this effect is proportional to the amount precipitated. Therefore, the hardening effect is also a function of composition, aging temperature, and time. Holding or aging the preparations for too long a period at a given temperature may also cause them to lose their hardness. This effect is known as overaging (54). The implications of age-hardening on the overall performance criteria (such as dissolution, disintegration, and tableting) of pharmaceutical solid dispersions remain to be further investigated. In addition to the hardening effect, the precipitation also has caused intergranular corrosion with changes in electrical properties, heat resistance, and specific density (55).

Aging Effects of Glass Solution—Since a glass solution is a metastable form, it may be subjected to aging transformation, yielding a more stable form. This may take place rapidly or extremely slowly, as in the case of untreated ordinary window glass kept at room temperature. Small-angle X-ray scattering and electron microscope methods were used to study the kinetics of a metastable amorphous phase separation from CaO–MgO–SiO_2 glass at 825° (146). The growth of amorphous particles was found to be rate-limited by the diffusion process. Their average radius is proportional to the square root of annealing time. The crystallization of iopanoic acid and chloramphenicol palmitate dispersed in polyvinylpyrrolidone 10,000 (5% w/w) was detected by polarizing microscope visualization of crystal needles in unpulverized and pulverized samples. These samples were kept at ambient temperature for several months (41). The effect of such precipitation on the dissolution rate should be further studied.

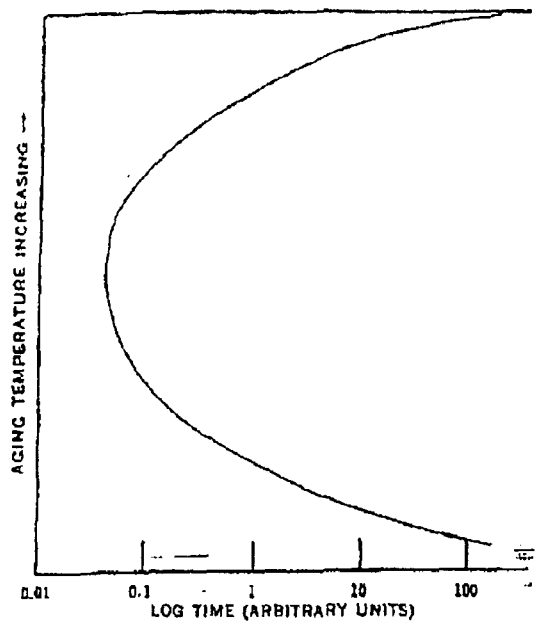


Figure 18—*Diagram illustrating the time for 100% of precipitation from a supersaturated solid solution as a function of aging temperature (from* Reference 54, *p. 240, reprinted with permission).*

Aging Effects of Metastable Polymorphic Forms in Solid Dispersions—The amorphous and other metastable crystalline forms of the dispersed drug in solid dispersions are also subject to aging changes. The importance of this aspect can be seen from the marked difference of dissolution and absorption characteristics between various polymorphic forms of drugs (47). Metastable forms may range from being extremely stable to extremely unstable. Diamond, a crystalline form of carbon, is a good example of the first case. Amorphous form and Form C of chloramphenicol palmitate are examples of the latter case (127).

The methodology for the detection of polymorphic transitions was well reviewed (47). Recently, X-ray diffraction techniques were utilized to study the kinetics of the transformation of amorphous sulfathiazole dispersed in urea at eutectic compositions and their effect on the dissolution rate (56).

REVIEW OF *IN VIVO* STUDIES

Sulfathiazole-Urea Systems—The potential of pharmaceutical applications of solid dispersions was early demonstrated in the human studies of the sulfathiazole-urea system (17). The oral administration of the solidified "eutectic mixture" resulted in a faster and higher rate of absorption than the 50–100-mesh sulfathiazole particles alone on the basis of blood levels and urinary excretion data. The cumulative excretion of the drug and its metabolites in 8 hr. was also 23% higher from the "eutectic mixture." The excretion rate data are shown in Fig. 19. The presence of the urea was found not to interfere with the absorption of the sulfathiazole. The *in vitro* dissolution rate of sulfathiazole will probably be diminished in the presence of urea due to its decreasing solubility in the aqueous solution of urea (17).

Chloramphenicol-Urea Systems—In oral suspension studies in rabbits (51), the solid dispersion of 20% chloramphenicol-80% urea produced a faster and higher absorption in the 1st hr. than the pure chloramphenicol with a similar particle-size distribution (50–100 mesh). The peak value was about 70% higher for the solid dispersion. However, the total areas under the blood level-time curve from both dosage forms were almost the same. When administered in capsule form, the solid dispersion produced a much higher blood level in the first 4 hr. In the first 2 hr., the ratio of blood levels gave a threefold difference. Such marked difference in absorption characteristics obtained in both suspension and capsule forms has not been entirely explained. It is believed that in the capsule case, this difference is a reflection of better wetting and dispersion of solid in the urea system than in the pure, poorly soluble chloramphenicol system. These advantages would become less significant when administered in suspension form. The solid dispersion with eutectic composition (76% chloramphenicol–24% urea) was shown to be inferior in absorption than the pure compound when studied in either the capsule or suspension form.

The finer particle sizes of chloramphenicol obtained in the low concentration of the mixture were proposed to have contributed to its better absorption and the attainment of supersaturation from the lower concentration dispersed form (50, 51). Unfortunately, these studies were conducted on rabbits whose rate of stomach emptying in the feeding and fasting state differs markedly from man. The lack of suitability of using rabbits in evaluating drug absorption was recently raised by Chiou *et al.* (147).

Reserpine–Bile Acid Coprecipitates—A more rapid onset of blepharoptotic activity as well as a significantly increased potency relative to reserpine base was shown in mice after oral administration of reserpine-deoxycholic acid coprecipitates (39). The enhancement generally increased as the concentration of reserpine in the coprecipitates decreased. The only exception was that of the lowest concentration dispersion studied (1:32 molar amounts of reserpine–desoxycholic acid). The physical mixture was also more potent than the reserpine base. These findings were attributed to the enhancement of oral absorption of the drug dispersed

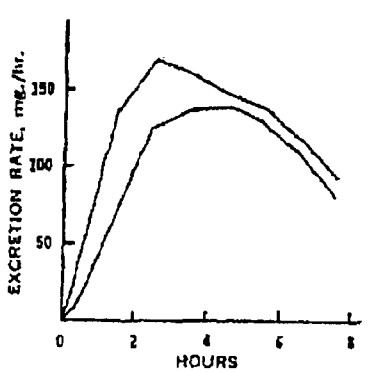


Figure 19—*Average excretion rates of total sulfathiazole in urine after administration of 2 g. of sulfathiazole as a eutectic mixture (top curve) and pure compound (lower curve) to a human subject (from* Reference 17, *Fig. 11, reprinted with permission).*

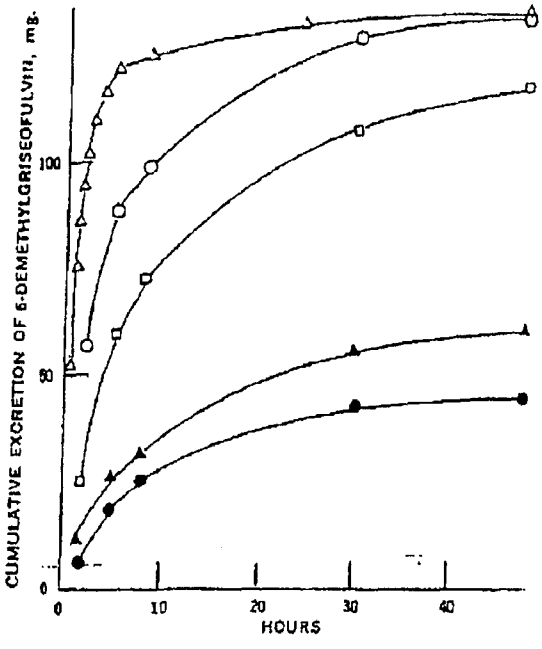


Figure 20—*Average cumulative urinary excretion of 6-demethylgriseofulcin, a major metabolite, after oral and intravenous doses of griseofulcin in dogs. Key:* △, *intravenous dose;* ○, *griseofulcin in polyethylene glycol 400 solution;* □, *griseofulcin dispersed in polyethylene glycol 6000 (10% w/w);* ▲, *commercial capsule of micronized griseofulcin; and* ●, *commercial tablet of micronized griseofulcin (all data corrected for 250-mg. dose) (from* Reference 27, *Fig. 2, reprinted with permission).*

in the bile acid. A rank correlation with the *in vitro* dissolution rate was found (88). Similar phenomena of increased blepharoptotic activity in mice were also reported for the reserpine coprecipitates with other bile acids (87). The general application of drug coprecipitates in increasing drug absorption remains to be explored.

Griseofulvin–Polyethylene Glycol Polymers—In none of the *in vivo* studies of three solid dispersion systems discussed here were comparisons made with micronized or microcrystalline powders of pure drugs. The solid dispersion approach will certainly appear unique and valuable if it proves to yield better oral absorption than that obtainable with the commercially available micron-size powders. Such critical evaluation was first carried out in dogs (27) and man (28, 29) for micronized griseofulvin and griseofulvin dispersed in polyethylene glycol.

In the dog studies, the total areas under the blood concentration curves in the first 8 hr. for the micronized griseofulvin, either in tablet or capsule form, were found to be approximately only 25% of those obtained from capsule forms of 10% griseofulvin–90% polyethylene glycol prepared by melting methods. By analyzing the total excretion of the major metabolite in 48 hr., it was found that approximately 88% of dispersed griseofulvin, 45% of micronized griseofulvin in capsule form, and 33% of micronized griseofulvin in tablet form were absorbed. The griseofulvin dissolved in polyethylene glycol 400 was found to be completely absorbed. Their cumulative excretion plots are shown in Fig. 20. From the analysis of the excretion rate data, it was found that oral absorption of griseofulvin in dogs could proceed for more than 40 hr. The amounts absorbed were shown to correlate linearly with the logarithm of the *in vitro* dissolution rates. The solid dispersion of 5% griseofulvin–95% polyethylene glycol 4000 also produced about fourfold the blood area in the first 8 hr. than did the micronized griseofulvin in a dog (12). In a preliminary study, the presence of polyethylene glycol 4000 in a physical mixture was found not to affect the oral absorption of micronized griseofulvin (12).

To test its practical application, the absorption studies were further carried out in human subjects. The 10 and 20% griseofulvin dispersions in polyethylene glycol 6000 were found to be almost completely absorbed in eight trials, while only 43% of micronized griseofulvin was absorbed. More strikingly, the absorption from dispersed forms was almost complete within 2 hr. after administration. The absorption from the micronized product was found to continue for 30–80 hr. after dosing. The average cumulative excretion of urinary metabolites (6-demethylgriseofulvin and its glucuronide) obtained from administration of various forms is plotted in Fig. 21. The rapid and complete absorption of the insoluble antibiotic in man was mainly attributed to the molecular and colloidal dispersion of the drug in a highly water-soluble carrier. It is predicted that the polyethylene glycol can act as one

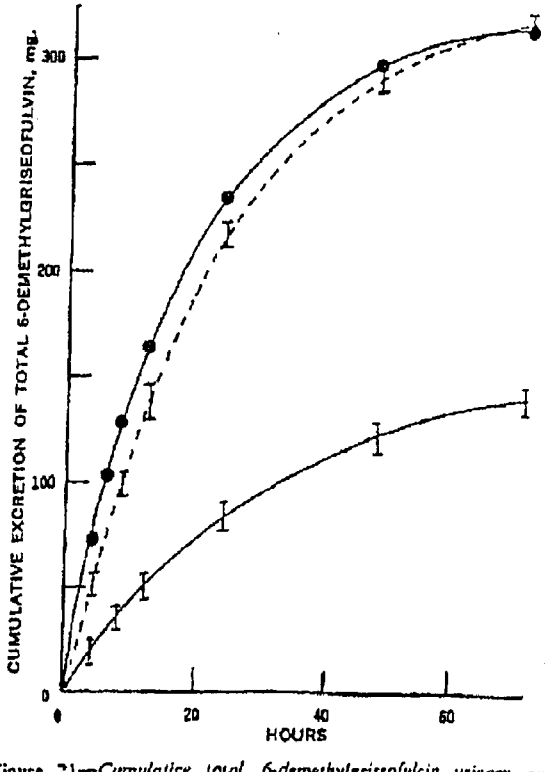


Figure 21—*Cumulative total 6-demethylgriseofulcin urinary excretion data after intravenous and oral administration of griseofulcin to two human subjects (intravenous data only for a subject; others are mean values of eight trials). Key:* ●, *intravenous dose;* - - -, *griseofulcin dispersed in polyethylene glycol 6000 (10 and 20% w/w); and* ——, *tablets of micronized griseofulcin (all data corrected for 500-mg. dose) (from* Reference 28, *reprinted with permission).*

of the ideal universal carriers for most poorly soluble drugs.

MISCELLANEOUS APPLICATION

A unique method in formulating a liquid drug or chemical in a solid dosage form was recently introduced by Chiou and Smith (40). A liquid drug such as methyl salicylate, vitamin E, clofibrate, benzyl benzoate, and benzonatate was mixed by mechanical stirring with the melted liquid of polyethylene glycol 6000 at a temperature below 70°. The mixture was then rapidly cooled, and the resultant "solid" mass was pulverized, encapsulated, and tableted. The method is particularly valuable for drugs with low therapeutic doses because the maximum concentration that can be incorporated into a solid form only ranged between 5 and 10% (w/w). It is believed that other thermoplastic polymers with low melting points can also function as carriers for such purposes.

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ACKNOWLEDGMENTS AND ADDRESSES

Received from the *College of Pharmacy, Washington State University, Pullman, WA 99163, and from the ‡School of Pharmacy, University of California, San Francisco, CA 94122

This work was supported in part by the National Institutes of Health, Grant FR056866.

The authors express their gratitude to Dr. Art Miodozeniec of Hoffmann-La Roche, Inc. for his valuable comments on the manuscript. Permission from various publishers for reproduction of the figures in this article is also gratefully acknowledged.

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Ex. 4

United States Patent [19]

Klimesch et al.

[11] **Patent Number: 5,073,379**

[45] **Date of Patent: * Dec. 17, 1991**

[54] **CONTINUOUS PREPARATION OF SOLID PHARMACEUTICAL FORMS**

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[*] Notice: The portion of the term of this patent subsequent to Jan. 31, 2006 has been disclaimed.

[21] Appl. No.: **398,663**

[22] Filed: **Aug. 25, 1989**

[30] **Foreign Application Priority Data**

Sep. 7, 1988 [DE] Fed. Rep. of Germany 3830353

[51] **Int. Cl.**[5] **A61K 9/44**; A61K 9/20

[52] **U.S. Cl.** **424/467**; 424/400; 424/464; 424/465; 424/468

[58] **Field of Search** 424/465, 467, 441, 440; 425/407

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[57] **ABSTRACT**

A mixture of one or more pharmaceutical active compounds and one or more thermoplastic polymers is tabletted by a process in which the mixture is extruded and the still moldable extrudate is pressed to give tablets, between two belts, or a belt and a roller, which make contact in parts, rotate in opposite directions and run parallel along the contact zone, the shape-imparting indentations, which may be present in complementary pairs, being located in both or in only one of the revolving shape-imparting elements.

20 Claims, 3 Drawing Sheets

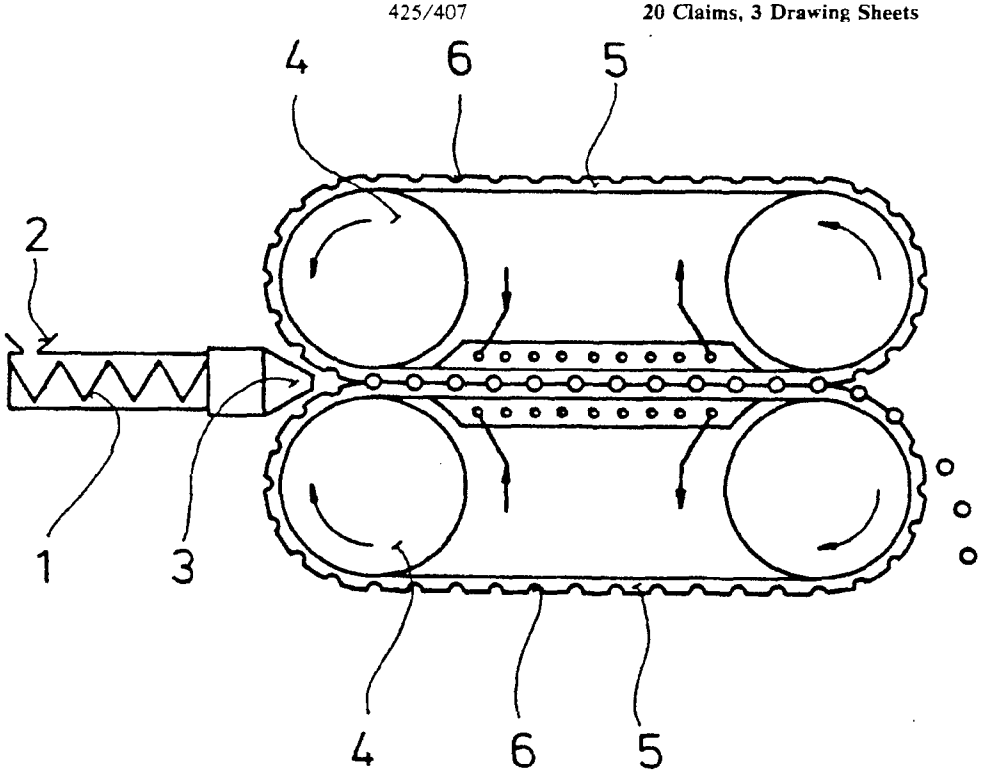


FIG.1

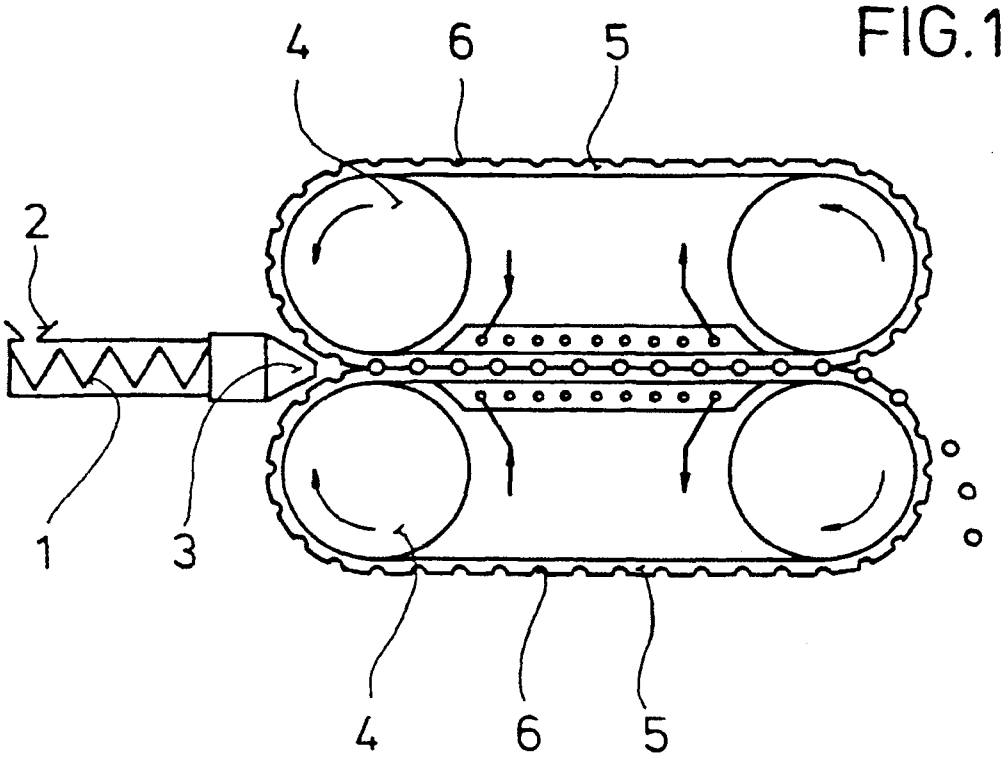
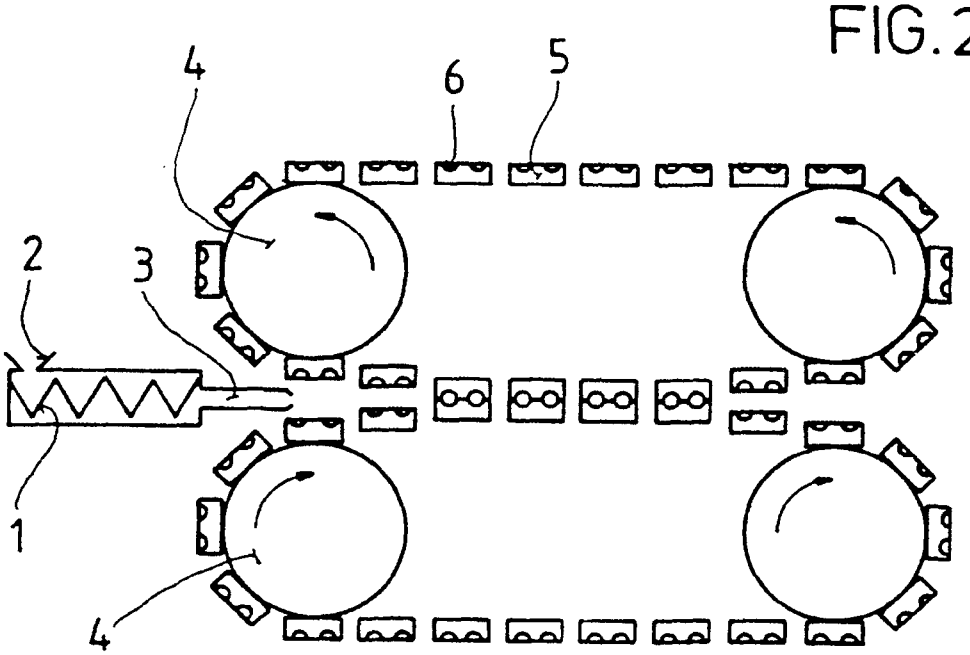


FIG.2



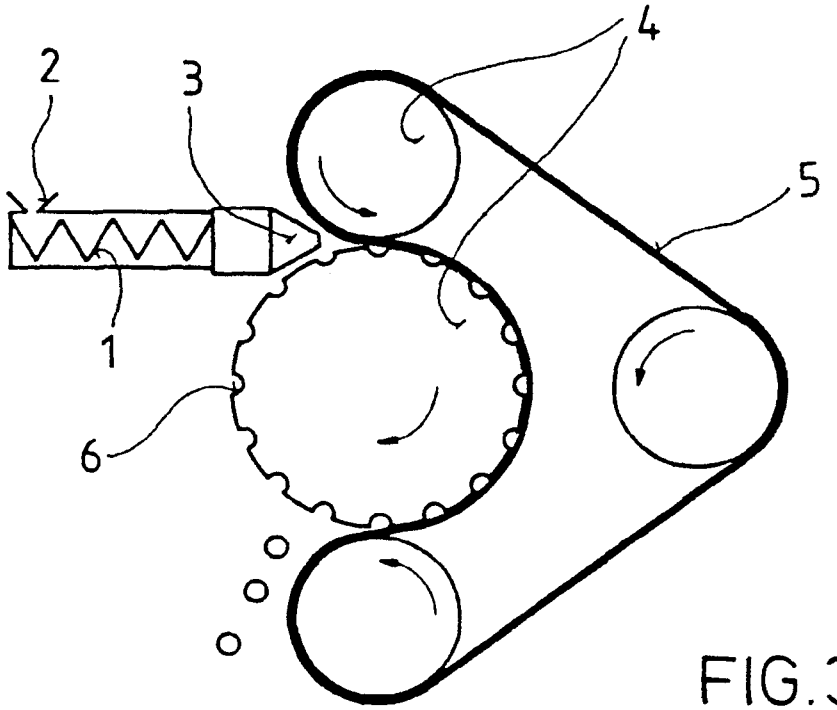


FIG. 3

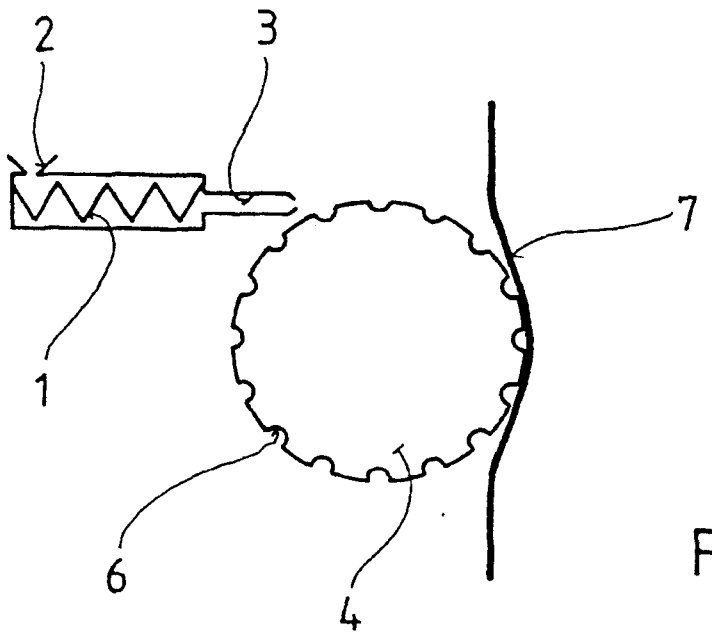


FIG. 4

FIG.5

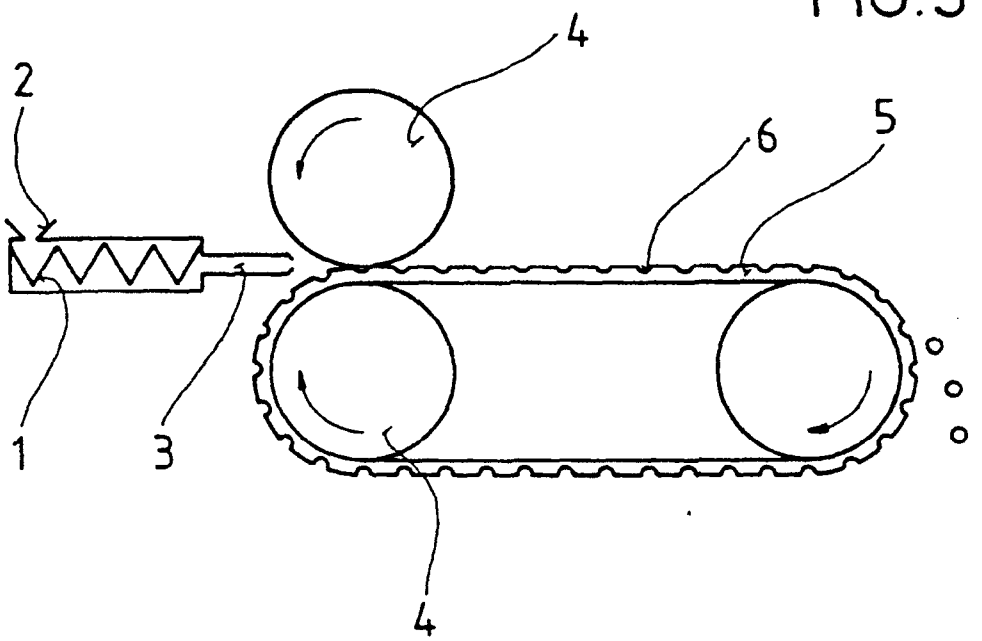
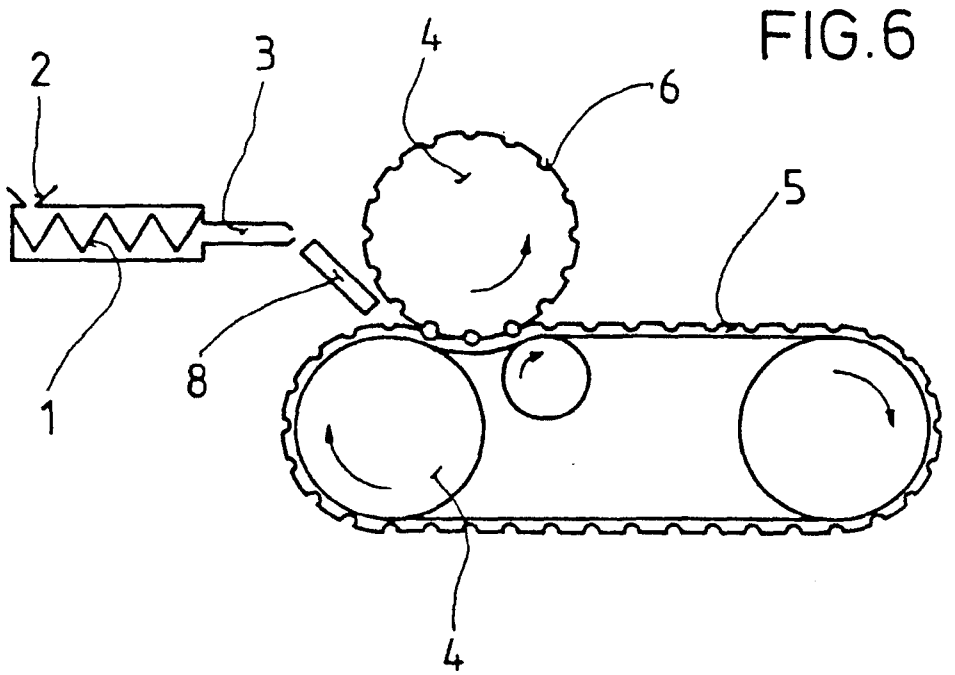


FIG.6



CONTINUOUS PREPARATION OF SOLID PHARMACEUTICAL FORMS

The present invention relates to a continuous process for the preparation of solid pharmaceutical forms by extruding a polymer melt containing the active compound and forming the still plastic extrudate between a belt and a roller or two belts.

It is known that polymer melts containing pharmaceutical active compounds can be extruded and can be formed by injection molding or calendering (EP-A-240 904 and 240 906). The injection molding process is not completely continuous but involves cyclic operations which, owing to the required cooling times, cannot be accelerated to the extent necessary for mass production. In the case of calendering too, the production rate is limited because the rollers make contact only along a line, so that it is only when the rollers are running slowly that the cooling time is sufficient to cool the hot, still plastic extrudate sufficiently for the resulting moldings to be dimensionally stable.

It is an object of the present invention to provide a process for the continuous preparation of solid pharmaceutical forms, which on the one hand permits large-scale production and on the other hand also allows the processing of only slowly hardening melts.

We have found that these objects are achieved by the processes and apparatuses described in the claims.

Although there may be cases where premixing is advantageous, so that a simple extruder is sufficient, it is as a rule substantially more advantageous if the extruder is in the form of a conventional single-screw or multi-screw mixing extruder, so that premixing is unnecessary. The mixing extruder (1) may have a plurality of feed hoppers (2), if necessary for the separate addition of solid and liquid components of the mixture, and a pipe connection for blanketing with inert gas (as a rule nitrogen) and/or devolatilization. In order to increase the throughput, the extruder may have more than one die (3).

To ensure reliable transport of the extrudate and to avoid breaking it off downstream of the die, extrusion is advantageously carried out obliquely downward. The most advantageous angle in each case depends on the product properties and the procedure (eg. extrusion temperature and extrusion rate).

Shaping takes place directly after the extrusion process. The still plastic extrudate is passed, if necessary with the aid of a suitable guide channel (8), through the shaping apparatuses described in claims **18** to **23**.

In general, it is practical to cool the shaping parts (roller and belt or double belt) to 10–20° C. Unless very expensive steps are taken, lower temperatures are disadvantageous owing to the expected condensation. The shaping parts are therefore preferably provided with the conventional cooling apparatuses for cooling with a cooling liquid. In some cases, natural air cooling is also sufficient. It may also be advantageous to heat the shaping parts.

If the extruder has more than one die, each die is associated with one or more rows of revolving shapeimparting indentations in the roller and/or in the belt or (in the case of a double belt) in one or both belts.

In the case of the resilient belts as claimed in claims **2** and **18** (FIG. **1**), the belts are provided with shape-imparting indentations which are opposite one another and, in pairs, determine the tablet shape. The apparatus

advantageously contains a conventional control and regulation means which ensures that the two mold halves meet exactly. The belts consist of a fillercontaining elastomer, for example polypropylene, acrylonitrile/butadiene/styrene copolymer, polyamide, polycarbonate or a blend of these, each of which contains, for example, aluminum powder or flakes as a filler, the filler improving the thermal conductivity; the belt thickness is slightly greater than the depth of the mold halves.

Metal link belts (FIG. **2**) may consist of various metals, such as brass, bronze, copper or, preferably, corrosion-resistant or abrasion-resistant steel. The belts are divided into segments (links) which contain shape-imparting indentations. A plurality of shapeimparting indentations may be engraved per segment, both in the longitudinal direction and side by side.

In the case of smooth belts in combination with engraved rollers as claimed in claims **4** and **20** (FIG. **3**), the belts may consist both of elastomers and of metal, thin steel belts being preferred.

The smooth belt may furthermore be replaced by a stationary smooth wall which is flat or, preferably, curved in a concave shape to match the roller (claims **5** and **21**; FIG. **4**).

In the case of the apparatus stated in claim **22** (FIG. **5**), a resilient belt provided with shape-imparting indentations, as described above, is used in combination with a smooth roller, preferably of metal, in particular corrosion-resistant steel.

Finally, the roller (4) and the belt (5) may be provided with shape-imparting indentations (6) which correspond to one another in pairs (claims **7** and **23**; FIG. **6**).

Because of the longer contact times between the belts or between the belt and the roller, the cooling time is substantially longer compared with the pair of rollers described in EP-A-240 906, which pair of rollers makes contact only along a line. On the one hand, this permits the throughput to be increased by increasing the speed of rotation compared with the pair of rollers, while on the other hand also making it possible to process pharmaceutical mixtures which solidify only very slowly.

The cooling time is the longest when two belts are used (cf. FIGS. **1** and **2**). A similar situation occurs in the arrangement according to claim **22** and FIG. **5** (belt with indentations and smooth roller). Here, however, the mold is open at the top during the major part of the cooling time. The belt is cooled from below.

When an engraved roller is used in combination with a smooth belt, an arrangement according to FIG. **3** or one based on the principle of FIG. **6** is possible. In the arrangement according to FIG. **3**, it is advantageous if only the roller is cooled, while in the arrangement based on the principle of FIG. **6** the roller and belt may be cooled; however, in special cases, it is also possible to cool the belt and to heat the roller. In both arrangements, the angle of wrap (the roller segment surrounded by the belt) can of course be greater or smaller than in the drawing.

The elements of the apparatus should each be arranged so that the molding can fall downward at the end of the cooling zone. However, it is advisable, as a precaution, also to provide a stripping roller which ensures reliable removal from the mold without damaging the moldings. The stripping roller therefore advantageously has soft bristles. It simultaneously cleans the mold.

Extrudable pharmaceutical mixtures are mixtures of one or more pharmaceutical active compounds with one or more auxiliaries which are conventionally used in the preparation of pharmaceutical tablets and are pasty and therefore extrudable due to the melting or softening of one or more components. These are, in particular, mixtures which contain pharmacologically acceptable polymers (the glass transition temperature of the mixture being below the decomposition temperature of all components of the mixture), for example polyvinylpyrrolidone (PVP), copolymers of N-vinylpyrrolidone (NVP) and vinyl acetate, copolymers of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate, polyvinyl alcohol, ethylene/vinyl acetate copolymers, polyhydroxyethyl methacrylate, copolymers of methyl methacrylate and acrylic acid, cellulose esters, cellulose ethers, polyethylene glycol and polyethylene. The K values (according to H. Fikentscher, Cellulose-Chemie 13 (1932). 58-64 and 71 and 74) of the polymers are from 10 to 100, preferably from 12 to 70, in particular from 12 to 35, and those of PVP are from 12 to 70, preferably from 12 to 35, in particular from 12 to 17.

In the total mixture of all components, the polymeric binder must soften or melt at from 50 to 180° C., preferably from 60 to 130° C., so that the mass is extrudable. The glass transition temperature of the mixture must thus in any case be less than 180° C., preferably less than 130° C. If required, it is reduced by means of conventional pharmacologically acceptable plasticizers, such as long-chain alcohols, ethylene glycol, propylene. . glycol, trimethylolpropane, triethylene glycol, butanediols, pentanols, hexanols, polyethylene glycols, silicones, aromatic carboxylic esters (eg. dialkyl phthalates, trimellitic esters, benzoic esters or terephthalic esters) or aliphatic dicarboxylic esters (eg. dialkyl adipates, sebacic esters, azelaic esters, citric esters and tartaric esters) or fatty acid esters.

NVP polymers which, when mixed with the active compound and, if required, conventional pharmaceutical auxiliaries, with or, preferably, without added plasticizers, melt or soften in the desired temperature range are preferred. Melting or softening below a certain temperature may be necessary where there is a possibility of thermal and/or oxidative damage not only to the active compound but also to the NVP polymer. The latter may undergo yellowing during extrusion, and it is for this reason that NVP polymers have not usually been extruded in the past. However, there is little danger at extrusion temperatures below 180° C., especially below 130° C., if the polymer has not been prepared in aqueous solution using hydrogen peroxide as the initiator, but in an organic solvent or in water using an organic peroxide as the initiator, for example by the process described in EP-A-273 238 or by the process of US 4 520 179 or 4 520 180.

If the K value is greater than 17, in particular greater than 30 or even 40, and no components with a powerful plasticizing effect are present, the only suitable NVP polymers are those having a glass transition temperature Tg of less than 120° C., preferably less than 100° C., or the NVP polymer (including homopolymers) must not have been prepared in water using H:O: as the initiator. This would give rise to polymer terminal groups which would lead to yellowing at elevated temperatures.

Depending on the intended use, the NVP polymer can be rendered hydrophilic via the type and amount of comonomers to as great or as small an extent that the tablets prepared therefrom dissolve or swell in the mouth (buccal tablet) or in the stomach or only in the intestine (rapidly or slowly) so that they release the active compound. They have adequate swelling properties when they absorb more than 10% by weight of water on storage at 90% relative humidity. If it is required that carboxyl-containing binders do not release the active compound until they reach the alkaline medium of the intestine, the above data on water absorption applies only to the neutralized form (salt form) of the polymer (in which the protons of the carboxyl groups have been completely or partly replaced by ammonium, sodium or potassium ions).

Suitable comonomers for NVP are unsaturated carboxylic acids, eg. methacrylic acid, crotonic acid, maleic acid and itaconic acid, and their esters with alcohols of 1 to 12, preferably 1 to 8, carbon atoms, as well as hydroxyethyl or hydroxypropyl acrylate and methacrylate, (meth)acrylamide, the anhydrides and halfesters of maleic acid and itaconic acid (the half-esters preferably being formed only after the polymerization), N-vinylcaprolactam and vinyl propionate. Preferred comonomers are acrylic acid and, in particular, vinyl acetate. Preferred NVP polymers are therefore those which contain either only NVP or vinyl acetate as the sole comonomer in copolymerized form. Vinyl acetate and vinyl propionate may be complefely or partly hydrolyzed after the polymerization.

Conventional pharmaceutical auxiliaries, whose total amount may be up to 100% by weight, based on the polymer, are, for example, extenders, such as silicates or diatomaceous earth, stearic acid or its salts with, for example, magnesium or calcium, methylcellulose, sodium carboxymethylcellulose, talc, sucrose, lactose, cereal starch or corn starch, potato starch and polyvinyl alcohol, as well as wetting agents, preservatives, disintegrants, adsorbents, colorants and flavorings (cf. for example H. Sucker et al., Pharmazeutische Technologie, Thieme-Verlag, Stuttgart 1978).

If desired, the tablets prepared according to the invention may also be provided with a conventional coating to improve the appearance and/or the flavor (coated tablet, film tablets) or for further delaying the release of active compound. For oral tablets with delayed release of active compound, it may be advantageous if the tablet is prepared by one of the known techniques in a form having closed pores, so that it floats in the stomach and thus remains there longer. Furthermore, the novel process can be used to produce very small tablets, which are advantageously filled into capsules, instead of conventional granules. For the purposes of the present invention, the term tablet is associated with neither a certain shape nor oral administration. Instead, it also includes suppositories (which do not melt at body temperature) for rectal use.

For the purposes of the present invention, pharmaceutical active compounds are all substances having a pharmaceutical action and a very low level of side effects, provided that they do not decompose under the processing conditions. The amount of active compound per unit dose and the concentration may vary within wide limits, depending on the efficacy and rate of release. The only condition is that they are sufficient to achieve the desired effect. For example, the concentration of active compound may be from 0.1 to 95, preferably from 20 to 80, in particular from 30 to 70, % by weight. Combinations of active compounds can also be

used. For the purposes of the present invention, active compounds include vitamins.

The novel process is suitable, for example, for processing the following active compounds: betamethasone, thiocticacid, sotalol, salbutamol, norfenefrine, silymarin, dihydergotamine, buflomedil, etofibrate, indomethacin, oxazepam, β-acetyldigoxin, piroxificam, haloperidol, ISMN, amitriptyline, diclofenac, nifedipine, verapamil, pyritinol, nitrendipine, doxycycline, bromhexin, methylprednisolone, clonidine, fenofibrate, allopurinol, pirenzepine, levothyroxine, tamoxifen, metildigoxin, o-(β-hydroxyethyl)-rutoside, propicillin, acyclovir mononitrate, paracetamol, naftidrofuryl, pentoxifylline, propafenone, acebutolol, L-thyroxine, tramadol, bromocriptine, loperamide, ketotifen, fenoterol, Ca dobelisate, propranolol, minocycline, nicergoline, ambroxol, metoprolol, β-sitosterine, enalapril hydrogen maleate, bezafibrate, ISDN, gallopamil, xanthinol nicotinate, digitoxin, flunitrazepan, bencyclan, dexapanthenol, pindolol, lorazepam, diltiazem, piracetam, phenoxymethylpenicillin, furosemide, bromazepam, flunarizine, erythrom.ycin, metoclopramide, acemetacin, ranitidine, biperiden, metamizol, doxepin, dipotassium chlorazepate, tetrazepam, estramustine phosphate, terbutaline, captopril, maprotiline, prazosine, atenolol, glibenclamide, cefaclor, etilefrine, cimetidine, theophylline, hydromorphone, ibuprofen, primidone, clobazam, oxaceprol, medroxyprogesterone, flecainide, Mg pyridoxal-5-phosphate glutaminate, hymechromone, etofylline clofibrate, vincamine, cinnarizine, diazepam, ketoprofen, flupentixol, molsidomine, glibornuride, dimetinden, melperone, soquinolol, dihydrocodeine, clomethiazole, clemastine, glisoxepide, kallidinogenase, oxyfedrine, baclofen, carboxymethylcysteine, thioridacine, betahistine, L-tryptophan, myrtol, bromelaine, prenylamine, salazosulfapyridine, astemizol, sulpirid, benzerazide, dibenzepine, acetylsalicylic acid, miconazole, nystatin, ketoconazole, Na picosulfate, colestyramine, gemfibrocil, rifampicin, fluocortolone, mexiletine, amoxicillin, terfenadine, mucopolysaccharidepolysulfuric ester, triazolam, mianserin, tiaprofenic acid, amezinium metilsulfate, mefloquine, probucol, quinidine, carbamazepine, Mg L-aspartate, penbutolol, piretanide, amitriptyline, cyproterone, Na valproinate, mebeverine, bisacodyl, 5-aminosalicylic acid, dihydralazine, magaldrate, phenprocoumone, amantadine, naproxen, carteolol, famotidine, methyldopa, auranofin, estriol, nadolol, levomepromazine, doxorubicin, medofenoxate, azathioprine, flutamide, norfloxacin, fendiline, prajmalium bitartrate and aescin.

Solid solutions of the following active compounds are particularly preferred: acetaminophen (=paracetamol), acetohexamide, acetyldigoxin, acetylsalicylic acid, acromycin, anipamil, benzocaine, β-carotene, chloramphenicol, chlordiazepoxide, chlormadinone acetate, chlorothiazide, cinnarizine, clonazepam, codeine, dexamethasone, diazepam, dicumarol, digitoxin, digoxin, dihydroergotamine, drotaverine, flunitrazepam, furosemide, gramicidine, griseofulvin, hexobarbital, hydrochlorothiazide, hydrocortisone, hydroflumethiazide, indomethacin, ketoprofen, lonetil, medazepam, mefruside, methandrostenolone, methylprednisolone, methylsulfadiazine (=sulfaperin), nalidixinic acid, nifedipine, nitrazepam, nitrofurantoin, nystatin, estradiol, papaverine, phenacetin, phenobarbital, phenylbutazone, phenytoin, prednisone, reserpine, spironolactone, streptomycin, sulfadimidine (=sulfamethazine), sulfamethizole, sulfamethoxazole, sulfamethoxydiazine (=sulfameter), sulfaperin, sulfathiazole, sulfisoxazole, testosterone, tolazamide, tolbutamide, trimethoprim and tyrothricin.

The term solid solutions is familiar to the skilled worker, for example from the literature cited at the outset. In solid solutions of pharmaceutical active compounds in polymers, the active compound is present in molecular disperse form in the polymer.

The formation of solid solutions of the stated active compounds in NVP polymers could not be foreseen and is all the more surprising since many active compounds which are sparingly soluble in water do not form solid solutions (with molecular disperse distribution) in other polymers but are included in the particular polymer in the form of solid particles which can be detected by electron microscopy. Crystalline active compounds also exhibit a Debye-Scherrer pattern, in contrast to the solid solutions.

In the Examples which follow, parts and percentages are by weight.

Examples 1 to 32: Double link belt according to FIG. 2

EXAMPLE 1

45 parts of a copolymer having a K value of 30 and consisting of 60% by weight of N-vinylpyrrolidone and 40% by weight of vinyl acetate, 5 parts of stearyl alcohol and 50 parts of theophylline were mixed and extruded in a twin-screw extruder. The temperatures of the six shots of the extruder barrel were 30, 60, 60, 60, 80 and 100° C.; the die was heated to 100° C. The resulting extrudate was pressed directly to give oblong tablets, using a double link belt which was cooled to 15° C.. Rigid tablets were formed.

The tablets thus obtained were stable to mechanical effects and showed no abrasion during transport and packaging.

EXAMPLE 2

50 parts of the copolymer of Example 1 and 50 parts of theophylline were mixed and extruded in a twin-screw extruder. In contrast to Example 1, the temperatures of the shots were brought to 30, 60, 60, 60, 90 and 120° C. The die was likewise at 120° C. The extrudate obtained was pressed to give oblong tablets similarly to Example 1. The temperature of the double link belt was 15° C. These tablets obtained similarly to Example 1 were also stable to mechanical effects.

EXAMPLE 3

47.5 parts of a copolymer having a K value of 30 and consisting of 60% by weight of N-vinylpyrrolidone and 40% by weight of vinyl acetate, 2.5 parts of crosslinked PVP as a tablet disintegrant and 50 parts of theophylline were mixed and extruded in a twin-screw extruder. The temperatures of the five shots were each 120° C., and the die was at 130° C. The still plastic extrudate was pressed to give oblong tablets as in Example 1 (temperature of the double link belt: +15° C.). The tablets were stable to mechanical effects.

EXAMPLE 4

50 parts of a copolymer having a K value of 52 and consisting of 30% by weight of N-vinylpyrrolidone and 70% by weight of vinyl acetate and 50 parts of theophylline were mixed and extruded in a twin-screw extruder. The temperatures of the five shots were 30, 60, 100, 100 and 120° C. The die was likewise heated to 120° C. The still plastic extrudate was pressed to give me-

chanically stable oblong tablets as in Example 1 (temperature of the double link belt +15° C.).

EXAMPLES 5 TO 8

A mixture of 50% by weight of a N-vinylpyrrolidone homopolymer (PVP), having the K value stated in each case in the Table, and 50% by weight of theophylline was melted and extruded in a single-screw extruder at the temperature stated in each case in the Table, and the extrudate was formed into tablets as in Example 1.

Example	K value	T [°C.] 1st	2nd	3rd Shot	4th	5th	Die	Temp. of the double link belt [°C.]
5	12	115	125	135	135	135	145	10
6	17	125	125	135	145	145	155	10
7	25	145	155	165	175	175	175	15
8	30	150	160	160	170	180	180	15
8a	60	150	160	160	170	180	180	15

EXAMPLE 9

40 parts of a copolymer of 60% by weight of N-vinylpyrrolidone and 40% by weight of vinyl acetate, having a K value of 30, 10 parts of polyhydroxyethyl methacrylate and 50 parts of theophylline were processed to give mechanically stable tablets similarly to Example 1. Temperatures of the shots: 70, 80, 80, 80 and 80° C. Die: 90° C. Double link belt: +30° C.

EXAMPLE 10

50 parts of a commercial, 80% hydrolyzed polyvinyl acetate and 50 parts of theophylline were processed similarly to Example 1. The temperatures of the 5 shots were 100, 100, 110, 120 and 130° C. Die: 150° C. Double link belt: +32° C.

EXAMPLE 11

50 parts of polyhydroxyethyl methacrylate having a K value of 30 and 50 parts of theophylline were processed similarly to Example 1. Temperatures of the shots: 120, 130, 150, 160 and 160° C. Die: 170° C. Double link belt: +30° C.

EXAMPLES 12 TO 14

36 parts of a copolymer of 60% by weight of N-vinylpyrrolidone and 40% by weight of vinyl acetate, having a K value of 30, 4 parts of stearyl alcohol and 40 parts of theophylline and 20 part of

Example 12) starch
Example 13) lactose
Example 14) sucrose

were fixed in a 6-shot twin-screw extruder and formed into tablets similarly to Example 1. The temperatures of the shots were 90, 100, 110, 120, 120 and 130° C. and the

temperature of the die was 135° C. Double link belt: +15° C.

EXAMPLES 15 TO 17

50 parts of the copolymer of Examples 12 to 14 and 50 parts of verapamil were formed into tablets similarly to Examples 12 to 14.

The following were carried out similarly to the above Examples. The processing conditions and the release rates in the half-change test (cf. R. Voigt, Lehrbuch der pharmazeutischen Technologie, 5th edition, Verl. Chemie, Weinheim; Deerfield Beach, Florida; Basle, 1984, page 627, in conjunction with the paddle method according to USP 21) are tabulated. A heatable double link belt (Examples 18 to 32), a heatable double belt (Examples 33 to 53) and an engraved roller together with a smooth belt (Examples 54 to 85) were used for shaping.

TABLE 1

Double link belt according to FIG. 2

Example No.	Active compound	Polymer	Auxiliary	Weight ratio of active compound/ polymer/ auxiliary	T1	T2	T3	T4 [°C.]	T5	T6	Die	Release rate	Temperature double link belt [°C.]
18	Pseudoephedrine 47.5 Diphenhydramine 2.5	A	./.	50/50/0	60	80	100	120	120	120	120	100% in 1 h	16
19	Propafenone	A	starch	40/40/20	60	70	90	110	110	110	110	100% in 1 h	16
20	Propafenone	A	StA	60/35/5	80	90	100	120	140	140	140	100% in 2 h	15
21	Propafenone	A	StA	60/30/10	80	90	100	120	130	130	140	52% in 6 h	15
22	Propafenone	A	StS	60/30/5	70	90	100	110	115	115	115	42% in 6 h	15
23	Propafenone	B	StA	50/40/10	65	80	95	110	110	110	110	100% in 6 h	15
24	Propafenone	A	MgSt	60/35/5	60	70	80	80	95	100	100	95% in 6 h	10
25	Propafenone	A	MgSt	50/40/10	60	70	80	80	95	100	100	80% in 6 h	10
26	Anipamil	A	MgSt	50/40/10	30	30	40	40	60	60	60	100% in 2 h	10
27	Vitamin B1	B	./.	50/50/0	40	40	50	60	80	80	80	100% in 1 h	10
28	Nicotinic acid	A	./.	50/50/0	60	70	80	95	95	100	100	100% in 1 h	10
29	Biperiden	A	StA	50/45/5	80	90	100	120	120	130	135	100% in 4 h	16
30	Biperiden	A	./.	50/50/0	80	90	110	120	140	140	140	100% in 1 h	16
31	Canthaxanthine	B	./.	50/50/0	30	30	40	40	60	60	60	100% in 1 h	20
32	Canthaxanthine	A	./.	50/50/0	40	40	55	60	60	80	80	100% in 1 h	20

TABLE 2

Double belt according to FIG. 1

Example No.	Active compound	Polymer	Auxiliary	T1	T2	T3	T4 [°C.]	T5	T6	Die	Temperature of the double link belt [°C.]
33	Indomethacin	A		50	60	70	80	80	80	80	10
34	Indomethacin	B		60	80	100	120	120	120	120	10
35	Anipamil	A		30	30	40	50	50	60	60	15

TABLE 2-continued

Example No.	Active compound	Polymer	Auxiliary	T1	T2	T3	T4 [°C.]	T5	T6	Die	Temperature of the double link belt [°C.]
				Double belt according to FIG. 1							
36	Anipamil	B		30	30	40	50	50	60	60	15
37	Benzocaine	D		60	80	95	100	120	120	140	20
38	Benzocaine	D		60	80	95	100	120	130	140	20
39	Benzocaine	F		30	30	40	50	50	60	60	10
40	Benzocaine	B		60	80	100	120	120	120	120	10
41	5,5-Diphenhydramine	B		60	80	100	120	120	120	120	15
42	Paracetamide	B		60	80	100	120	120	120	120	15
43	Sulfathiazole	B		70	90	100	100	100	100	120	10
44	Sulfathiazole	E		70	90	100	100	100	110	120	15
45	Benzocaine	A		30	30	40	50	60	70	70	10
46	5,5-Diphenhydramine	A		60	80	100	120	120	120	130	10
47	Paracetamol	A		60	80	100	120	120	120	130	10
48	Sulfathiazole	A		70	90	100	100	100	100	130	10
49	Vitamin C	C		75	95	95	120	120	120	120	20
50	Benzocaine	E		60	70	80	120	130	130	130	15
51	Benzocaine	G		60	70	70	80	80	80	120	15
52	Benzocaine	H		50	60	60	60	80	90	110	10
53	Benzocaine	I		50	60	70	70	75	75	80	10

TABLE 3

Example No.	Active compound	Polymer	Auxiliary	Weight ratio of active compound/ polymer/ auxiliary	T1	T2	T3	T4 [°C.]	T5	T6	Die	Temp. of the roller [°C.]
				Engraved roller + smooth belt according to FIG. III								
54	Metoprolol	A	StA	40/55/5	60	70	80	80	90	80	80	18
55	Ranitidine	A	—	46/54/0	60	70	80	80	90	90	80	18
56	Diclophenac	A	StA	40/55/5	65	70	80	90	90	90	90	18
57	Furosemide	A	StA	30/60/10	65	75	80	90	100	100	100	18
58	Nifedipine	A	StA	20/70/10	60	70	80	80	80	80	80	18
59	Gallopamil	A	StA	40/54/6	50	60	70	80	80	70	70	16
60	Gallopamil	A	StA	40/48/12	50	60	70	80	80	70	70	16
61	Gallopamil	A	StA	40/42/18	50	60	70	80	80	70	70	16
62	Gallopamil	A	StS	40/54/6	50	60	70	80	80	70	70	16
63	Gallopamil	A	StS	40/48/12	50	60	70	80	80	70	70	16
64	Gallopamil	A	StS	40/42/18	50	60	70	80	80	70	70	16
65	Anipamil	A	StA	34/54.4/13.6	50	60	65	65	60	60	55	10
66	Biperiden	A	StA	6/89/5	45	55	60	65	65	65	60	15
67	Biperiden	A	StA	6/84/10	45	55	50	65	65	65	60	15
68	Biperiden	A	StA	6/79/15	45	55	60	65	65	65	60	15
69	Biperiden	A	StA	6/74/20	50	50	60	60	50	50	50	10
70	Biperiden	A	StA	6/69/25	40	50	55	60	60	50	50	10
71	Biperiden	A	StA	6/64/30	40	50	55	60	60	50	50	10
72	Biperiden	A	StA	6/59/35	40	50	55	60	60	50	50	10
73	Bezafibrate	A	—	61.5/38.5/0	60	70	80	80	80	80	80	15
74	Bezafibrate	A	StA	61.5/34/4.5	60	70	80	80	80	70	70	15
75	Bezafibrate	A	StA	61.5/29.5/9.0	40	45	50	50	50	50	50	15
76	Metoprolol	A	Starch	40/45/15	60	70	80	80	80	80	80	15
77	Metoprolol	A	Starch	40/35/25	55	60	65	70	70	70	70	16
78	Anipamil	A	Lactose	32/43/25	55	60	70	80	70	70	65	10
79	Anipamil	A	Cellulose	32/61.2/6.8	55	60	70	80	65	65	60	10
80	Anipamil	A	Lactose	32/34.4/13.6	55	60	70	80	65	65	60	10
81	Anipamil	A	Starch	32/54.4/13.6	55	60	70	80	65	65	60	15
82	Caffeine powder	A	StA	50/45/5	65	75	90	90	90	90	100	18
83	Caffeine powder	A	—	50/50/0	65	75	90	90	90	90	100	18
84	Caffeine powder	A	StA	50/45/5	65	70	70	75	75	90	80	20
85	Caffeine powder	A	—	50/50/0	65	70	70	75	75	90	80	20

A = Copolymer of 60% by weight of NVP and 40% by weight of vinyl acetate, K value about 33
B = PVP, K value 12
C = PVP, K value 17
D = Mowiol ® 30–92 (92% hydrolyzed polyvinyl alcohol)
E = Mowiol ® 4–80 (80% hydrolyzed polyvinly alcohol)
F = Copolymer of NVP, vinyl acetate and hydroxypropyl acrylate in a weight ratio of 30:40:30, K value about 18
G = Cellulose acetate
H = Cellulose acetate phthalate
I = Copolymer of vinyl acetate/crotonic acid, K value about 30
StA = Stearyl alcohol
StS = Stearic acid
MgSt = Magnesium stearate

We claim:

1. A process for tabletting a mixture of one or more pharmaceutical active compounds, one or more pharmacologically acceptable thermoplastic polymers, said polymers having a Fikentscher K value of from 10 to 100, and optional pharmaceutical auxiliaries,

said mixture having a glass transition temperature below the decomposition temperature of all components of said mixture

wherein said mixture is heated, without thermal and/or oxidative degradation, at a temperature of from 50° to 180° to render the mixture extrudable and said heated mixture is extruded at from 50° to 180° and the still formable extrudate is pressed between two belts or a belt and a roller to give tablets, said two belts or said belt and a roller making contact in parts, rotating in opposite directions and running parallel along a contact zone, at least one of said two belts or at least one of said belt and a roller having shape-imparting indentations.

2. A process as claimed in claim **1**, wherein two resilient belts having indentations which are opposite one another and, in pairs, determine the tablet shape are used.

3. A process as claimed in claim **1**, wherein two metal link belts which contain the shape-imparting indentations in corresponding pairs are used.

4. A process as claimed in claim **1**, wherein a rotating roller having shape-imparting indentations engraved on the lateral surface of the roller is used together with a smooth belt which rests against a segment of the lateral surface of the roller and revolves with the said surface.

5. A process as claimed in claim **4**, wherein the revolving, smooth belt is replaced by a stationary, smooth wall.

6. A process as claimed in claim **1**, wherein a rotating smooth roller is used together with a resilient belt which has the shape-imparting indentations in the contact surface.

7. A process as claimed in claim **2**, wherein, instead of the second belt, a roller which rotates synchronously in contact with the first belt and on whose lateral surface engraved shape-imparting indentations correspond in pairs with those of the belt is used.

8. A process as claimed in claim **1**, wherein the thermoplastic polymer used is a solvent-free N-vinylpyrrolidone polymer which has a water content of not more than 3.5% by weight and contains not less than 20% by weight of N-vinylpyrrolid-2-one (NVP) as copolymerized units, all comonomers which may be copolymerized containing nitrogen and/or oxygen.

9. A process as claimed in claim **8**, wherein the thermoplastic polymer used contains not less than 60% by weight of NVP as copolymerized units.

10. A process as claimed in claim **8**, wherein the thermoplastic polymer used consists of polyvinylpyrrolidone or contains only vinyl acetate as copolymerized units in addition to NVP.

11. A process as claimed in claim **8**, wherein a thermoplastic polymer is used whose comonomers are selected from the following group: acrylic acid, methacrylic acid, crotonic acid, maleic acid (anhydride), itaconic acid (anhydride), esters of the stated acids or halfesters of the stated dicarboxylic acids with alcohols of 1 to 12 carbon atoms, hydroxyethyl and hydroxypropyl acrylate and methacrylate, acrylamide, methacrylamide, N-vinylcaprolactam and vinyl propionate.

12. A process as claimed in claim **8**, wherein the thermoplastic polymer used is an NVP polymer which has been prepared either in an organic solvent or using an organic peroxide in water.

13. A process as claimed in claim **8**, wherein not more than 20% by weight, based on the polymer, of plasticizers are used.

14. A process as claimed in claim **1**, wherein the active compound used is one which is sparingly soluble in water, forms a molecular disperse phase in the polymer melt without the addition of solvents or water and forms a solid solution after solidification of the melt.

15. A process as claimed in claim **14**, wherein one or more active compounds from the following group are used: acetaminophen (=paracetamol), acetohexamide, acetyldigoxin, acetylsalicylic acid, acromycin, anipamil, benzocaine, β-carotene, chloramphenicol, chlordiazepoxide, chlormadinone acetate, chlorothiazide, cinnarizine, clonazepam, codeine, dexamethasone, diazepam, dircumarol, digitoxin, digoxin, dihydroergotamine, drotaverine, flunitrazepam, furosemide, gramicidin, griseofulvin, hexobarbital, hydrochlorothiazide, hydrocortisone, hydroflumethiazide, indomethacin, ketoprofen, lonetil, medazepam, mefruside, methandrostenolone, methylprednisolone, methylsulfadiazine (=sulfaperin), nalidixic acid, nifedipine, nitrazepam, nitrofurantoin, nystatin, estradiol, papaverine, phenacetin, phenobarbital, phenylbutrazone, phenytoin, prednisone, reserpine, spironolactone, streptomycin, sulfadimidine(=sulfamethazine), sulfamethizole, sulfamethoxazole, sulfamethoxydiazine (=sulfameter), sulfaperin sulfathiazole, sulfisoxazole, testosterone, tolazamide, tolbutamide, trimethoprim and tyrothricin.

16. A process as claimed in claim **1**, wherein an NVP polymer having a Fikentscher K value of from 10 to 50 is used.

17. A process as claimed in claim **1**, wherein an NVP polymer having a Fikentscher K value of from 12 to 35 is used.

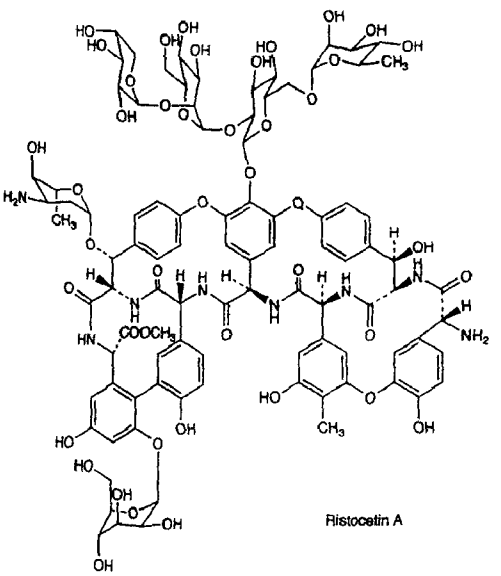
18. A process as claimed in claim **1**, wherein said mixture is heated at a temperature of from 60 to 130° C.

19. A process as claimed in claim **1**, wherein said mixture has a glass transition temperature less than 180° C.

20. A process as claimed in claim **19**, wherein said mixture has a glass transition temperature less than 130° C.

* * * * *

1, D. Gottlieb, P. Shaw, Eds. (Springer-Verlag, New York, 1967) pp 84-89.



Crystalline sulfates. Sol in acidic aq solns; much less sol in the neutral pH range. Generally insol in organic solvents. Both components show good stability in aq acidic solns, but are readily inactivated above pH 7.0. Commercial prepns are mixtures of both with > 90% ristocetin A.

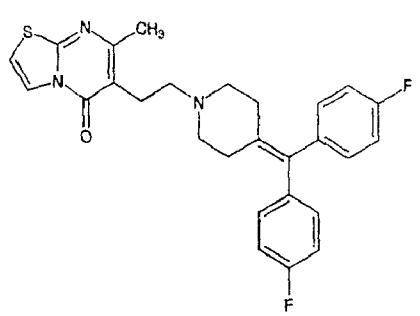
Ristocetin A, $C_{95}H_{110}N_8O_{44}$, *ristomycin A*. Cryst sulfate, $[\alpha]_D$ −120° to −133° (water).

Ristocetin B, *ristomycin B*. Cryst sulfate, $[\alpha]_D$ −144° to −149° (water).

USE: Tool for investigation of platelet aggregation: Howard, Firkin, *Thromb. Diath. Haemorrh.* **26**, 362 (1971).

THERAP CAT: Antibacterial.

8399. Ritanserin. *6-[2-[4-[Bis(4-fluorophenyl)methylene]-1-piperidinyl]ethyl]-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one;* R-55667; Tiserton. $C_{27}H_{25}F_2N_3OS$; mol wt 477.58. C 67.90%, H 5.28%, F 7.96%, N 8.80%, O 3.35%, S 6.71%. Selective serotonin ($5\text{-}HT_2$) receptor antagonist. Prepn: L. E. J. Kennis *et al.*, **Eur. pat. Appl. 110,435**; *eidem*, U.S. pat. **4,533,665** (1984, 1985 both to Janssen). Pharmacological profile: F. Awouters *et al., Drug Dev. Res.* **15**, 61 (1988). GC/MS determn in plasma and pharmacokinetics: P. Timmerman *et al, Biomed. Environ. Mass Spectrom.* **18**, 498 (1989). Clinical studies: G. Nappi *et al., Headache* **30**, 439 (1990); G. Bersani *et al., Acta Psychiat. Scand.* **83**, 244 (1991); J. M. Monti *et al., Sleep* **16**, 647 (1993).

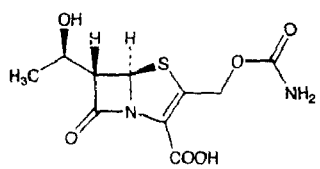


Crystals from acetonitrile, mp 145.5°. LD_{50} in male, female mice, rats, dogs (mg/kg): 28.2, 28.2, 20.0, 22.2, 24.1, 33.2 i.v.; 626, 993, 956, 515, ~1280, 640-1280 orally (Awouters).

L-Tartrate, $C_{27}H_{25}F_2N_3OS.C_4H_6O_6$, solid from 2-prop… mp 198.7°.

THERAP CAT: Anxiolytic; antidepressant.

8400. Ritipenem. *[5R-[5α,6α(R*)]]-3-[[(Aminocarb… yl)oxy]methyl]-6-(1-hydroxyethyl)-7-oxo-4-thia-1-azabi… [3.2.0]hept-2-ene-2-carboxylic acid;* (5*R*,6*S*,8*R*)-6α-hydr… ethyl-2-carbamoyloxymethyl-2-penem-3-carboxylic … (5*R*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-3-(hydroxymethyl)-7-… 4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid … carbamate. $C_{10}H_{12}N_2O_6S$; mol wt 288.28. C 41.66%, … 4.20%, N 9.72%, O 33.30%, S 11.12%. Prepn: M. Alp… *et al.*, Ger. pat. **3,245,270**; M. Foglio *et al.*, U.S. pat. **4,… 565** (1983, 1984 both to Carlo Erba). Synthesis: G. … ceschi *et al., J. Antibiot.* **36**, 938 (1983). Total synth… W. Cabri *et al., Tetrahedron Letters* **34**, 3491 (1993). … ity study: M. Brughera *et al., J. Antimicrob. Chemother.* … Suppl. C, 129 (1989). Series of articles on synthesis, *in … activity, metabolism: ibid.*, 1-204 (1989). Clinical pha… cokinetics of acid and ester forms: S. R. Norrby *et al.*, … **25**, 371 (1990); A. M. Lovering *et al., ibid.* **29**, 179 (1… HPLC determn in serum and urine: R. Mendez *et al.*, … *Chromatog.* **579**, 115 (1992).

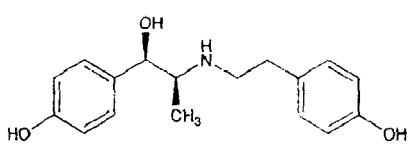


Sodium salt, $C_{10}H_{11}N_2NaO_6S$, *FCE-22101.* $[\alpha]_D^{20}$ … uv max (H_2O): 258, 306 nm (ε 4150, 6030). LD_{50} in … female mice, male, female rats (mg/kg): 3872, 4393, … 2201 i.v. (Brughera).

Acetoxymethyl ester, $C_{13}H_{16}N_2O_8S$, *ritipenem ace… FCE-22891.* LD_{50} in male, female mice, male, female … (mg/kg): 4363, 6167, > 5000, > 5000 orally (Brughera).

THERAP CAT: Antibacterial.

8401. Ritodrine. *(R*,S*)-4-Hydroxy-α-[1-[[2-(4-hy… oxyphenyl)ethyl]amino]ethyl]benzenemethanol; erythro-4-hydroxy-α-[1-[(p-hydroxyphenethyl)amino]ethyl]benzyl alcohol; N*-[2-(*p*-hydroxyphenyl)ethyl]-*N*-[2-(*p*-hydroxyphenyl)-2-hydroxy-1-methylethyl]amine; 1-(4-hydroxyphenyl)-2-[(4-hydroxyphenyl)ethylamino]propanol; *N*-(*p*-hydroxyphenylethyl)-4-hydroxynorephedrine. $C_{17}H_{21}NO_3$; mol … 287.36. C 71.06%, H 7.37%, N 4.87%, O 16.70%. … Adrenergic agonist. Prepn: **Belg. pat. 660,244** (1965 … N.V. Philips); Claassen *et al.*, U.S. pat. **3,410,944** (1968 … No. Am. Philips). Clinical investigations: Coutinho *et al. Am. J. Obstet. Gynecol.* **104**, 1053 (1969); Landesman *et al. ibid.* **110**, 111 (1971); Wesselius-De Casparis *et al., Acta Med. J.* **3**, 144 (1971). Clinical efficacy in treatment of … term labor: J. F. Larsen *et al., Obstet. Gynecol.* **67**, … (1986).



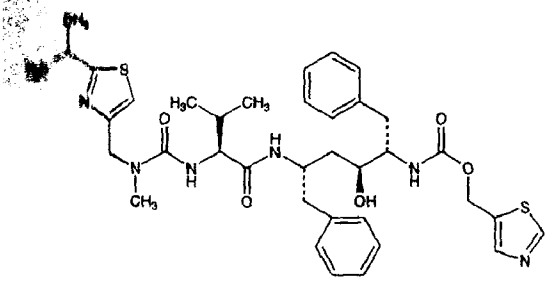
Base, resinous mass, mp 88-90°.

Hydrochloride, $C_{17}H_{21}NO_3.HCl$, *DU-21220, Miolan, Prempar, Pre-Par, Utemerin, Utopar, Yutopar.* mp 193-1… (dec) from ethanol-ether. uv max: 267.5 nm (ε 3310).

THERAP CAT: Tocolytic.

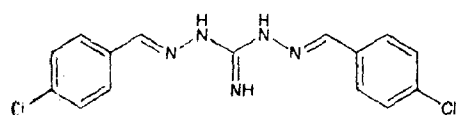
8402. Ritonavir. *[5S-(5R*,8R*,10R*,11R*)]-10-H… oxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid 5-thiazolylmethyl ester;* (2*S*,3*S*,5*S*)-5-[… [*N*-[[*N*-methyl-*N*-[(2-isopropyl-4-thiazolyl)methyl]amino]carbonyl]valinyl]amino]-2-[*N*-[(5-thiazolyl)methoxycarbo… yl]amino]-1,6-diphenyl-3-hydroxyhexane; A-84538; Abb… 84538; ABT-538. $C_{37}H_{48}N_6O_5S_2$; mol wt 720.96. C 61.… H 6.71%, N 11.66%, O 11.10%, S 8.90%. Peptidomimet… HIV-1 protease inhibitor. Prepn: D. J. Kempf *et al.*, PCT

Appl. 94 14,436 (1994 to Abbott). Antiretroviral pharmacokinetics: *idem et al., Proc. Nat. Acad.* 92, 2484 (1995). Structural model for drug resis- M. Markowitz *et al., J. Virol.* 69, 701 (1995). Evalu- HIV-infected patients: D. D. Ho *et al., Nature* 373,



THERAP CAT: Antiviral.

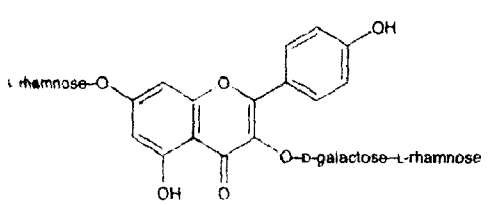
8403. Robenidine. *Bis[(4-chlorophenyl)methylene]carbonimidic dihydrazide; 1,3-bis[(p-chlorobenzylidene)amino]guanidine.* $C_{15}H_{13}Cl_2N_5$; mol wt 334.21. C 53.91%, H Cl 21.22%, N 20.96%. Prepn: Tomcufcik, Ger. pat. 113 (1970 to Am. Cyanamid), *C.A.* **72,** 90113c (1970). activity studies: Kantor *et al., Science* **168,** 373 (1970); *et al., Biochem. Biophys. Res. Commun.* **46,** 621 Metabolism: Zulalian *et al.,* 163rd Am. Chem. Soc. (Boston, April 1972) *Abstracts of Papers,* PEST 12, Animal studies: Millard, *Res. Vet. Sci.* **11,** 394 (1970); Norton, *ibid.* **13,** 279 (1972).



Hydrochloride, $C_{15}H_{13}Cl_2N_5$.HCl, *robenzidene, Cycostat,* Crystals from ethanol, mp 289-290°.

THERAP CAT (VET): Coccidiostat

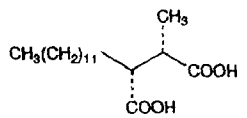
8404. Robinin. *3-[[6-O-(6-Deoxy-α-L-mannopyranosyl)-β-D-galactopyranosyl]oxy]-7-[(6-deoxy-α-L-mannopyranosyl)oxy]-5-hydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one;* kaempferol 3-robinoside 7-rhamnoside. $C_{33}H_{40}O_{19}$; mol wt 740.67. C 53.51%, H 5.44%, O 41.04%. Dimorphic flavanol isolated from the leaves and flowers of *Robinia pseudoacacia* L., *Leguminosae:* C. Zwenger, F. Dronke, *Ann.* 1, 257 (1861); C. Sando, *J. Biol. Chem.* **94,** 675 Structure: Zemplén, Bognár, *Ber.* **74B,** 1783 Total synthesis and structure: L. Farkas *et al., Chemistry* **15,** 215 (1976)



Form. Yellow crystals, mp 250-254° (Farkas); also reported as straw-yellow needles from alc, mp 249-250° (Sando). uv max (ethanol): 352, 368 nm (log ε 4.14, 4.18), Horowitz, *J. Org. Chem.* **22,** 1619 (1957). Sol in hot water, hot alc; practically insol in ether. On hydrolysis yields kaempferol, *q.v.*

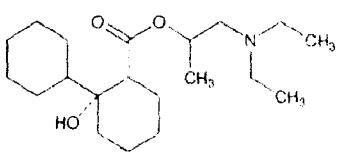
Form. Obtained by crystallization from water and dehydrating, mp 195-197° (Sando). Also reported as hydrate, yellow needles from aq methanol, mp 196-199° (Farkas).

8405. Roccellic Acid. *[S-(R*,S*)]-2-Dodecyl-3-methylbutanedioic acid; (2R,3S)-2-dodecyl-3-methylsuccinic acid; d-α-dodecyl-β-methylsuccinic acid; d-α-methyl-α'-dodecylsuccinic acid.* $C_{17}H_{32}O_4$; mol wt 300.44. C 67.96%, H 10.74%, O 21.30%. Occurs in lichens. Isoln from *Lecanora sordida* (Pers.) Th. Fries, *Parmeliaceae:* Hesse, *J. Prakt. Chem.* **58,** 497 (1898); Kennedy *et al., Sci. Proc. Roy. Dublin Soc.* **21,** 557 (1937); from *Roccella montagnei, Graphidaceae:* Subbaraya, Seshadri, *Proc. Indian Acad. Sci.* **12A,** 466 (1940); from *Crocynia membranacae* (Dicks.) Zahlbr., *Chrysotrichaceae:* Akermark *et al., Acta Chem. Scand.* **13,** 1855 (1959). Structure: Kennedy *et al., loc. cit.* Absolute configuration: Akermark, *Acta Chem. Scand.* **16,** 599 (1962).



Rectangular rods from acetone, mp 132-133°. $[\alpha]_D^{20}$ +18° (c = 1.84 in ethanol). Practically insol in water. Freely sol in alcohol, ether; sol in aq sodium bicarbonate solns. Forms a water-sol sodium salt.

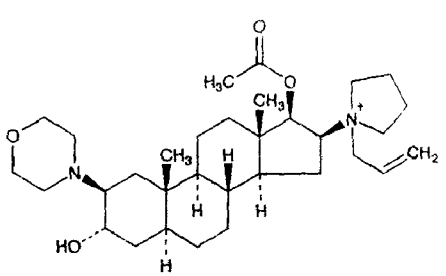
8406. Rociverine. *1-Hydroxy[1,1'-bicyclohexyl]-2-carboxylic acid 2-(diethylamino)-1-methylethyl ester;* 2-(diethylamino)-1-methylethyl *cis*-1-hydroxy[bicyclohexyl]-2-carboxylate; LG-30158; Rilaten. $C_{20}H_{37}NO_3$; mol wt 339.52. C 70.75%, H 10.98%, N 4.13%, O 14.14%. Spasmolytic agent with balanced neurotropic and myotropic properties. Prepn: L. Turbanti, S. Afr. pat. 67 **05649,** *C.A.* **70,** 47117d (1969) and U.S. pat. **3,700,675** (1968, 1972 both to Guidotti). Antispasmodic activity *in vitro* and *in vivo:* G. Toson *et al., Arzneimittel-Forsch.* **28,** 1130 (1978). Effect in cystitis or bladder spasm: A. Manganelli, *Farmaco Ed. Prat.* **34,** 384 (1979). Clinical studies: M. Petrillo *et al., Curr. Med. Res. Opin.* 7, 73 (1980); R. Assisi, S. deStefano, *Acta Ther.* 6, 353 (1980); F. Marsala, *Minerva Med.* **73,** 2179 (1982).



Oil, $bp_{0.1}$ 148-150°. n_D^{20} 1.4820. Sol in alc, ether, chloroform, benzene, dil mineral acids. Insol in water.

THERAP CAT: Antispasmodic.

8407. Rocuronium. *1-[(2β,3α,5α,16β,17β)-17-(Acetyloxy)-3-hydroxy-2-(4-morpholinyl)androstan-16-yl]-1-(2-propenyl)pyrrolidinium;* 1-allyl-1-(3α,17β-dihydroxy-2β-morpholino-5α-androstan-16β-yl)pyrrolidinium 17-acetate. $[C_{32}H_{53}N_2O_4]^+$. Non-depolarizing neuromuscular blocking agent. Prepn: D. S. Savage *et al.,* Eur. pat. **Appl. 287,150;** T. Sleigh *et al.,* U.S. pat. **4,894,369** (1988, 1990 both to Akzo). Pharmacology: A. W. Muir *et al., Brit. J. Anaesth.* **63,** 400 (1989); K. Khuenl-Brady *et al., Anesthesiology* 72, 669 (1990). Clinical pharmacodynamics: T. J. Quill *et al., Anesth. Analg.* **72,** 203 (1991); and pharmacokinetics in the elderly: R. S. Matteo *et al., ibid.* **77,** 1193 (1993). Comparative clinical trial: T. Magorian *et al., Anesthesiology* **79,** 913 (1993). HPLC determn: U. W. Kleef *et al., J. Chromatog.* **621,** 65 (1993). Review: T. C. Wicks, *J. Am. Assoc. Nurse Anesthet.* **62,** 33-38 (1994)



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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 May 2001 (17.05.2001)

PCT

(10) International Publication Number
WO 01/34119 A2

(51) International Patent Classification[7]: A61K 9/14

(21) International Application Number: PCT/US00/31072

(22) International Filing Date:
10 November 2000 (10.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/438,994 12 November 1999 (12.11.1999) US

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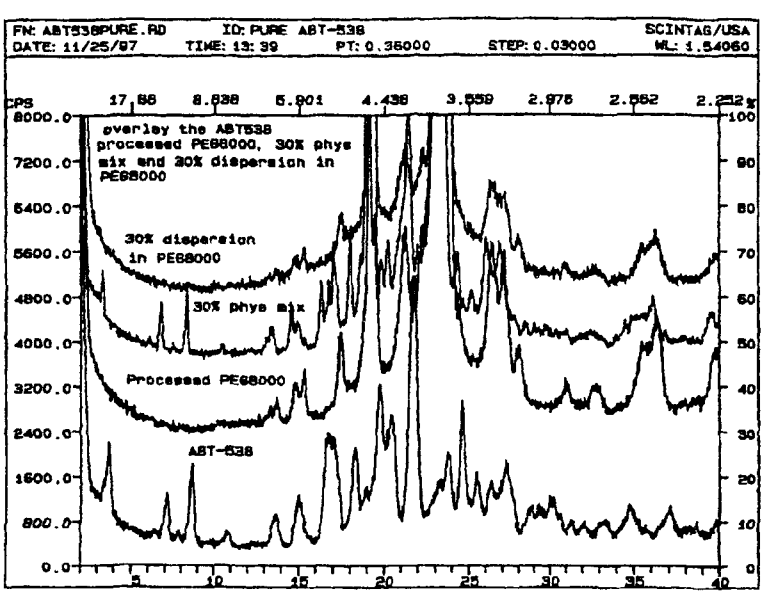
(81) Designated States *(national)*: CA, JP, MX.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
Without international search report and to be republished upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INHIBITORS OF CRYSTALLIZATION IN A SOLID DISPERSION



(57) Abstract: A pharmaceutical composition is disclosed which comprises a solid dispersion of a pharmaceutical compound in a water soluble carrier, such as polyethylene glycol (PEG), and a crystallization inhibitor, such as polyvinylpyrrolidone or hydroxypropylmethylcellulose. The solid dispersion may optionally be encapsulated in hard gelatin capsules, compressed into a tablet, or may be granulated with a pharmaceutically acceptable granulating agent. Also disclosed are methods of making said solid dispersion and methods of treatment employing said solid dispersion.

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INHIBITORS OF CRYSTALLIZATION IN A SOLID DISPERSION

Technical Field of the Invention

The instant invention relates to the fields of pharmaceutical and organic chemistry, and provides novel solid dispersion pharmaceutical formulations which demonstrate an inhibition of crystallization.

Background of the Invention

One measure of the potential usefulness of an oral dosage form of a pharmaceutical agent is the bioavailability observed after oral administration of the dosage form. Various factors can affect the bioavailability of a drug when administered orally. These factors include aqueous solubility, drug absorption throughout the gastrointestinal tract, dosage strength, and first pass effect. Aqueous solubility is one of the most important of these factors. When a drug has poor aqueous solubility, attempts are often made to identify salts or other derivatives of the drug which have improved aqueous solubility. When a salt or other derivative of the drug is identified which has good aqueous solubility, it is generally

identified which has good aqueous solubility, it is generally accepted that an aqueous solution formulation of this salt or derivative will provide the optimum oral bioavailability. The bioavailability of the aqueous oral solution formulation of a drug is then generally used as the standard or ideal bioavailability against which other oral dosage forms are measured.

For a variety of reasons, including patient compliance and taste masking, a solid dosage form, such as a capsule or tablet, is usually preferred over a liquid dosage form. However, oral solid dosage forms of a drug generally provide a lower bioavailability than oral solutions of the drug. One goal of the development of a suitable solid dosage form is to obtain a bioavailability of the drug that is as close as possible to the ideal bioavailability demonstrated by the oral aqueous solution formulation of the drug.

An alternative dosage form is a solid dispersion. The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (or fusion), solvent, or melting-solvent methods. (Chiou and Riegelman, *Journal of Pharmaceutical Sciences*, *60*, 1281 (1971)). The dispersion of a drug or drugs in a solid diluent by

mechanical mixing is not included in this category. Solid dispersions may also be called solid-state dispersions.

Retroviral protease inhibiting compounds are useful for inhibiting HIV proteases *in vitro* and *in vivo*, and are useful for inhibiting HIV (human immunodeficiency virus) infections and for treating AIDS (acquired immunodeficiency syndrome). HIV protease inhibiting compounds typically are characterized by having poor oral bioavailability. Examples of HIV protease inhibiting compounds include

2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir);

(2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl]-amino-1,6-diphenylhexane (ABT-378);

N-(2(R)-hydroxy-1 (S)-indanyl -2(R)-phenylmethyl -4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide (indinavir);

N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide (saquinavir);

5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;

1 -Naphthoxyacetyl-beta-methylthio-Ala-(2S, 3S)-3-amino-2-hydroxy-4-butanoyl 1,3-thiazolidine-4-t-butylamide;

5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;

[1S-[1R-(R-),2S*])-N^1 [3-[[[(1,1 -dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide;

VX-478; DMP-323; DMP-450; AG1343(nelfinavir);

BMS 186,318; SC-55389a; BILA 1096 BS; and U-140690, or combinations thereof.

While some drugs would be expected to have good solubility in organic solvents, it would not necessarily follow that oral administration of such a solution would give good bioavailability for the drug.

Polyethylene glycol (PEG) solid dispersion formulations are generally known to improve the dissolution and bioavailability of many compounds. However, Aungst *et al.* has recently demonstrated that this was unable to improve the bioavailability of an HIV protease inhibitor with a cyclic urea structural backbone, called DMP 323

(Aungst *et al.*, *International Journal of Pharmaceutics*, *156*, 79 (1997)).

In addition, some drugs tend to form crystals when placed in solution, which can be problematic during formulation.

Polyvinylpyrrolidone (PVP) is known to inhibit crystallization of drugs (Yohioka, M. et al., J. Pharm. Sci., 84, 983, 1995). However, prior to the instant invention, the incorporation of PVP into a second polymer matrix, such as polyethylene glycol, has never been established.

U.S. 4,610,875 teaches a process for the preparation of a stable pharmaceutical dipyridamole composition containing PVP.

U.S. 4,769,236 teaches a process for the preparation of a stable pharmaceutical composition with a high dissolution rate in the gastrointestinal tract containing PVP, wherein the pharmaceutical agent is hydroflumethiazide, dipyridamole, hydrochlorothiazide, cyclothiazide, cyclopenthiazide, polythiazide, methyldopa, spironolactone, quinidine, cyanidol, metronidazole, ibuprofen, naproxen, erythromycin, glaphenin, furosemide, suloctidil, nitrofurantoin, indomethacin, flavoxate,

phenobarbitol, cyclandelate, ketoprofen, natridrofuryl, or triamterene.

Thus, it would be a significant contribution to the art to provide a stable solid dispersion pharmaceutical formulation which demonstrates a lack of crystallization.

Summary of the Invention

The instant invention provides a stable solid dispersion pharmaceutical formulation comprising a pharmaceutical compound, a water soluble carrier, such as polyehtylene glycol (PEG), and a crystallization inhibitor, such as polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose (HPMC).

Also provided by the instant invention is a pharmaceutical composition comprising a stable solid dispersion as described above with additional pharmaceutically acceptable carriers, diluents, or excipients.

Additionally provided by the instant invention is a method for preparing a stable solid dispersion as described above.

The instant invention still further provides methods of treatment comprising administering an effective amount of a stable solid dispersion as described above to a mammal in need of such treatment.

Brief Description of the Figures

Figure 1 illustrates the PXD patterns showing that Amorphous ABT-538 can be isolated within PEG alone.

Figure 2 illustrates the PXD patterns showing that Amorphous ABT-538 can be isolated with a PVP/PEG matrix.

Figure 3 illustrates the DSC thermograms of PEG, ABT-538, a physical mixture of the two and a solid dispersion. The absence of ABT-538 melting in the dispersion confirms the above PXD data showing amorphous ABT-538 present in the dispersion.

Figure 4 illustrates the DSC thermograms of PVP/PEG, ABT-538, a physical mixture of the two and a solid dispersion. The absence of ABT-538 melting in the dispersion confirms the above PXD data showing amorphous ABT-538 present in the dispersion.

Figure 5 illustrates the effect of PEG or PVP on the crystallization rate of amorphous ritonavir. The heat of fusion was used to calculate percent crystallized. In the presence of PVP the crystallization rate is slower.

Figure 6 illustrates the inhibition of crystallization using PVP.

Figure 7 illustrates PXD patterns of ABT-538 dispersions with and without PVP stored at 50°C. The data

demonstrate the improved physical stability of amorphous ABT-538 on storage.

Figure 8 illustrates PXD patterns of fenofibrate dispersions with and without PVP.

Figure 9 illustrates PXD patterns of fenofibrate dispersions with and without PVP and PEG.

Figure 10 illustrates PXD patterns of fenofibrate dispersions with and without PEG.

Figure 11 illustrates PXD patterns of fenofibrate dispersions with and without 10% PVP and PEG.

Figure 12 illustrates PXD patterns of griseofulvin dispersions with and without PEG.

Figure 13 illustrates PXD patterns of griseofulvin dispersions with and without PEG and PVP.

Figure 14 illustrates PXD patterns of griseofulvin dispersions with and without PEG.

Figure 15 illustrates PXD patterns of griseofulvin dispersions with and without PEG and PVP.

Detailed Description of the Invention

This invention pertains to the preparation of solid dispersion systems for pharmaceuticals which demonstrate a lack of crystallization.

The invention involves dispersion in a hydrophilic matrix of pharmaceuticals which exhibit poor aqueous solubility. The intent of such a formulation is to improve the aqueous dissolution properties and ultimately achieve improved bioavailability. Typically, the intent of such systems is to generate a dispersion of amorphous (high energy) drug within the matrix. The presence of the high energy drug form usually improves the dissolution rate. However, these systems are not often physically stable. The drug can crystallize over time, causing the loss of the desired properties and reduced shelf-life. The current invention enhances the physical stability of such formulations, thereby making this type of formulation more feasible.

In the instant invention, PEG 8000 is used as the hydrophilic matrix. Also employed in this formulation is polyvinylpyrrolidone (PVP), which is an example of a hydrophilic, amorphous polymer, and is used to inhibit crystallization. Other hydrophilic, amorphous polymers

include hydroxypropylmethylcellulose (HPMC), or other pharmaceutically acceptable hydrophilic, amorphous polymers. Specifically, PVP PF 17 is used within the PEG matrix to inhibit the crystallization of the drug of interest. A range of 1%-95% (w/w) of PVP can be employed, with a range of 1%-15% (w/w) being preferred.

The benefits of incorporating PVP into the PEG matrix are two fold. Firstly, processing PVP can be difficult due to its hygroscopicity. Secondly, when PVP dissolves a viscous layer at the solid-liquid interface forms. This viscous region can hinder dissolution of the drug. Another benefit of adding PVP is an increase in amorphous volume of the polymer matrix where drugs may reside. Since polyethylene glycols tend to be highly crystalline, this increase in amorphous volume could be important for fast dissolution. PVP has the added advantage of having a high Tg, which imparts stabilization of amorphous regions by reducing mobility. Therefore, this invention affords the benefits of the PEG properties in a dispersion along with those of PVP.

A solid (molecular) dispersion comprising an HIV protease inhibiting compound may be prepared by dissolving or dispersing the HIV protease inhibiting compound in a sufficient amount of an organic solvent followed by

dispersion into a suitable water soluble carrier. Suitable organic solvents include pharmaceutically acceptable solvents such as methanol, ethanol, or other organic solvents in which the protease inhibitor is soluble. Suitable water soluble carriers include polymers such as polyethylene glycol (PEG), pluronics, pentaeythritol, pentaeythritol tetraacetate, polyoxyethylene stearates, poly-ε-caprolactone, and the like.

The organic solvent (preferably ethanol) may then be evaporated away, leaving the drug dispersed/dissolved in the molten matrix, which is then cooled. The solid matrix has the compound finely dispersed (molecular dispersion) in such a way that dissolution of the drug is maximized, thus improving the bioavailability of a drug exhibiting dissolution rate limited absorption. Ease of manufacturing is also an attribute to this type of formulation. Once the organic solvent is evaporated to yield a solid mass, the mass may be ground, sized, and optionally formulated into an appropriate delivery system. Thus, by improving the dissolution of a poorly water soluble drug, the drug in a suitable carrier may be filled into a gelatin capsule as a solid, or the matrix may potentially be compressed into a tablet.

The delivery system of the present invention results in increased solubility and bioavailability, and improved dissolution rate of the HIV protease inhibiting compound.

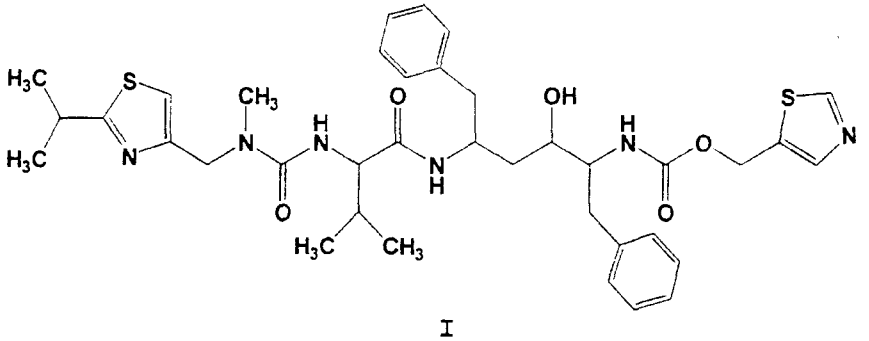
Other pharmaceutically-acceptable excipients may be added to the formulation prior to forming the desired final product. Suitable excipients include lactose, starch, magnesium stearate, or other pharmaceutically-acceptable fillers, diluents, lubricants, disintegrants, and the like, that might be needed to prepare a capsule or tablet.

The resulting composition comprising the pharmaceutical compound may be dosed directly for oral administration, diluted into an appropriate vehicle for oral administration, filled into capsules, or made into tablets for oral administration, or delivered by some other means obvious to those skilled in the art. The composition can be used to improve the oral bioavailability and solubility of said HIV protease inhibiting compound.

Total daily dosing of the pharmaceutical compound may be administered to a human in single or divided doses in amounts, for example, from 0.001 to 1000 mg/kg body weight daily, but more usually 0.1 to 50 mg/kg body weight daily. Dosage unit compositions may contain such amounts of

submultiples thereof to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, rate of excretion, drugs administered in combination and the severity of the particular disease undergoing therapy.

One type of pharmaceutical compound that may be employed in the practice of the present invention is an HIV protease inhibitor. An example of an HIV protease inhibitor is ABT-538 (ritonavir), the chemical structure of which is represented hereinbelow as a compound of formula I

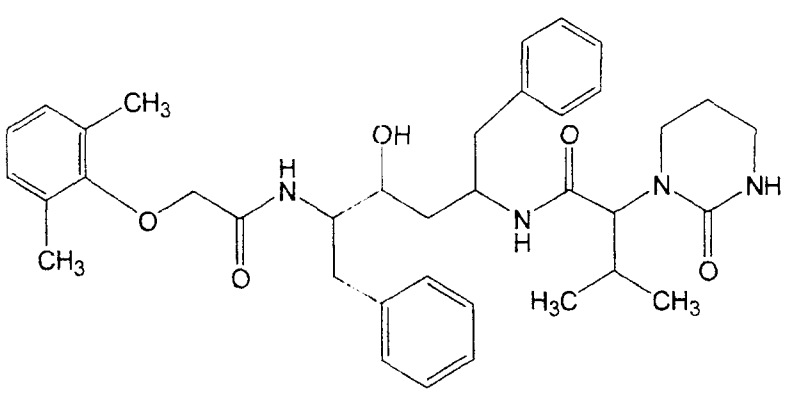


I

A compound of formula I is an HIV protease inhibitor marketed by Abbott Laboratories under the tradename Norvir®, with the common name ritonavir [(2S,3S,5S)-5-(N-(N-((N-

methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane]. This and other compounds as well as methods for preparing same are disclosed in U.S. Patent Nos. 5,648,497 and 5,541,206, the disclosures of which are herein incorporated by reference.

Additional HIV protease inhibitors which may be formulated into a solid dispersion of the instant invention include compounds of formula II



II

A compound of formula II is known as ABT-378 ((2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2S-(1-tetrahydropyrimid-2-onyl)-3-methyl-butanoyl)amino-1,6-diphenylhexane). This and other compounds, as well as methods for preparing same, are identified in U.S. Patent No. 5,914,332, the disclosure of which is herein incorporated by reference.

Other types of pharmaceutical compounds which may be employed in the practice of the present invention include but are not limited to antibacterial agents, antifungal agents such as griseofulvin, chemotherapeutic agents, agents for treating hyperlipidemia such as fenoifibrate, and the like.

The following Examples are provided to further illustrate the present invention.

EXAMPLES

Equipment:

DSC

DSC measurements were made using a Mettler DSC 30 unit. Samples (4-7mg) were sealed in standard 40 μl aluminum crucibles with a single hole punched in the lids. An empty crucible of the same type was used as a reference.

X-ray Powder Diffraction Analysis

An X-ray powder diffraction (XPD) pattern was obtained with a Scintag® XDS 2000 θ/θ diffraction system equipped with a 2 kW normal focus X-ray tube and a liquid nitrogen cooled germanium solid state detector.

Isothermal Calorimetry (TAM)

The recrystallization reactions of 30% ABT-538 in PEG or PEG:PVP (95:5) solid dispersions were monitored via isothermal calorimetry (Thermometric 2277 Calorimeter) at 40 °C. Since crystallization is an exothermic process, a positive power output indicates

crystallization. The magnitude of the power output at any time is proportional to the rate of crystallization. XPD was used to confirm crystallization.

HPLC

The potency values of all the dispersions as well as the dissolution sample concentrations were determined via HPLC.

The effect of PVP on the crystallization rate of the drug in each dispersion system (drug with polymer) was investigated with the appropriate experimental technique. The results of these studies are provided in Figures 1-15.

Three pharmaceuticals of different properties were employed to demonstrate the general applicability of the instant invention. These compounds are identified in Table 1 below:

Table 1

Model Compounds

Property/Compound	ABT-538	Fenofibrate	Griseofulvin
MW (g/mole)	720.96	360.84	352.77
T_m (°C)	124	79	218.13
T_g (°C)	45.8	-21.7	91

Example 1

Dispersion Preparations

A. Ritonavir (ABT-538) Dispersion Preparation:

The samples were prepared by dissolving ABT-538 in a small volume of 200 proof ethanol in a 250 ml round bottom flask. The flask was vortexed and then placed in a water bath maintained at 75 °C. The PEG 8000 was added to the hot alcohol solution with continual swirling until the PEG melted. The flask was then attached to a rotary evaporator, immersed in the water bath (75 °C) under vacuum for 15 minutes to remove the ethanol. After the majority of ethanol had evaporated, the flask was immersed in an ice

bath for 15 minutes. The contents of the flask were then vacuum dried at room temperature overnight to remove residual alcohol. The dispersion was removed from the flask, gently ground, and sized to 40-100 mesh size. The drug loads used for these dispersions were 10, 20 and 30% w/w.

B. ABT-378 Dispersion Preparation:

The solid dispersion of 30% ABT-538 in 95:5 PEG8000:PVP was prepared by dissolving the ABT-538 and PVP 17 PF in a small volume of 200 proof ethanol in a 250 ml round bottom flask. The remainder of the process was as described above. A 30% ABT-538 dispersion in 85:15 PEG8000:PVP was also prepared similarly as were dispersions of 10 or 20% PVP 17PF in PEG 8000 without drug.

C. Fenofibrate Dispersion Preparation:

15% Fenofibrate in PEG 8000:

Both fenofibrate and PEG 8000 were sized to 40-100 mesh prior to mixing with a spatula on weighing paper. The mixture was then added to a 25 ml beaker and heated to 85°C in a water bath until the all the material had

melted. The molten solution was then poured onto a chilled X-ray sample holder to rapidly solidify the solution. The solid sample was immediately used to monitor the crystallization rate via X-ray powder diffraction.

15% Fenofibrate in 90:10 PEG 8000:PVP:

Fenofibrate (40-100 mesh) was added to the 90:10 PEG 8000:PVP control dispersion (see above) which was also sized to 40-100 mesh and mixed with spatula on a piece of weighing paper. The mixture was then processed as described above for the 15% fenofibrate dispersion in PEG 8000.

D. Griseofulvin Dispersion Preparation:

15% griseofulvin in PEG 8000:

Both griseofulvin and PEG 8000 were sized to 40-100 mesh prior to mixing on a weighing paper with a spatula. The sample was then added to an 4 ml stainless steel vessel which was sealed under a N_2 atmosphere. The vessel was then immersed into an oil bath maintained at 180°C. The sample was occasionally shaken to mix the molten contents. After 5 minutes the vessel was immersed into a

liquid N_2 bath for 30 minutes. The contents of the vessel were removed, gently ground and sized to 40-100 mesh.

15% griseofulvin in 80:20 PEG 8000:PVP:

This dispersion was prepared in a similar manner as describe above for the 15% griseofulvin in PEG 8000 dispersion using the 80:20 PEG8000:PVP control dispersion.

E. Results:

ABT-538:

Figure 1 shows the X-ray powder diffraction (XPD) pattern of ABT-538, processed PEG 8000, a physical mixture of the two components and the 30% solid dispersion. A similar plot is shown in Figure 2 with PVP incorporated into the matrix. It is apparent from these figures that ABT-538 is not crystalline within either matrix. Figure 3 shows the DSC thermograms of ABT-538, PEG8000, the 30% physical mixture and the dispersion. A similar plot is seen in Figure 4 for the PEG:PVP dispersion. The endotherm associated with drug melting can clearly be discerned from the other components. Thus, it is possible to follow the kinetics of ABT-538

crystallization via DSC measurements. Crystallization kinetics were determined by heating the samples to 85°C, holding them isothermally for predetermined times followed by heating through the melting transition temperature of ABT-538. The heats of fusion were determined and ratioed against the heat of fusion of the drug melting in the physical mixture, giving the fraction crystallized. The percent crystallized as a function of isothermal (85°C) hold time is shown in Figure 5. It is clear from this experiment that the presence of PVP within the matrix suppresses the crystallization rate of ABT-538.

The crystallization rate was also followed via the heat associated with crystallization of ABT-538 using a isothermal calorimetry. The shapes and magnitudes of the crystallization peaks in Figure 6 indicate that ABT-538 crystallizes more readily in the PEG matrix as compared to the PEG:PVP matrix. This stabilizing effect of PVP is also reflected in the times required for complete crystallization (time to reach baseline) which were <10 hours for PEG and >30 hours for PEG:PVP (95:5). These data support the previous DSC results.

An additional study was performed with a dispersion containing 15% PVP. The samples were held at 50°C (above

the T_g of ABT-538) and X-ray diffraction patterns were measured over time to monitor for the appearance of crystalline ABT-538. Figure 7 shows that in the presence of PVP, crystalline ABT-538 is not present after 272 hours, while in PEG8000 alone crystalline drug is detected at 233 hours (and before, data not shown).

Fenofibrate:

Figure 8 shows the XPD patterns of PEG 8000, fenofibrate, a 15% physical mixture and the 15% fenofibrate solid dispersion. The figure illustrates that the fenofibrate is X-ray-amorphous within the matrix. A similar plot with the XPD patterns for the 15% fenofibrate dispersion in a 90:10 PEG 8000:PVP matrix is presented in Figure 9. Again, the fenofibrate is amorphous. Upon storage at 25°C, the fenofibrate begins to crystallize in the PEG 8000 matrix within 1 hour (Figure 10). Additional crystallization follows upto 12 hours, when the experiment was terminated. In the presence of PVP (Figure 11), the fenofibrate does not crystallize in the timeframe of the experiment. This clearly demonstrates the inhibitory effects of PVP on crystallization within the PEG 8000 matrix.

Griseofulvin:

Similar XPD patterns for the griseofulvin dispersion in PEG 8000 and 80:20 PEG 8000:PVP matrices are shown in Figures 12 and 13, respectively. In both instances, amorphous griseofulvin is isolated within the respective matrices. The XPD rate of crystallization experiments show that after one hour at 25°C, griseofulvin begins to crystallize (Figure 14). However, in the presence of PVP (Figure 15), crystallization is not observed even after 15 hours under the same conditions. This again demonstrates the inhibitory effects of PVP amorphous drug crystallization within a PEG matrix.

E. Conclusions:

The data presented demonstrate that PVP incorporated within a hydrophilic matrix, such as PEG 8000, inhibits crystallization of drug molecules having varying physicochemical properties. Thus, the instant invention has a broad application to development of viable solid dispersion formulations where the high energy amorphous (non-crystalline) form of a drug is desired.

Example 2

Stability of Dispersion in Molten PEG 8000

The stability of the dispersion of ABT-538 in PEG 8000 in the molten state at 70 °C was examined. Individual approximately 5 mg quantities of the dispersion (aged for 6 weeks at room temperature) were placed in 4 ml glass vials. These vials, with the exception of the initial time point, were placed in a 70 °C oven which was sampled at pre-determined intervals, chilled in ice water and placed in the freezer until HPLC analysis. After all samples were collected, they were analyzed for ABT-538 content by HPLC. The HPLC system consisted of a Hitachi AS 4000 autosampler, SP 8800 ternary pump, Applied Biosystems 783 detector, and PE Nelson Data acquisition system. Other chromatographic details included a Regis Little Champ 5 cm C-18 column, a mobile phase consisting of an aqueous solution of 0.1% trifluoroacetic acid in 10 mM aqueous tetramethyl ammonium perchlorate (TMAP)/acetonitrile/methanol (55/40/5). The flow rate was 1 ml/minute, the wavelength of detection was 205 nm, and the injection volume was 100 µl. Standard curves of peak area of ABT-538 vs.

concentration in the range of interest were compared with experimentally obtained area counts.

Example 3

Protocol For Oral Bioavailability Studies

Dogs (beagle dogs, mixed sexes, weighing 7-14 kg) are fasted overnight prior to dosing, but are permitted water *ad libitum*. Each dog receives a 100 μg/kg subcutaneous dose of histamine approximately 30 minutes prior to dosing. Each dog receives a single solid dosage form corresponding to a 5 mg/kg dose of the drug. The dose is followed by approximately 10 milliliters of water. Blood samples are obtained from each animal prior to dosing and at 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours after drug administration. The plasma is separated from the red cells by centrifugation and frozen (- 30 °C) until analysis. The concentrations of parent drug is determined by reverse phase HPLC with low wavelength UV detection following liquid-liquid extraction of the plasma samples. The parent drug area under the curve is calculated by the trapezoidal method over the time course of the study. The absolute bioavailability of each test composition is calculated by comparing the area under the curve after oral dosing to

that obtained from a single intravenous dose. Each capsule or capsule composition is evaluated in a group containing at least six dogs. The values reported are averages for each group of dogs.

5

WE CLAIM:

1. A pharmaceutical composition comprising a solid dispersion of a pharmaceutical compound, a water soluble carrier, and a crystallization inhibitor selected from the group consisting of polyvinylpyrrolidone (PVP) and hydroxypropylcellulose (HPMC).

2. The composition of Claim 1 wherein said water soluble carrier is polyethylene glycol (PEG).

3. The composition of Claim 1 wherein said pharmaceutical compound is an HIV protease inhibitor dissolved in an organic solvent.

4. The composition of Claim 3 wherein said organic solvent is ethanol.

5. The composition of Claim 3 wherein said HIV protease inhibitor is 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).

6. The composition of Claim 3 wherein said HIV protease inhibitor is (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl-butanoyl] amino-1,6-diphenylhexane (ABT-378).

7. The composition of Claim 3 wherein said HIV protease inhibitor is a combination of 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

8. The composition of Claim 2 wherein said solid dispersion is encapsulated in a hard gelatin capsule.

9. The composition of Claim 2 wherein said solid dispersion is compressed into a tablet.

10. The composition of Claim 1 further comprising an additive or a mixture of additives independently selected

from the group consisting of pharmaceutically acceptable surfactants and antioxidants.

11. The composition of Claim 1 wherein said pharmaceutical compound is fenofibrate.

12. The composition of Claim 1 wherein said pharmaceutical compound is griseofulvin.

13. A method of preparing a composition of Claim 1 which comprises:

a) dissolving a pharmaceutical compound inhibitor into an organic solvent to form a solution;

b) adding a water soluble carrier to said solution to form a mixture;

c) adding PVP to said mixture of step b);

d) optionally flash evaporating said solvent;

e) optionally drying the resulting residue remaining after evaporation;

f) optionally grinding and sieving the solid dispersion to obtain a resultant product.

14. The method of Claim 13 additionally comprising encapsulating the solid dispersion in a hard gelatin capsule.

15. The method of Claim 13 additionally comprising compressing said solid dispersion into a tablet.

16. The method of Claim 13 wherein said pharmaceutical compound is an HIV protease inhibitor.

17. The method of Claim 16 wherein said HIV protease inhibitor is selected from the group consisting of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6)-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

18. The method of Claim 13 wherein said solvent is ethanol.

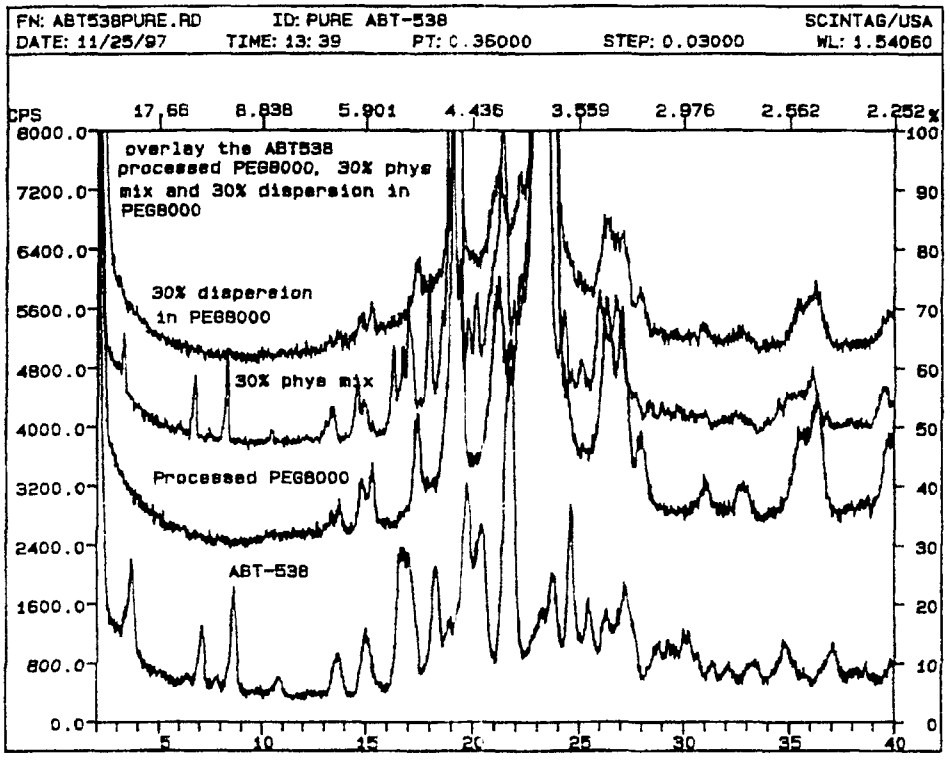
19. The method of Claim 13 wherein said water soluble carrier is polyethylene glycol (PEG).

20. A method of treating an HIV infection comprising administering an effective amount of a solid dispersion of Claim 1 to a mammal in need of such treatment, wherein said pharmaceutical compound is an HIV protease inhibitor.

21. The method of Claim 20 wherein said HIV protease inhibitor is selected from the group consisting of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6)-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-oryl)-3-methyl butanoyl] amino-1,6-diphenylhexane (AET-378).

22. A method of treating hyperlipidemia comprising administering an effective amount of a solid dispersion of Claim 1 to a mammal in need of such treatment, wherein said pharmaceutical compound is fenofibrate.

23. A method of treating a fungal infection comprising administering an effective amount of a solid dispersion of Claim 1 to a mammal in need of such treatment, wherein said pharmaceutical compound is griseofulvin.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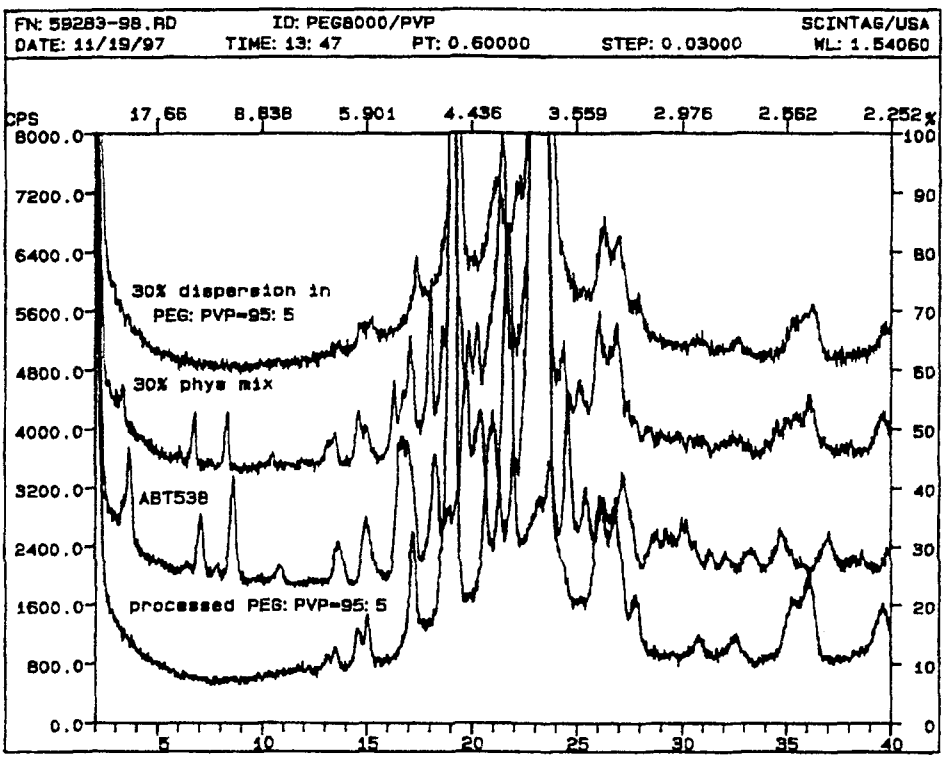
5.901
4.436
3.559
2.976
2.562
2.252
%
overlay the ABT538 processed PEG8000, 30% phys mix and 30% dispersion in PEG8000
30% dispersion in PEG8000
30% phys mix
Processed PEG8000
ABT-538

Figure 1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8.838
5.901
4.436
3.559
2.976
2.562
2.252
%
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
30% dispersion in PEG: PVP-95: 5
30% phys mix
ABT538
processed PEG: PVP-95: 5
5
10
15
20
25
30
35
40

Figure 2

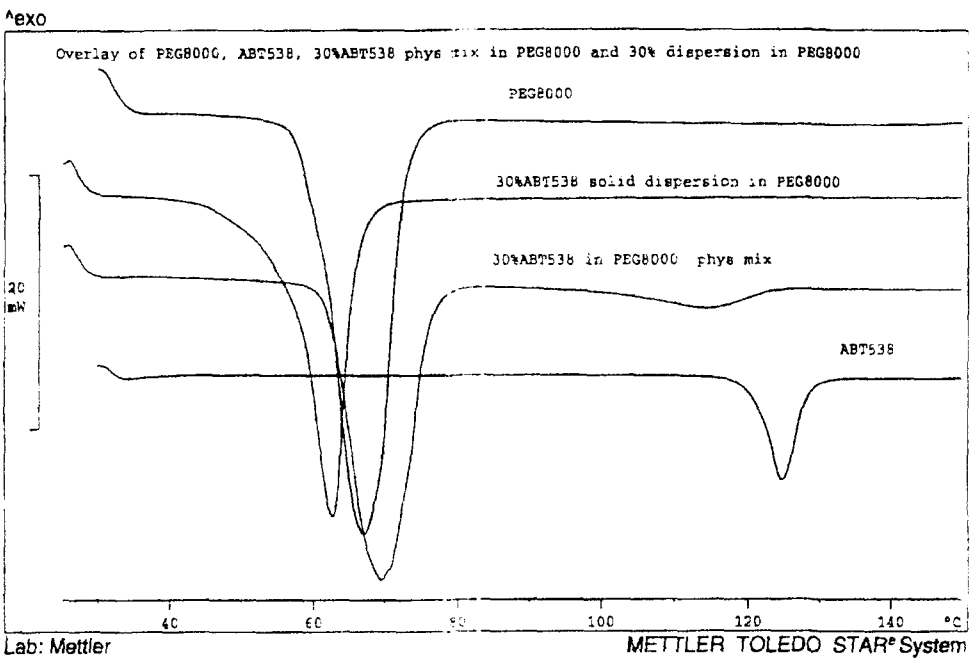

^exo
Overlay of PEG8000, ABT538, 30%ABT538 phys mix in PEG8000 and 30% dispersion in PEG8000
PEG8000
30%ABT538 solid dispersion in PEG8000
30%ABT538 in PEG8000 phys mix
ABT538
20
mW
40
60
100
120
140
°C
Lab: Mettler
METTLER TOLEDO STAR System

Figure 3

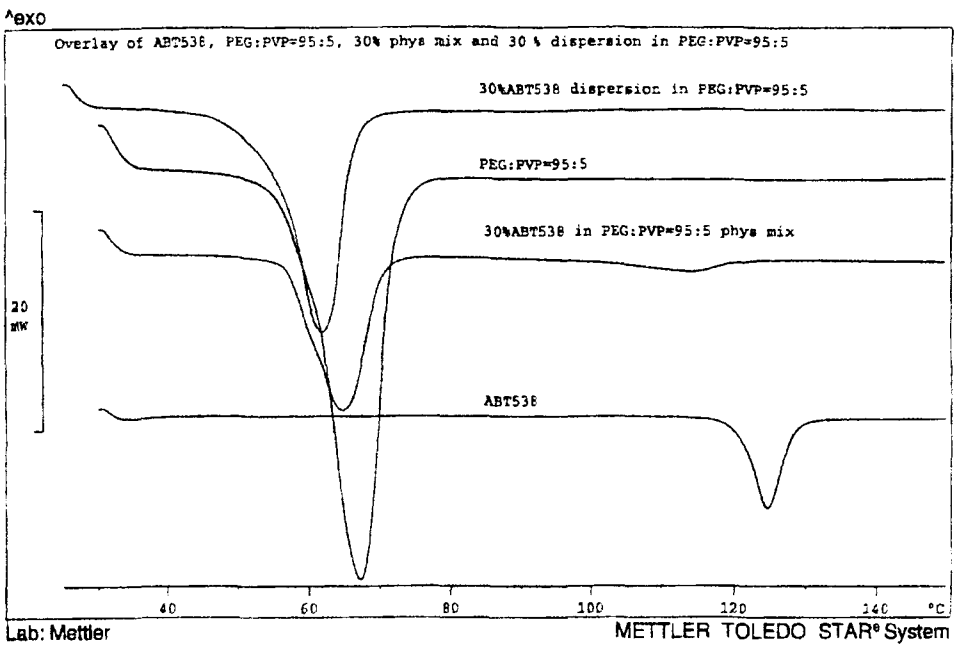

^exo
Overlay of ABT538, PEG:PVP=95:5, 30% phys mix and 30 % dispersion in PEG:PVP=95:5
30%ABT538 dispersion in PEG:PVP=95:5
PEG:PVP=95:5
30%ABT538 in PEG:PVP=95:5 phys mix
ABT538
20
mW
40
60
80
100
120
140
°C
Lab: Mettler
METTLER TOLEDO STAR° System

Figure 4

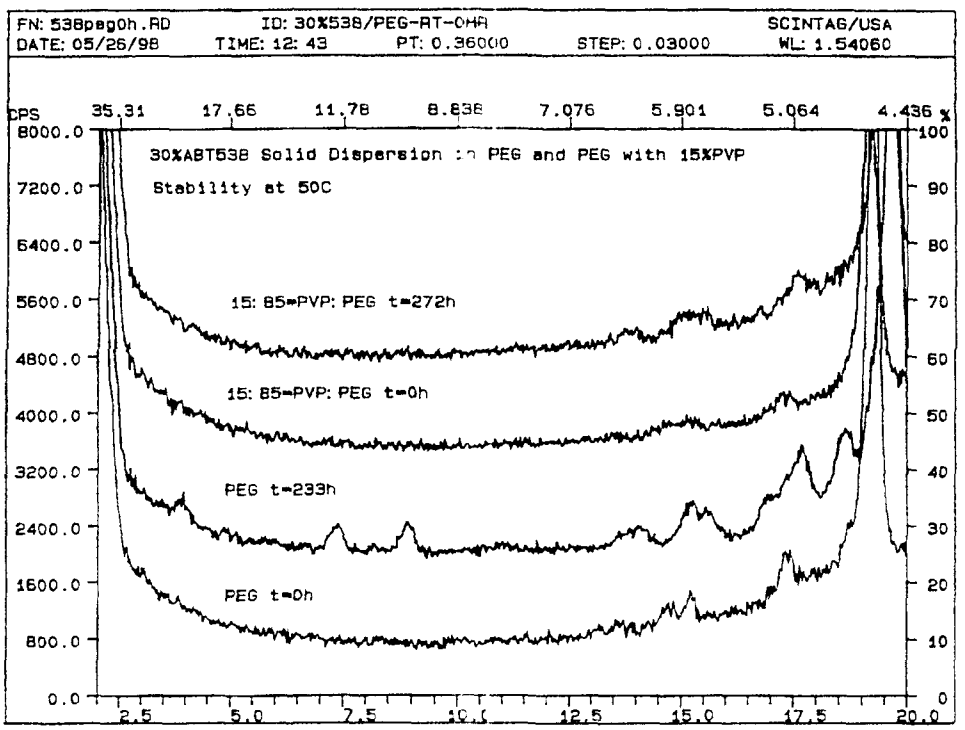
Missing at the time of publication

Figure 5

ABT-538 Isothermal Calorimetry (40°C)

Missing at the time of publication

Figure 6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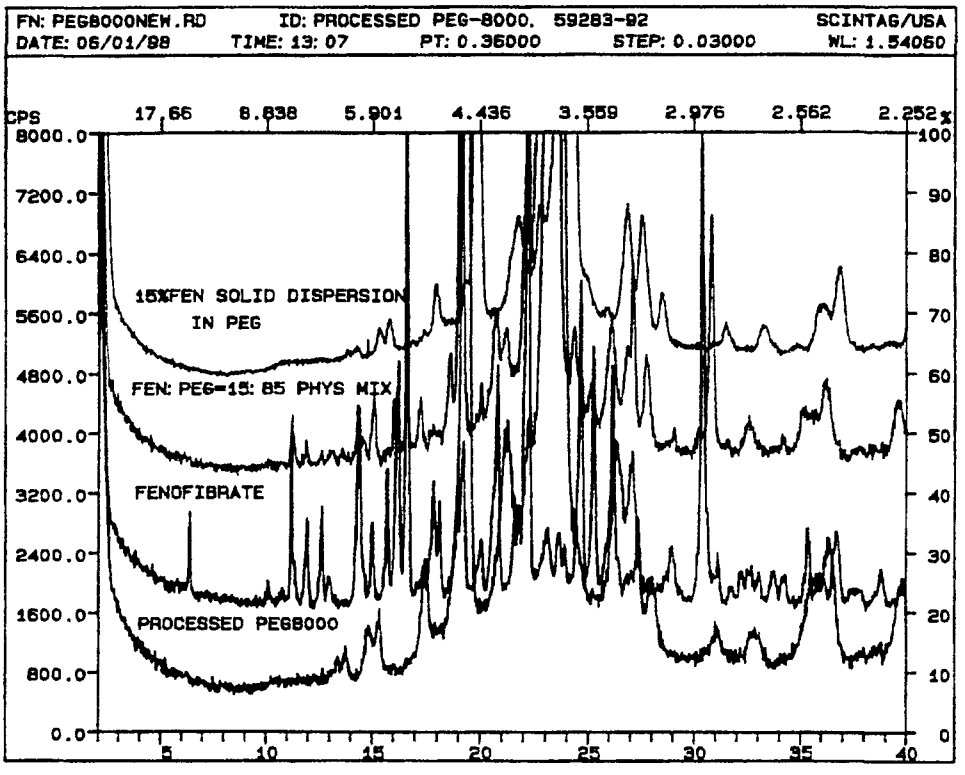
17.66
11.78
8.838
7.076
5.901
5.064
4.436 %
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
30%ABT538 Solid Dispersion in PEG and PEG with 15%PVP
Stability at 50C
15: 85=PVP: PEG t=272h
15: 85=PVP: PEG t=0h
PEG t=233h
PEG t=0h
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0

Figure 7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2.562
2.252
X
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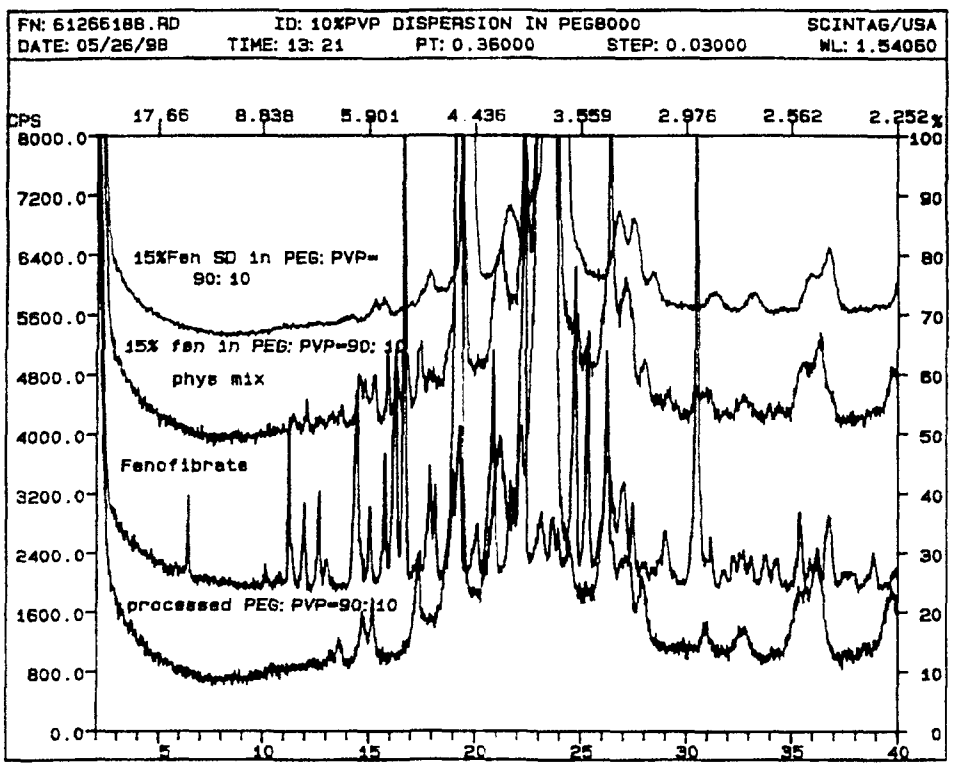
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
5
10
15
20
25
30
35
40
15%FEN SOLID DISPERSION IN PEG
FEN: PEG=15: 85 PHYS MIX
FENOFIBRATE
PROCESSED PEG8000

Figure 8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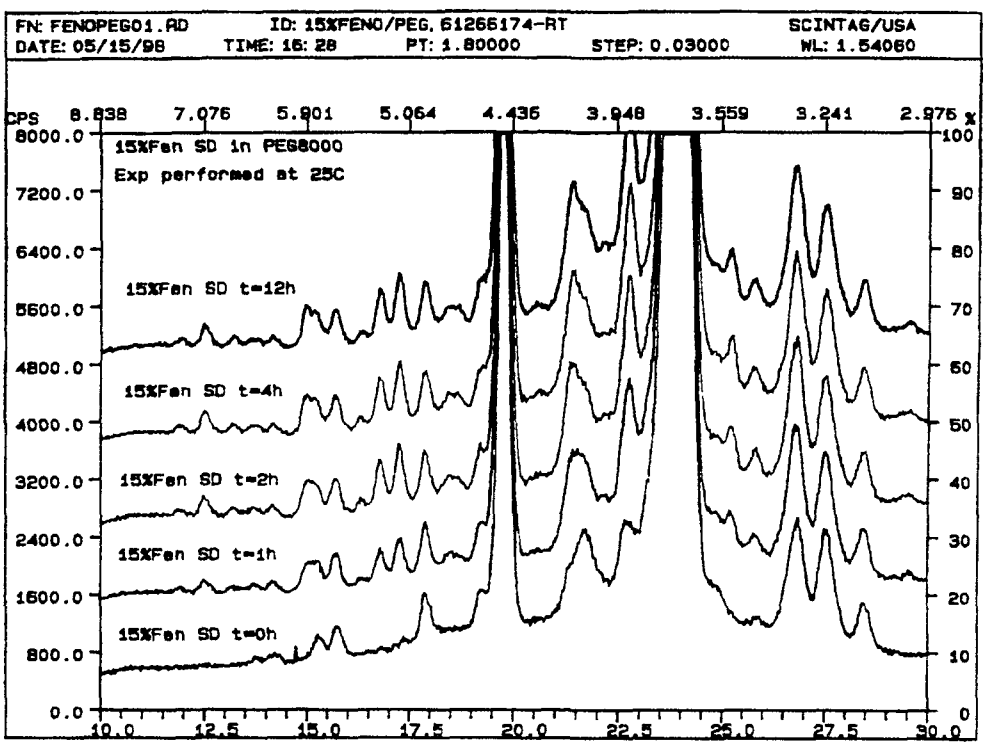
8.838
5.901
4.436
3.559
2.976
2.562
2.252
%
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
5
10
15
20
25
30
35
40
15%Fen SD in PEG: PVP=
90: 10
15% fen in PEG: PVP=90: 10
phys mix
Fenofibrate
processed PEG: PVP=90:10

Figure 9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7.076
5.901
5.064
4.436
3.948
3.559
3.241
2.976
%
15%Fen SD in PEG8000
Exp performed at 25C
15%Fen SD t=12h
15%Fen SD t=4h
15%Fen SD t=2h
15%Fen SD t=1h
15%Fen SD t=0h
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
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17.5
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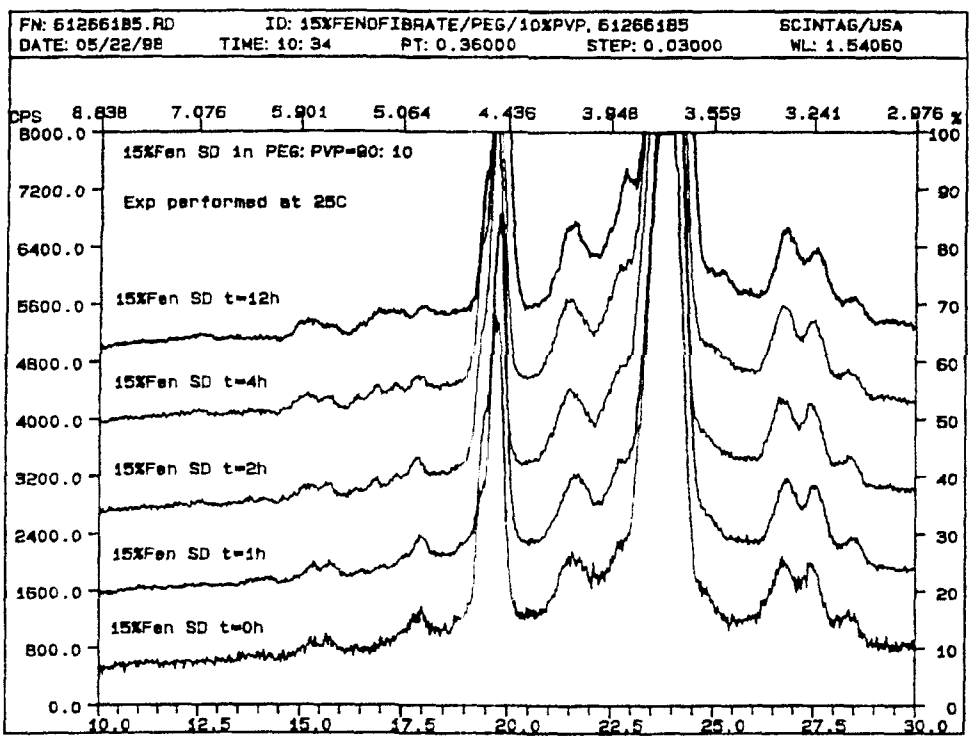
22.5
25.0
27.5
30.0

Figure 10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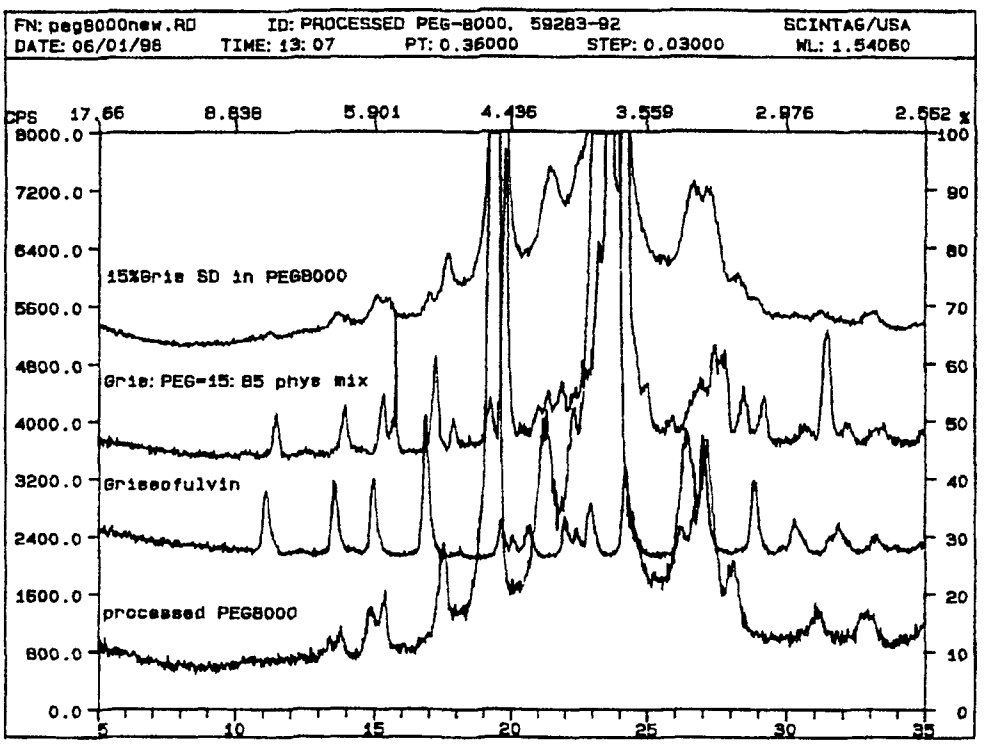
7.076
5.901
5.064
4.436
3.948
3.559
3.241
2.976
%
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
15%Fen SD in PEG: PVP=90: 10
Exp performed at 25C
15%Fen SD t=12h
15%Fen SD t=4h
15%Fen SD t=2h
15%Fen SD t=1h
15%Fen SD t=0h
10.0
12.5
15.0
17.5
20.0
22.5
25.0
27.5
30.0

Figure 11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CPS 17.66 8.838 5.901 4.436 3.559 2.976 2.552 x
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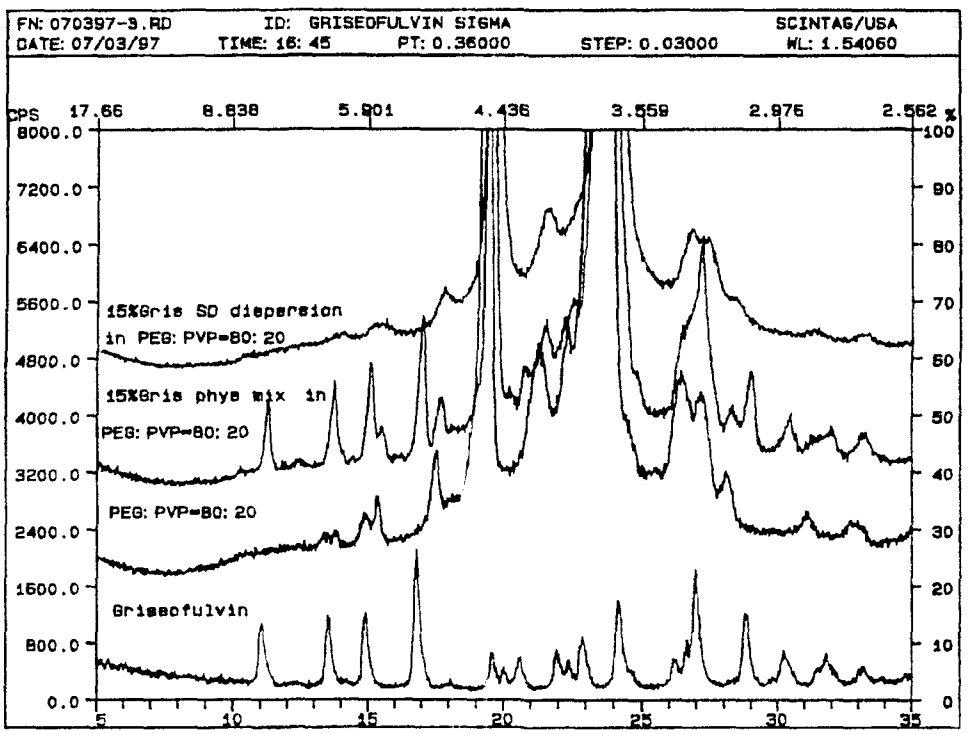
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
5 10 15 20 25 30 35
15%Gris SD in PEG8000
Gris: PEG-15: 85 phys mix
Griseofulvin
processed PEG8000

Figure 12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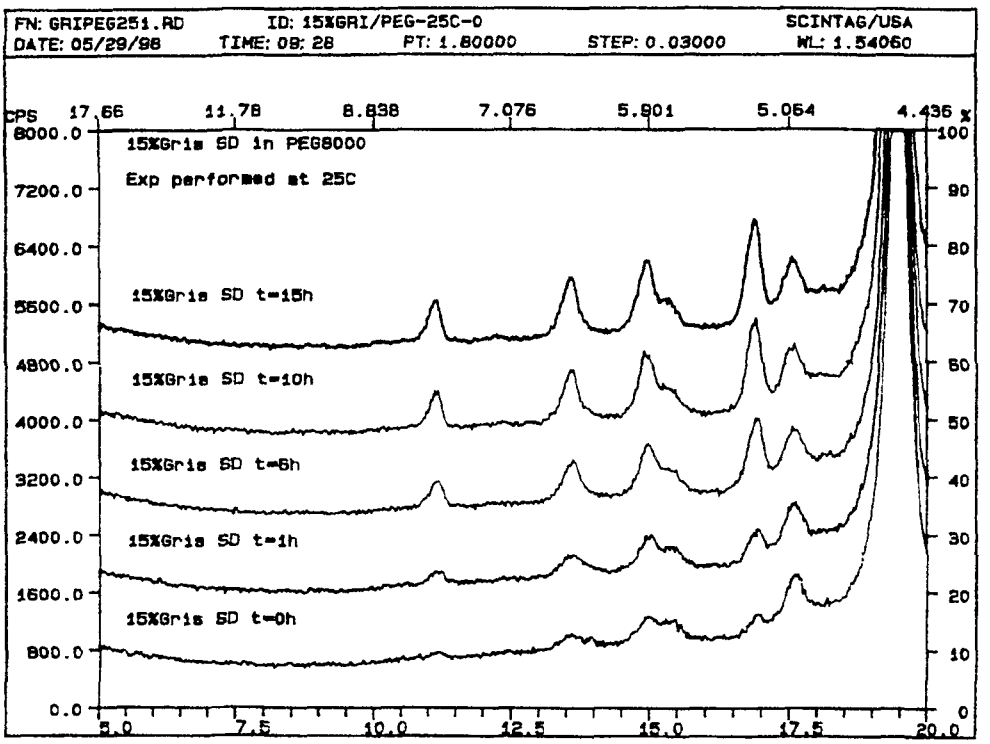
5.901
4.436
3.559
2.976
2.562
%
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
15%Gris SD dispersion in PEG: PVP=80: 20
15%Gris phys mix in PEG: PVP=80: 20
PEG: PVP=80: 20
Griseofulvin
5
10
15
20
25
30
35

Figure 13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11.78
8.838
7.076
5.901
5.064
4.436 x
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
15%Gris SD in PEG8000
Exp performed at 25C
15%Gris SD t=15h
15%Gris SD t=10h
15%Gris SD t=6h
15%Gris SD t=1h
15%Gris SD t=0h
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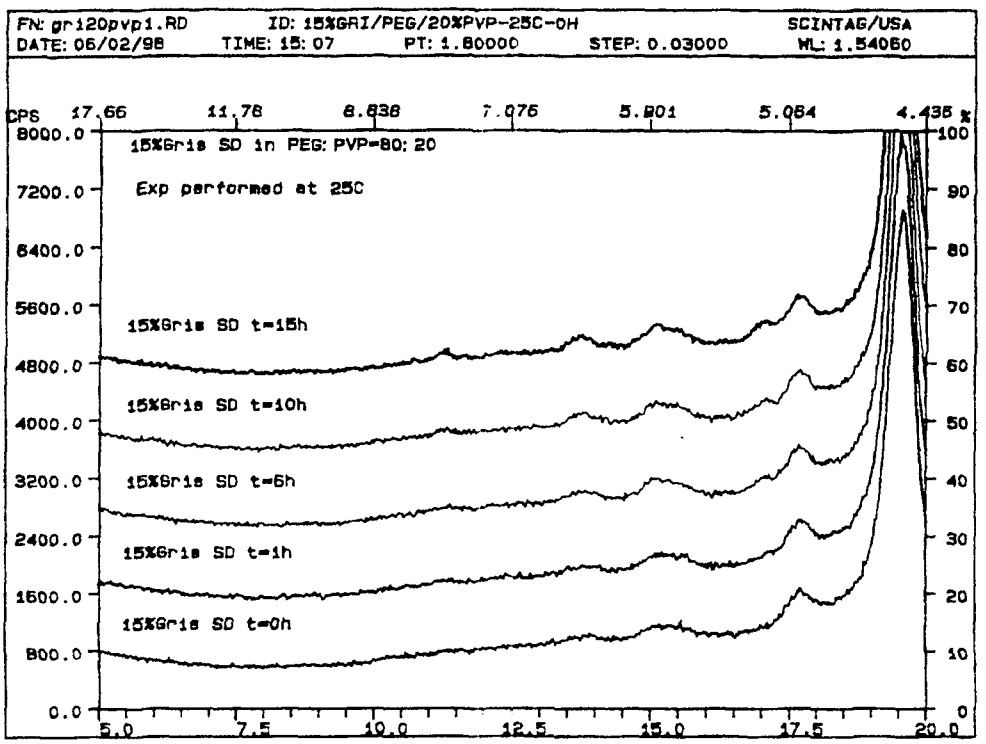
7.5
10.0
12.5
15.0
17.5
20.0

Figure 14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8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
15%Gris SD in PEG: PVP=80: 20
Exp performed at 25C
15%Gris SD t=15h
15%Gris SD t=10h
15%Gris SD t=6h
15%Gris SD t=1h
15%Gris SD t=0h
5.0
7.5
10.0
12.5
15.0
17.5
20.0

Figure 15

United States Patent [19]

Panoz et al.

[11] **Patent Number: 4,769,236**

[45] **Date of Patent: * Sep. 6, 1988**

[54] **MEDICAMENTS WITH A HIGH DEGREE OF SOLUBILITY AND METHOD FOR THEIR PRODUCTION**

[75] Inventors: **Donald E. Panoz**, Athlone; **Owen I. Corrigan**, Howth, both of Ireland

[73] Assignee: **Elan Corporation, PLC**, Athline, Ireland

[*] Notice: The portion of the term of this patent subsequent to Sep. 9, 2003 has been disclaimed.

[21] Appl. No.: **864,827**

[22] Filed: **May 19, 1986**

Related U.S. Application Data

[63] Continuation of Ser. No. 646,485, Aug. 31, 1984, Pat. No. 4,610,875, which is a continuation of Ser. No. 422,444, Sep. 23, 1982, abandoned.

[30] **Foreign Application Priority Data**

Apr. 19, 1982 [FR] France 82 06646

[51] **Int. Cl.**[4] **A61K 31/79**; A61K 9/14

[52] **U.S. Cl.** **424/80**; 424/78; 424/489; 424/497; 424/501; 514/951

[58] **Field of Search** 424/80, 78, 489, 497, 424/501

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Primary Examiner—Shep K. Rose

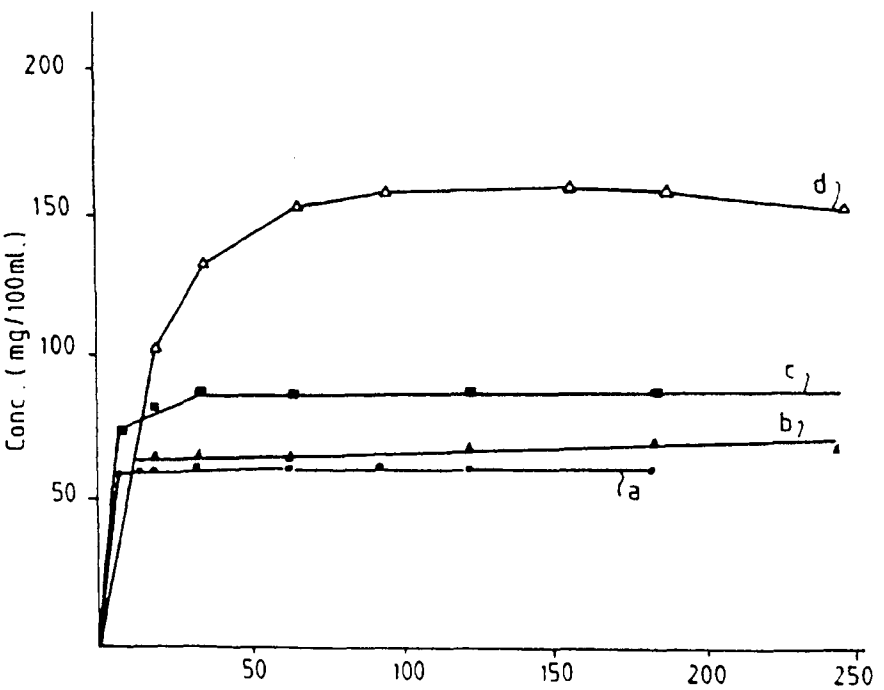
Attorney, Agent, or Firm—Robert H. Falk; Randall C. Brown

[57] **ABSTRACT**

The present invention relates to medicaments with a high degree of dissolution rate and solubility. These medicaments are characterized in that they are in amorphous form produced by spraying in the presence of a stabilizer and of an agent inhibiting the formation of crystals.

1 Claim, 2 Drawing Sheets

FIG. 1



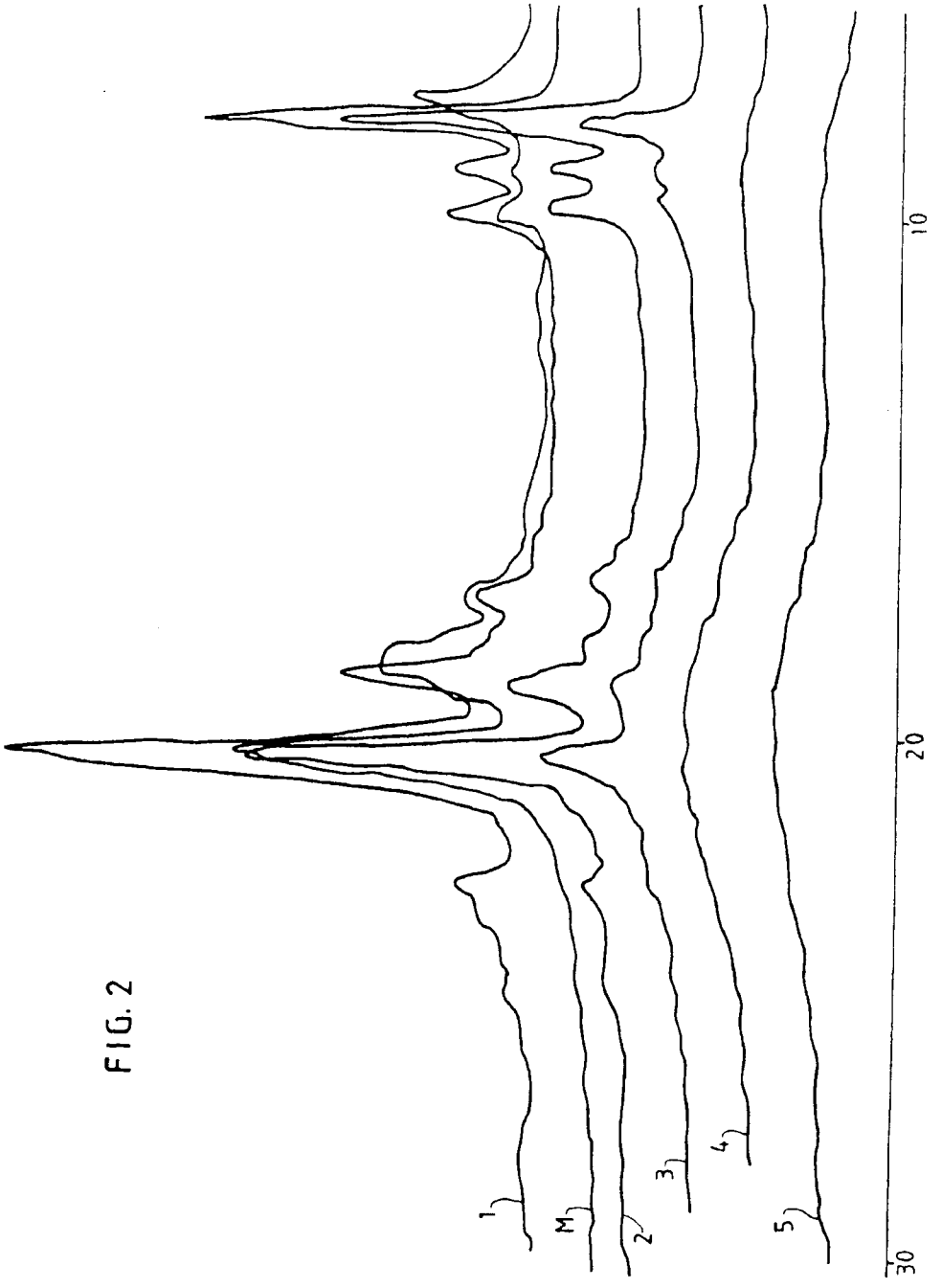


FIG. 2

MEDICAMENTS WITH A HIGH DEGREE OF SOLUBILITY AND METHOD FOR THEIR PRODUCTION

This application is a continuation of application Ser. No. 646,485, filed Aug. 31, 1984, now U.S. Pat. No. 4,610,875, which in turn is a continuation of Ser. No. 422,444, filed Sept. 23, 1982, now abandoned.

The present invention relates to medicaments with a high degree of dissolution rate and solubility and to a method for their production.

It is known and widely demonstrated that the dissolution rate and solubility of a medicament represents a determining factor in its therapeutic activity. It is known that therapeutic activity depends on the bioavailability of the medicament, which is a function of good and/or complete absorption. The latter depends on the degree of dissolution of the active principle forming the medicament. The good dissolution of a medicament is all the more indispensable as there exists a certain and very limited area of the gastro-intestinal tract adapted to absorb the medicament and the non-availability of a medicament following its poor or incomplete dissolution in contact with this area causes poor absorption and, thereby, a therapeutic action which ranges from reduced to very variable. It should be added also that a high degree of solubility of a medicament enables the preparation, if desired, of concentrated liquid forms. Now the liquid form of a medicament enables the posology to be easily varied, lends itself to coloring, to sweetening and to the aromatization of the medicament vehicle. Once diluted, medicaments are less irritaing than in cachets, powders, tablets or pills, pharmaceutical forms which place them in direct contact with the mucuous membranes, at which local irritation of the gastric mucous tissue can occur. Sometimes, the liquid form is indispensable as, for example, for hygroscopic products and liquid eutectic mixtures which cannot be put into powders or cachets.

It is known that crystalline forms (the most stable forms) are those which dissolve with most difficulty; thus for a long time attempts have been made to prepare medicaments containing the active principles in amorphous form, of which form the solubility is higher than that of the crystalline form (See review of J. Haleblain, *J. Pharm. Sci.* 64, 1269 (1975)). However, these amorphous forms present the problem that they are converted readily in time into crystalline forms, i.e., amorphous forms may not be physically stable, which is a very serious drawback for maintaining the enhanced dissolution of a substance for therapeutic use.

Accordingly it is an object of the present invention to provide a medicinal form with a high degree of solubility and dissolution preserving a physical and chemical stability necessary for any medicament.

According to the invention there is provided a medicament with a high degree of solubility characterized in that it is in amorphous form obtained by spraying in the presence of a stabilizer and of an agent inhibiting crystal formation.

According to an advantageous embodiment of the present invention, the stabilizer and the crystal-formation inhibiting agent are constituted by polyvinylpyrrolidone.

According to another advantageous embodiment of the present invention, the inhibiting agent is constituted by the mixture polyethyleneglycol-polyvinylpyrrolidone.

According to the invention the concentration of the inhibiting agent present at the time of spraying is comprised between 1 and 50% with respect to the active principle (weight/weight).

The amount of stabilizer and of crystal formation inhibiting agent added before the spraying is of course a function of the nature of the active principle utilized. The more physically unstable the medicinal substance in the amorphous phase or the more it tends to form crystals, the greater is the amount of inhibiting polymer added.

The inhibiting polymer must be added before the spraying of the medicament, since the simple mixing of the inhibitor with the active principle sprayed alone, without the inhibitor, leads to a product whose solubility dissolution characteristics are, by a long way, inferior to those obtained with the products according to the present invention.

Moreover, numerous analyses, and particularly differential scanning calorimetry (DSC) carried out by Applicant have enabled it to be envisaged that a large part of the medicinal substance is in the form of an amorphous complex: medicinal substance-polyvinylpyrrolidone.

According to another aspect of the present invention, there is provided a process for the preparation of medicaments, characterized in that the active principle and the inhibiting polymer are dissolved in a solvent, with heating if necessary, then atomized in a sprayer, the input and output temperatures being comprised respectively between 110° and 150° C. and 80° to 120° C.

According to an advantageous embodiment of the method according to the present invention, the solvent for dissolving the active substance and the inhibitor is constituted by water and/or a low molecular weight alcohol (C_1 to C_4).

Apart from the foregoing features, the invention also comprises other features which will emerge from the description which follows.

The present invention will be better understood by means of the additional description which follows, in which examples of the preparation of novel medicaments according to the present invention are given, as well as the characteristics of the various products obtained.

It must be well understood, however, that these examples are given purely by way of illustration of the invention of which they do not constitute in any way a limitation thereof.

EXAMPLES OF THE PREPARATION

Example 1

Preparation of hydroflumethiazide

In 50 parts of ethanol are dissolved 1 part of hydroflumethiazide and 0.1 parts of polyvinylpyrrolidone. This solution is then atomized (for example in a BUCHI 190 apparatus). The feed temperature is adjusted to 132° and the output temperature to 98° C. Atomizing flow rate: 750 ml/hour.

FIG. 1 shows the solubility graphs of unatomized hydroflumethiazide (graph a), hydroflumethiazide atomized in the absence of PVP (graph b), hydroflumethiazide atomized but mixed with 10% of PVP (graph c), and, hydroflumethiazide atomized according to Example 1 (graph d).

It is clearly seen that the process according to the present invention enables the solubility of the medicament to be considerably increased, while the latter is much less affected by a simple hydroflumethiazide + PVP mixture.

The product obtained according to Example 1 is practically unchanged in structure over at least four months, whilst a sample of hydrolumethiazide atomized without the presence of PVP is converted entirely into the crystalline form at the end of 12 days.

Example 2

Preparation of dipyridamole

Procedure was as described in Example 1, but solutions containing 0%, 5%, 10%, 20% and 35% of PVP with respect to the weight of dipyridamole, were prepared and them atomized.

FIG. 2 shows the X-ray diffraction curves of the different products obtained. It is to be noted that the diffraction curve of the mixture dipyridamole-PVP 3:1 (curve M) has an entirely different shape from the curve 5.

Curve 1 represents 0% of PVP.
Curve 2 represents 5% of PVP.
Curve 3 represents 10% of PVP.
Curve 4 represents 20% of PVP.
Curve 5 represents 35% of PVP.

The solubility of the product represented by curve 5 is twice greater than that of the mixture M.

Examples 3 to 25

Results as interesting as those described in Examples 1 and 2 were obtained by utilizing the following medicaments: hydrochlorthiazide, cyclothiazide, cyclopenthiazide, polythiazide, methyldopa, spironolactone, quinidine, cyanidol, metronidazole,ibuprofen, naproxen, erythromycin, glaphenin, furosemide, suloctidil, nitrofurantoin, indomethacin, flavoxate, phenobarbital, cyclandelate, ketoprofen, naftidrofuryl and triamterene.

It results from the foregoing description that whatever the types of application and embodiments adopted, medicaments which are stable over time and of course solubility are obtained, much superior to that of previously known medicaments.

Thus as emerges from the foregoing, the invention is in no way limited to those in its types of application, embodiments and uses which have just been described more explicitly; it encompasses thereof on the contrary all modifications which may come to the mind of the technician skilled in the art, without departing from the scope, nor the range, of the present invention.

We claim:

1. A process for the preparation of a stable pharmaceutical composition with a high dissolution rate in the gastrointestinal tract, in which an active principle is in an amorphous form which is stable against changing in time to the crystalline form, comprising the steps of:

dissolving, in a pharmaceutically acceptable solvent constituted by water, a low molecular weight C_1 to C_4 alcohol or mixtures thereof, an active non-amorphous principle soluble therein selected from the group consisting of hydroflumethiazide, dipyridamole, hydrochlorothiazide, cyclothiazide, cyclopenthiazide, polythiazide, methyldopa, spironolactone, quinidine, cyanidol, metronidazole, ibuprofen, naproxen, erythromycin, glaphenin, furosemide, suloctidil, nitrofurantoin, indomethacin, flavoxate, phenobarbital, cyclandelate, ketoprofen, naftidrofuryl and triamterene wherein said active principle is a medicament which exhibits poor solubility and sub-optional biopharmaceutical properties and which is normally in crystalline form, and a stabilizing and crystal-formation-inhibiting amount of between about 1 to 50% w/w with respect to the active principle of polyalkyleneglycol-polyvinylpyrrolidone to form a solution;

heating said solution to about 110° to about 150° C.; and

atomizing said heated solution at an input temperature of about 110° to about 150° C. in a sprayer such that the output temperature is between about 80° and about 120° C. to obtain a stable amorphous active principle-polyalkyleneglycol-polyvinylpyrrolidone composition.

* * * * *

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SURFACTANTS IN PHARMACEUTICAL PRODUCTS AND SYSTEMS

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INTRODUCTION

Surface-active agents (surfactants) are substances which, at low concentrations, adsorb onto the surfaces or interfaces of a system and alter the surface or interfacial free energy and the surface or interfacial tension. Surface-active agents have a characteristic structure, possessing both polar (hydrophilic) and nonpolar (hydrophobic) regions in the same molecule. Thus surfactants are said to be amphipathic in nature. The wide range of uses for surfactants in pharmaceutical products and systems is the subject of this article.

PHYSICOCHEMICAL BACKGROUND

Surface and Interfacial Tension; Surface and Interfacial Free Energy

Atoms and molecules at surfaces and interfaces possess energies significantly different from those of the same species in the bulk phase. The term "surface" is usually reserved for the region between a condensed phase (liquid or solid) and a gas phase or vacuum, while the term "interface" is normally applied to the region between two condensed phases.

In the case of a liquid–gas interface, molecules of the liquid in the boundary can only develop attractive cohesive forces with molecules situated below and adjacent to them. They can develop attractive adhesive forces with molecules of the gaseous phase. However at the gas–liquid interface, these adhesive forces are quite small. The net effect is that molecules at the surface of the liquid have potential energies greater than those of similar molecules in the interior of the liquid and experience an inward force toward the bulk of liquid. This force pulls the molecules of the interface together and the surface contracts.

Thus, the surface of a liquid behaves as if it were in a state of tension—the surface tension (γ)— due to the contracting force acting in all directions in the plane of the surface.

In order to extend the surface of a liquid it is necessary to bring molecules from the interior to the surface against the inward pull. The work required to increase the surface area by unit area is termed the *surface free energy*.

At the interface between two condensed phases, the dissimilar molecules in the adjacent layers facing each other have potential energies greater than those of similar molecules in the respective bulk phases. This is due to the fact that cohesive forces between like molecules tend to be stronger than adhesive forces between dissimilar molecules. Thus the interfacial tension is the force per unit length existing at the interface between two immiscible or partially miscible condensed phases and the interfacial free energy is the work required to increase the interface by unit area.

Adsorption Phenomena

Adsorption may be defined as the process of enrichment of one or more substances at a surface (1) or as the taking up of one substance at the surface of another (2). It can occur at any type of interface. However, in the context of pharmaceutical systems the interfaces where surfactant adsorption is important are the gas–liquid, liquid–liquid, gas–solid, and liquid–solid interfaces.

Adsorption at liquid–liquid and liquid–gas interfaces

Considering a system of two immiscible phases (e.g., heptane and water), a surface-active molecule that is adsorbed at the interface between the two liquids will tend to orient itself with its hydrophilic end toward the more polar liquid (water), and its hydrophobic end toward the less polar liquid (heptane). Thus the surfactant molecules replace water and/or heptane molecules of the original interface. The interaction across the interface is then between the hydrophilic group of the surfactant and the water molecules on one side of the interface, and between the hydrophobic group of surfactant and heptane on the other side of the interface. These interactions are much stronger than the original interactions between the unlike

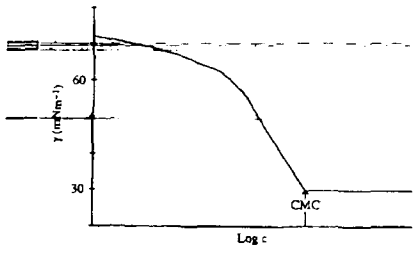

Fig. 1 Schematic plot of surface or interfacial tension (γ) versus logarithm of the surfactant concentration (c).

molecules of heptane and water; therefore the interfacial tension is significantly reduced by the adsorption of surfactant at the interface (i.e., the inward pull for each phase at the interface is reduced).

Air consists of molecules that are mainly nonpolar. Surface tension reduction by surfactants at the air–aqueous interface occurs due to adsorption of surfactants at the interface, with the hydrophilic end of the surfactant oriented toward the liquid. The presence of the surfactant molecules reduces the net inward pull toward the bulk liquid, and therefore reduces the surface tension.

The effect of a surfactant on the lowering of surface tension is shown in Fig. 1. The surface tension is lowered even at low concentrations of surfactant. As the surfactant concentration is increased, the surface layer becomes saturated with surfactant molecules, and micelles form within the bulk liquid as an alternative way of shielding the hydrophobic portions of the surfactants from the aqueous environment; the surface tension tends to a constant value. *Micelles are small aggregates of surfactant in which the* surfactant molecules are arranged in such a way that the hydrophobic ends are shielded from the surrounding aqueous environment. The concentration at which micelles first appear in solution is termed the critical micelle concentration (CMC).

Adsorption at solid–liquid interfaces

Adsorption of surfactant from an aqueous solution onto a solid surface may involve specific chemical interaction between the surfactant (adsorbate) and the surface (adsorbent).

Common interactions that can occur (3) include:

1. An ion-exchange process
2. An ion-pairing interaction
3. Acid–base interaction via either hydrogen bonding between substrate and adsorbate or Lewis acid–Lewis base reaction
4. Adsorption by polarization of π electrons, where the adsorbate contains electron-rich aromatic nuclei and the adsorbent has strongly positive sites
5. Adsorption by dispersion forces, i.e., London–van der Waals dispersion forces acting between adsorbate and adsorbent
6. Hydrophobic bonding.

Contact Angles and the Wetting of Solids

A drop of liquid when placed on a flat, homogeneous solid surface, comes to equilibrium, assuming a shape which minimizes the total free energy of the system. The angle between the liquid and the solid is called the contact angle (θ), the angle being measured through the liquid (Fig. 2). The contact angle may be calculated if the surface and interfacial tensions are known from Young's equation given in Eq. 1 or 2.

$$\gamma_{SA} = \gamma_{SL} + \gamma_{LA} \cos\theta \quad (1)$$

or

$$\cos\theta = \frac{\gamma_{SA} - \gamma_{SL}}{\gamma_{LA}} \quad (2)$$

where γ_{LA} is the surface tension of the liquid, γ_{SL} is the interfacial tension existing between the solid and liquid phases, and γ_{SA} is the surface tension (or surface free energy) of the solid. If $\theta < 90°$, wetting of the solid is said to take place. If $\theta > 90°$, wetting does not take place.

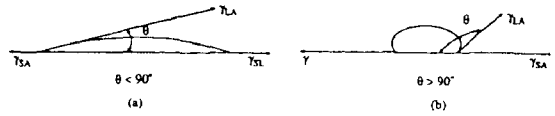

Fig. 2 Contact angles. In (a), $\theta < 90°$, and wetting of the solid occurs; in (b), $\theta > 90°$, and wetting does not take place.

The term "wetting" refers to the displacement from a surface of one fluid by another. It is most commonly applied to the displacement of air from a liquid or solid surface by water or an aqueous solution. The term "wetting agent" is applied to any substance that increases the ability of water or an aqueous solution to displace air from a liquid or solid surface.

For good wetting, cos θ should be as close as possible to 1; that is, θ should be as close as possible to 0. From Young's equation, it can be seen that if γ_{LA} or γ_{SL} was minimized, cos θ would be maximized, and wetting would be promoted.

Contact angles of water on powders of pharmaceutical importance are usually measured by preparing disks of the powder by compression or melting. However, *compaction may change the surface, so making the* measured result of little relevance. Contact angles on finely divided solids can also be determined by packing the powder into a tube and measuring the penetration of liquids into the packing.

Three types of wetting phenomena have been described (4): adhesional wetting, spreading wetting, and immersional wetting.

The way in which a particular system behaves depends on the interfacial energies between the solid substrate and any contacting liquid, and between the liquid and the second fluid (air). By manipulating these factors, the wetting process can be controlled. This may be achieved by the use of surfactants.

Modification of the wetting process by the use of surfactants

The effect of surfactants on the wetting process is a result of their adsorption at various interfaces with a resulting alteration of interfacial tensions. As has been noted from Young's equation, the wetting process is promoted if either γ_{LA} or γ_{SL} or both are reduced with γ_{SA} remaining unchanged. Surfactants almost always cause a reduction in γ_{LA}, however, the same cannot be said for γ_{SL} and the effect on the interfacial tension depends on the nature of the adsorption. Thus the addition of a surface-active agent to the system does not always promote wetting, and spreading may in fact be made more difficult (4).

If adsorption of the surfactant molecules at the solid–liquid interface occurs in such a manner that they are oriented with their polar ends toward the substrate and hydrophobic ends toward the liquid, the wettability of an aqueous solution is reduced. *This orientation of surfactants* molecules at the surface occurs if they are adsorbing to ionic or polar substrates (ion-exchange or ion-pairing mechanism). However, at higher concentrations of surfactant, the surfactant ions adsorb by hydrophobic interaction with the already adsorbed layer, thus exposing their hydrophilic ends to the solution in such a way that the surface becomes more readily wetted. Thus, the contact angle may first increase and subsequently decrease following the addition of more surfactant to a solution. *In contrast, where adsorption occurs onto nonpolar* surfaces by, for example, van der Waals attraction, the surfactant molecules are oriented with their hydrophilic groups toward the liquid, the hydrophilicity of the substrate is increased, and it becomes more wettable.

The adsorption of surfactants onto solid surfaces is important with respect to their detergent properties, their use as wetting agents in solid pharmaceutical dosage forms, and as stabilizers for suspension formulations. The mode of action of surfactants in each of these systems is discussed further below.

Micellization

As mentioned previously, surfactant molecules have the ability to form micelles in aqueous solution. These micelles are colloidal-sized clusters of molecules. Micellization is an alternative to interfacial adsorption for removing hydrophobic groups from contact with the aqueous environment, thereby reducing the free energy of the system. In micelles, the hydrophobic groups are directed toward the center of the surfactant aggregate. In cases where there is little distortion of the surrounding solvent by the hydrophobic group, there is little tendency for micellization to occur, such as in water when the *hydrophobic* group of the surfactant is short or in the case of nonaqueous solvents.

One of the most important applications of micellization in the context of pharmaceuticals is their ability to solubilize drugs of poor aqueous solubility.

Micelles are dynamic species; there is a constant rapid interchange of surfactant molecules between the micelle and the bulk solution. Micelles cannot, therefore, be regarded as rigid structures with a defined shape, although an average micellar shape may be considered.

The main types of micelles recognized (3) are:

1. Small spherical
2. Elongated cylindrical, rodlike micelles with hemispherical ends (prolate ellipsoids)
3. Large, flat lamellar micelles (disklike extended oblate spheroids)
4. Vesicles, more or less spherical structures, consisting of lamellar micelles arranged in one or more concentric spheres.

In nonaqueous solvents, surfactants may form "inverted micelles" where the hydrophilic heads of the surfactant

molecules are present in the center of the micelle with the hydrocarbon chains extending outward into the solvent. Dipole–dipole interactions hold the hydrophilic heads of the surfactant molecules together in the core, and in certain cases hydrogen bonding between head groups can also occur.

Micellar shape can be affected by changes in temperature, concentration and the presence of added electrolyte to the liquid phase. Changes in any of these factors may affect micellar size, shape, and aggregation number (number of surfactant monomers in the micelle).

Phase Behavior of Surfactants

Equilibrium phase structures

As the concentration of a surfactant solution is increased, structures of the types depicted in Fig. 3 may be encountered (5). At concentrations well above the CMC, a more ordered structuring of the solution occurs. Two main types of liquid crystalline phases may be identified: the middle phase, M_1, exhibiting a hexagonal array of indefinitely long, mutually parallel rods; and the neat phase, G, with a lamellar structure. The liquid crystalline hexagonal phase, like the micellar phase, can exist either in a normal or reverse orientation. The order of phase structures formed upon increasing surfactant concentration generally follows a well defined sequence (Fig. 4) with a "mirror plane" through the lamellar phase in such a way that normal phase structures can be considered to be "oil-in-water" and the reverse structures to be "water-in-oil" (5).

Modified phase structures

In addition to the equilibrium phase structures mentioned above, nonequilibrium surfactant phase structures exist that are also finding applications in drug delivery. Vesicular forms of surfactants are generally formed by dispersing lamellar phases in an excess of water (or nonaqueous polar

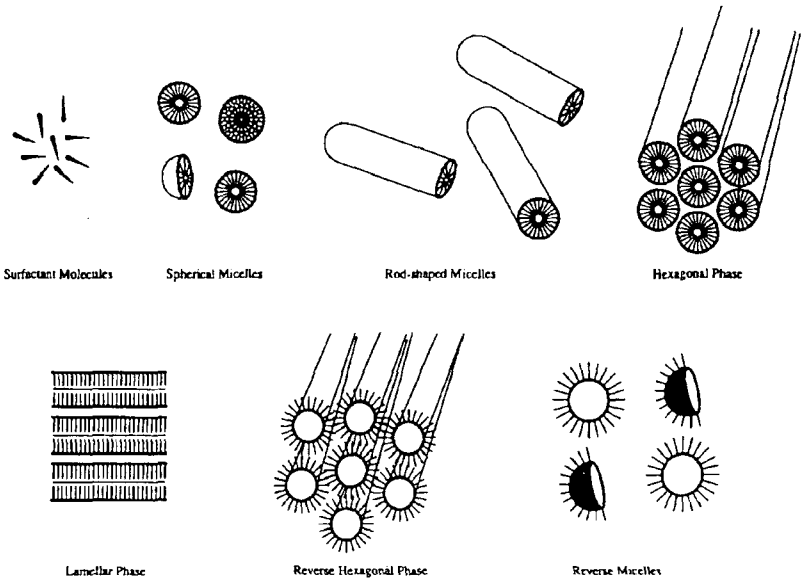

Fig. 3 Equilibrium phase structures of surfactant molecules. (From Lawrence, M.J. Chem. Soc. Rev. 1994, 23 (6), 417–424, reproduced by permission of the Royal Society of Chemistry.)

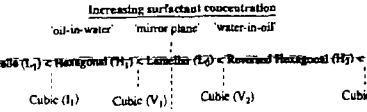

Fig. 4 Idealized phase sequence in surfactant-water systems. (From Lawrence, M.J. Chem. Soc. Rev. 1994, 23 (6), 417–424, reproduced by permission of the Royal Society of Chemistry.)

solvents such as ethylene glycol or dimethylformamide) or, in the case of reversed vesicles, in an excess of oil. With most surfactants, vesicles are nonequilibrium structures that will eventually re-equilibrate back into the lamellar phases from which they originated. Vesicles are structural analogs of liposomes (discussed later); they are approximately spherical structures and have the ability to "solubilize" both lipid soluble and water soluble agents.

Several of the phase structures produced by surfactants have potential as carriers and vehicles for drugs and also as targeting systems, used to direct the drug to a specific site in the body (5).

SURFACTANT CLASSIFICATION

Surfactant molecules may be classified based on the nature of the hydrophilic group within the molecule. The four main groups of surfactants are defined as follows:

1. *Anionic surfactants*, where the hydrophilic group carries a negative charge, such as carboxyl ($RCOO^-$), sulphonate (RSO_3^-) or sulphate ($ROSO_3^-$).
   Examples of pharmaceutical importance include potassium laurate, $CH_3(CH_2)_{10}COO^-K^+$, and sodium lauryl sulphate, $CH_3(CH_2)_{11}SO_4^-Na^+$.
2. *Cationic surfactants*, where the hydrophilic group carries a positive charge (e.g., quaternary ammonium halides, $R_4N^+Cl^-$). Examples of pharmaceutical importance include cetrimide, a mixture consisting mainly of tetradecyl (ca. 68%), dodecyl (ca. 22%), and hexadecyltrimethylammonium bromides (ca. 7%), as well as benzalkonium chloride, a mixture of alkylbenzyldimethylammonium chlorides of the general formula $[C_6H_5CH_2N^+(CH_3)_2R]Cl^-$, where R represents a mixture of the alkyls from C_8H_{17} to $C_{18}H_{37}$.
3. *Ampholytic surfactants (also called zwitterionic surfactants)*, where the molecule contains, or can potentially contain, both a negative and a positive charge, (e.g., the sulfobetaines, $RN^+(CH_3)_2CH_2CH_2SO_3^-$). Examples of pharmaceutical importance include *N*-Dodecyl-*N*,*N*-Dimethylbetaine, $C_{12}H_{25}N^+(CH_3)_2.CH_2COO^-$.
4. *Nonionic surfactants*, where the hydrophile carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene ($OCH_2.CH_2O$—) groups. Examples of pharmaceutical importance include polyoxyethylated glycol monoethers (e.g. cetomacrogol), sorbitan esters (Spans®) and polysorbates (Tweens®).

Tables 1–4 in the article *Surfactants in Pharmaceutical Products and Systems* in Volume 14 of the first edition of this encyclopedia (6), together with the references cited therein, give listings of some of the surfactants most commonly used in pharmaceuticals, along with the purpose(s) for which they are usually employed.

SURFACTANT USES IN PHARMACEUTICAL PREPARATIONS

Because of their unique functional properties, surfactants find a wide range of uses in pharmaceutical preparations. These include, depending on the type of product, improving the solubility or stability of a drug in a liquid preparation, stabilizing and modifying the texture of a semisolid preparation, or altering the flow properties of a granulate, thus aiding in the processing of the final tablet dosage form. In addition to their use as excipients to improve the physical and chemical characteristics of the formulation, surfactants may be included to improve the efficacy or bioperformance of the product. The properties of surfactants are such that they can alter the thermodynamic activity, solubility, diffusion, disintegration, and dissolution rate of a drug. Each of these parameters influence the rate and extent of drug absorption. Furthermore, surfactants can exert direct effects on biological membranes thus altering drug transport across the membrane. The overall effect of inclusion of a surfactant in a pharmaceutical formulation is complex and may be beyond those initially intended.

Surfactants may reduce the effectiveness of antimicrobials or preservatives included in a formulation (7). They also have the capacity to damage biological membranes.

LIQUID SYSTEMS

Solutions

Surfactants as solubilizing agents

Solubilization can be defined as "the preparation of a thermodynamically stable isotropic solution of a substance normally insoluble or very slightly soluble in a given solvent by the introduction of an additional amphiphilic component or components" (4). The amphiphilic components (surfactants) must be introduced at a concentration at or above their critical micelle concentrations. Simple micellar systems (and reverse micellar) as well as liquid crystalline phases and vesicles referred to above are all capable of solubilization. In liquid crystalline phases and vesicles, a ternary system is formed on incorporation of the solubilizate and thus these anisotropic systems are not strictly in accordance with the definition given above (4).

Solubilization by micelles

The location of a solubilized molecule in a micelle is determined primarily by the chemical structure of the solubilizate. Solubilization can occur at a number of different sites in a micelle:

1. On the surface, at the micelle–solvent interface,
2. Between the hydrophilic head groups,
3. In the palisades layer, i.e., between the hydrophilic groups and the first few carbon atoms of the hydrophobic groups that comprise the outer regions of the micelle core,
4. More deeply in the palisades layer, and
5. In the micelle inner core.

In aqueous systems, nonpolar additives such as hydrocarbons tend to be intimately associated with the hydrocarbon core of the micelle. Polar and semipolar materials, such as fatty acids and alcohols are usually located in the palisades layer, the depth of penetration depending on the ratio of polar to nonpolar structures in the solubilizate molecule.

In reverse micelles (formed in nonpolar solvent systems containing surfactant), polar additives may be solubilized in the core where a polar interaction of head groups occurs.

A preferred location of the solubilizate molecule within the micelle is largely dictated by chemical structure. However, solubilized systems are dynamic and the location of molecules within the micelle changes rapidly with time. Solubilization in surfactant aqueous systems above the critical micelle concentration offers one pathway for the formulation of poorly soluble drugs (7). From a quantitative point of view, the solubilization process above the CMC may be considered to involve a simple partition phenomenon between an aqueous and a micellar phase. Thus the relationship between surfactant concentration C_m and drug solubility C_{tot} is given by Eq. 3.

$$C_{tot} = C_s + PC_sC_m \quad (3)$$

where C_s is the drug solubility in the absence of surface-active agent and P is the distribution coefficient of drug between the micelle and bulk phases. A plot of C_{tot} versus C_m is linear with a slope of PC_s, which is the solubilizing capacity of the micelle (8).

The effect of altering the pH of the vehicle, in the case of a partly ionized drug will be to alter the apparent partition coefficient. Thus the effect of increasing the pH of a vehicle containing an acidic drug is to reduce the proportion of drug in the micellar phase. If the surfactant is a weak electrolyte, it may induce a concentration-dependent change in pH thus altering drug partitioning and solubility (9).

In general the solubilizing capacity for surfactants with the same hydrocarbon chain length increases in the order *anionic < cationic < nonionic, the effect being attributed* to a corresponding increase in the area per head group, leading to looser micelles with less dense hydrocarbon cores which can accommodate more solute.

The solubilizing capacity for a given surfactant system is a complex function of the physicochemical properties of the two components which, in turn, influence the location or sites where the drug is bound to the micelle. The molar volume of the solubilizate together with its lipophilicity are important factors, the former reducing and the latter increasing solubilization (9).

Many pharmaceutical products contain a number of solutes potentially capable of being solubilized within the micellar phase. Thus competition can occur between solutes resulting in an altered solubilizing capacity. Furthermore, the addition of a second highly solubilized component to form a mixed micellar system may greatly alter the structure, size and solubilizing capacity of the system, thereby greatly enhancing drug solubility.

Solubilization has been used for many years in the formulation of phenolic antiseptic and disinfectant solutions. In the case of Cresol and Soap Solution (Lysol) and Chloroxylenol Solution B.P., soap micelles are used to solubilize the phenolic substances. The soap (anionic surfactant) is formed by reaction of potassium hydroxide with a suitable oil such as linseed oil (in Cresol and Soap Solution) or castor oil (in Chloroxylenol Solution). The solubilizing potential of surfactant solutions for hydrophobic species has also been exploited in the design of cholelitholytic solvents for gallstone dissolution with some limited success.

Stability of drugs in solubilized systems

Solubilization of a drug by incorporation into micelles may affect its stability (7). In the micelle, the molecular environment of the drug molecules changes their proximity and orientation with respect to each other, which may affect activity. In a micelle, the drug molecules may be protected from attacking species such as hydronium or hydroxide ions and the stability of the drug may be increased. The difference in environment between the micellar and bulk aqueous phases may be such that reaction rates may be radically changed by the transfer of solute to micelles. Micellar systems may be used to deliberately alter the rates and directions of chemical reactions (7).

AB block copolymer micelles

It is well known that block copolymers in a selective solvent (a good solvent for one block but a nonsolvent for the other) form a micellar structure through the association of the insoluble segments (10). In contrast with micelles formed from low molecular weight surfactants, block copolymer micelles dissociate slowly to free polymeric chains. They have a greater capacity for solubilizing aromatic molecules and express lower CMCs. The AB block copolymers are considered useful vehicles for hydrophobic drugs.

Only a few block copolymers form micellar structures in aqueous milieu. One example is a series of polyethylene oxide/polypropylene oxide/polyethylene oxide block copolymers known as Pluronics (tradename) or poloxamers. The poloxamers have been used widely in pharmaceuticals, particularly as emulsifiers for intravenous lipids (7). At low concentrations, poloxamer monomers are thought to form monomolecular micelles by a change in configuration in solution (7). At higher concentrations, aggregation of the monomolecular micelles occurs. The aggregates so formed show the ability to solubilize drugs and increase the stability of solubilized materials. Poloxamers have low toxicity and their solubilization capabilities might prove useful in the delivery of hydrophobic drugs, although multimolecular micelle formation with core-shell structure is uncertain under physiological conditions (11).

Other block copolymers have been prepared and studied as formulation adjuvants for hydrophobic drugs, e.g., poly(ethylene oxide)/poly(aspartic acid) and poly (ethylene oxide)/poly(β-benzyl-L-asparate) block copolymers have been used with adriamycin (12, 13).

Suspensions

If a suspension is to be produced by a dispersion technique (as opposed to precipitation techniques), surfactants may be used in the formulation to aid dispersion of the solid particles in the liquid. This is particularly important if the powder is not readily wetted by the liquid vehicle. Surfactants can reduce the interfacial tension between the solid particles and the liquid vehicle. The advancing contact angle is reduced, and wetting of the solid particles promoted. Such a system is said to be deflocculated. The inclusion of a surface-active agent to improve powder wettability can often improve the bioavailability of the formulation.

The forces at the surface of a particle affect the degree of flocculation and agglomeration in a suspension. Particles dispersed in a liquid medium may become charged in one of two main ways. Ionic species present in solution may be adsorbed at the surface or, alternatively charges on the surface may arise due to ionization of groups (such as carboxyl groups for example) which may be located at the surface. The surface charge will influence the distribution of ions in the aqueous medium surrounding the solid particles. The result is the formation of what is known as an "electric double layer." If the surface charge is positive, immediately adjacent to the surface will be a region of tightly bound solvent molecules and negative counterions. Thus, the first layer is tightly bound, while the second layer (which still contains an excess of negative ions) is more diffuse (14). As two particles approach each other in aqueous medium, a weak attractive force exists just beyond the range of the double-layer-repulsive forces. This region is responsible for the particle interaction termed "flocculation."

Flocculated particles are weakly bonded, settle rapidly, do not form a cake and so are easily resuspended. For this reason it is frequently desirable to promote flocculation in a suspension.

The inclusion of surfactants in the formulation is one way of achieving what is known as "controlled flocculation." Surfactants can cause dispersed solids to flocculate by a number of different mechanisms (3). The first is where there is an electrostatic attraction of surfactant ions to oppositely charged sites on the particle surface, resulting in a lowering of the electrical energy

barrier to the close approach of two particles to each other. Flocculation may also occur by a bridging mechanism. A long, (usually polymeric), surfactant molecule containing functional groups at various sites may adsorb onto sites on the surface of adjacent particles, holding the particles together in a loose arrangement. Alternatively if the surfactant molecules adsorb in such a manner that the molecule extends into the liquid phase, interaction of the extended portions of surfactant molecules adsorbed to different particles result in bridging of those particles.

Another method of employing surfactants to achieve flocculation is to first treat the particles with an ionic surfactant to disperse them. A readily soluble electrolyte is then added which has the effect of compressing the electrical double layer surrounding each particle, allowing flocculation to occur. Subsequent dilution of this type of system will redisperse it (due to a decrease in electrolyte concentration).

Emulsions

Emulsification is one of the most important applications of surface-active agents in pharmaceutical systems. The phenomenon has been extensively studied and many books and chapters of books have been devoted to the subject.

Macroemulsions are either oil in water (o/w) or water in oil (w/o). The type of emulsion formed depends largely on the emulsifying agent used; the process and relative proportions of the oil and water phases are less important. In general, o/w emulsions are produced by emulsifying agents that are more soluble in the water phase than in the oil phase, and w/o emulsions are produced by emulsifying agents that are more soluble in the oil phase. It is also possible to form a multiple emulsion. For example, a small water or aqueous solution droplet may be enclosed in a larger oil droplet which is itself dispersed in an aqueous phase. Such a system is referred to as a "water-in-oil-in-water" (w/o/w) emulsion. It is also possible to from an o/w/o emulsion.

Many medicinal agents which have an unpalatable taste or texture can be made more acceptable for oral administration when formulated as emulsions. Mineral-oil-based laxatives, oil soluble vitamins and high-fat nutritive preparations are frequently administered in the form of o/w emulsions. It has been shown that in some cases the absorption of drugs may be enhanced if formulated as emulsions (15). Emulsions (o/w) have also been used for the intravenous administration of lipid nutrients. Radiopaque emulsions have been used as diagnostic agents in X-ray examinations.

Emulsification is widely used in pharmaceutical products for external application such as lotions and creams, and in aerosol products to form foams. Semisolid emulsified formulations are discussed below.

Based on the size of the dispersed particles or droplets, emulsions may be classified (16) into

1. Macroemulsions, droplets ~0.1–50 μm, opaque emulsions
2. Microemulsions, droplets 10–100 nm, transparent dispersions.

Stabilization of the dispersion of one immiscible liquid in another requires the addition of an emulsifying agent which is commonly a surfactant or a mixture of surfactants.

In the formation of an emulsion, one of the two immiscible liquids is broken up into droplets which are dispersed in the other liquid. The dispersion of one liquid in another immiscible liquid leads to a large increase in interfacial free energy because of the increase in the area of the interface. The emulsifying agent stabilises the emulsion by adsorbing at the liquid–liquid interface as an oriented interfacial film. This film reduces the interfacial tension between the liquids and also decreases the rate of coalescence of the dispersed droplets by forming mechanical, steric and/or electrical barriers around them.

A strong mechanical barrier lessens the chance of droplets coalescing on collision. For maximum mechanical stability, the interfacial film of the adsorbed surfactants should be close packed with strong lateral interactions. For this reason, a mixture of two or more surfactants is commonly used as the emulsifying agent, such as a combination of a water-soluble surfactant and an oil-soluble surfactant. In pharmaceutical (o/w) systems a mixture of a sorbitol ester (Span®) with a polyoxyethylenated sorbitol ester (Tween®) is often used. The water soluble Tween tends to a have a greater interaction with the aqueous phase, its hydrophilic group extending further into the water than that of the nonoxyethyleneated ester. This is believed to facilitate interaction of the hydrophobic groups of the molecules, as they can approach each other more closely in the interfacial film.

The interfacial film can also stabilize the emulsion by producing repulsive electrical forces between approaching droplets. This repulsion is due to surface charge on the droplets. The surface charge effect is believed to be important only in the case of o/w emulsions. The source of surface charge is the hydrophilic head of the surfactant molecules which is oriented toward the aqueous continuous phase. In emulsions containing ionic surfactant molecules, the charge on the disperse phase droplets

is due to the amphipathic ion. In the case of nonionic surfactants, the charge may arise either from adsorption of ions from the aqueous phase or from frictional contact between droplets and the aqueous phase. In the latter case, the phase with the higher dielectric constant is positively charged (3).

Microemulsions

Microemulsions consist of large or "swollen" micelles, containing an internal phase similar to that found in a solubilized solution (16). Unlike macroemulsions, they appear as clear, transparent solutions. They tend to be more thermodynamically stable than macroemulsions and can have essentially infinite lifetimes assuming no change in composition, temperature and pressure. This is in contrast to macroemulsions which, although they may remain stable for long periods of time, will ultimately undergo phase separation to attain a minimum in free energy. Microemulsions can generally be obtained by gentle mixing of the ingredients of the emulsion. In this respect, they differ from macroemulsions which require intense agitation for their formation. Microemulsions are usually prepared with more than one surfactant or using a mixture of surfactant and cosurfactant (e.g., a polar compound of intermediate chain length).

Microemulsions have been studied as drug delivery systems, in particular for topical and transdermal drug delivery (17, 18).

Microspherical particles prepared by emulsification processes

Emulsification–evaporation processes are widely used in the preparation of polymer based microspherical drug-loaded particulates. For example, hydrophobic drug-loaded PLA (polylactic acid) or PGLA (polylactide-*co*-glycolide) biodegradable microspheres are often prepared from emulsions containing a non aqueous dispersed phase of dichloromethane containing the drug and polymer in an aqueous continuous phase. For the preparation of hydrophilic drug loaded microspheres a double-emulsion process may be necessary. The nature of the surfactants used to stabilize the emulsion phases can greatly influence the size, size distribution, surface morphology, loading, drug release, and bioperformance of the final multiparticulate product.

Aerosols

Surfactants are found in both solution and suspension formulations of metered dose inhalers (MDIs). The most common surfactants found in pressurised aerosol preparations include sorbitan trioleate (Span 85), oleic acid, and lecithins at concentrations of 0.1–2.0% (w/w). These agents are nonvolatile liquids which dissolve in the propellant blend. Their function in the formulation is to provide lubrication for the metering valves and, in the case of suspension formulations, to maintain the disperse nature of the drug.

The three surfactants commonly used in chlorofluorocarbon (CFC)-based MDI formulations are insoluble in the CFC-replacement propellants, hydrofluoroalkane (HFA) 134a and HFA 227. Possible formulation alternatives involve the use of an adjuvant such as ethanol to aid dissolution of the surfactant or a novel surfactant. Several companies have investigated novel materials among which are fluorosurfactants, polyoxyethylenes and drugs coated with surfactant (19).

Controlled flocculation in metered-dose aerosol suspensions

Controlled flocculation is a widely used technique for stabilizing suspended systems. The aim is to alter particle surface charge or to achieve particle separation via steric hindrance with the help of appropriate stabilizing excipients. However this is particularly difficult to achieve in nonpolar systems such as suspensions in CFC (or HFA) propellants. Controlled flocculation to optimise the stabilisation of MDIs has been recommended by Ranucci et al. (20) but disputed by Hickey et al. (21).

Liposomes

Liposomes are single- or multilayered phospholipids vesicles. They are roughly spherical in shape and consist of lipid bilayers alternating with aqueous regions.

Liposomes have shown potential as drug delivery systems. The exact location of a drug molecule in a liposome depends on its physicochemical composition and the composition of the lipids. Water soluble drugs may be included in the aqueous phase, and oil-soluble drugs may be added to the membrane-forming phospholipid. An extensive account of the pharmaceutical use of liposomes is found in the article "*Liposomes as Pharmaceutical Dosage Forms*," by Y. Barenholz, and D.J.A., Crommelin, Volume 9 of the first edition of this encyclopedia (22).

SEMISOLID SYSTEMS

Surfactants are major constituents of pharmaceutical, cosmetic, and food semisolid formulations, many of which are emulsions, either oil in water (o/w) or water in oil (w/o). They are included for their stabilizing, wetting,

solubilizing, detergent and penetration-enhancing properties.

Water-in-oil emulsions traditionally contain surfactants of natural origin such as cholesterol, wool fat, wool alcohols, lanolin, divalent salts of fatty acids soaps, calcium oleate and/or synthetic agents of low hydrophilic-lipophilic balance (HLB) (indicating high lipophilicity), such as Spans (fatty acid esters of sorbitan). An example of such a product is Oily Cream B.P. which consists of a 1:1 mixture of wool alcohols and water.

Oil-in-water creams, for topical use, generally contain mixed emulsifiers/surfactants; one of which is a water soluble surfactant with a high HLB, the other being an amphiphile, usually a long chain fatty alcohol (e.g., of chain length C_{14} to C_{18}) or acid (e.g., palmitic or stearic). The water soluble surfactant may be anionic (e.g., sodium lauryl sulphate), cationic (e.g., cetrimide), or nonionic (e.g., cetomacrogol, Tweens).

These mixed-surfactant systems are used not only for their ability to form complex condensed films at the liquid–liquid interface, enhancing the stability of the emulsion, but also because of their ability to impart "body" to the product, resulting in a semisolid product rather than a liquid. Mixed emulsifiers control the consistency of a cream by forming a viscoelastic network throughout the continuous phase of the emulsion. The network results from the interaction of the mixed emulsifier with water, forming a liquid crystalline phase.

Foams

Emulsification is used in aerosol products to produce foams which are generally formulated as o/w emulsions. The liquified propellant forms the disperse phase of the emulsion, and the medication is usually in the aqueous continuous phase. On discharge from the pressurised container, the propellant vaporizes to form bubbles which remain trapped within the aqueous phase giving rise to a foam. These are referred to as "stable foam" products. Nonaqueous stable foams may also be formulated, where the water is replaced by various glycols such as polyethylene glycol. "Quick breaking foams" result when the propellant is in the external phase. The product is emitted as a foam and collapses into a liquid.

Biological Effects on Percutaneous Absorption

Surfactants—traditionally common constituents and stabilizers of topical vehicles, ranging from hydrophobic agents such as oleic acid to hydrophilic sodium lauryl sulphate—have been tested as penetration enhancers to improve transdermal drug delivery. Ionic surfactants are thought to enhance transdermal absorption by disordering the lipid layer of the stratum corneum and by denaturation of keratin. The use of penetration enhancers in general, and surfactants in particular, in transdermal therapeutic systems has been reviewed by Walters (23).

SOLID DOSAGE FORMS

Surface-active agents have been widely shown to enhance drug dissolution rates. This may be due to wetting effects, resulting in increased surface area, effects on solubility and effective diffusion coefficient or a combination of effects. Consequently surfactants have been included in tablet and capsule formulations to improve wetting and deaggregation of drug particles and thus increase the surface area of particles available for dissolution.

This wetting effect is found to be operative at concentrations below the CMC. The effect of surfactants on the dissolution of solids is complex. In addition to effects on the available surface area, surfactants in concentrations above the CMC can increase drug solubility and hence the effective concentration gradient. However they also reduce the effective rate of drug diffusion as a consequence of drug solubilization within micelles. Models to quantify the effect of surfactant concentration on drug dissolution have been developed (24). For solids whose dissolution is under significant surface control, surfactants may further influence the dissolution process. In this regard the enhancing effect of surfactants on the dissolution rate of cholesterol has been widely studied (25).

Hard Gelatin Capsules and Tablets

Wetting agents

Surfactants are used in capsule (26) and tablet formulations as wetting agents to aid dissolution.

Lubricants, anti-adherents, and glidants

The primary function of tablet lubricants is to reduce the friction arising at the interface of tablet and die walls during compression and ejection. Lubricants also possess antiadherent (prevention of sticking to the punch and, to a lesser extent, to the die wall) and glidant (improvement of flow characteristics of powders or granulates) characteristics and are useful in the processing of hard gelatin capsules.

Magnesium stearate is used extensively as a lubricant in tablet manufacture. It is an example of a "boundary lubricant," that is, the polar regions of the molecule adhere to the metal surface of the die wall (in tablet manufacture). Adsorption of magnesium stearate to the powder or granule surfaces also prevents agglomeration of the feed material and aids flow.

Lubricants may be classified as water-soluble or water-insoluble. The latter are generally more effective than water-soluble lubricants and can be used at a lower concentration (27). Common water-insoluble lubricants (which are surfactants) include magnesium stearate, calcium stearate, sodium stearate, and stearic acid; water-soluble lubricants include sodium lauryl sulphate and magnesium lauryl sulphate.

Sodium lauryl sulphate is used in the production of hard gelatin capsules where it is added to the gelatin solution during the preparation stage. The stainless steel molds are lubricated prior to dipping into the gelatin solution and sodium lauryl sulphate is added to reduce the surface tension of the mix and cause the mold pins to wet more uniformly (28).

Solid Dispersion Systems

The bioavailability of hydrophobic drugs can be increased by strategies designed to enhance the dissolution rate of the drug. This has been achieved in many cases by forming a solid dispersion of the drug in a suitable carrier, often a hydrophilic polymer such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP). The drug is dispersed in the carrier by coprecipitation from a suitable solution containing both drug and carrier, by melting both components together, or by some other process involving a phase change. By using relatively high concentrations of carrier and a rapid precipitating process, the drug may form as an amorphous or molecularly dispersed high energy phase in the carrier. A number of workers have used surfactants as the carrier material to achieve this enhanced dissolution effect. Among the surfactants employed are polyoxyethylene stearate, Renex 650, poloxamer 188, Texafor AIP deoxycholic acid, and Tweens and Spans. Surfactants have also been added to conventional drug–polymer solid dispersions to further improve drug release properties. Sjokvist et al. (29) found that the incorporation of sodium dodecyl sulphate (1–2%) in griseofulvin (3–10%)-PEG solid dispersions eliminated any traces of crystalline drug, griseofulvin being present as a solid solution. Other three-component solid dispersions containing surfactants have also been reported such as Tween 20-Griseofulvin-PEG and Tween 20-Oxodipine-PEG (30). Problems have been reported however as to the physical stability of surfactant containing systems, dissolution rates decreasing over a 12-month period (31).

Matrix Systems

Drug release from nondisintegrating inert matrices, fabricated from hydrophobic carriers such as polyethylene, is improved by the presence of surfactants in the dissolution medium. Drug release was shown to be a function of the pore size distribution of the matrix and the permeation pressure of the release media defined by its surface tension and contact angle. Inclusion of dioctyl sodium succinate, which reduced the contact angle below 90°, greatly enhanced drug release; increasing the concentration of polysorbate in the range of 0.001–0.1% had the same effect (32). Surfactants have also been included in matrix-type drug delivery systems to aid penetration of the dissolution medium thus increasing the rate and extent of drug release.

Suppositories

Several nonionic surface-active materials have been developed as suppositories vehicles. Many of these bases, known as water-dispersible bases, can be used for the formulation of both water-soluble and oil-soluble drugs (33). The surfactants most commonly used are the polyoxyethylene sorbitan fatty acid esters (Tweens), the polyoxyethylene stearates, and the sorbitan fatty acid esters (Spans). These surfactants may be used alone, blended, or with other suppository base materials to yield a wide range of melting points and consistencies.

Surface-active agents are widely used in combination with other suppository bases. The inclusion of these agents in the formulation may improve the wetting and water-absorption properties of the suppository. In addition, emulsifying surfactants help to keep insoluble substances suspended in a fatty base suppository (33).

The inclusion of a surfactant in the suppository formulation may enhance the rectal absorption of drugs. The effect has been attributed to the formation of mixed micelles. It has been suggested that the presence of the micelle facilitates the incorporation of the lipid component of the mixed micelle into the biological membrane. This lipid then enhances the fluidity and permeability of the membrane to the poorly absorbed drug. It appears that the colorectal mucous membrane is more sensitive to the effects of mixed micelles than the gastrointestinal membrane of the small intestine.

Surfactant Influence on Drug Absorption from the Gastrointestinal Tract

In the context of oral dosage forms containing surfactants, these agents may play a role in reducing the rate of gastric emptying and retarding the movement of drug to the absorption site by increasing the viscosity of the formulation. This is thought to be especially true of polyoxyethylene derivatives. Bile salts, which are physiological surfactants, have been shown to affect the rate of gastric emptying. The presence of bile salts in the stomach has also been shown to affect ionic movement across the gastric mucosa, thus increasing the movement of hydrogen and chloride ions out of the lumen.

Surfactants may also affect the rate and extent of drug absorption by exerting an influence on the permeability of the biomembrane. Competitive binding of the surfactant to the membrane protein is considered to be partially responsible for enhanced drug absorption in many cases. Alternatively, the enhancement may be due to allosteric rearrangement of the membrane protein which is triggered by the binding of one or more permeating species.

Nakanishi et al. (34) studied the effect of a range of surfactants on the rectal absorption of sulphaguanidine and found absorption to be increased. The increase was associated with histological changes in rectal membrane, increasing the rectal permeability. The same authors found that surfactants such as sodium deoxycholate and sodium dodecyl sulphate used together with the chelating agent EDTA could increase the rectal absorption of macromolecules such as inulin, insulin, and albumin.

The membrane effects of surfactants are explained by a combination of membrane-surfactant binding, disruption of membranes through solubilization into lipoproteins, proteins, and mixed micelles, protein–protein interactions, and selective solubilization of some membrane components by the surfactant. The structure of the surfactant may play a role in determining the range and extent of the influence of a particular surfactant on drug absorption. It appears that the greatest effect is achieved by molecules having a C12–C16 hydrocarbon chain, polyoxyethylene chain lengths between 10 and 20, and molecular areas between 1.0 and 1.6 nm^2 (4). These effects, in the case of drugs of low aqueous solubility, are in addition to the higher absorption rate, arising from an increase in drug solubility (35, 36).

Surfactants, at high concentrations, exhibit some toxicity and have the ability in many cases to disrupt a membrane. Both ionic and nonionic surfactants have been shown to assist the breakdown of the mucous layer covering the epithelium and at high concentrations are thought to interfere with the membrane itself, which may lead to disruption of membrane metabolism, particularly with regard to enzyme systems associated with the membrane. Adverse reactions to drug formulation agents including surfactants have been reviewed by Weiner and Bernstein (37).

DIRECT ACTIONS OF SURFACTANTS

Detergents

Detergents are surfactants that are used for the removal of foreign matter from a solid surface. The process involves many of the actions specific to surfactant molecules. The surfactant requires good wetting properties to ensure good contact with the solid surface. It must also have the ability to remove dirt into the bulk liquid. This is achieved by a lowering the dirt–liquid and solid–liquid interfacial tensions, thus reducing the work of adhesion between the dirt and the solid and enabling the dirt to be readily detached. Once detached, adsorption of surfactant at the dirt particle surface prevents deposition, allowing the dirt to be washed away. If the dirt is oily it may be emulsified or solubilized by the surfactant.

Antimicrobial Activity

Significant antimicrobial effects have been associated with cationic surfactants, in particular the quaternary compounds. The action mechanism of quaternary surfactants involves disruption of the cell membrane, protein denaturation, and enzyme inhibition. Quaternary compounds are able to lyse cells at relatively low concentration, resulting in leakage of cell contents into the surrounding medium. Quaternary ammonium and some phosphonium surfactants are used as topical disinfectants in commercial dermatological products, in surgical hand scrubs, and in the irrigation of skin wounds. The most commonly used quaternary compounds employed for their antimicrobial effects are cetylpyridinium chloride, benzalkonium chloride, benzethonium chloride and cetyltrimethylammonium bromide (38). Other surfactants, containing more than one quaternary (or positively ionizable group) are among the most active substances known in terms of antimicrobial activity. Included in this group are dequalinium acetate and chlorhexidine gluconate which have been used in throat lozenges and mouthwashes. The lysis of cells can also occur in the presence of anionic surfactants, although these are in general weaker in their antimicrobial activity. A wide range of anionics, in particular sodium lauryl sulphate and its homologs, finds wide application in mouthwashes (38).

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Respiratory Distress Syndrome (RDS)

In 1959, surfactant deficiency was identified as the major pathogenic factor in respiratory distress syndrome in infants (39). Pulmonary surfactant is a complex mixture of phospholipids, neutral lipids, and specific proteins which spread as a monolayer at the air-liquid interfaces of the lung and lower surface tension at end-expiration thus preventing alveolar collapse. If the amount or quality of endogenous surfactant is inadequate, inspiratory pressure and the work of breathing must increase in order to re-expand the alveoli with each breath and permit adequate gas exchange. As the infant grows tired, progressive respiratory failure occurs.

Phosphatidylcholine is the major component of endogenous surfactant, constituting about 60% of total phospholipids, and dipalmitoylphosphatidylcholine (DPPC) is the primary surface-tension lowering phospholipid.

The surfactant replacement therapy treatment used may be either "natural" or "artificial." Natural surfactants are derived from bovine or porcine animal lungs or human amniotic fluid. Synthetic or artificial surfactants are composed of DPPC and spreading agents such as unsaturated phosphatidylglycerol or tyloxapol and hexadecanol (40).

NATURALLY OCCURRING SURFACTANTS

Of the naturally occurring surfactants, the bile salts and phospholipids are of particular importance.

Phospholipids

The phospholipids are widely found in biological membranes and can be used as emulsifiers especially for intravenous fat emulsions, and as a key component of liposomes. The elucidation of factors governing the solubilization of drugs in phospholipid dispersions can provide some clues as to the biological role of interactions with lipid systems in vivo (4). Phospholipids have been discussed above and in reference (22) in the context of liposomes.

Bile Salts

Bile salts are carboxylic acids (C22–C28) with a cyclopentenophenanthrene nucleus containing a branched chain of 3–9 carbon atoms ending in a carboxyl group. Structurally they form micelles which are different from the conventional spherical micelles synonymous with amphiphiles having a distinct hydrocarbon chain. The hydrophobic feature of the bile salts is associated with one surface of the steroid nucleus and consequently intermolecular association is much more restricted. Primary and secondary micelles have been proposed, the former consisting of two to four molecules, the latter being composed of aggregates of the primary micelles. The CMC is less distinct and is highly dependent on the structure of the specific bile salt, in particular the number of hydroxy groups and their orientation.

Many studies have been completed in order to assess the effect of bile salts on the bioavailability of poorly soluble drugs. Bile salts for example, have been shown to enhance the absorption of sulphaguanidine and urogastrone. Bile salts may also play a role in enhancing the transport of a compound from the lumen of the intestine to the systemic circulation. Such absorption involves overcoming the resistance of the aqueous boundary layer and the membrane epithelium to the passage of the drug.

Bile salts readily form mixed micelles with lipid-like molecules such as lecithins or fatty acids. These mixed micelles are structurally very different from the simple micelles and generally have a much greater solubilizing capacity for hydrophobic molecules, both biological and synthetic. The solubility of DDT, a nonpolar, water insoluble molecule, for example, in bile salt micellar solution can be increased to a far greater extent by the addition of unsaturated long chain fatty acids, probably because of mixed micelle formation.

Saponins

Saponins are glycosides found in certain plants which are characterized by their property of producing a frothing aqueous solution. The term "saponin" is derived from the Latin "sapo" meaning soap. Plant materials containing saponins have been used for a long time in many parts of the world for their detergent properties, for example, in Europe, the root of *Saponaria officinalis* and in South America the bark of *Quillaja saponaria* (41).

The saponin structure is either of the steroidal (commonly tetracyclic triterpenoids) or pentacyclic triterpenoid type. Triterpenoid saponins are found, for example in Quillaia bark and in liquorice root. Quillaia B.P. is defined as the dried inner part of the bark of *Quillaja saponaria* and other species of *Quillaja* and is used as an emulsifying agent. Liquorice, the root of which also contains triterpenoid saponins, has long been used in pharmacy as a flavoring agent, demulcent, and mild expectorant.

Iscoms

Iscoms (immune-stimulating complexes) are stable complexes of cholesterol, phospholipid, and Quil A (derived from *Quillaja saponaria*) in size ranges from 40 to 100 nm. They are promising carriers for antigens in subunit vaccines. Iscoms are considered to be multimicellar structures, shaped and stabilized by hydrophobic interactions, electrostatic repulsion, steric factors and possibly hydrogen bonds (42). Protection has been achieved after immunization with iscom-based vaccines, against viruses like the Epstein–Barr virus (43) and the measles virus (44).

SURFACE ACTIVITY OF DRUGS

A large number of drug molecules exhibit surface activity, that is, they tend to accumulate at interfaces, depress surface tension and associate to form aggregates in solution. Although the hydrophobic groups of most drugs are aromatic, they still behave like typical surfactants (which possess flexible hydrophobic chains), inasmuch as these aromatic groups have a high degree of flexibility. (Drugs that exhibit association characteristics typical of surface active agents and may reduce surface tension are reviewed in Ref. 4.)

Most of the drugs form micelles at concentrations that they do not attain in vivo. It is therefore their surface activity, rather than their self-association tendency which is more important biologically. Surface-active drugs will tend to bind hydrophobically to proteins and other macromolecules and to associate with other amphipathic substances such as bile salts, phospholipids, and receptors. As with other surface-active agents, surface-active drugs may interact directly with biological membranes. The possible biological implications of surface activity is discussed by Attwood and Florence (4) in relation to the phenothiazine tranquillisers and local anesthetics.

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Ex. 9

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Application No	Ref.	Date
04 816 820.7 - 1219	M/43260-EP	17.04.2009

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Result of consultation

A copy of the result of consultation of 09.04.2009 is enclosed for your information.

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For the Examining Division

Enclosure(s): Copy of result of consultation (Form 2036)

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Consultation by telephone with the applicant / representative

Despatch for information

Participants

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Result of consultation

In the telephone conversation of today 09 April 2009 which took place between the representative W. Thalhammer and the examiner S. Muller, S. Muller states that the set of claims as filed with letter of 04 April 2008 lacks inventive step in view of D2 (WO/01034119).
W. Thalhammer will contact S. Muller again next week.

09.04.2009
.....
Date

Muller, Sophie
.....
Examiner