RESEARCH REROPT

In the course of the study for meeting the requirements of patentability, we tested actual data that belong to tangible and intangible (information) objects, as well as specific objects of study.

To resolve the tasks, the Performer used:

- Methods of matching and comparison, synthesis, and analysis;
- The provisions of regulatory acts and references listed in the previous section.

The invention (utility model) is the result of human intellectual activity in any field of technology [1].

According to the art. 6 of the Law [1]:

"2. The scope of invention, which is legally protected under this Law, may be presented by:

product (device, substance, strain of microorganism, plant and animal cell culture, etc.);

process (method), and the new intended use of a known product or process".

The volume of legal protection for the invention is defined by the formula of invention, which contains all the essential features. In other words, formula of the invention is a brief verbal description of the invention essence containing its cumulative essential features [3, cl.7.1]. According to cl. 6.6.1. of the Regulations [3]: *"The invention essence is expressed with the set of its essential features sufficient to achieve a technical result provided by the invention (utility model)*".

The structure of the formula of invention may be single-link or multi-link and include, respectively, one or more points. Single-link formula is used to characterize one invention with a set of essential features that have no development or clarification on certain cases of its performance or use. Multi-link formula of invention (utility model) is used to characterize one invention (utility model) with development and (or) specification of its cumulative features in respect of some cases of performance and the invention use or to characterize a group of inventions. Multi-link formula characterizing one invention has one independent claim and the subsequent one (several) following it dependent claim(s). Multi-link formula characterizing a group of inventions has several independent claims, each of which describes one of the inventions of the group. At this, each group of inventions can be characterized involving dependent claims subordinated to the respective independent claim [3, cl.7.2]. So, an independent claim of the formula of invention must relate to only one invention [3, cl. 7.3.2].

Claims of formula are divided into restrictive and distinctive sections. The known features inherent to prototype of the invention are placed in the first (restrictive) section of the formula, and new ones, created by an inventor, – in the following, distinctive section. That means that restrictive section of the formula of invention contains the essential features of the invention, which coincide with the essential features of the closest analogue (prototype), and distinctive section – contains important features that distinguish the invention from the prototype.

Essential are features, each of which is necessary, and all together – are sufficient to achieve the technical result. In other words, the signs are essential if they affect the technical result, i.e. they are in the cause-effect relationship with it [4, p. 121; 5, p.125].

Description of the research object:

The invention under the patent of Ukraine No. 85564 dated 10.02.2009.

Bibliographic data of the patent of Ukraine
No. **85564** dated 10.02.2009 for invention

(11) Patent Number	**85564**
(24) Registration date	10.02.2009
(21) Application Number	a200603276
(22) Filing Date	23.08.2004
(24) Date of Effect	10.02.2009
(31) Priority Application Number under the Paris Convention	10/650,178
(32) Priority Application Filling Date under the Paris Convention	28.08.2003
(33) Two-Letter Country Code where the prior application was filed	US
(54) Title	Solid pharmaceutical dosage form containing HIV protease inhibitor, its preparation method
(73) The owner	ABBVIE INC. (US)

Formula of invention under the patent of Ukraine No. **85564** has the following wording:

"1. The solid pharmaceutical dosage form comprising a solid dispersion of at least one inhibitor of HIV protease in at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant, at this, the specified inhibitor of HIV protease is (2S,3S,5S)-5-(N-(N-(N-methyl-N-((2-isopropyl-4-thiasolil)-methyl)-amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiasolil)methoxy-carbonyl)-amino)-amino-1,6-difenyl-3-hydroxyhexan (ritonavir) and each of the above components is at least one pharmaceutically acceptable water-soluble polymer, which has a Tg of at least about 50 °C and the indicated dosage form comprises from about 50 to about 85% by weight of the entire dosage form of said pharmaceutically acceptable water-soluble polymer.

2. The dosage form of cl. 1, distinguished in that the specified solid dispersion is a glass solution or a solid solution and consists of one phase.

3. The dosage form of cl. 2, distinguished in that the specified pharmaceutically acceptable surfactant has HLB value from about 4 to about 10.

4. The dosage form of cl. 3, distinguished in that the specified solid dispersion additionally comprises other pharmaceutically acceptable surfactant.

5. The dosage form of cl. 2, distinguished in that the specified pharmaceutically acceptable surfactant is a sorbitan fatty acid ester.

6. The dosage form of the cl. 2, distinguished in that it includes from about 5 to about 30% by weight relative to weight of the dosage form of the specified inhibitor of HIV protease, from about 2 to about 20% by weight of the specified surfactant, and from about 0 to about 15% by weight of additives.

7. The dosage form of cl. 1, distinguished in that it shows the dose-dependent AUC of ritonavir concentration in dog plasma in the absence of fasting for at least about 9 μg.h/ml/100 mg.

8. The dosage form of cl. 2, distinguished in that at least one HIV protease inhibitor contains ritonavir and (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimide-2-onyl)-3-methylbutanoil]-amino-1,6-difenylhexan (lopinavir).

9. The dosage form of cl. 8, distinguished in that it shows the dose-dependent AUC of ritonavir concentration in dog plasma in the absence of fasting for at least about 9 μg.h/ml/100 mg and dose-dependent AUC of lopinavir concentration in dog plasma in the absence of fasting for at least about 20 μg.h/ml/100 mg.

10. The dosage form of cl. 2, distinguished in that the specified water-soluble polymer has a Tg from about 80 to about 180 °C.

11. The dosage form of cl. 2, distinguished in that this specified water-soluble polymer is homopolymer or copolymer of N-vinylpyrrolidone.

12. The dosage form of cl. 2, distinguished in that the specified water-soluble polymer in it is a copolymer of N-vinylpyrrolidone and vinyl acetate.

13. The dosage form of cl. 2, distinguished in that it contains at least one additive selected from the regulators of fluidity, disintegration agents, agents that increase the volume, lubricating agents.

14. The dosage form of cl. 2, distinguished in that at storage for about 6 weeks at about 40 °C and 75% humidity it contains for at least about 98% of the claimed initial content of HIV protease inhibitor.

15. The dosage form of cl. 1, distinguished in that the specified water-soluble polymer has a Tg from about 80 to about 180 °C, the above pharmaceutically acceptable surfactant has HLB value from about 4 to about 10 and is present in an amount from about 2 to about 20% by weight relative to the weight of the dosage form.

16. The dosage form of cl. 1, distinguished in that the specified water-soluble polymer is a copolymer of N-vinylpyrrolidone and vinyl acetate, the specified pharmaceutically acceptable surfactant is a sorbitan fatty acid ester, and it has HLB value from about 4 to about 10 and is present in an amount from about 2 to about 20% by weight relative to the weight of the dosage form.

17. A method for preparation of a solid dosage form of cl. 1, comprising:

obtaining a melt containing at least one HIV protease inhibitor, at least one specified pharmaceutically acceptable water-soluble polymer and at least one specified pharmaceutically acceptable surfactant; and

leaving the melt for solidification to obtain a solid dispersion of the product.

18. The method of cl. 17, distinguished in that it additionally includes grinding of the specified solid dispersion of the product with compressing the specified solid dispersion of the product into a tablet.

19. The solid pharmaceutical dosage form comprising a solid dispersion of ritonavir and lopinavir in at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant, at this, the specified water-soluble polymer has a Tg for about 50 °C, and is present in an amount from about 50 to about 85% by weight relative to the weight of the dosage form, and the specified pharmaceutically acceptable surfactant has HLB value from about 4 to about 10 and is present in an amount from about 2 to about 20% by weight relative to the weight of the dosage form.

20. The dosage form of cl. 19, distinguished in that the specified solid dispersion is a glass solution or a solid solution and consists of one phase.

21. The dosage form of cl. 19, distinguished in that the specified water-soluble polymer has a Tg from about 80 to about 180 °C.

22. The dosage form of cl. 19, distinguished in that the specified water-soluble polymer is a copolymer of N-vinylpyrrolidone and vinyl acetate, and the specified pharmaceutically acceptable surfactant is a sorbitan fatty acid ester.

23. The dosage form of cl. 19, distinguished in that the specified water-soluble polymer is a homopolymer or copolymer of N-vinylpyrrolidone, and the specified pharmaceutically acceptable surfactant is a sorbitan fatty acid ester.

24. The dosage form of cl. 19, distinguished in that the specified water-soluble polymer is copovidone, and the specified surfactant is sorbitan monopalmitate.

25. The dosage form of cl. 19, distinguished in that it contains at least one additive selected from the regulators of fluidity, disintegration agents, agents that increase the volume, lubricating agents.

26. The solid pharmaceutical dosage form comprising glass solution or solid solution of ritonavir and lopinavir in a matrix containing sorbitan fatty acid ester and a copolymer of N-vinylpyrrolidone and vinyl acetate, which indicates ritonavir and lopinavir presence in an amount of from 5 to about 30% by weight relative to weight of dosage form; the specified copolymer is present in an amount of from 50 to about 85% by weight relative to the weight of the dosage form, and the specified sorbitan fatty acid ester is present in an amount of from 2 to about 20% by weight relative to the weight of the dosage form.

27. The dosage form of cl. 26, distinguished in that the specified polymer in it is copovidone, and the specified sorbitan fatty acid ester is sorbitan monopalmitate."

The invention under the patent of Ukraine *No.* **85564** contains four objects. The objects of the invention are:

The solid pharmaceutical dosage form (composition) characterized by an independent claim 1 of the formula of the invention and dependent claims 2 – 16 of the formula of invention;

A method for preparation of the solid dosage form, characterized by an independent claim 17 of the formula of the invention and a dependent claim 18 of the formula of invention;

The solid pharmaceutical dosage form (composition), characterized by an independent claim 19 of the formula of the invention and dependent claims 20 – 25 of the formula of invention;

The solid pharmaceutical dosage form (composition), characterized by an independent claim 26 of the formula of the invention and a dependent claim 27 of the formula of invention.

Furthermore, according to section 5 of Art. 6 of the Law [1], interpretation of the formula shall be made within the description of invention and corresponding drawings. Therefore, the application materials and description of the invention should include not only references to the assignment of the claimed object of invention (for new chemical compounds – its possible intended use), but also description of the means and methods by which the invention may be used in the form as it is described in any claim of the formula, and a proof of such implementation. That is, the description of the invention must contain a proof of hall-marks set out in the formula of invention within the average specialist scope of knowledge.

According to Art. 7 of the Law [1]:

"1. The invention meets the patentability requirements if it is new, achieves an inventive step and is industrially applicable.

2. The utility model meets the patentability if it is new and industrially applicable.

3. The invention (utility model) should be considered new if it is not a part of the prior art. To determine the novelty of an invention, objects that are a part of the prior art should be considered only separately.

4. The prior art includes all information that became public in the world before the date of filing the application to the Institution or, if priority is claimed, before the priority date.

5. The prior art also includes the contents of any application for granting a patent in Ukraine (including an international application, which includes Ukraine) in the wording in

which this application was filed first, provided that the date of its filing (if priority is claimed, the priority date) precedes the date indicated in section four of this Article and that it was published on that date or after that date.

<...>

7. The invention achieves an inventive step if it is not obvious for a specialist, i.e. it does not obviously follow from the prior art. In assessing the inventive step, content of applications referred to in part five of this Article, is not taken into account.

8. The invention (utility model) shall be considered industrially applicable if it can be used in industry or in other field."

The specialist should be referred to as a person who has knowledge in the relevant field, based on the information that became public before the priority date, and in its absence, before the date of application to the public service and are contained in manuals, handbooks, monographs, textbooks on this field.

The source of such information may be descriptions of patents for inventions (utility models) or scientific publications, if the invention relates to the field of exploration that is so new that the relevant knowledge is not yet available from other sources [6].

The obvious (which evidently derive from the prior art) are solutions obtained by conventional engineering design based on the known means and methods that give a known result [4].

In accordance with clause 6.5.3. of the Consideration Rules [2]:

"The invention achieves an inventive step if it is not obvious for a specialist, i.e. it does not follow obviously from the prior art. At determining the inventive step, the claimed invention is compared not only to individual documents or parts thereof, but to a combination of documents or parts thereof (the so-called collective prototype) when merging the documents or parts thereof is obvious to a specialist.

<...>

6.5.3.2. When checking the inventive step, the awareness of influence of cumulative features of the claimed invention on the achievement of the claimed by an applicant technical result is established from the prior art. If such awareness is not established, the invention is recognized to be meeting the inventive step requirement.

<...>

6.5.3.5. *The present invention is generally recognized as such that does not meet the inventive step requirement if it is based on:*

adding to the known media of any known part(s) that is (are) attached (added) to it by the known rules to achieve a technical result, for which the influence of exactly these additions was established;

replacement of any part(s) of the known media by another known part(s) to achieve the technical result for which the influence of exactly this change was established;

removal of any media (element, action) with a simultaneous removal of its function caused by its presence, and achievement of a technical result (simplification, reduction of weight, dimensions, material consumption, increase of reliability, reduction of the process time, etc.), which is normal for such a removal;

increasing the number of similar elements or actions to strengthen the technical result which is caused by the presence in the media of exactly such elements or actions;

production of the known media or its part(s) of the known material to achieve a technical result, which is caused by the known properties of this material;

creating a medium consisting of well-known parts, the selection of which and the connection between which is made according to the known rules, guidelines, and thus the achieved technical result is caused only by the known properties of these parts and the connections between them;

use of formerly known product (device, substance, microorganism strain, etc.) or the method for the new application, if its new application is caused by its known properties, structure, performance and it is known that exactly these properties, structure, performance are necessary to implement the said purpose;

change of the quantitative parameter(s), showing such parameters in the relationship or in change of its type provided that the fact of the influence of each of the parameter on the specified technical result is known and the new values of these parameters or their relationship could be obtained on the basis of the known dependencies, regularities".

In accordance with clause 25.2.2. of Methodological guidelines [6]:

"Checking the inventive step is carried out on the cumulative essential features described in an independent claim of the formula by comparing these cumulative features with the information obtained as a result of search about objects that are part of the prior art."

In accordance with clause 25.5.2. of Methodological guidelines [6]:

"Should the invention be acknowledged under an independent claim as such that did not achieve an inventive step, the invention is generally acknowledged as such that did not achieve an inventive step".

In accordance with clause 6.5.4.2. of the Consideration Rules [2]:

"If a group of inventions is claimed, then the check for the patentability is carried out for each invention of the group separately. The group of inventions is recognized as such that meets the patentability requirements if all the inventions of the group meet the patentability requirements".

In accordance with clause 26.3. of Methodological guidelines [6]:

"The group of inventions is recognized as such that meets the established requirements if all the inventions of the group meet the patentability requirements".

Thus, to answer the question, it is necessary to study each of the four objects of the group of inventions under the patent of Ukraine No. **85564** regarding its compliance with the patentability requirements.

Clause 6.5.2. of the Procedure for consideration [2] provides clarification on certain documents which are the prior art:

"The prior art includes all information that became public in the world before the date of filing the application to the State service or, if priority is claimed, before the priority date.

<...>

The prior art also includes the contents of any application for granting a patent in Ukraine (including an international application, which includes Ukraine) in the wording in which this application was filed first, provided that the date of its filing (if priority is claimed, the priority date) precedes the date of filing of the application to the public service or, if priority is claimed, the priority date and that it was published on that date or after that date.

The content of the application in the wording in which this application was initially filed is determined by the content of the application documents submitted to the public service on the filing date, and if the application claims the priority – by its content, which coincides with the content of the materials that have been the basis for the assignment of the priority right.

If the earlier application is withdrawn or considered withdrawn before its publication, but the data on such an application were published since the preparation for it was conducted, the content of such an application is not included to the prior art. "

However, according to clause 6.5.2.1 of the Procedure for consideration [2], the date that determines the inclusion of information source to the prior art is:

for published descriptions to security documents – the publication date indicated on them;

for published information on the application for a patent for an invention, which is submitted to the public service – the publication date indicated on them;

for printed matters – the date of publication, and, in the absence of the possibility to establish this date – the last day of the month or December 31 of the year specified in the publication if the publication date is determined only by the month or year;

for deposited manuscripts, articles, reviews, monographs, etc. – the date of their deposit;

for reports of scientific researches, explanatory notes to development works and other engineering, technology, and project documentation, which is in the organs of scientific and technical information, – the date of receipt by these organs;

for regulatory and technical documentation – the date of its registration with the competent authority;

for materials of theses and dissertations abstracts published as a manuscript – the date of receipt by the library;

for works accepted for the competitive tendering – the date of their presentation for review supported by documents relating to the competition;

for sources that are perceived visually (posters, models, products, etc.), – the documented date on which their review becomes possible;

for exhibits placed on exhibitions – the documented start date of the show;

for oral reports, lectures, speeches, etc. – the date of the report, lecture, speech, if they are recorded using a sound recording equipment or shorthand in the prescribed manner, existing at that date;

for information about technical tools that have become known as a result of their use – the documented date on which the information became public;

for radio, television, cinema messages – the date of such a message, if it is recorded on the appropriate storage media under the established procedure existing at that date.

To answer the questions for examination proceeding we had to provide the information base for the preparation of the Opinion, therefore, we conducted patent search in an international patent databases and information databases with the aim of identifying documents that constitute the prior art (documents that became known before the priority date) of the said patent of Ukraine for invention No. **85564.**

The following Table 1 presents the list of the found documents relating to the object of invention under the patent of Ukraine for invention No. **85564.**

Table 1

A list of relevant documents relating to the case, and analysis of which will be conducted in the preparation of the Opinion.

Number	Document	Date of publication
D1	WO 01/34119	17.05.2001
D2	L. Dias et al., "Physical and Oral Dog Bioavailability Evaluation of ABT-538:PVP Co-Precipitates", *Pharmaceutical Research* (1996), Vol. 13, no. 9 suppl., pp. 351	September 1996
D3	A. Forster et al., "Characterization of glass solutions of poorly water-soluble drugs produced by melt extrusion with hydrophilic amorphous polymers", *Journal of Pharmacy and Pharmacology*, 2001, 53: 303-315	2001
D4	J. Rosenberg et al., "Meltrex®-Formulations Containing Solid Solutions of Nearly Insoluble Drugs: Formation of	2001

	Nanoparticles on Dissolution in Water", *28th Int. Symp. on Controlled Release of Bioactive Materials and 4th Consumer & Diversified Products Conference* (2001), Vol. 1, pp. 738-739	
D5	Abu T.M. Serajuddin, "Solid Dispersion of Poorly Water-Soluble Drugs: Early Promises, Subsequent Problems, and Recent Breakthroughs", *Journal of Pharmaceutical Sciences,* vol. 88, No. 10, October 1999, pages 1058-1066	October 1999
D6	O.I. Corrigan, "Surfactants in Pharmaceutical Products and Systems", *Encyclopedia of Pharmaceutical Technology*, vol. 14, 2002, pages 2639-2653	2002
D7	J. Breitenbach, "Melt extrusion: from process to drug delivery technology", *European Journal of Pharmaceutics and Biopharmaceutics,* vol. 54, (2002), pages 107-117	2002
F8	US6599528	29.07.2003

Further, an analysis of relevant documents and answers to Customer questions is provided.

1. Does the patent of Ukraine for invention No. 85564 meet the patentability requirements?

The document **D1** contains the following information:

- (p. 10, lines 3-5):

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

- (p. 29, lines 3-7):

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).

- (p. 10, line 20 – p. 11, line 6):

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.

- (p. 11, lines 16-18):

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

- (p. 14, lines 10-12):

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

- (p. 15, line 8 – p. 16, line 4):

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

- (p. 20, lines 5-6):

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.

- (p. 20, lines 9-12):
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

- (p. 30, line 23 – p. 31, line 2):
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.

Further, there is a translation of the above information:
- (p. 10, lines 3-5):
"This invention relates to preparation of solid dispersion systems for pharmaceutical agents that show the absence of crystallization"

- (p. 29, lines 3-7):
"1. A pharmaceutical composition comprising a solid dispersion of pharmaceutical compound, water-soluble carrier and crystallization inhibitor selected from the group consisting of polyvinylpyrrolidone (PVP) and hydroxypropycellulose (HPMC)."

- (p. 10, line 20 – p. 11, line 6):
"In the present invention, PEG 8000 is used as a hydrophilic matrix. This formulation also uses polyvinylpyrrolidone (PVP), which is an example of a hydrophilic, amorphous polymer and used to inhibit crystallization. Other hydrophilic amorphous polymers include hydroxypropylcellulose (HPMC) or other pharmaceutically acceptable hydrophilic amorphous polymers. Specifically, PVP PF 17 is used in the PEG matrix to inhibit crystallization of the drug of interest. PVP can be used in a range of 1%-95% (wt./wt.), where the primary range is of 1% to 15% (wt./wt.)."

- (p. 11, lines 16-18):

"... PVP has the further advantage because of the high Tg that stabilizes the amorphous regions by reducing mobility. ..."

- (p. 14, lines 10-12):

"... An example of the HIV protease inhibitor is AVT-538 (ritonavir), the chemical structure of which is presented hereinafter as compound of formula I..."

- (p. 15, line 8 – p. 16, line 4):
- *"Additional HIV protease inhibitors, which can be formulated in a solid dispersion of the present invention are compounds of formula II*
- *The compound of formula II is known as the AVT-378 ((2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-(2S-(1-tetrahydropyrimide-2-onyl)-3-methylbutanoil)amino-1,6-difenylhexan). ..."*
-
- - (p. 20, lines 5-6):
- *"The sample was prepared by dissolving AVT-538 in a small volume of ethanol 200 proof in 250 ml roundbottomed flask. The flask was shaken and placed into a water bath at 75 C. PEG 8000 was added to the hot ethanol solution with continuous shaking to PEG melting. Then the flask was attached to rotor evaporator, and immersed into a water bath (75°C) in a vacuum for 15 minutes to remove the ethanol. After evaporation of the major part of ethanol, the flask was immersed in an ice bath for 15 minutes. The contents of the flask was then dried under vacuum at room temperature overnight to remove residual alcohol. Dispersion was removed from the flask, gently crushed to the size of 40-100 mesh. The content of the drug in these dispersions was 10, 20 and 30% wt./wt."*
-
- - (p. 20, lines 9-12):
- *"The solid dispersion 30% AVT-538 in 95:5 PEG 8000:PVP by dissolving AVT-538 and PVP 17 PF in a small volume of ethanol 200 proof in 250 ml roundbottomed flask. ..."*

- (p. 30, line 23 – p. 31, line 2):
- *"10. The composition of claim 1, additionally comprising an additive or mixture of additives independently selected from the group consisting of pharmaceutically acceptable surfactants and antioxidants."*
-
- That is, Document **D1** describes the solid pharmaceutical dispersion dosage form containing surfactant and HIV protease inhibitor (ritonavir) dispersed in a water-soluble polymer, the content of which is 70 to 90 wt.% and which has a high Tg. The above solid pharmaceutical dispersion dosage form may additionally comprise a compound of formula II known as AVT-378 ((2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-(2S-(1-tetrahydropyrimide-2-onyl)-3-methylbutanoil)amino-1,6-difenylhexan), as well as lopinavir. Also Document **D1** describes a method of preparation of the solid pharmaceutical dispersion dosage form, which involves melting the components with the subsequent hardening.
-
- Document **D2** contains the following information:

- (PDD 7475, lines 1-4):

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.

- (PDD 7475, the last 5 lines):

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.

Further follows the translation of the above information:

- (PDD 7475, lines 1-4):

"Polyvinylpyrrolidone (PVP) is used to prepare co-precipitates of the insoluble antiviral compound AVT-538, for which attempts were made to increase the bioavailability of this drug. Co-precipitates of PVP: the drug was prepared using the method of solvent evaporation."

- (PDD 7475, the last 5 lines):

"Co-precipitates of PVP: drug also shows an additional increase in bioavailability when combined with surfactants and acidifiers. Initial results showed that the significant increase in AVT-538 bioavailability can be obtained using techniques of formulation modifying."

That is, Document **D2** describes the use of polyvinylpyrrolidone for preparation of ritonavir formulations with increased bioavailability. Bioavailability can be further improved due to the use of surfactant.

Document **D3** contains the following information:

- (p. 308, the right column, the second paragraph):

The Tg is an important indicator of the stability of the amorphous state and it has been suggested that the Tg should be at least 50°C above the storage temperature to ensure stability over the shelf-life of the product (Yoshioka et al 1995). Therefore, an important part of

«Tg is an important indicator of the amorphous state stability, and it is believed that Tg should be at least more than 50°C higher from the temperature storage to ensure stability during the term of the product storage (Yoshioka et al 1995). ...."

Document **D3** shows that the glassification temperature Tg of solid amorphous compositions should be sufficiently high, at least above 70°C, taking as a starting point the recommended temperature of the storage of drugs at 20°C.

Document **D4** contains the following information:

- (p. 738, the left column, the last sub-paragraph):

Meltrex®-formulations were prepared by melt extrusion. A powder mixture of the drugs (drug compound A: solubility in water 0.007 mg/ml, drug compound B: solubility in water 0.005 mg/ml, total drug load 20.84%), polymer (Kollidon® VA-64, BASF, 72.16%) and 7 % of different Span emulsifiers (sample 1: Span 20; sample 2: Span 40; sample 3: Span 60) was fed into a lab-scale twin-screw extruder (screw diameter: 18 mm). The drug-containing thermoplastic melt was shaped into oblong-type tablets of approx. 950 mg by on-line calendering[2)] between two con-rotating rollers. The calculated

- (p. 739, the left column, the last sub-paragraph – the right column, the first sub-paragraph):

The results show that colloidal solubilization of nearly insoluble drug compounds can be achieved by proper choice of suitable emulsifiers. The HLB value of Span 60 (HLB 4.7) seems to be too low compared to Span 40 (HLB 6.7) or even Span 20 (HLB 8.6). A physical mixture of drug A, drug B, PVP and Span 20 did not produce a colloidal solution in water, whereas a Meltrex® tablet consisting of the same ingredients in the same percent ratio showed self-emulsifying properties in water. This shows that Meltrex® technology can be used successfully for colloidal solubilization of nearly insoluble drug compounds.

Further follows the translation of the above information:

- (p. 738, the left column, the last sub-paragraph):

"Meltrex® formulations were obtained by melt extrusion. The powder mixture of drugs (drug compound A: solubility in water 0.007 mg/ml, drug compound B: solubility in water 0.005 mg/ml, total drug load 20.84%), polymer (Kollidon® V A-64, BASF, 72.16%) and 7% of different Span emulsifiers (sample 1: Span 20, sample 2: Span 40, sample 3: Span 60) were injected into lab-scale twin-screw extruder (screw diameter: 18 mm). The drug-containing thermoplastic melt was shaped into oblong-type tablets of approx. 950 mg by online calendering between two con-rotating rollers. ...."

- (p. 739, the left column, the last sub-paragraph – the right column, the first sub-paragraph):

"The results showed that colloidal solubilization of nearly insoluble drug compounds can be achieved by the proper choice of suitable emulsifiers. The HLB value of Span 60

(hydrophilic-lipophilic balance) *(HLB 4.7) seems to be too low compared to Span 40 (HLB 6.7) or even Span 20 (HLB 8.6). A physical mixture of drug A, drug B, PVP and Span 20 did not produce colloidal solutions in water, whereas a Meltrex® tablet consisting of the same ingredients in the same percent ratio showed self-emulsifiying properties in water. This shows that Meltrex® technology can be used successfully for colloidal solubilization of nearly insoluble drugs."*

Document **D4** shows that solid solutions of nearly insoluble drugs derived by Meltrex® technology, with a total content of drug compounds 20.84% containing polymer (Kollidon® Va-64, BASF, 72.16%, where Kollidon® VA-64 is a water soluble copolymer of N-vinylpyrrolidone and vinyl acetate (60:40) with a Tg nearly 103°C) and 7% emulsifier Span (Span 20, sorbitan monostearate, HLB 8.6; Span 40, sorbitan monopalmitate, HLB 6.7; Span 60, sorbitan monostearate, HLB 4.7) as a carrier.

Document **D5** contains the following information:

- (p. 1058, the left column, the first sub-paragraph):

Abstract □ Although there was a great interest in solid dispersion systems during the past four decades to increase dissolution rate and bioavailability of poorly water-soluble drugs, their commercial use has been very limited, primarily because of manufacturing difficulties and stability problems. Solid dispersions of drugs were generally produced by melt or solvent evaporation methods. The materials, which

- (p. 1062, the right column, the first sub-paragraph):

Because the water-soluble carrier dissolved more rapidly than the drug, drug-rich layers were formed over the surfaces of dissolving plugs, which prevented further dissolution of drug from solid dispersions. The dissolution

- (p. 1063, the left column, the last sub-paragraph):

Bioavailability Enhancement—The reports on the bioavailability enhancement by solid dispersion in surface-active carriers are promising. The human bioavailability

- (p. 1063, the right column, the last sentence of the first sub-paragraph):

350 mg, respectively. The bioavailability of ritonavir (Norvir, Abbott), another poorly soluble HIV protease inhibitor (solubility < 1 μg/mL at pH > 2), was enhanced by formulation as a solid dispersion in a mixture of such surface-active carriers as Gelucire 50/13, polysorbate 80 and polyoxyl 35 castor oil.[84]

Further follows the translation of the above information:

- (p. 1058, the left column, the first sub-paragraph):

"Abstract Although there was a great interest in solid dispersions systems during the past four decades to increase dissolution rate and bioavailability of poorly water-soluble drugs, their commercial use has been very limited, primarily, because of manufacturing

difficulties and stability problems. Solid dispersions of drugs were generally produced from the melt or by solvent evaporation method. ...."

- (p. 1063, the left column, the last sub-paragraph):

"Bioavailability Enhancement – The report on the bioavailability enhancement by solid dispersions in surface-active carriers are promising. ..."

- (p. 1063, the right column, the last sentence, the first sub-paragraph):
- *"...The bioavailability of ritonavir (Norvir, Abbott), another poorly soluble HIV protease inhibitor (solubility <1 μg/ml at pH > 2), was enhanced by its formulation as a solid dispersion in a mixture of such surface active carriers as Gelucire 50/13, polysorbate 80, and polyoxyl 35 castor oil. "'*
-
- From Document **D5** it is known that solid dispersions containing surfactants such as polysorbate 80 and polyoxyl 35 castor oil, enhance the bioavailability of the poorly soluble drugs, including HIV protease inhibitors, such as ritonavir, and such dispersions may be produced from the melt.
-
- Document D6 contains the following information:

- (p. 2649, the left column):

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 A1P deoxycholic acid, and Tweens and Spans. Surfactants have also been added to

Further follows the translation of the above information:

- (p. 2649, the left column): *"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 **solid dispersions** 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 the carrier and a rapid precipitaion process, the drug can 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, as well as Tweens and Spans.*

From Document **D6** it is known that solid dispersions containing polyvinylpyrrolidone (PVP) as a carrier and surfactants such as polyoxyethylene stearate, as well as Tweens and Spans, enhance the bioavailability of poorly water-soluble hydrophobic drugs, and such dispersions can be produced from the melt.

Document **D7** contains the following information:

- (p. 113, the right column, the third sub-paragraph from below):

A number of glass solutions of poorly soluble drugs have been developed using the melt extrusion process with a drug load ranging from 30 to 60% with real time stability up to 9 years. During this time period no crystallization could be

- (p. 113, the right column, the last two sub-paragraphs – p. 114, the left column, the first sub-paragraph):

Glass solutions of a lipophilic drug substance by melt extrusion technology which on dissolution forms nanoparticles and thereby increases the dissolution kinetics have been presented recently [92]. PVP or a vinylpyrrolidone–vinylacetate copolymer have been studied together with different surfactants.

17-Estradiol hemihydrate as a poorly water-soluble drug was improved with respect to its solubility and dissolution rate by melt extrusion. Different compositions of excipients such as PEG 6000, PVP or a vinylpyrrolidone–vinylacetate-copolymer were used as polymers and Sucroester®WE15 or Gelucire® 44/14 as additives. The solid dispersions resulted in a significant increase in dissolution rate when compared to the pure drug or to the physical mixtures. A 30-fold increase in dissolution rate was obtained for a formulation containing 10% 17-Estradiol, 50% PVP and 40% Gelucire™ 44/14. The solid dispersions were then processed into tablets. The improvement in the dissolution behavior was also maintained with the tablets [93].

Further follows the translation of the above information:

- (p. 113, the right column, the third sub-paragraph from below):

"A number of glass solutions of poorly soluble drugs have been developed using the melt extrusion process with a drug load ranging from 30 to 60% with real time stability up to 9 years. ..."

- (p. 113, the right column, the last two sub-paragraphs – p. 114, the left column, the first sub-paragraph):

"Glass solutions of a lipophilic drug substance by melt extrusion technology which on dissolution forms nanoparticles and thereby increases the dissolution kinetics have been presented recently [92]. PVP or vinylpyrrolidone-vinyl acetate copolymer have been studied together with different surfactants.

17-Estradiol hemihydrate as poorly water-soluble drug was improved with respect to its solubility and dissolution rate by melt extrusion. Different compositions of excipients such as PEG 6000, PVP or vinylpyrrolidone-vinyl acetate copolymer were used as polymers and Sucroester®WE15 and for Gelucire® 44/14 as additives. The solid dispersions resulted in a significant increase in dissolution rate compared to the pure drug or to the physical mixtures. A 30-fold increase in dissolution rate was obtained for a formulation containing 10% 17-Estradiol, 50% PVP and 40% Gelucire® 44/14. The solid dispersions were then processed into tablets. The improvement in the dissolution behavior was also maintained with the tablets [93]."

Document **D7** shows that solid glass solutions of lipophilic drugs prepared by melt extrusion, which contain polyvinylpyrrolidone (PVP) or vinylpyrrolidone-vinyl acetate copolymer as the carrier and surfactants such as polyoxyethylene stearate, as well as Tweens and Spans, which enhance the bioavailability of poorly water-soluble hydrophobic drugs, and such dispersions can be produced from the melt.

Document F8 contains the following information:

- (column 5 – column 6):

1. A mechanically stable pharmaceutical presentation for oral administration, comprising one or more active ingredients, at least one melt-processable matrix-forming excipient selected from the group consisting of homo- and copolymers of N-vinylpyrrolidone, acrylate polymers and cellulose derivatives, and more than 10 and up to 40% by weight of a surface-active substance with an HLB of from 2 to 18, which is liquid at 20° C. or has a drop point in the range from 20 to 50° C., obtainable by mixing the starting materials in the melt without addition of solvents and subsequently shaping.

- (column 2, lines 47-50):

Particularly suitable active ingredients are immunosuppressants, protease inhibitors, reverse transcriptase inhibitors, cytostatics or antimycotics, in addition to CNS-active substances or dihydropyrimidine derivatives.

- (column 3, lines 29-37):

Pharmaceutically acceptable polymers are, in particular, homo- and copolymers of N-vinylpyrrolidone such as polyvinylpyrrolidone with Fikentscher K values of from 12 to 100, in particular K 17 to K 30, or copolymers with vinyl carboxylates such as vinyl acetate or vinyl propionate, for example copovidone (VP/VAc-60/40).

Also suitable are polyvinyl alcohol or polyvinyl acetate, which may also be partially hydrolyzed, or acrylate polymers of the Eudragit type.

Further follows the translation of the above information:

- (column 5 – column 6):

"1. A mechanically stable pharmaceutical presentation for oral administration, comprizing one or more active ingredients, at least one melt-processable matrix-forming excipient selected from the group consisting of homo- and copolymers of N-vinylpyrrolidone, acrylate polymers and cellulose derivatives, and more than 10 and up to 40% by weight of a surface-active substance with an HLB of from 2 to 18, which is liquid at 20° C or has a drop point in the range from 20 to 50° C obtainable by mixing the starting materials in the melt without addition of solvent and subsequently shaping."

- (column 2, lines 47-50):

"Particularly suitable active ingredients are immunosuppressants, protease inhibitors, reverse transcriptase inhibitors, cytostatics or antimycotics, in addition to CNS-active substances or dihydropyrimidine derivatives."'

- (column 3, lines 29-37):

"Pharmaceutically acceptable polymers are, in particular, homo- and copolymers of N-vinylpyrrolidone such as polyvinylpyrrolidone with Fikentscher K values of from 12 to 100, in particular K 17 to K 30, or copolymers with vinyl carboxylates such as vinyl acetate or vinyl propionate, for example, copovidone (VP/VAc-60/40).

Also suitable are polyvinyl alcohol or polyvinyl acetate, which can also be partially hydrolyzed, or acrylate polymers of the Eudragit type."'

Document **D8** shows solid compositions (produced from the melt), which may include, in particular, protease inhibitors, water-soluble homo- and copolymers of N-vinylpyrrolidone, acrylate polymers and cellulose derivatives, and more than 10 to 40% by weight of surfactant with HLB from 2 to 18, which is obtained by mixing the starting materials in the melt without adding of solvent and subsequent formation.

Thus, at the priority date, according to the results found in patent research materials, a pharmacy specialist has learnt:

- solid pharmaceutical dispersion dosage form containing surfactant and HIV protease inhibitor (ritonavir) dispersed in a water-soluble polymer, the content of which is 70 to 90 wt.% and which have a high Tg **(D1).** Dispersion dosage form may additionally comprise a compound AVT-378 ((2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-(2S-(1-tetrahydropyrimide-2-onyl)-3-methylbutanoil)amino-1,6-difenylhexan), also known as lopinavir;

- In addition, Document **D1** shows the method of preparation of the specified in the preceding sub-paragraph solid pharmaceutical dispersion dosage form, which involves melting the components with subsequent hardening to form a dispersion;

- Document **D2** shows of the use of polyvinylpyrrolidone for obtaining formulations of ritonavir with enhanced bioavailability where bioavailability can be further enhanced through the use of a surfactant;

- Document **D3** shows that the glassification temperature Tg of solid amorphous compositions should be sufficiently high, at least above 70° C, taking as a starting point the recommended temperature of the storage of medicines at 20°C;

- Document **D4** shows that solid solutions of nearly insoluble drugs derived by Meltrex® technology, with a total content of drug compounds 20.84% containing polymer (Kollidon® Va-64, BASF, 72.16%, where Kollidon® VA-64 is a water soluble copolymer of N-vinylpyrrolidone and vinyl acetate (60:40) with a Tg nearly 103°C) and 7% emulsifier Span (Span 20, sorbitan monostearate, HLB 8.6; Span 40, sorbitan monopalmitate, HLB 6.7; Span 60, sorbitan monostearate, HLB 4.7) as a carrier.

- Document **D5** shows that solid dispersions containing surfactants such as polysorbate 80 and polyoxyl 35 castor oil enhance the bioavailability of poorly soluble drugs, including HIV protease inhibitors, such as ritonavir, and such dispersions may be produced from melt;

- Document **D6** shows that solid dispersions containing polyvinylpyrrolidone (PVP) as a carrier and surfactants such as polyoxyethylene stearate, as well as Tweens and Spans, enhance the bioavailability of poorly water-soluble hydrophobic drugs, and such dispersions can be produced from the melt;

- Document **D7** shows that solid glass solutions of lipophilic drugs prepared by the melt extrusion, which contain polyvinylpyrrolidone (PVP) or vinylpyrrodilone-vinyl acetate copolymer as the carrier and surfactants such as polyoxyethylene stearate, as well as Tweens and Spans, which enhance the bioavailability of poorly water-soluble hydrophobic drugs, and such dispersions can be produced from the melt;

- Document **F8** shows solid compositions (produced from the melt), which may include, in particular, protease inhibitors, water-soluble homo- and copolymers of N-vinylpyrrolidone, acrylate polymers and cellulose derivatives, and more than 10 to 40% by weight of surfactant with HLB from 2 to 18, which is obtained by mixing the starting materials in the melt without adding of the solvent and subsequent formation.

Therefore, taking into account the fact that:

- The presented document **(D1)** describes a solid pharmaceutical dosage form comprising a solid dispersion of at least one HIV protease inhibitor in at least one pharmaceutically acceptable water-soluble polymer, and at least one pharmaceutically acceptable surfactant, at that, the specified HIV protease inhibitor represents ritonavir, and, at that, each of these pharmaceutically acceptable water-soluble polymers has a Tg of at least about 50°C and the specified dosage form comprises from about 50 to about 85% by weight of the entire dosage form of the specified pharmaceutically acceptable water-soluble polymer from claim 1 of the patent of Ukraine for the invention No. 85564, as well as the fact that it describes a process for the preparation of solid pharmaceutical dosage form comprising the preparation of a melt containing at least one HIV protease inhibitor, at least one pharmaceutically acceptable water-soluble polymer, and at least one pharmaceutically acceptable surfactant; and leaving the melt for hardening to obtain a solid dispersion product from claim 17 of the patent of Ukraine for the invention No. 85564, these objects of the invention by the independent claims 1 and 17 of the patent of Ukraine for the invention No.

85564 does not meet the requirements of patentability "novelty", as they are part of the prior art **(D1),** and they do not meet the requirements of patentability "inventive step";

- None of the cited documents for prior art **(D1-D8)** describes cumulative features under the independent claims 19 and 26 of the patent of Ukraine for the invention No. 85564, and therefore, the invention objects for the independent claims 19 and 26 of the patent of Ukraine for the invention No. 85564 meet the patentability requirement "novelty";

- In addition, taking into account the fact that the documents on prior art show the use of solid pharmaceutical dosage forms **(D4-D8)** of poorly soluble drugs **(D5-D7),** such as ritonavir **(D1, D2, D5)** and lopinavir **(D1)** in form of dispersion **(D1, D5, D6)** to enhance their bioavailability, that contain water-soluble polymers such as polyvinylpyrrolidone and vinylpyrrolidone-vinyl acetate copolymers **(D4, D7)** in an amount in the range from 50 to 85 wt.% **(D1, D4)** having a glassification temperature Tg above 50□C (**D3, D4),** and additionally contain at least one surfactant that must enhance the bioavailability of poorly soluble substances present in the solid pharmaceutical dosage form by improving their solubility **(D1, D2, D4-D8),** the content of which is in the range of 2 to 20 wt.% **(F4, F8)** with HLB (hydrophilic-lipophilic balance) ranging from 4 to 10 **(D4, D7, D8),** solid pharmaceutical dosage form comprising a solid dispersion of ritonavir and lopinavir in at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant, at that, pharmaceutically acceptable water-soluble polymer has a Tg of at least about 50 °C, and is present in an amount from about 50 to about 85% by weight relative to the mass of the dosage form, and the specified pharmaceutically acceptable surfactant with HLB value from about 4 to about 10 and is present in an amount from about 2 to about 20% by weight relative to the mass of the dosage form under an independent claim 19 of the patent of Ukraine for invention No. 85564 does not meet the requirements of patentability "inventory level", because it is obvious for this field specialist and explicitly follows the prior art.

In particular, the ordinary pharmaceutical specialist solving the problem of enhancement the oral bioavailability of poorly soluble HIV protease inhibitors, such as ritonavir and lopinavir **(D1),** without hesitation and any inventiveness, taking into account only the documents on prior art would suggest to replace the poorly soluble compounds used in the solid solution obtained by Meltrex® technology **(D4),** with the poorly soluble HIV protease inhibitors, such as ritonavir and lopinavir **(D1)** with obtaining a solid pharmaceutical dosage form under an independent claim 19 of the patent of Ukraine for the invention No. 85564. That is, the object of the invention under claim 19 of the patent of Ukraine for the invention No. 85564 was produced by replacement of some part(s) of the known medium by another known part(s) to achieve the technical result for which it was established the influence of exactly such a replacement;

- In addition, taking into account the fact that the prior art documents show the use of solid pharmaceutical dosage forms **(D4-D8)** of poorly soluble drugs **(D5-D7)** content of which is in the range of 10 to 30 wt.% **(D1, D4),** such as ritonavir **(D1, D2, D5)** and lopinavir **(D1)** to enhance their bioavailability, that contain water-soluble polymers such as polyvinylpyrrolidone and vinylpyrrolidone and vinyl acetate copolymers as a carrier**(D4, D7)** in an amount in the range of 50 to 85 wt.% **(D1, D4)** with a glassification temperature Tg above 50□C **(D3, D4)**, and additionally contain at least one surfactant that must enhance the bioavailability of poorly soluble substances present in the solid pharmaceutical dosage form by improving their solubility **(D1, D2, D4-F8)**, the content of which is in the range of 2 to 20 wt.% **(F4, F8)** with HLB (hydrophilic-lipophilic balance) ranging from 4 to 10 **(F4, F7, F8)**, and which, for example, is sorbitan fatty acid ester such as Span (Span 20 sorbitan monostearate, HLB 8.6; Span 40, sorbitan monopalmitate, HLB 6.7; Span 60, sorbitan monostearate, HLB 4.7) **(D4, D6, D7)** solid pharmaceutical dosage form comprising glass solution or solid solution of lopinavir and ritonavir in the matrix containing sorbitan fatty acid

ester and N-vinylpyrrolidone and vinyl acetate copolymer, where indicated ritonavir and lopinavir present in an amount of from 5 to about 30% by weight relative to the weight of the dosage form, specified copolymer is present in an amount of from 50 to about 85% by weight relative to weight of the dosage form, and specified sorbitan fatty acid ester presented in an amount of from 2 to about 20% by weight relative to weight of the dosage form under an independent claim 26 of the patent of Ukraine for invention No. 85564 does not meet the requirements of patentability "inventory level", because it is obvious to a specialist in this field of art and explicitly follows the prior art.

In particular, the ordinary pharmaceutical specialist solving the problem of enhancement the oral bioavailability of poorly soluble HIV protease inhibitors, such as ritonavir and lopinavir **(D1)** without hesitation and any inventiveness, taking into account only the documents on prior art would suggest to replace the poorly soluble compounds used in the solid solution obtained by Meltrex® technology **(D4),** with the poorly soluble HIV protease inhibitors, such as ritonavir and lopinavir **(D1)** with obtaining a solid pharmaceutical dosage form under an independent claim 19 of the patent of Ukraine for the invention No. 85564. That is, the object of the invention under claim 26 of the patent of Ukraine for the invention No. 85564 was produced by replacement of some part(s) of the known medium by another known part(s) to achieve the technical result for which it was established the influence of exactly such a replacement;

Based on the above, it is obvious that solid pharmaceutical dosage form under claim 1 of the patent of Ukraine No. 85564 for invention and the manner of its preparation according to claim 17 of the patent of Ukraine No. 85564 for invention have neither novelty nor inventive step, while solid pharmaceutical dosage forms under claims 19 and 26 of the patent of Ukraine No. 85564 for invention are new, but they have no inventive step.

Information described in the patent of Ukraine No. 85564 for invention gives no reason for ordinary pharmaceutical specialist to call into question the repeatability and ability to use in industry the objects of invention under the patent of Ukraine No. 85564 for invention, because the invention under claims 1, 17, 19, and 26 of the patent of Ukraine No. 85564 for invention meet the patentability requirement "industrial applicability".

Therefore, according to the stated above, the following conclusions regarding the patentability of the patent of Ukraine No. 85564 for invention, concerning the solid pharmaceutical dosage form containing HIV protease inhibitor, and method of its preparation, namely:

1. The objects of invention under claims 1 and 17 of the patent of Ukraine No. 85564 for invention do not meet the patentability requirements "novelty" and "inventive step" and meet the patentability requirement "industrial applicability", and objects of the invention under claims 19 and 26 meet the patentability requirements "novelty" and "industrial applicability", and do not meet the patentability requirement "inventive step".

_____. _____ V. M. Otsaliuk

30 January 2017

To: **Commercial Court of the City of Kyiv**

44-B B. Khmelnytskoho Str., the City of Kyiv, 01030

Plaintiff: **Charitable organisation "All-Ukrainian Network of People Living with HIV / AIDS"**

Correspondence address:
52, B. Khmelnytskoho Str., the City of Kyiv, AEQUO LLC,
6th Floor (BC Vector)
tel. + 38044 233 6599, fax + 38044 237 7769

Defendant-1: **The State Intellectual Property Service of Ukraine**

Defendant-2: **AbbVie Inc.**
.

Case No.: **910/10050/16**
Judge: **O. V. Marchenko**

MOTION
for Admission of Evidence

1. The The Commercial Court of the city of Kyiv is considering the case No. 910/10050/16 under the claim of the Charitable organisation "All-Ukrainian Network of People Living with HIV/AIDS" (hereinafter also referred to as the "**Plaintiff**") against the State Intellectual Property Service of Ukraine (hereinafter also referred to as the "**Defendant-1"**) and AbbVie Inc. (hereinafter also referred to as the "**Defendant-2**"). One of the Plaintiff's claims in this case is the invalidation of the patent of Ukraine No. 85564 for invention "*Solid Pharmaceutical Dosage Form For Inhibitors Of HIV Protease And Method For Manufacture Thereof*" (hereinafter also referred to as the "**Invention**").

2. The necessity to satisfy the Plaintiff's claim is justified by non-compliance of the Invention with the patentability criteria "novelty" and "inventive level".

3. The Plaintiff attached an Expert Opinion conducted by a patent attorney of Ukraine V. M. Otsaliuk dated 29.12.2015, which is based on the results of the examination of patentability requirements of the invention under the patent of Ukraine No. 85564 (hereinafter referred to as the "**Expert Opinion**"), to the statement of claim *(a copy of the Report is attached to the statement of claim in this case in Annex 4*). According to this Report, "***Obviously, the solid pharmaceutical dosage form of claim 1 of patent***

of Ukraine No. 85564 for the invention and the method of production thereof of claim of 17 of patent of Ukraine No. 85564 for the invention have neither novelty, nor inventive step, while solid pharmaceutical dosage forms of claims 19 and 26 of patent of Ukraine No. 85564 for the invention are new, but have no inventive step" (page 25 of the Expert Opinion).

4. According to page 10 of the Expert Opinion, the expert analysed the following eight documents while preparing it:

Number	***Document***	***Date of Publication***
D1	WO 01/34119 (International Application published according to Patent Cooperation Treaty No. WO 01/34119)	17/05/2001
D2	L. Dias et al., "Physical and Oral Dog Bioavailability Evaluation of ABT-538:PVP Co-Precipitates", *Pharmaceutical Research* (1996), Vol. 13, no. 9 suppl., pp. 351	September, 1996
D3	A. Forster et al., "Characterization of glass solutions of poorly water-soluble drugs produced by melt extrusion with hydrophilic amorphous polymers", *Journal of Pharmacy and Pharmacology*, 2001, 53: 303-315	2001
D4	J. Rosenberg et al., "Meltrex®-Formulations Containing Solid Solutions of Nearly Insoluble Drugs: Formation of Nanoparticles on Dissolution in Water", *28th Int. Symp. on Controlled Release of Bioactive Materials and 4th Consumer & Diversified Products Conference* (2001), Vol. 1, pp. 738-739	2001
D5	Abu T.M. Serajuddin, "Solid Dispersion of Poorly Water-Soluble Drugs: Early Promises, Subsequent Problems, and Recent Breakthroughs", *Journal of Pharmaceutical Sciences,* vol. 88, No. 10, October 1999, pages 1058-1066	October 1999
D6	O.I. Corrigan, "Surfactants in Pharmaceutical Products and Systems", *Encyclopedia of Pharmaceutical Technology*, vol. 14, 2002, pages 2639-2653	2002
D7	J. Breitenbach, "Melt extrusion: from process to drug delivery technology", *European Journal of Pharmaceutics and Biopharmaceutics,* vol. 54, (2002), pages 107-117	2002
D8	US6599528 (patent of the USA No. US6599528)	29/07/2003

5. Since the claims in case No. 910/10050/16, refer to invalidation of the patent of Ukraine No. 85564 for the invention due to the non-compliance with patentability requirements such as "novelty" and "inventive level", the circumstances thereof are to be proven in this case. Documents D1 - D8 (*copies with translation are provided in Annexes 1 - 8*), based on which the Expert Opinion is made, contain data on such circumstances and thus should be admitted as written evidence to materials of the case No. 910/10050/16.

6. Furthermore, the patent attorney of Ukraine V. M. Otsalyuk analysed additional documents and concluded the results in an Additional Expert Report dated 25.11.2016

regarding the compliance of the invention under patent of Ukraine No. 85564 "*Solid Pharmaceutical Dosage Form For Inhibitors Of HIV Protease And Method For Manufacture Thereof*" with the patentability requirements (hereinafter also referred to as the "**Additional Expert opinion**", a *copy of which is provided in Annex 9*).

7. According to the Additional Expert opinion, "***a Group of inventions under the patent of Ukraine No. 85564 for invention " Solid Pharmaceutical Dosage Form For Inhibitors Of HIV Protease And Method For Manufacture Thereof" does not comply with the patentability requirements "inventive level"*** *(page 21 of the Additional Expert Opinion)* ***based on the materials provided for the examination and considering the previously reviewed materials.***

8. Thus, the Additional Expert Opinion confirmed the non-compliance of the Invention under the patent of Ukraine No. 85564 with the patentability requirement "novelty" and "inventive level" as of the claimed priority date.

9. As stated on page 1 of the Expert Opinion, for its preparation, two additional documents were analysed: (*copies with translation are provided in Annexces 10 and 11*):

Number	Document
D9	R. Witteler et. al., «Chemistry and physicochemical properties of Povidone» BASF ExAct, no. 2, July 1999, pp. 1-8.
D10	C. Leuner et al., «Improving drug solubility for oral delivery using solid dispersions», European Journal of Pharmaceutics and Biopharmaceutics, vol. 50 (2000), pages 47-60.

10. Since the claims in case No. 910/10050/16, refer to invalidation of the patent of Ukraine No. 85564 for an invention due to the non-compliance with patentability requirements such as "novelty" and "inventive level", the circumstances thereof are to be proven in this case. The Additional Expert Opinion and documents D9 and D10 contain data on such circumstances and thus should be admitted as written evidence to the materials of the case No. 910/10050/16.

Taking into account the above, being guided by Articles 22, 32, 36 of the Commercial Procedural Code of Ukraine,

I hereby request :

To admit the following documents into the case No. 910/10050/16 file:

1. Certified copy of the International Application published according to Patent Cooperation Treaty No. WO 01/34119 and its translation into Ukrainian.
2. Certified copy of the publication "L. Dias et al., "Physical and Oral Dog Bioavailability Evaluation of ABT-538:PVP Co-Precipitates", *Pharmaceutical Research* (1996), Vol. 13, no. 9 suppl., pp. 351" and its translation into Ukrainian.
3. Certified copy of the publication "A. Forster et al., "Characterization of glass solutions

of poorly water-soluble drugs produced by melt extrusion with hydrophilic amorphous polymers", *Journal of Pharmacy and Pharmacology*, 2001, 53: 303-315" and its translation into Ukrainian.

4. Certified copy of the publication "J. Rosenberg et al., "Meltrex®-Formulations Containing Solid Solutions of Nearly Insoluble Drugs: Formation of Nanoparticles on Dissolution in Water", *28th Int. Symp. on Controlled Release of Bioactive Materials and 4th Consumer & Diversified Products Conference* (2001), Vol. 1, pp. 738-739" and its translation into Ukrainian.
5. Certified copy of the publication "Abu T. M. Serajuddin, "Solid Dispersion of Poorly Water-Soluble Drugs: Early Promises, Subsequent Problems, and Recent Breakthroughs", *Journal of Pharmaceutical Sciences,* vol. 88, No. 10, October 1999, pages 1058-1066" and its translation into Ukrainian.
6. Certified copy of the publication "O. I. Corrigan, "Surfactants in Pharmaceutical Products and Systems", *Encyclopedia of Pharmaceutical Technology*, vol. 14, 2002, pages 2639-2653" and its translation into Ukrainian.
7. Certified copy of the publication "J. Breitenbach, "Melt extrusion: from process to drug delivery technology", *European Journal of Pharmaceutics and Biopharmaceutics,* vol. 54, (2002), pages 107-117" and its translation into Ukrainian.
8. Certified copy of the data on patent of the United States of America No US6599528 and its translation into Ukrainian.
9. Certified copy of the Additional Expert Report dated 25.11.2016 regarding the compliance of the invention under patent of Ukraine No. 85564 "Solid Pharmaceutical Dosage Form For Inhibitors Of HIV Protease And Method For Manufacture Thereof" with the patentability requirements
10. Certified copy of the publication of R. Witteler et. al., "Chemistry and physicochemical properties of Povidone" BASF ExAct, no. 2, July 1999, pp. 1-8, and its translation into Ukrainian.
11. Certified copy of the publication of C. Leuner et al., "Improving drug solubility for oral delivery using solid dispersions", European Journal of Pharmaceutics and Biopharmaceutics, vol. 50 (2000), pages 47-60, and its translation into Ukrainian.

Annexes:

1. Certified copy of the International Application published according to Patent Cooperation Treaty No. WO 01/34119 and its translation into Ukrainian.
2. Certified copy of the publication "L. Dias et al., "Physical and Oral Dog Bioavailability Evaluation of ABT-538:PVP Co-Precipitates", *Pharmaceutical Research* (1996), Vol. 13, no. 9 suppl., pp. 351" and its translation into Ukrainian.
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Representative of Charitable Organisation
"All-Ukrainian Network of People Living with HIV / AIDS"
acting under the PoA [*signature*] N. O. Dryuk
(a copy of the PoA contains in the case file)