A SOLID PHARMACEUTICAL DOSAGE FORMULATION

Field of the Invention

The present invention relates to a pharmaceutical dosage formulation, and more particularly, relates to a pharmaceutical dosage formulation comprising an HIV protease inhibitor.

Background of the Invention

Millions of people around the world are suffering from HIV/AIDS, and millions more are likely to become infected each year. Many medications are currently available for the treatment of HIV/AIDS including HIV protease inhibitors (PI's), nucleoside/nucleotide reverse transcriptase inhibitors (NRTI's) and non-nucleoside reverse transcriptase inhibitors (NNRTI's). Most current treatment regimens require a combination of at least three medications, most commonly two NRTI's and either a PI or a NNRTI.

PI's are poorly soluble and are very difficult to formulate. Originally, PI's were provided as liquid formulations in which the PI component was dissolved. Currently, the most widely used PI dosage forms are gelatin capsules containing a fill solution in which the active ingredient is dissolved. The fill solutions required to dissolve the PI often contain excipients that cause discomfort or irritate the gastrointestinal system. Furthermore, only a limited amount of the PI can be dissolved in these dosage forms which therefore limits the amount of the PI loaded in each gelatin capsule.

In order to obtain the necessary dose of an individual PI, a patient must take several gelatin capsules at any given dosing period, which is repeated several times in a day. As mentioned above, therapy for HIV patients includes multiple medications that commonly includes a PI. Moreover, these patients often times require additional medications such as antibiotics and lipid lowering agents to control opportunistic infections and other diseases or conditions they may be afflicted with. Consequently, these patients can take an extraordinary number of medications in a variety of different dosage forms over the course of a given day.

Such treatment regimens are further complicated by the fact that some of the dosage forms (including some PI's) require refrigerated storage conditions to prevent degradation of

the active ingredients. For subjects residing in economically challenged or developing countries where refrigerators are not as common in households, such storage conditions represent a particularly challenging dilemma.

It has also been observed that upon administration of a PI from gelatin capsules there is variability in the blood levels of the active ingredient from subject to subject and even within the same subject. That is, some patients receiving treatment can have very high or very low blood levels of the PL In turn, this can lead to unwanted adverse events in those patients experiencing high blood levels of the drug or rendering the treatment less effective or ineffective in those patients experiencing low blood levels of the drug.

In order to increase the bioavailability of PI's it is recommended that patients take the gelatin capsule formulation following a meal to increase the overall bioavailability of the active ingredient. Bioavailability can further vary depending on fat content in each meal. Unfortunately, many patients do not always adhere to this routine due to the complexity of their treatment regimens or otherwise. Often patients will take the medication on an empty stomach that leads to low bioavailability of the drug, and perhaps ineffective treatment.

Therefore, it is desirable to have a PI dosage form that reduces or eliminates gastrointestinal adverse events. It is also desirable to have such a dosage form that can be loaded with more active ingredient to reduce the pill burden on patients. Furthermore, it is desirable to have a dosage form that provides little variability in the blood levels of the PI within a subject and throughout a patient population. Another desirable feature would be a dosage form that provides similar blood levels of a PI regardless of whether or not a patient takes the medication following a meal. Yet another desirable feature would be a dosage form that does not have to be refrigerated to prevent degradation of the PI.

Summary of the Invention

Surprisingly, it has been discovered that by formulating an undissolved form of a PI (in particular lopinavir and a lopinavir/ritonavir combination) in a pharmaceutical dosage form, all of the aforementioned disadvantages associated with dosage forms containing a dissolved PI can be overcome. In particular, pharmaceutical dosage forms containing the undissolved PI reduce pill burdens on HIV patients, in large measure because the drug load in these formulations can be increased. Additionally, such formulations can be stored at room temperature and do not require refrigeration. Moreover, these formulations provide a more

consistent blood level of the PI among patients taking such therapy which helps insure an effective therapeutic benefit and less adverse events. Further, these consistent blood levels can be achieved with the formulation provided herein without regard to whether or not the patient has eaten or what type of meal was eaten. It is believed that this is the first time that an undissolved form of lopinavir has been formulated in a solid dosage form. Given the advantages attendant to such formulation, this represents the next breakthrough in HIV therapy which will help ease the complicated treatment regimens currently prescribed for HIV patients.

In the Drawings

In the drawings,

Figure 1 shows Box (lower and upper quartiles) and Whiskers (5^{th} and 95^{th} percentiles) Plots for Lopinavir AUC Under Various Meal Conditions; and

Figure 2 shows Box (lower and upper quartiles) and Whiskers (5^{th} and 95^{th} percentiles) Plots for Lopinavir Cmax Under Various Meal Conditions.

Detailed Description of the Invention

Definitions

The term "AUC∞" is the area under the concentration time curve (AUC) extrapolated to infinity or the AUC to the last measured time point + (last measured concentration/elimination rate constant).

The term "Cmax" is defined as the observed maximum plasma concentration of an active ingredient.

"Pharmaceutically acceptable" as used herein means moieties or compounds mat are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio.

The term "weight percent" or "percent by weight" or "wt %" is defined as the weight of the individual component in the formulation divided by the total weight of all components of the formulation and then multiplied by 100. In some cases where a formulation has an outer coating, then weight of the coating can either be included or excluded in the total weight.

The phrase "fasting/fasted state or condition" generally is defined as 10 hours of abstinence from eating prior to dosing and 4 hours post-dosing, although those skilled in the art will recognize various other timings that would also qualify as a fasting or fasted state.

The phrase "moderate-fat meal condition" is defined as receiving a meal that is approximately 500-600 KCal wherein 20-30% of the calories are from fat served approximately 30 minutes prior to dosing.

The phrase "high-fat meal condition" is defined as receiving a meal that is approximately 1000 Kcal wherein 50-55% of the calories are from fat served approximately 30 minutes prior to dosing and is used herein to refer to a "fed state" although those skilled in the art will recognize various meal conditions that would also qualify as a fed state.

The term "solid solution" is defined as a system in a solid state wherein the drug is molecularly dispersed throughout a matrix such that the system is chemically and physically uniform or homogenous throughout.

The term "solid dispersion" is defined as a system having small particles, typically of less than 400 um in size, more typically less than 100 μm in size, and most typically less than 10 fun in size, of one phase dispersed in another phase (the carrier phase).

Suitable PI's for use in accordance with the present invention include but are not limited to (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-3hydroxyhexane (ritonavir); (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]-amino-1,6-diphenylhexane (ABT-378; lopinavir); 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-4t-butylamide; 5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-tbutylamide; [1S-[1R-(R-),2S*])-N[1] [3-[[[(1,1-dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide; amprenavir (VX-478); DMP-323; DMP-

450; AG1343 (nelfinavir); atazanavir (BMS 232,632); tipranavir; palinavir; TMC-114; RO033-4649; fosamprenavir (GW433908); P-1946; BMS 186,318; SC-55389a; BILA 1096 BS; and U-140690, or any combinations thereof, whether used for PI activity or otherwise, such as with the case of ritonavir that can sometimes be employed as a cytochrome P450 monooxygenase inhibitor (variously referred to as a "pK booster). Preferred PIs are lopinavir and ritonavir alone, or in combination.

Generally, dosage forms of the present invention will comprise a therapeutically effective amount of at least one PL The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and other factors known to those of ordinary skill in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. Typically, however, a pharmaceutical dosage form of the present invention will comprise from about 5 to about 30 % by weight of the total dosage form, preferably from about 10 to about 25 % by weight of the total dosage form, of an HIV protease inhibitor or a combination of HIV protease inhibitors. Preferably, the dosage form will contain between about 10 mg to about 1500 mg of a PL Most preferably, the dosage form will comprise lopinavir and ritonavir in a ratio of about 4:1 respectively. The preferred dose of lopinavir and ritonavir is 400 mg and 100 mg respectively which can be divided evenly between multiple dosage forms, preferably two. It will be understood that multiple doses, typically two, can be given in a given day.

Pharmaceutical dosage forms provided herein generally will comprise an "undissolved" PL In contradistinction to existing gelatin capsules filled with a PI dissolved in a solvent, undissolved PI's as used herein means that the PI is in a solid form and not dissolved in a liquid carrier in its final dosage form. Solid forms of a PI may include, for example, crystalline, micronized crystalline, crystalline nanoparticulates, amorphous, micronized amorphous, amorphous nanoparticulates, or preferably amorphous solid forms of a PI.

Many pharmaceutical dosage forms are acceptable for use in accordance with the present invention; the choice of which is well within the skill of a person of ordinary skill in this art based upon the properties of the dosage forms provided herein. For example, orally administered solid dosage forms include but are not limited to capsules, dragees, granules, pills, powders, and tablets. Excipients commonly used to formulate such dosage forms include encapsulating materials or formulation additives such as absorption accelerators, antioxidants, binders, buffers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, and mixtures thereof. Excipients for orally administered compounds in solid dosage forms include agar, alginic acid, aluminum hydroxide, benzyl benzoate, 1,3-butylene glycol, castor oil, cellulose, cellulose acetate, cocoa butter, corn starch, corn oil, cottonseed oil, ethanol, ethyl acetate, ethyl carbonate, ethyl cellulose, ethyl laureate, ethyl oleate, gelatin, germ oil, glucose, glycerol, groundnut oil, isopropanol, isotonic saline, lactose, magnesium hydroxide, magnesium stearate, malt, olive oil, peanut oil, potassium phosphate salts, potato starch, propylene glycol, talc, tragacanth, water, safflower oil, sesame oil, sodium carboxymethyl cellulose, sodium lauryl sulfate, sodium phosphate salts, soybean oil, sucrose, tetrahydrofurfuryl alcohol, and mixtures thereof.

A preferred dosage form, will generally comprise at least one HIV protease inhibitor in a therapeutically effective amount, at least one phannaceutically acceptable water-soluble polymer and at least one phannaceutically acceptable surfactant.

More preferably, a solid solution or solid dispersion can be formed into one of the above pharmaceutical dosage forms. Such solutions or dispersions can be manufactured with suitable pharmaceutically acceptable water-soluble polymers including but not limited to water-soluble polymers having a Tg of at least about 50 °C, preferably at least about 60°C, most preferred from about 80 °C to about 180 °C. Methods for determining Tg values of the organic polymers are described in "Introduction to Physical Polymer Science", 2nd Edition by L.H. Sperling, published by John Wiley & Sons, Inc., 1992. The Tg value can be calculated as the weighted sum of the Tg values for homopolymers derived from each of the individual monomers, i.e., that make up the polymer: Tg = S Wi Xj where W is the weight percent of monomer i in the organic polymer, and X is the Tg value for the homopolymer derived from monomer L Tg values for the homopolymers may be taken from "Polymer

Handbook", 2nd Edition by J. Brandrup and E.H. Immergut, Editors, published by John Wiley & Sons, Inc., 1975.

Water-soluble polymers having a Tg as defined above allow for the preparation of solid solutions or solid dispersions that are mechanically stable and, within ordinary temperature ranges, sufficiently temperature stable so that the solid solutions or solid dispersions may be used as dosage forms without further processing or be compacted to tablets with only a small amount of tableting aids.

The water-soluble polymer comprised in the preferred dosage form is a polymer that preferably has an apparent viscosity, when dissolved at 20 °C in an aqueous solution at 2 % (w/v), of about 1 to about 5000 mPa.s., and more preferably of about 1 to about 700 mPa.s, and most preferred of about 5 to about 100 mPa.s.

Water-soluble polymers suitable for use in the preferred dosage form of the present invention include but are not limited to homopolymers and copolymers of N-vinyl lactams, especially homopolymers and copolymers of N-vinyl pyrrolidone, e.g. polyvinylpyrrolidone (PVP), copolymers of N-vinyl pyrrolidone and vinyl acetate or vinyl propionate, cellulose esters and cellulose ethers, in particular methylcellulose and ethylcellulose, hydroxyalkylcelluloses, in particular hydroxypropylcellulose, hydroxyalkylalkylcelluloses, in particular hydroxypropylmethylcellulose, cellulose phthalates or succinates, in particular cellulose acetate phthalate and hydroxypropyhnethylcellulose phthalate, hydroxypropyhnethylcellulose succinate or hydroxypropyhnethylcellulose acetate succinate; high molecular polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide, polyacrylates and polymethacrylates such as methacrylic acid/ethyl acrylate copolymers, methacrylic acid/methyl methacrylate copolymers, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymers, poly(hydroxyalkyl acrylates), poly(hydroxyalkyl methacrylates), polyacrylamides, vinyl acetate polymers such as copolymers of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate (also referred to as partially saponified "polyvinyl alcohol"), polyvinyl alcohol, oligo- and polysaccharides such as carrageenans, galactomannans and xanthan gum, or mixtures of one or more thereof.

Of these, homopolymers or copolymers of N-vinyl pyrrolidone, in particular a copolymer of N-vinyl pyrrolidone and vinyl acetate, are preferred. A particularly preferred

polymer is a copolymer of about 60 % by weight of the copolymer, N-vinyl pyrrolidone and about 40 % by weight of the copolymer, vinyl acetate.

According to the preferred dosage form of the present invention, the pharmaceutical dosage form comprises from about 50 to about 85 % by weight of the total dosage form, preferably from about 60 to about 80 % by weight of the total dosage form, of a water-soluble polymer or any combination of such polymers.

The term "pharmaceutically acceptable surfactant" as used herein refers to a pharmaceutically acceptable non-ionic surfactant. In one embodiment, the present invention provides a dosage form comprising at least one surfactant having an hydrophilic lipophilic balance (HLB) value of from about 4 to about 10, preferably from about 7 to about 9. The HUB system (Fiedler, H.B., Encylopedia of Excipients, 5th ed., Aulendorf: ECV-Editio-Cantor-Verlag (2002)) attributes numeric values to surfactants, with lipophilic substances receiving lower HLB values and hydrophilic substances receiving higher HLB values.

Surfactants having an HLB value of from about 4 to about 10 suitable for use in the present invention include but are not limited to polyoxyethylene alkyl ethers, e.g. polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether; polyoxyethylene alkylaryl ethers, e.g. polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether; polyethylene glycol fatty acid esters, e.g. PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate; alkylene glycol fatty acid mono esters, e.g. propylene glycol monolaurate (Lauroglycol®); sucrose fatty acid esters, e.g. sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate; or sorbitan fatty acid mono esters such as sorbitan mono laurate (Span® 20), sorbitan monooleate, sorbitan monopalmitate (Span® 40), or sorbitan stearate, or mixtures of one or more thereof.

The sorbitan mono fatty acid esters are preferred, with sorbitan mono laurate and sorbitan monopalmitate being particularly preferred.

A preferred dosage form of the present invention comprises from about 2 to about 20 % by weight of the total dosage form, preferably from about 3 to about 15 % by weight of the total dosage form, of the surfactant or combination of surfactants.

Besides the surfactant having an HLB value of from about 4 to about 10, the preferred dosage form may comprise additional pharmaceutically acceptable surfactants such as

polyoxyethylene castor oil derivates, e.g. polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor® EL; BASF Corp.) or polyoxyethyleneglycerol oxystearate such as polyethylenglycol 40 hydrogenated castor oil (Cremophor® RH 40) or polyethylenglycol 60 hydrogenated castor oil (Cremophor® RH 60); or block copolymers of ethylene oxide and propylene oxide, also known as polyoxyethylene polyoxypropylene block copolymers or polyoxyethylene polypropyleneglycol, such as Poloxamer® 124, Poloxamer® 188, Poloxamer® 237, Poloxamer® 388, Poloxamer® 407 (BASF Wyandotte Corp.); or a mono fatty acid ester of polyoxyethylene (20) sorbitan, e.g. polyoxyethylene (20) sorbitan monooleate (Tween® 80), polyoxyethylene (20) sorbitan monostearate (Tween® 60), polyoxyethylene (20) sorbitan monopalmitate (Tween® 40), polyoxyethylene (20) sorbitan monolaurate (Tween® 20).

Where such additional surfactants are used, the surfactant having an HLB value of from about 4 to about 10 generally accounts for at least about 50 % by weight, preferably at least about 60 % by weight, of the total amount of surfactant used.

The dosage form of the present invention can include additional excipients or additives such as, for example, flow regulators, lubricants, bulking agents (fillers) and disintegrants. Such additional excipients may comprise from about 0 to about 15 % by weight of the total dosage form.

The preferred solid dispersion or solid solution based dosage form of the present invention can be produced by preparing a solid solution or solid dispersion of the HIV protease inhibitor, or the combination of HIV protease inhibitors, in a matrix of a water-soluble polymer and a surfactant, and then shaping into the required tablet form. Alternatively, the solid solution or solid dispersion product can be subdivided to granules, e.g. by grinding or milling, and the granules may subsequently be compacted to tablets.

Various techniques exist for preparing solid solutions or solid dispersions including melt-extrusion, spray-drying and solution-evaporation with melt-extrusion being preferred.

The melt-extrusion process comprises the steps of preparing a homogeneous melt of the HIV protease inhibitor or the combination of HIV protease inhibitors, the water-soluble polymer and the surfactant, and cooling the melt until it solidifies. "Melting" means a transition into a liquid or rubbery state in which it is possible for one component to get embedded homogeneously in the other. Typically, one component will melt and the other components will dissolve in the melt thus forming a solution. Melting usually involves

heating above the softening point of the water-soluble polymer. The preparation of the melt can take place in a variety of ways. The mixing of the components can take place before, during or after the formation of the melt. For example, the components can be mixed first and then melted or be simultaneously mixed and melted. Usually, the melt is homogenized in order to disperse the active ingredients efficiently. Also, it may be convenient first to melt the water-soluble polymer and then to mix in and homogenize the active ingredients.

Usually, the melt temperature is in the range of about 70 to about 250 °C, preferably from about 80 to about 180 °C, most preferred from about 100 to about 140 °C.

The active ingredients can be employed as such or as a solution or dispersion in a suitable solvent such as alcohols, aliphatic hydrocarbons or esters. Another solvent which can be used is liquid carbon dioxide. The solvent is removed, e.g. evaporated, upon preparation of the melt.

Various additives may be included in the melt, for example flow regulators such as colloidal silica; lubricants, fillers, disintegrants, plasticizers, stabilizers such as antioxidants, light stabilizers, radical scavengers, stabilizers against microbial attack.

The melting and/or mixing takes place in an apparatus customary for this purpose. Particularly suitable ones are extruders or kneaders. Suitable extruders include single screw extruders, intermeshing screw extruders or else multiscrew extruders, preferably twin screw extruders, which can be corotating or counterrotating and, optionally, be equipped with kneading disks. It will be appreciated that the working temperatures will also be determined by the kind of extruder or the kind of configuration within the extruder that is used. Part of the energy needed to melt, mix and dissolve the components in the extruder can be provided by heating elements. However, the friction and shearing of the material in the extruder may also provide a substantial amount of energy to the mixture and aid in the formation of a homogeneous melt of the components.

The melt ranges from pasty to viscous. Shaping of the extrudate conveniently is carried out by a calender with two counter-rotating rollers with mutually matching depressions on their surface. A broad range of tablet forms can be attained by using rollers with different forms of depressions. Alternatively, the extrudate is cut into pieces, either before (hot-cut) or after solidification (cold-cut).

Optionally, the resulting solid solution or solid dispersion product is milled or ground to granules. The granules may then be compacted. Compacting means a process whereby a

powder mass comprising the granules is densified under high pressure in order to obtain a compact with low porosity, e.g. a tablet. Compression of the powder mass is usually done in a tablet press, more specifically in a steel die between two moving punches. Where a solid dosage form of the invention comprises a combination of more than one HIV protease inhibitor (or a combination of an HIV protease inhibitor with one or more other active ingredients) it is of course possible to separately prepare solid solution or solid dispersion products of the individual active ingredients and to blend the milled or ground products before compacting.

At least one additive selected from flow regulators, disintegrants, bulking agents (fillers) and lubricants is preferably used in compacting the granules. Disintegrants promote a rapid disintegration of the compact in the stomach and keeps the granules which are liberated separate from one another. Suitable disintegrants are crosslinked polymers such as crosslinked polyvinyl pyrrolidone and crosslinked sodium carboxymethylcellulose. Suitable bulking agents (also referred to as "fillers") are selected from lactose, calcium hydrogenphosphate, microcrystalline cellulose (Avicell®), silicates, in particular silicium dioxide, magnesium oxide, talc, potato or corn starch, isomalt, polyvinyl alcohol.

Suitable flow regulators are selected from highly dispersed silica (Aerosil®), and animal or vegetable fats or waxes.

A lubricant is preferably used in compacting the granules. Suitable lubricants are selected from polyethylene glycol (e.g., having a Mw of from 1000 to 6000), magnesium and calcium stearates, sodium stearyl fumarate, and the like.

Various other additives may be used, for example dyes such as azo dyes, organic or inorganic pigments such as aluminium oxide or titanium dioxide, or dyes of natural origin; stabilizers such as antioxidants, light stabilizers, radical scavengers, stabilizers against microbial attack.

Dosage forms according to the invention may be provided as dosage forms consisting of several layers, for example laminated or multilayer tablets. They can be in open or closed form. "Closed dosage forms" are those in which one layer is completely surrounded by at least one other layer. Multilayer forms have the advantage that two active ingredients which are incompatible with one another can be processed, or that the release characteristics of the active ingredient(s) can be controlled. For example, it is possible to provide an initial dose by including an active ingredient in one of the outer layers, and a maintenance dose by including

the active ingredient in the inner layer(s). Multilayer tablets types may be produced by compressing two or more layers of granules. Alternatively, multilayer dosage forms may be produced by a process known as "coextrusion". In essence, the process comprises preparation of at least two different melt compositions as explained above, and passing these molten compositions into a joint coextrusion die. The shape of the coextrusion die depends on the required drug form. For example, dies with a plain die gap, called slot dies, and dies with an annular slit are suitable.

In order to facilitate the intake of such a dosage form by a mammal, it is advantageous to give the dosage form an appropriate shape. Large tablets that can be swallowed comfortably are therefore preferably elongated rather than round in shape.

A film coat on the tablet further contributes to the ease with which it can be swallowed. A film coat also improves taste and provides an elegant appearance. If desired, the film-coat may be an enteric coat. The film-coat usually includes a polymeric film-forming material such as hydroxypropyl methylcellulose, hydroxypropylcellulose, and acrylate or methacrylate copolymers. Besides a film-forming polymer, the film-coat may further comprise a plasticizer, e.g. polyethylene glycol, a surfactant, e.g. a Tween® type, and optionally a pigment, e.g. titanium dioxide or iron oxides. The film-coating may also comprise talc as anti-adhesive. The film coat usually accounts for less than about 5 % by weight of the dosage form.

The benefits provided by the present invention are presently believed to be attributable to the pharmacokinetic (pK) properties of the dosage form. Pharmacokinetic properties are generally understood to mean the manner and extent to which a drug is absorbed. Common pK parameters include AUC (or "area under the curve"), which typically refers to the amount of drug that is measurable in blood or blood products of a person taking the drug over time. AUC is variously referred to as a patients exposure to a drug. Cmax is another pK term which refers to the maximum blood (or blood product) level over the course of a given regimen of a drug. Drug regimens for which pK parameters are measured include "clinical studies." Some clinical studies are performed in a finite population of healthy volunteer patients and are designed to determine the pK parameters of a drug (such as those mentioned above), and not to treat a patient. Each patient is thus called a member of the study population. While such clinical studies are carefully controlled and monitored, pK parameters can vary between clinical studies in large measure because different clinical

studies are performed on different populations of patients. Although variances exist between clinical studies, those skilled in the art readily recognize that once a particular set of pK parameters is generally known, it is a matter of routine to formulate a drug to achieve a similar set of pK parameters.

As previously mentioned, the present invention provides a dosage form that can be taken without regard to whether a patient has eaten, sometimes referred to as "without regard to meals", "can be taken with or without food", "no food effect" or similar phrases. In particular, the Cmax of the drug and AUC of the drug is similar in patients that have eaten ("fed state") as compared to patients that have not eaten ("fasted state"). Hence, the dosage form provided herein advantageously can be taken at any time regardless of whether or not patients have recently eaten.

Notwithstanding the previous definition, there is no completely standard definitions for fed and fasted states. Generally, however, a fasted state refers to the fact that a patient has not eaten for a given amount of time before taking a dose of medication, as well as not eating for a given amount of time after taking the dosage form. These time periods before and after dosing are a matter of choice, and can range between, for example 2 hours to 24 hours. A fed state generally refers to the fact that a patient has eaten within a given time period of taking a particular medication. This time period is variable but may constitute, for example, a meal just before, during, or just after taking the medication, typically a meal is eaten within about an hour of dosing. The quantity of food eaten that will qualify as a fed state is also variable but generally can comprise between about 500 to about 1500 Kcal of food.

The dosage forms provided herein will have substantially the same Cmax and AUC_∞ values in patients in a fasted state as well as in a fed state, regardless of the dose given. In particular, the mean of the individual patient ratios in a patient population for either the Cmax or AUCoo in the fed state to fasted state will be in the range of about 0.7 to about 1.43; more preferably between about 0.75 and about 1.35; and most preferably between about 0.8 and about 1.25. Thus for example, in study population of 30 individuals each patient is given a dose of drug in a fed state and, after an appropriate time period, a dose of the drug in a fasted state. The AUCoo and Cmax for both meal conditions are calculated for each patient. The AUCoo value for the fed state is then divided by the AUCoo for the fasted state for each patient. The individual patient values are then added together and then divided by the number of patients completing the study to arrive at a mean AUCoo value for all patients

completing the study. The mean Cmax value is calculated in a similar manner. If the mean value of the fed to fasted ratio for all patients' Cmax or AUC∞ values in a given study is within 0.7 to 1.43, for example, then the dosage form provided to the patients would be considered to capable of administration without regard to whether or not the patient was in a fed or fasted state.

As also previously mentioned, the dosage forms provided herein have less variability than other gelatin capsule based formulations containing a dissolved form of the drug or drugs. This lack of variability is evidenced in Figure 1 and Figure 2 which compare AUCoo and Cmax data of an embodiment of the present invention and the data from a marketed gelatin capsule containing a dissolved PL As shown by the Figures, the AUCoo and Cmax data associated with an embodiment of the present invention shows less variation. In particular, the graphs are a "box and whiskers" plot of the data comparing the two formulations wherein the bottom of any given "whisker" (labeled A in the first box and whisker plot of Figure 1) is called the "5th percentile", meaning that 5% of the patients in the study fell below the designated AUCoo or Cmax value for the particular whisker. The top of the whisker (labeled D in first box and whisker plot of Figure 1) represents the "95th percentile", meaning that 5% of the patients in the study had a AUCoo or Cmax value above the value designated by the top of any particular whisker. Similarly, the bottom of any particular box (labeled B in first box and whisker plot of Figure 1) represents the 25th percentile and the top of any particular box (labeled C in first box and whisker plot of Figure 1) represent the 75th percentile. The line running through any particular box is the 50th percentile or median of any particular study population.

As seen by the Figures, the data generally demonstrates that the variability associated with the embodiment of the present invention is less than that associated with the existing gelatin capsule formulation. Looking at the dosage forms given under fasting conditions of Figure 1 (for example), the difference between 95th percentile and 5th percentile of the gelatin capsule is greater than the difference between 95* percentile and 5th percentile of the embodiment of the present invention. This translates into the fact that a greater portion of the study population is getting a therapeutic benefit from the PI without experiencing adverse events do to overexposure of the drug. For purposes of, for example, reducing side effects and achieving therapeutic levels, it is generally preferred that the difference between the 95th percentile of AUCoo and 5th percentile of AUC∞ of any given study population taking a

dosage form as provided herein (regardless of whether the population is fed or fasted) is less than about 180, more preferably less than about 175, even more preferably less than about 165, and most preferably less than about 160. Under fasting conditions, it is preferable that the difference between the 95th percentile of AUC_∞ and 5th percentile of AUC_∞ of any given study population taking a dosage form as provided herein is less than about 170, more preferably less than about 160, and most preferably less than about 150. Under fed conditions, it is preferable that the difference between the 95* percentile of AUCoo and 5th percentile of AUCoo of any given study population taking a dosage form as provided herein is less than about 130, more preferably less than about 120, and most preferably less than about 110.

Similarly to the differences between the 95th and 5* percentiles provided above, the difference between the 75th percentile and 25th percentile of the AUC data in Figure 1 is also very important in demonstrating the lack of variability in dosage forms of the present invention. It is generally preferred that the difference between the 75th percentile of AUCoo and 25th percentile of AUCoo of any given study population taking a dosage form as provided herein (regardless of whether the population is fed or fasted) is less than about 60, more preferably less than about 55, even more preferably less than about 50. Under fasting conditions, it is preferable that the difference between the 75th percentile of AUCoo and 25th percentile of AUCoo of any given study population taking a dosage form as provided herein is less than about 65, more preferably less than about 60, and most preferably less than about 55. Under fed conditions, it is preferable that the difference between the 75th percentile of AUCoo and 25th percentile of AUCoo of any given study population taking a dosage form as provided herein is less than about 60, more preferably less than about 50, and most preferably less than about 40.

In terms of ranges of AUCoo values, it is preferred that under fasted conditions the 5th percentile to the 95th percentile of AUCoo of any given study population taking a dosage form as provided herein ranges between about 33 μg•h/mL and about 175 μg•h/mL; and the 25th percentile to the 75th percentile of AUCoo of any given study population taking a dosage form as provided ranges between about 54 μg•h/mL and about 107 μg•h/mL. Under fed conditions it is preferred that the 5th percentile to the 95th percentile of AUCoo of any given study population taking a dosage form as provided herein ranges between about 57 μg•h/mL and about 142 μg•h/mL; and the 25th percentile to the 75th percentile of AUC_∞ of any given

study population taking a dosage form as provided herein ranges between about 75 μg•h/mL and about 109 μg•h/mL. It is also preferred that the 5th percentile of the AUC∞ of any given study population taking a dosage form as provided herein greater than about 30 μg•h/mL under fasted conditions, and greater than about 50 μg•h/mL under fed conditions. Finally with respect to AUC∞, it is preferred mat under fasting conditions the mean AUC∞ is between about 60 μg•h/mL and about 95 μg•h/mL. for any given study population taking a dosage form provided.

Similarly to the AUC parameters associated with Figure 1, the Cmax parameters shown in Figure 2 also demonstrates lack of variability associated with dosage forms provided herein. For example, looking at the box and whiskers plot of Figure 2 for patients under fasting conditions taking a dose of PI formulated according to the present invention, it is preferred that difference between the 95th percentile and the 5th percentile is less than about 15, more preferably less than about 13, and most preferably less than about 11. Under fasted conditions it is also preferable that the 5th percentile of Cmax of a given study population taking a dose of active ingredient fonuulated according to the present invention is greater that about 2.5 μg /mL. Turning to the box and whiskers plot of Figure 2 for fed conditions taking a dosage form of the present invention, it is preferred that difference between the 95th percentile and the 5* percentile is less than about 12, more preferably less than about 11.

With respect to the description of the figures provided above, it should be pointed out that when a patient is referred to as taking a dosage form of the present invention, they received a dose of a PI in multiple dosage forms. Specifically, the so called dosage form contained 400 mg of lopinavir and 100 mg of ritonovir evenly divided between two dosage forms. Lopinavir was the only drug measured in these studies due to the fact mat ritonavir is supplied not for its action as a PI but as a pharmacokinetic enhancer or booster (ritonavir inhibits the metabolism of lopinavir). Further, it will be understood that the when ritonavir is employed it can be separately dosed instead of part of a combination dosage form. Moreover, it will be understood that the values given can vary due to, for example, changes in meal timings and quantities, as well as the constitution of the study population. It is well known that study populations from different nationalities may have different drug metabolism rates. Accordingly, in cases where study data is taken from such populations, the data may have to be normalized as is well known in the art Moreover, in cases where an increase in the dose or a decrease in the dose of lopinovir, for example, is provided to a study

population, the data resulting from such dosing may require normalization using appropriate modeling as is well known in the art Last, with respect to the above discussion concerning the figures, a "High Fat Meal" as described in the figures is considered to be a fed state.

In addition to providing methods of treating a human patient afflicted with HIV/AIDs, the present invention provides methods of reducing the side effects associated with HIV therapy, methods of increasing the bioavailability of a PI, methods of decreasing the pill burden of an HIV/AIDs patient, methods of decreasing the variability of blood levels of a PI in a patient taking PI therapy, and methods of providing a PI to a patient taking PI therapy. All of these methods comprise the step of providing a pharmaceutical dosage form comprising a therapeutically effective amount of an undissolved form of a PI to a patient. Preferably, the PI is (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]-amino-1,6-diphenylhexane (ABT-378; lopinavir). More preferably, the dosage form will comprise (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-3hydroxyhexane (ritonavir).

Examples

The following examples are provided to further understand and illustrate the present invention and not to limit the spirit and scope of the present invention as it is defined in the appended claims.

Example 1

Component	Weight %	Weight %	Weight %
Ritonavir	18-22.5 in total	4.17	4.17
Lopinavir		16.67	16.67
Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40)	65 – 75	71.16	70.12
Span 20 (Sorbitan monolaurate)	4-10	7.0	5.02
Cremophor RH40 (polyoxyethylene-glycerol oxystearate)	0-10	-	3.02
Colloidal silica	0-3	1.0	1.0

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40) was mixed with ritonavir (4.17 parts by weight), lopinavir (16.67 parts by weight) and colloidal silica (1.0 part by weight). The powdery mixture was then fed into a twin-screw extruder (screw diameter 18 mm) at a rate of 2.0 kg/h and a melt temperature of 133 °C. The clear, fully transparent melt was fed to a calender with two counter-rotating rollers having mutually matching cavities on their surfaces. Tablets of 1080 mg were thus obtained. DSC and WAXS analysis did not reveal any evidence of crystalline drug material in the formulation.

The bioavailability of the formulation was assessed using beagle dogs (mixed sexes, weighing approximately 10 kg) which received a balanced diet with 27 % fat and were permitted water ad libitum. Each dog received a 100 µg/kg subcutaneous dose of histamine approximately 30 minutes prior to dosing. A single dose corresponding to about 200 mg lopinavir, about 50 mg ritonavir, or about 200 mg lopinavir and about 50 mg ritonavir, respectively, was administered to each dog. The dose was followed by approximately 10 milliliters of water. Blood samples were obtained from each animal prior to dosing and 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours after drug administration. The plasma was separated from the red cells by centrifugation and frozen (-30 °C) until analysis. Concentrations of HIV protease inhibitors were determined by reverse phase HPLC with low wavelength UV detection following liquid-liquid extraction of the plasma samples. The area under the curve (AUC) was calculated by the trapezoidal method over the time course of the study. Each dosage form was evaluated in a group containing 8 dogs; the values reported are averages for each group of dogs.

The dose-adjusted AUC in dogs was 0.52 µg.h/ml/100 mg for ritonavir and 4.54 µg.h/ml/100 mg for lopinavir. This example shows that solid solutions or solid dispersions of HIV protease inhibitors without added surfactant yield a very poor bioavailability.

Example 2

Component	Weight %	Weight %
Ritonavir	18 – 22.5	20.8
Lopinavir	-	-
Copovidone (N-vinyl pyrrolidone/vinyl acetate	60 – 75	63.15

copolymer 60:40)		
Span 20 (Sorbitan monolaurate)	5 15 in total	-
Cremophor RH40 (polyoxyethyleneglycerol oxystearate)		10.00
PEG 6000	0-8	5.00
Colloidal silica	0-3	1.04

The above composition is processed by melt extrusion. The resulting extrudate can be used as such or milled and compressed into tablets, preferably by the use of suitable tabletting aids such as sodium stearyl fumarate, colloidal silica, lactose, isomalt, calcium silicate, and magnesium stearate, cellulose or calcium hydrogenphosphate.

Example 3

Component	Weight %
Ritonavir	4.16
Lopinavir	16.67
Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40)	78.17
Colloidal silica	1.0

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 78.17 parts by weight) was mixed with ritonavir (4.16 parts by weight), lopinavir (16.67 parts by weight) and colloidal silica (1.0 part by weight). The powdery mixture was then fed into a twin-screw extruder (screw diameter 18 mm) at a rate of 2.0 kg/h and a melt temperature of 133 °C. The clear, fully transparent melt was fed to a calender with two counter-rotating rollers having mutually matching cavities on their surfaces. Tablets of 1080 mg were thus obtained. DSC and WAXS analysis did not reveal any evidence of crystalline drug material in the formulation.

Example 4

Component	Weight %
Ritonavir	4.17
Lopinavir	16.67
Copovidone	68.17
Cremophor RH40	10.00

colloidal silica	1.0
lactose monohydrate	6.0
crosslinked PVP	6.0
colloidal silica	1.0
magnesium stearate	0.51

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 68.17 parts by weight) was blended with Cremophor RH40 (polyoxyethyleneglycerol oxystearate; 10.00 parts by weight) in a Diosna high-shear mixer. The resulting granules were mixed with ritonavir (4.17 parts by weight), lopinavir (16.67 parts by weight) and colloidal silica (1.00 parts by weight). The powdery mixture was then fed into a Leistritz Micro 18 twin-screw extruder at a rate of 2.3 kg/h and a melt temperature of 126 °C. The extrudate was cut into pieces and allowed to solidify. The extruded pieces were milled using a high impact universal mill. The milled material (86.49 parts by weight) was blended in a bin blender with lactose monohydrate (6.00 parts by weight), crosslinked PVP (6.00 parts by weight), colloidal silica (1.00 part by weight) and magnesium stearate (0.51 parts by weight). The powdery blend was compressed to tablets of 1378.0 mg on a Fette E 1 single punch tablet press. The tablets were then film-coated in a coating pan by spraying an aqueous dispersion for film coating (Opadry, available from Colorcon) at a temperature of 60 °C.

The bioavailability of the formulation was assessed using beagle dogs as in Example 1. The dose-adjusted AUC in dogs was 0.60 µg.h/ml/100 mg for ritonavir and 7.43 µg.h/ml/100 mg for lopinavir. This example shows that inclusion of a surfactant into solid solutions or solid dispersions of HIV protease inhibitors improves the bioavailability attained.

Example 5

Component	Weight (mg)
Ritonavir	50
Lopinavir	200
Copovidone	853.8
Span 20	83.9
colloidal silica	12

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 853.8 parts by weight) was blended with Span 20 (Sorbitan monolaurate; 83.9 parts by weight) in a Diosna high-shear mixer. The resulting granules were mixed with ritonavir (50 parts by weight),

lopinavir (200 parts by weight) and colloidal silica (12 parts by weight). The powdery mixture was then fed into a twin-screw extruder (screw diameter 18 mm) at a rate of 2.1 kg/h and a melt temperature of 119 °C. The extrudate was fed to a calender with two counter-rotating rollers having mutually matching cavities on their surfaces. Tablets of 1120 mg were thus obtained.

The bioavailability of the formulation was assessed using beagle dogs as in Example 1. The dose-adjusted AUC in dogs was 10.88 µg.h/ml/100 mg for ritonavir and 51.2 µg.h/ml/100 mg for lopinavir. This example shows that inclusion of a surfactant having an HLB of 4 to 10 into solid solutions or solid dispersions of HIV protease inhibitors markedly improves the bioavailability attained.

Example 6

Example 5 was repeated, however, the extrudate was cut into pieces and allowed to solidify. The extruded pieces were milled to a particle size of about 250 µm, using a high impact universal mill. The milled material was blended in a bin blender with sodium stearyl fumarate (12.3 parts by weight) and colloidal silica (8.0 parts by weight) for 20 min. The powdery blend was compressed on a rotary tablet machine with 3 punches (6500 tablets/h). The tablets were then film-coated in a coating pan by spraying an aqueous dispersion for film coating (Opadry, available from Colorcon) at a temperature of 60 °C.

The bioavailability of the formulation was assessed using beagle dogs as in Example 1. The dose-adjusted AUC in dogs was 14.24 µg.h/ml/100 mg for ritonavir and 52.2 µg.h/ml/100 mg for lopinavir.

Example 7

Component	Weight (mg)
Ritonavir	50
Lopinavir	200
Copovidone	841.3
Span 20	60.2
Cremophor RH40	36.2
colloidal silica	12

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 841.3 parts by weight) was blended with Cremophor RH40 (polyoxyethyleneglycerol oxystearate; 36.2 parts

by weight), Span 20 (Sorbitan monolaurate; 60.2 parts by weight) in a Dipsna high-shear mixer. The resulting granules were mixed with ritonavir (50 parts by weight), lopinavir (200 parts by weight) and colloidal silica (12 parts by weight). The powdery mixture was then fed into a twin-screw extruder (screw diameter 18 mm) at a rate of 2.1 kg/h and a melt temperature of 114 °C. The extrudate was fed to a calender with two counter-rotating rollers having mutually matching cavities on their surfaces. Tablets of 1120 mg were thus obtained.

The bioavailability of the formulation was assessed using beagle dogs as in Example 1. The dose-adjusted AUC in dogs was 10.96 µg.h/ml/100 mg for ritonavir and 46.5 µg.h/ml/100 mg for lopinavir. This example shows that a combination of a surfactant having an HLB of 4 to 10 and a further surfactant can successfully be used.

Example 8

Example 7 was repeated, however, the extrudate was cut into pieces and allowed to solidify. The extruded pieces were milled to a particle size of about 250 µm, using a high impact universal mill. The milled material was blended in a bin blender with sodium stearylfumarate (13.9 parts by weight), colloidal silica (7.0 parts by weight), isomalt DC100 (159.4 parts by weight) and calcium silicate (7.0 parts by weight) for 20 min. The blend was compressed and then film-coated in a coating pan by spraying an aqueous dispersion for film coating (Opadry, available from Colorcon) at a temperature of 60 °C.

The bioavailability of the formulation was assessed using beagle dogs as in Example 1. The dose-adjusted AUC in dogs was 10.38 µg.h/ml/100 mg for ritonavir and 42.7 µg.h/ml/100 mg for lopinavir.

Example 9

Component	Weight (mg)
Lopinavir	200
Copovidone	683.3
Span40	67.2
colloidal silica	9.6
Sodium stearylfumarate	7.9
colloidal silica	11.3
Isomalt DC 100	129.1
Sodium dodecyl sulfate	15.6

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 683.3 parts by weight) was blended with Span 40 (sorbitan monopalmitate; 67.2 parts by weight) in a Diosna high-shear mixer. The resulting granules were mixed with lopinavir (200 parts by weight) and colloidal silica (9.6 parts by weight). The powdery mixture was then fed into a twin-screw extruder (screw diameter 18 mm) at a rate of 2.1 kg/h and a melt temperature of 119 °C. The extrudate was cut into pieces and allowed to solidify. The extruded pieces were milled using a high impact universal mill. The milled material was blended in a bin blender with sodium stearylfumarate (7.9 parts by weight), colloidal silica (11.3 parts by weight), isomalt DC100 (129.1 parts by weight) and sodium dodecyl sulfate (15.6 parts by weight). The blend was compressed and then film-coated in a coating pan by spraying an aqueous dispersion for film coating (Opadry, available from Colorcon) at a temperature of 60 °C.

The bioavailability of the formulation was assessed using beagle dogs as in Example 1. Tablets corresponding to 200 mg lopinavir were coadministered to dogs together with 50 mg ritonavir. The dose-adjusted AUC of lopinavir was 38,8 µg.h/ml/100 mg.

Example 10

Component	Weight (mg)
Ritonavir	50
Copovidone	151.5
Cremophor RH40	24
colloidal silica	3.8
PEG 6000	12
Isomalt DC 100	31.9
Calcium silicate	4.2

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 151,5 parts by weight) was blended with Cremophor RH40 (24 parts by weight) and PEG 6000 (12 parts by weight) in a Diosna high-shear mixer. The resulting granules were mixed with ritonavir (50 parts by weight) and colloidal silica (2.4 parts by weight). The powdery mixture was then fed into a twin-screw extruder and was melt-extruded. The extrudate was cut into pieces and allowed to solidify. The extruded pieces were milled using a high impact universal mill. The milled material was blended in a bin blender with colloidal silica (1.4 parts by weight), isomalt DC100 (31.9 parts by weight) and calcium silicate (4.2 parts by weight). The blend was compressed and then film-coated in a coating pan by spraying an aqueous dispersion for film coating (Opadry, available from Colorcon) at a temperature of 60 °C.

Example 11

Component	Weight %
Extrusion	
Ritonavir	3.53
Lopinavir	14.11
Copovidone	57.71
Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)	8.47
Colloidal silicon dioxide	1.28
Post extrusion	
Lactose	5.88
Crospovidone	5.88
Magnesium stearate	0.49
Colloidal silicon dioxide	0.55
Film coating	2.12

The extruded material was milled, compressed with tableting excipients, and coated. The formulation consisted of lopinavir (200 mg/tablet), ritonavir (50 mg/tablet), copovidone as the carrier polymer, and polyoxyl 40 hydrogenated castor oil as the surfactant. For compression, outer phase excipients were added to the milled extrudate. The surfactant was incorporated prior to extrusion by granulation with a portion of the polymer.

Example 12

Component	Weight %
Extrusion	
Ritonavir	3.48
Lopinavir	13.91
Copovidone	58.06
Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)	1.67
Sorbitan monopalmitate (Span 40)	4.67
PEG 6000	0.83
Colloidal silicon dioxide	0.84
Post extrusion	
Isomalt	11.29
Calcium silicate	1.47
Sodium stearyl fumarate	0.59
Sodium lauryl sulfate	0.88
Colloidal silicon dioxide	0.49
Fihn coating	1.81

The tablet formulation was compressed from separately extruded lopinavir and ritonavk powder mixtures. The surfactant was incorporated prior to extrusion by granulation with a portion of the polymer.

Example 13

Component	Weight %
Extrusion	
Ritonavk	4.03
Lopinavir	16.10
Copovidone	68.74
Sorbitan monolaurate (Span 20)	6.76
Colloidal silicon dioxide	0.97
Post extrusion	
Sodium stearyl fumarate	0.99
Colloidal silicon dioxide	0.64
Film coating	1.77

The formulation was prepared by milling the extrudate, mixing with tableting excipients and compressing into tablets. An aqueous, hydroxypropyl methylcellulose based film coating was applied to the compressed tablets to enhance pharmaceutical elegance. The surfactant was incorporated prior to extrusion by granulation with a portion of the polymer.

Example 14

Component	Weight %
Extrusion	
Ritonavk	3.54
Lopinavir	14.15
Copovidone	59.54
Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)	2.56
Sorbitan monolaurate (span 20)	4.26
Colloidal silicon dioxide	0.85
Post extrusion	
Isomalt	11.28
Calcium silicate	0.50
Sodium stearyl fumarate	0.98
Colloidal silicon dioxide	0.50
Film coating	1.84

The formulation was prepared by milling the extrudate, mixing with tableting excipients and compressing into tablets. An aqueous, hydroxypropyl methylcellulose based film coating was applied to the compressed tablets to enhance pharmaceutical elegance. The surfactant was incorporated prior to extrusion by granulation with a portion of the polymer.

Example 15

Component	Weight %
Extrusion	
Ritonavir	4.17
Lopinavir	16.67
Copovidone	71.17
Sorbitan monolaurate (span 20)	6.99
Colloidal silicon dioxide	1.00

The formulation was extruded in the shape of a tablet without the additional processing steps of milling, compression and coating. The formulation composition included ritonavir, lopinavir, copovidone, surfactant, and colloidal silicon dioxide with the two formulations differing in the type of surfactant used. The extruded tablet formulation contained sorbitan monolaurate as the surfactant that was incorporated prior to extrusion by granulation with a portion of the polymer.

Example 16

Component	Weight %
Extrusion	
Ritonavir	4.17
Lopinavir	16.67
Copovidone	70.13
Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)	3.02
Sorbitan monolaurate (span 20)	5.02
Colloidal silicon dioxide	1.00

The formulation was extruded in the shape of a tablet without the additional processing steps of milling, compression and coating. The formulation composition included ritonavir, lopinavir, copovidone, surfactant, and colloidal silicon dioxide with the two formulations differing in the type of surfactant used. The extruded tablet formulation contained both polyoxyl 40 hydrogenated castor oil and sorbitan monolaurate as the

surfactants. The surfactants were incorporated prior to extrusion by granulation with a portion of the polymer.

This dosage form was characterized by an excellent stability and, in particular, exhibit high resistance against recrystallization or decomposition of the active ingredient(s). Thus, upon storage for 6 weeks at 40 °C and 75% humidity (e.g., when kept in high density polyethylene (HDPE) bottles without desiccant), the dosage forms according to the present invention did not exhibit any sign of crystallinity (as evidenced by DSC or WAXS analysis) and contained at least about 98 % of the initial active ingredient content (as evidenced by HPLC analysis).

In vitro dissolution tests were performed on several of the formulation disclosed in the Examples above. The testing method and conditions are shown in the table below.

Apparatus:	USP Apparatus 2 (paddle)
Agitation:	75 rpm
Medium:	0.06M POE10LE (Polyoxyethylene 10 Lauryl Ether)
Temperature:	37°C
Profile Times:	15, 30, 60, 90, 120 and 150 minutes with medium replacement
Proposed Specification:	Q = 80% in 120 minutes

The results are shown below. Table 1 shows the mean % lopinavir releaseded in minutes for the formulations disclosed in Examples 9-10 and 12-16.

Table 1. Mean % lopinavir dissolved in minutes.

Example No.	Mean % Lopinavir Dissolved (minutes)						
	15	30	45	60	90	120	150
9	30.4	56.0	75.1	88.7	100.6	101.1	100.9
10	-	-	-	-	-	-	-
12	21.6	473	67.1	82.0	96.0	100.8	101.1
13	20.6	43.0	61.3	75.4	**92.2**	98.1	**99.2**
13	23.1	473	-	80.0	93.9	98.1	98.8
14	21.0	47.6	69.9	85.6	98.5	101.1	101.7
15	36.9	63.0	**81.7**	**93.2**	102.0	103.0	103.1
16	32.1	57.0	74.9	86.5	**95.9**	99.2	99.6

Table 2 shows the mean % ritonavir dissolved in minutes for the formulations disclosed in Examples 9-10 and 12-16.

Table 2. Mean % ritonavir dissolved in minutes

Example No.	Mean % Ritonavir Dissolved (minutes)						
	15	30	45	60	90	120	150
9	-	-	-	-	-	-	-
10	-	76.5	91.1	95.0	96.9	-	-
12	21.8	46.4	65.6	79.8	93.3	98.1	98.3
13	19.8	41.6	59.4	73.4	90.0	**96.2**	97.5
13	**23.1**	46.0	-	78.0	92.0	96.3	96.9
14	21.0	45.4	66.5	**82.3**	95.1	100.1	**98.2**
15	34.4	59.1	76.9	88.0	96.6	67.6	97.7
16	30.5	54.4	71.7	83.1	92.3	95.4	96.0

Therefore, in one embodiment the present invention provides for example, a pharmaceutical dosage form comprising lopinavir in a therapeutically effective amount, said dosage form providing an in vitro dissolution profile wherein about 20 % to about 30 % of lopinavir is released from about 0 to about 15 minutes using a USP apparatus 2 (paddle) at 75 rpm with a 0.06M POE10LE (Polyoxyethylene 10 Lauryl Ether) medium at 37°C.

In one embodiment the present invention provides for example, a pharmaceutical dosage form comprising lopinavir in a therapeutically effective amount, said dosage form providing an in vitro dissolution profile wherein about 20 % to about 30 % of lopinavir is released from about 0 to about 15 minutes using a USP apparatus 2 (paddle) at 75 rpm with a 0.06M POE10LE (Polyoxyethylene 10 Lauryl Ether) medium at 37°C.

In one embodiment the present invention provides for example, a pharmaceutical dosage form comprising lopinavir in a therapeutically effective amount, said dosage form providing an in vitro dissolution profile wherein about 43 % to about 63 % of lopinavir is released from about 15 to about 30 minutes using a USP apparatus 2 (paddle) at 75 rpm with a 0.06M POE10LE (Polyoxyethylene 10 Lauryl Ether) medium at 37°C.

In one embodiment the present invention provides for example, a pharmaceutical dosage form comprising lopinavir in a therapeutically effective amount, said dosage form providing an in vitro dissolution profile wherein about 61.3 % to about 81.7 % of lopinavir is released from about 30 to about 45 minutes using a USP apparatus 2 (paddle) at 75 rpm with a 0.06M POE10LE (Polyoxyethylene 10 Lauryl Ether) medium at 37°C.

In one embodiment the present invention provides for example, a pharmaceutical dosage form comprising lopinavir in a therapeutically effective amount, said dosage form

providing an in vitro dissolution profile wherein about 75.4 % to about 93.2 % of lopinavir is released from about 45 to about 60 minutes using a USP apparatus 2 (paddle) at 75 rpm with a 0.06M POE10LE (Polyoxyethylene 10 Lauryl Ether) medium at 37°C.

In one embodiment the present invention provides for example, a pharmaceutical dosage form comprising ritonavrr in a therapeutically effective amount, said dosage form providing an in vitro dissolution profile wherein about 19.8 % to about 34.4 % of ritonavir is released from about 0 to about 15 minutes using a USP apparatus 2 (paddle) at 75 rpm with a 0.06M POE10LE (Polyoxyethylene 10 Lauryl Ether) medium at 37°C.

In one embodiment the present invention provides for example, a pharmaceutical dosage form comprising ritonavir in a therapeutically effective amount, said dosage form providing an in vitro dissolution profile wherein about 41.6 % to about 76.5 % of ritonavir is released from about 15 to about 30 minutes using a USP apparatus 2 (paddle) at 75 rpm with a 0.06M POE10LE (Polyoxyethylene 10 Lauryl Ether) medium at 37°C.

In one embodiment the present invention provides for example, a pharmaceutical dosage form comprising ritonavir in a therapeutically effective amount, said dosage form providing an in vitro dissolution profile wherein about 59.4 % to about 91.1 % of ritonavir is released from about 30 to about 45 minutes using a USP apparatus 2 (paddle) at 75 rpm with a 0.06M POE10LE (Polyoxyethylene 10 Lauryl Ether) medium at 37°C.

In one embodiment the present invention provides for example, a pharmaceutical dosage form comprising ritonavir in a therapeutically effective amount, said dosage form providing an in vitro dissolution profile wherein about 73.4 % to about 95 % of ritonavir is released from about 45 to about 60 minutes using a USP apparatus 2 (paddle) at 75 rpm with a 0.06M POE10LE (Polyoxyethylene 10 Lauryl Ether) medium at 37°C.

In one embodiment the present invention provides for example, a pharmaceutical dosage form comprising lopinavir in a therapeutically effective amount, said dosage form providing an in vitro dissolution profile using a USP apparatus 2 (paddle) at 75 rpm with a 0.06M POE10LE (Polyoxyethylene 10 Lauryl Ether) medium at 37°C wherein:
about 20 % to about 30 % of lopinavir is released from about 0 to about 15 minutes;
about 43 % to about 63 % of lopinavir is released from about 15 to about 30 minutes;
about 61.3 % to about 81.7 % of lopinavir is released from about 30 to about 45 minutes; and
about 75.4 % to about 93.2 % of lopinavir is released from about 45 to about 60 minutes.

In one embodiment the present invention provides for example, a pharmaceutical dosage form comprising ritonavir in a therapeutically effective amount, said dosage form providing an in vitro dissolution profile using a USP apparatus 2 (paddle) at 75 rpm with a 0.06M POE10LE (Polyoxyethylene 10 Lauryl Ether) medium at 37°C wherein:
about 19.8 % to about 34.4 % of ritonavir is released from about 0 to about 15 minutes;
about 41.6 % to about 76.5 % of ritonavir is released from about 15 to about 30 minutes;
about 59.4 % to about 91.1 % of ritonavir is released from about 30 to about 45 minutes; and
about 73.4 % to about 95 % of ritonavir is released from about 45 to about 60 minutes.

In one embodiment the present invention provides for example, a pharmaceutical dosage form comprising ritonavir and lopinavir in a therapeutically effective amount, said dosage form providing an in vitro dissolution profile using a USP apparatus 2 (paddle) at 75 rpm with a 0.06M POE10LE (Polyoxyethylene 10 Lauryl Ether) medium at 37°C wherein:
about 19.8 % to about 34.4 % of ritonavir is released and about 20 % to about 30 % of lopinavir is released from about 0 to about 15 minutes;
about 41.6 % to about 76.5 % of ritonavir and about 43 % to about 63 % of lopinavir is released from about 15 to about 30 minutes;
about 59.4 % to about 91.1 % of ritonavir and about 61.3 % to about 81.7 % of lopinavir is released from about 30 to about 45 minutes; and
about 73.4 % to about 95 % of ritonavir and about 75.4 % to about 93.2 % of lopinavir is released from about 45 to about 60 minutes.

In order to understand lopinavir exposure among humans receiving the dosage form of the present invention and currently marketed Kaletra gelatin capsule, probability distributions were constructed from studies described below. It was assumed that the natural logarithms of lopinavir Cmax and AUC∞ followed normal distributions with mean (μ) and variance (σ^2) for each formulation. These values were taken from single 400/100 mg lopinavir/ritonavir dose, 4 or 5 period, randomized, open-label cross-over studies in healthy human volunteers under controlled meal conditions (either fasting, moderate-fat, or high-fat). Each study had between 48 and 63 subjects with a washout between periods of at least 7 days. The mean values for lopinavir Cmax and AUC∞ under moderate-fat meal condition were obtained from the central values in a cross-study meta-analysis of bioequivalence as generally known by those having ordinary skill in the art. The variance values for the distribution were obtained from the between-subject variability estimated for the dosage form

of the present invention and the currently marketed Kaletra gelatin capsule using the SAS Procedure Mixed as generally known by those having ordinary skill in the art.

The probability distributions of lopinavir Cmax and AUCoo under fasting and high-fat meal conditions were adjusted using the point estimates from Studies C and A described below for the dosage form of the present invention and currently marketed Kaletra gelatin capsule. The variance for each of fasting and high-fat meal conditions were projected according to the magnitude of the variability relative to that of the moderate-fat meal conditions using data from studies A, B and C described below in more detail.

The probability density in relation to AUC∞ for each formulation was calculated based on the mean and variance using the following formula:

$$\frac{1}{\sqrt{2\pi}\sigma}\frac{e^{-(\log x-\mu)^2/(2\sigma^2)}}{AUC_\infty}$$

The probability distribution of lopinavir Cmax was constructed in the same manner.

Study A was a single-dose (lopinavir/ritonavir 400/100 mg), five-period, randomized, open-label, pivotal bioavailability study in 63 healthy subjects. The first four periods were conducted according to a complete-crossover design. Subjects were equally randomized to four sequences of Regimens A, B, C and D for Periods 1 through 4. Five subjects from each sequence group who completed Periods 1 through 4 were randomly chosen to participate in Period 5 and received Regimen E. A washout interval of at least 7 days separated the doses of the five study periods. The five regimens were:

Regimen A: Three lopinavir/ritonavir 133.3/33.3 mg currently marketed Kaletra gelatin capsules following a moderate-fat breakfast;
Regimen B: Three lopinavir/ritonavir 133.3/33.3 mg currently marketed Kaletra gelatin capsules under fasting conditions;
Regimen C: Two lopinavir/ritonavir 200/50 mg dosage forms of the present invention following a moderate-fat breakfast;
Regimen D: Two lopinavir/ritonavir 200/50 mg dosage forms of the present invention under fasting conditions; and
Regimen E: Two lopinavir/ritonavir 200/50 mg dosage forms of the present invention following a high-fat breakfast.

Study B was a single-dose (lopinavir/ritonavir 400/100 mg), non-fasting, moderate-fat, open-label, four-period, randomized, complete-crossover, pivotal bioavailability study in 48 healthy subjects. Subjects were randomly assigned in equal numbers to receive one of four sequences of Regimens A, B, C and D defined as follows:

Regimen A: Two lopinavir/ritonavir 200/50 mg dosage forms of the present invention (Lot 1);

Regimen B: Two loprnavir/ritonavir 200/50 mg dosage forms of the present invention (Lot 2);

Regimen C: Two loprnavir/ritonavir 200/50 mg dosage forms of the present invention (Lot 3);

Regimen D: Three lopinavir/ritonavir 133.3/33.3 mg currently marketed Kaletra gelatin capsules.

The single doses were administered in the morning on Study Day 1 of each period following a moderate-fat breakfast. A washout interval of 7 days separated the doses of the four study periods.

Study C was a Phase 1, single-dose, fasting and non-fasting, open-label, randomized, five-period, partial crossover, single-center study in 56 healthy subjects. The currently marketed Kaletra liquid and gelatin capsule formulations were administered to provide a single dose of lopinavir/ritonavir 400/100 mg. Both formulations were given under fasting conditions and following moderate and high-fat meals.

It has been discovered that the dosage form of the present invention provides a substantially lower variation in Cmax and AUC∞ from the 5th to the 95th percentiles for lopinavir when administered to a subject whether fed or fasted than the gelatin capsule formulation. That is, the dosage form of the present invention provides a smaller A Cmax and A AUCoo from the 5th to the 95th percentiles for lopinavir than the Kaletra gelatin capsule formulation. This is shown both graphically in Figures 1 and 2 as well as numerically in Tables 3-5.

The dosage form of the present invention also provides a substantially lower variation in Cmax and AUCoo from the 25th to the 75th percentiles for lopinavir when administered to a subject whether fed or fasted than the gelatin capsule formulation. That is, the dosage form of the present invention provides a smaller A Cmax and A AUCoo from the 25^{rt*} to the 75^{tli}

percentiles for lopinavir than the Kaletra gelatin capsule formulation. This is shown both graphically in Figures 1 and 2 as well as numerically in Tables 3-5.

Table 3. Lopinavir bioavailability from Kaletra® Gelatin Capsule v. Claimed Dosage Form under Fasted Conditions.

Dosage Form	Percentile	AUC∞ (µg•h/mL)	Cmax (µg/mL)
Gelatin Capsule	5	10.6	1.31
	25	26.67	2.698
	50	52.22	4.946
	75	102.2	9.057
	95	268.5	21.52
Solid Dosage Form	5	33.15	3.051
	25	54.09	4.882
	50	76.02	6.809
	75	106.8	9.379
	95	174.3	15.03

Table 4. Lopinavir bioavailability from Kaletra® Gelatin Capsule v. Claimed Dosage Form under Moderate-Fat Meal Conditions.

Dosage Form	Percentile	AUCoo (µg•h/mL)	Cmax (µg/mL)
Gelatin Capsule	5	28.43	2.615
	25	52.9	4.433
	50	81.45	6.424
	75	125,41	9.314
	95	233.5	16.316
Solid Dosage Form	5	46.06	3.829
	25	71.27	5.91
	50	96.54	8.004
	75	130.8	10.89
	95	202.3	16.77

Table 5. Lopinavir bioavailability from Kaletra® Gelatin Capsule v. Claimed Dosage Form under High-Fat Meal Conditions.

Dosage Form	Percentile	AUCoo (µg•h/mL)	Cmax (µg/mL)
Gelatin Capsule	5	37.56	2.865
	25	68.05	4.882
	50	102.9	7.066
	75	155.5	10.28
	95	287.7	17.47
Solid Dosage Form	5	57.77	3.302
	25	75.26	5.011

	50	90.46	6.713
	75	108.7	8.993
	95	141.67	13.683

For example, it is shown in Table 3 that the Kaletra gelatin capsule formulation provides a A AUC∞ of 257.9 µg•h/mL from the 5th to the 95th percentile, and A Cmax of 20.21 µg/mL from the 5th to the 95th percentile. In contrast, the dosage form of the present invention provides a A AUCoo of 141.15 µg•h/mL from the 5th to the 95th percentile, and A Cmax of 11.98 µg/mL from the 5* to the 95th percentile.

In other words, 90 % of the study subjects in Table 3 will have a A AUCoo of 257.9 µg•h/mL and A Cmax of 20.21 µg/mL upon dosing of the Kaletra gelatin capsule formulation, while 90 % of the study subjects will have a A AUCoo of 141.15 µg•h/mL and A Cmax of 11.98 µg/mL upon dosing of dosage form of the present invention.

Again, looking at Table 3, this difference is even evident at the 25th to the 75th percentile wherein the Kaletra gelatin capsule formulation provides a A AUCoo of 75.53 µg•h/mL and A Cmax of 6.36 µg/mL for 50 % of the study subjects. In stark contrast, the dosage form of the present invention provides a A AUCoo of 52.71 µg•h/mL and A Cmax of 4.5 µg/mL for 50 % of the study subjects.

The dosage form of the present invention demonstrates no food effect. The ratio "X" of AUCoo fed to AUCoo fasted for lopinavir is calculated using the formula below,

$$\frac{\text{AUCoo (fed)}}{\text{AUCoo (fasted)}} = X.$$

The calculation is performed for each individual member of a study population in a given trial. The mean value is calculated by adding up the "X" values of every subject and then dividing the total by the number of subjects in the trial. When the "X" value is in the range of about 0.7 to about 1.43, it is determined that the dosage form has no food effect. That is, the dosage form will have substantially the same bioavailability whether it is administered on a full or empty stomach.

The ratio "Y" of Cmax fed to Cmax fasted for lopinavir is calculated using the formula below,

$$\frac{\text{Cmax (fed)}}{\text{Cmax (fasted)}} = X.$$

The calculation is performed for each individual member of a study population in a given trial. The mean value is calculated by adding up the "Y" values of every subject and then dividing the total by the number of subjects in the trial. When the "Y" value is in the range of about 0.7 to about 1.43, it is determined that the dosage form has no food effect. That is, the dosage form will have substantially the same bioavailability whether it is administered on a full or empty stomach.

Table 6 below better illustrates how "X" and "Y" values are calculated from individual members of a study population totaling 20 subjects.

Table 6. Fed/Fasted Ratio of Cmax and AUC for individual subjects.

Subject	Cmax (fed) / Cmax (fasted)	AUC∞ (fed) / AUC∞ (fasted)
1	1.10	0.93
2	0.86	0.86
3	0.74	1.25
4	1.69	2.70
5	0.89	1.07
6	1.36	1.25
7	0.97	1.25
8	0.77	1.05
9	1.30	1.77
10	1.48	2.23
11	1.12	1.45
12	0.60	0.67
13	0.94	0.75
14	1.48	1.82
15	1.19	1.32
16	0.94	0.93
17	0.41	0.62
18	0.98	1.49
19	0.95	1.01
20	1.05	1.13
Total number of subjects (N)	20	20
Total value	20.82	25.55
Mean value	(20.82 / 20) = 1.04	(25.55 / 20) = 1.28

Table 6. shows the mean Cmax value is 1.04 and the mean AUC∞ value is 1.28. These values are both individually within the range of about 0.7 to about 1.43 and show that the dosage form of the present invention has no food effect.

In conducting several studies comparing the dosage form of the present invention to the currently marketed Kaletra gelatin capsule formulation it has also been found that the dosage form of the present invention minimizes or eliminates many adverse events. Particularly, it has been found that the dosage form of the present invention minimizes or eliminates gastrointestinal adverse events. Table 7. below compares the number and types of adverse events in terms of percentage of study populations when administered the dosage form of the present invention versus the currently marketed Kaletra gelatin capsule formulation.

Table 7. Percentage of study population suffering adverse event by type.

Type of adverse event	Presently claimed dosage form (% of study subjects)	Currently marketed Kaletra gelatin cvapsule formulation (% of study subjects)
Abdominal pain	13	20
Asthenia	0	23
Headache	13	23
Diarrhea	17	50
Flatulence	4	14
Nausea	9	23
Taste Perversion	4	11