Title: PHARMACEUTICAL COMPOSITION CONTAINING NON-LIPOPHILIC HYDROPHOBIC DRUG AND PROCESS FOR THE PREPARATION THEREOF

Abstract: The present invention relates to a pharmaceutical composition comprising a therapeutically effective quantity of a non-lipophilic, hydrophobic active ingredient, such as aprepitant or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and a lipid/surfactant based drug delivery system in order to enhance the solubility/bioavailability of said active ingredient and a process for the preparation thereof.
PHARMACEUTICAL COMPOSITION CONTAINING NON-LIPOPHILIC HYDROPHOBIC
DRUG AND PROCESS FOR THE PREPARATION THEREOF

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising a therapeutically effective quantity of a non-lipophilic hydrophobic active ingredient, such as aprepitant or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and a lipid/surfactant based drug delivery system in order to enhance the solubility/bioavailability of said active ingredient and a process for the preparation thereof.

Moreover, the present invention relates to a pharmaceutical composition comprising of non-lipophilic, hydrophobic active ingredient such as aprepitant or a pharmaceutically acceptable salt, prodrug, or derivative thereof with improved physicochemical characteristics, which help in the effective delivery of aprepitant.

BACKGROUND OF THE INVENTION

Aprepitant is a NK1 receptor antagonist used for the treatment of emesis associated with chemotherapy. Aprepitant's chemical name is 5-\([(2R,3S)-2-[(lR)-l-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4morpholinyl]methyl\)- 1,2-dihydro-3H- 1,2,4-triazol-3-one and its chemical structure is presented by the following Formula I.

![Formula I](image)

Aprepitant is a white to off-white crystalline solid powder that is practically insoluble in water, sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile. The solubility of the drug in different solvents values and different pH is given below in Table 1 and 2, respectively.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>40mg/mL</td>
</tr>
<tr>
<td>ACN</td>
<td>10/10 mL</td>
</tr>
<tr>
<td>Water</td>
<td>Insoluble (10mg/100mL)</td>
</tr>
</tbody>
</table>

Table 1: Solubility of Aprepitant in different solvents.
Table 2: Solubility of Aprepitant in different pH values.

<table>
<thead>
<tr>
<th>pH</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>Insoluble (10mg/100 mL)</td>
</tr>
<tr>
<td>3.0</td>
<td>Insoluble (10mg/100 mL)</td>
</tr>
<tr>
<td>4.5</td>
<td>Insoluble (10mg/100 mL)</td>
</tr>
<tr>
<td>6.8</td>
<td>Insoluble (10mg/100 mL)</td>
</tr>
<tr>
<td>7.2</td>
<td>Insoluble (10mg/100 mL)</td>
</tr>
<tr>
<td>8.0</td>
<td>Insoluble (10mg/100 mL)</td>
</tr>
</tbody>
</table>

The poor solubility of aprepitant in aqueous media and poor permeability and delivery characteristics pose a tremendous challenge to the pharmaceutical formulation scientist in its delivery in adequate concentrations into the systemic circulation. Additionally, the delivery of aprepitant is also fraught with inter-patient variability when delivered as a tablet formulation, thereby requiring a nanoparticulate capsule-based composition to overcome this problem.

Moreover, Aprepitant is characterized as a hydrophobic compound with logP 1.1 and melting point of approximately 255°C.

It is well known, that poor water solubility is a significant obstacle for drug absorption. Approximately 40% of the drugs worldwide are insoluble in water and therefore, are difficult to formulate. It has been reported that since 1995, 90% of drugs released into the market have limited solubility and/or poor permeability. Therefore, improving the solubility will benefit patients and consumers by rendering previously poorly absorbed compounds more bioavailable and hence more effective for a given dose.

Problems in bioavailability (including plasma concentration fluctuations) have been observed during the administration of oral dosage forms of Aprepitant due to the low aqueous solubility of the active ingredient.

Various methods are already known for the industrial preparation of oral dosage forms comprising aprepitant or a pharmaceutically acceptable salt, prodrug or derivative thereof, as an active ingredient due to its useful therapeutical properties. However, the prior art has encountered substantial difficulties in the production of bioavailable composition of aprepitant.

EP-B-0 644 755 discloses a pharmaceutical composition of aprepitant, wherein in order to overcome these drawbacks, the particle size of the active ingredient is decreased to nanoscale by using a wet-milling method. The composition comprises excipients aiding in the reduction of the active ingredient particle size, "forcing" the obtained nanoparticles to remain separated during and after coating onto microcrystalline cellulose beads, preventing agglomeration of beads and allowing the particles of the active ingredient to re-disperse from the beads in vivo having the maintained nano-size. Further, it discloses a manufacturing process comprising the steps of: (1) production of a slurry of water, with a cellulose based excipient and Aprepitant, (2) pre-milling, (3) addition of an aqueous surfactant dispersion, (4) media milling of the above dispersions to form a new nanosized colloidal dispersion, (5) addition of an aqueous sucrose dispersion, (6) spray-coating of the nanosized colloidal dispersion on microcrystalline cellulose beads,
(7) sieving of the coated beads, (8) blending of coated beads with several excipients, and finally (9) encapsulating of the blended beads in hard gelatin capsules.

WO-A-2013/076659 discloses the use of alternative polymorph or co-crystals of aprepitant in order to increase the drug dissolution rate and/or achieve transient solubilization.

EP 2254 555 discloses solubility-enhanced forms of aprepitant, wherein said aprepitant is in the form of a complex with cyclodextrins in order to achieve a sustained solubilization of the drug.

Although each of the above patents represents an attempt to overcome the solubility/bioavailability problems associated with pharmaceuticals compositions comprising aprepitant, there still exists a need for improving Aprepitant's aqueous solubility/bioavailability of such pharmaceutical compositions in a less complicated production approach.

SUMMARY OF THE INVENTION

It is, therefore, an object of the present invention to provide a pharmaceutical composition for oral administration comprising a non-lipophilic hydrophobic active ingredient, such as aprepitant or a pharmaceutically acceptable salt, prodrug, or derivative thereof, with enhanced solubility/bioavailability of said active ingredient, which overcomes the deficiencies of the prior art.

Still, it is another object of the present invention to provide a pharmaceutical composition for oral administration comprising a non-lipophilic hydrophobic active ingredient, such as aprepitant or a pharmaceutically acceptable salt, prodrug, or derivative thereof, with improved physicochemical characteristics and enhanced bioavailability of aprepitant.

Moreover, it is another object of the present invention to provide a suitable process for the preparation of a pharmaceutical composition for oral administration comprising a therapeutically effective quantity of a non-lipophilic hydrophobic active ingredient, and in particular aprepitant or a pharmaceutically acceptable salt, prodrug, or derivative thereof, which is cost effective and reproducible.

In accordance with the above objects of the present invention, a pharmaceutical composition for oral administration is provided comprising a therapeutically effective quantity of a non-lipophilic hydrophobic active ingredient, such as aprepitant or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and a lipid/surfactant based drug delivery system in order to increase the solubility/bioavailability of the active ingredient.

According to another embodiment of the present invention, a process for the preparation of a pharmaceutical composition for oral administration comprising a therapeutically effective quantity of a non-lipophilic hydrophobic active ingredient, and in particular aprepitant or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and a lipid/surfactant based drug delivery system in order to increase the solubility/bioavailability of the active ingredient, wherein said active ingredient is mixed or suspended or dissolved with the lipid/surfactant based drug delivery system.

Further preferred embodiments of the present invention are defined in dependent claims 2 to 7.
Other objects and advantages of the present invention will become apparent to those skilled in the art in view of the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

In general, when working with low bioavailability compounds of Class II (poorly soluble, highly permeable) and/or Class IV (poorly soluble, poorly permeable) according to Biopharmaceutics Classification System (BCS), two approaches are common in order to increase the bioavailability:

1) solid dosage forms developed to increase dissolution rate, and
2) dosage forms containing the compound in lipid/surfactant solution-suspension system.

The first approach includes solid dosage forms wherein the dissolution rate is enhanced by: 1) increasing the available active ingredient surface area (e.g. nanoparticles), 2) using an alternative polymorph/co-crystals, 3) using a salt of the drug substance, 4) preparing eutectic mixtures and/or solid dispersions (stabilizing an amorphous or molecular form of the compound in polymers), and 5) preparing an inclusion complexes using cyclodextrins or others.

The second approach, lipid/surfactant-based drug delivery systems, have become an essential tool in the development of formulations of water-insoluble drugs for oral administration as said compounds have become increasingly important in therapy.

It has been surprisingly found that the object of the present invention is achieved by employing a lipid/surfactant-based drug delivery system in order to improve the solubility/bioavailability of Aprepitant or pharmaceutically acceptable salt, prodrug or derivative thereof.

A lipid/surfactant-based drug delivery system (LSBDDS) typically is composed of lipids and/or surfactants, and may also contain a hydrophilic co-solvent.

The drug is generally present in the dosage form dissolved in the formulation, and remains solubilized after dispersion of the dosage form in the GI tract. Absorption by the intestinal mucosal cells is facilitated by the rapid release of drug from the high surface area of the small emulsion or microemulsion droplets.

LSBDDS circumvent the dissolution step in the gastrointestinal tract by complex processes often involving digestion of the excipients, formation of different colloid phases and transfer of the drug between these phases. The active ingredient will be transferred from being a solution (into the formulation) to partition into lamellar or hexagonal phases formed during digestion and then transferred into mixed micelles.

Some of said drug delivery systems are characterized as Self-Emulsifying Drug Delivery Systems (SEDDS) such that they form an emulsion upon gentle agitation in water. Emulsions are considered metastable systems, with droplet sizes of 100-1000nm. Some other drug delivery systems, such as Self-Microemulsifying Drug Delivery Systems (SMEDDS), form microemulsions that are thermodynamically stable systems with droplet diameters <100 nm, wherein said microemulsions are visually transparent or translucent.
Both said drug delivery systems have attracted increasing interest primarily due to their ability to be delivered as pre-concentrates in a capsule following the generation of a drug containing (micro)-emulsion with a large surface area upon dispersion in the GIT. This emulsion will further facilitate the absorption of the drug due to a faster digestion by gastrointestinal enzymes and subsequent transfer to mixed micelles or possible absorption directly from the emulsion particle, by partitioning of drug into the aqueous phase of intestinal fluids. Usually said drug delivery systems comprise an oil, a surfactant, a co-surfactant or solubilizer, a co-solvent and a drug. The principle of said systems is that when they come in contact with the gastrointestinal fluids, they spontaneously form oil-in-water micro-emulsions under mild mechanical agitation thus improving the bioavailability of said drug. Compared with emulsions/micro-emulsions, both said drug delivery systems have the same advantage of facilitating the bioavailability of hydrophobic drugs, but also overcomes the drawback of instability (chemical and physical) as being a thermodynamic-stable system.

Even though BCS class II and IV drugs are hydrophobic with various logP values and low solubility and dissolution rate, said drugs still have different properties, e.g. said active ingredients may be divided into two groups depending on their lipophilicity. Non-lipophilic hydrophobic drugs (also called "brick dust") have a tight crystal lattice and are not very soluble in lipids, while lipophilic hydrophobic drugs ("grease balls") are more soluble in lipids than the brick dust category. Aprepitant with logP 1.1 is considered to be a brick dust active ingredient.

According to one embodiment, the pharmaceutical composition of the present invention comprises of a pharmaceutically effective amount of the Aprepitant, an oil phase and/or a surfactant and/or a co-surfactant.

According to another embodiment of the present invention, the lipids used may be of animal, vegetable or mineral origin, which are substantially inert, non-toxic hydrocarbon fats and oils and derivatives thereof, and may comprise any of the commonly commercially available fats or oils approved for pharmaceutical use. The lipid(s) may be liquid or solid at room temperature.

Lipids, which can be used individually or in combination in the present invention, may be selected, but not limited, from the following categories:

- Fatty acids,
- Natural oils and fats,
- Semi-synthetic mono-, di-, and triglycerides,
- Semi-synthetic PEG derivatives of glycerides and fatty acids,
- Polyglyceryl fatty acid esters
- Cholesterol and phospholipids

Fatty acids are monocarboxylic acid derivatives of saturated or unsaturated aliphatic hydrocarbons. Saturated fatty acids with eight or fewer carbons are flowable liquids while fatty acids of 10 or more carbons in chain length are semi solids at room temperature. Examples of fatty acids include, but not limited to: formic, acetic, propionic, butyric, valeric, caproic, caprylic, capric, lauric, myristic, myristoleic, palmitic, palmitoleic, margaric, stearic, oleic, ricinoleic, linoleic, linolenic, arachidic, gadoleic, gondoic, behenic, erucic, lignoceric fatty acids.
Naturally occurring oils and fats are comprised of mixtures of various triglycerides which are referred to as triacylglycerols, since chemically they are fatty acid tri-esters of glycerol. Several naturally oils and fats have been hydrogenated to decrease the number of double bonds, thereby conferring resistance to oxidative degradation. Examples of such include, but not limited to: arachis, castor, canola, coconut, corn, cottonseed, olive, palm, peanut, repeseed, sesame, soybean, sunflowerseed, vegetable oils, sweet orange oil and oleic acid.

Additionally to the naturally occurring triglycerides, there are several commercially available semi-synthetic glycerides. Examples of semi-synthetic mono-, di-, and triglycerides include, but not limited to: Glyceryl triacetate (triacetin), Glyceryl mono-, di-, tribehenate, Glyceryl tribehenenate (tribehehnen), Glyceryl tributyrurate (tributyrin), Glyceryl mono- and dicaprate, Glyceryl tricaprate (tricaprin), Glyceryl mono- and dicaprylate, Glyceryl tricaprylate (tricaprylin), Glyceryl mono- and dicaprylate/caprate, Glyceryl tricaprylate/caprate (medium chain triglycerides), Glyceryl tricaprylate/ caprate/laurate, Glyceryl tricaprylate/ caprate/linoate, Glyceryl tricaprylate/ caprate/stearate, Glyceryl tricaprylate/ caprate/succinate, Glyceryl monolaurate, Glyceryl dilaurate, Glyceryl trilaurate (trilaurin), Glyceryl monolinoleate, Glyceryl trimyristate (trimyristin), Glyceryl monooleate, Glyceryl mono- and dioleate, Glyceryl trioleate (triolein), Glyceryl tripalmitolate (tripalmitin), Glyceryl palmitostearate, Glyceryl monostearate, Glyceryl distearate, Glyceryl mono-, di-, and tristearate, Glyceryl tristearate (tristearin), Glyceryl tri-undecanoate (triundecanoin), Hard fat.

Examples of semi-synthetic PEG derivatives of glycerides and fatty acids include, but not limited to: PEG-4 glyceryl caprylate/caprate, PEG-6 glyceryl caprylate/caprate, PEG-6 glyceryl linoleate, PEG-6 glyceryl oleate, PEG-8 glyceryl caprylate/caprate, PEG-32 glyceryl laurate, PEG-32 glyceryl palmitostearate, PEG-35 castor oil, PEG-40 castor oil, PEG-40 hydrogenated castor oil.

The polyglyceryl fatty acid esters are composed of a chain of glycerol molecules, linked together by ether linkages, which are esterified with one or more fatty acid molecules. Examples include, but not limited to: Polyglyceryl-3 olate, Polyglyceryl-3 dioleate, Polyglyceryl-3 stearate, Polyglyceryl-3 diostearate, Polyglyceryl-6 dioleate, Polyglyceryl-6 octaesterate, Polyglyceryl-10 mono, dioleate, Polyglyceryl-10 decaoleate.

Finally, examples of cholesterol and phospholipids include, but not limited to: Sodium cholesteryl sulfate, L-a-Lecithin, Egg lecithin, Phosphatidic acid, Dioleoylphosphatidic acid, Dipalmitoylphosphatidic acid, Phosphatidylcholine, Dierucoylphosphatidylcholine, Dilauroylphosphatidylcholine, Dilinoleoylphosphatidylcholine, Dimyristoylphosphatidylcholine, Dioleoylphosphatidylcholine, Dipalmitoylphosphatidylcholine, Palmitoyl-oleoylphosphatidylcholine, Disteroylphosphatidylcholine, Hydrogenated egg phosphatidylcholine, Hydrogenated soy phosphatidylcholine, Phosphatidylcholine and lyso-phosphatidylcholine, Phosphatidyl-ethanolamine, Dioleoylphosphatidylethanolamine, Distearoylphosphatidylethanolamine, Phosphatidylglycerol, Dimyristoylphosphatidylglycerol, Dioleoylphosphatidylglycerol, Dipalmitoylphosphatidylglycerol, Distearoylphosphatidylglycerol, Palmitoyl- oleoylphosphatidylglycerol, Phosphatidylinositol, Phosphatidylerine, Dioleoylphosphatidylerinerine, Palmitoyl -oleoylphosphatidylerinerine, Sphingomyelin.
These lipids can be used alone or in combination. In the composition of the present invention, it is preferred that the lipids are present in amounts ranging from about 0% to 100% by weight of the excipient.

In another embodiment of the present invention the surfactants/co-surfactants used may be any of those known in the art, which includes, but is not limited to: cationic, anionic, and nonionic surfactants. The surfactant/co-surfactant used in the present invention should possess a Hydrophilic Lipophilic Balance (HLB) value of greater than about 1 according to the HLB system which is well known to those skilled in the art. The HLB value provides a means for ranking surfactant/co-surfactant according to the balance between the hydrophilic and lipophilic portions of the surfactant agent. That is, the higher the HLB value, the more hydrophilic the surfactant agent. Typically, the surfactant/co-surfactant used in the present invention has a HLB value ranging from about 1 and above. Examples of suitable surfactant/co-surfactant include, but are not limited to: polyoxyethylene-sorbitan-fatty acid esters, e.g., mono- and tri-lauryl, palmityl, stearyl and oleyl esters; polyoxyethylene fatty acid esters, e.g., polyoxyethylene stearic acid esters; polyoxy-ethylene castor oil derivatives; a-tocopherol, a-tocopheryl polyethylene glycol succinate (vitamin E TPGS), a-tocopherol palmitate and a-tocopherol acetate; PEG glyceryl fatty acid esters; propylene glycol mono- and di-fatty acid esters, such as propylene glycol laurate, propylene glycol caprylate/caprate and diethylene glycol-monoethylether (DGME); sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene co-polymers; glycerol triacetate; and monoglycerides and acetylated monoglycerides.

These surfactants/co-surfactants can be used alone or in combination. In the composition of the present invention, it is preferred that the surfactant/co-surfactant is present in amounts ranging from about 1% to about 99% by weight of the composition and more preferably in an amount ranging from about 10% to about 90% by weight.

The co-solvent carrier used in the present invention must be non-toxic and well tolerated physiologically. In addition, the carrier should allow the incorporation of the drug into the carrier. According to the present invention, the hydrophilic carrier includes, but is not limited to ethanol, glycol ethers, isopropanol, propylene glycol, glycerin, diethylene glycol monoethylether, polyethylene glycol etc. Also, nitrogen-containing co-solvent may be selected. Examples include, but is not limited to: dimethylformamide, dimethylacetamide, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N- alkylcaprolactam and mixtures thereof wherein alkyl is a C1-12 branched or straight chain alkyl. Any of the above-mentioned carriers can be used alone or in combination with one or more carriers. In the composition of the present invention, it is preferred that the carrier is present in amounts ranging from about 1% to about 99% by weight of the composition and more preferably in an amount ranging from about 2% to about 80% by weight.

In another embodiment of the present invention lipid excipients vulnerable to oxidation may be protected by inclusion of an antioxidant as stabilizing component of the formulation. The addition of the antioxidant is particularly important to formulations with high content of unsaturated fatty acids or derivatives thereof. Examples of the antioxidants useful in the composition of the present invention include, but are not limited to, butylated hydroxytoluene (BHT), sodium bisulfite, α-tocopherol, vitamin C (ascorbic acid), β-carotene, ascobylpalmitate,
tocopherol acetate, fumaric acid, malic acid, butylated hydroxyanisole (BHA), propyl gallate, sodium ascorbate, tertiary-butyl hydroquinone (lipid soluble) and propyl gallate (lipid soluble). Such antioxidants can be added in the range of 0.0001-10% of the total amount of composition.

The lipid/surfactant-based drug delivery system of the present invention may include further additives (alone or in a combination) such as absorbents, acids, adjuvants, anticaking agents, glidants, antitacking agents, antifoamers, antimicrobials, antiseptics, diluents, binders, chelating agents, sequestrants, coating agents, colorants, dyes, pigments, complexing agents, softeners, crystal growth regulators, denaturants, desiccants, dehydrating agents, dispersants, solubilizers, emollients, emulsifiers, fillers, flavor masking agents, gelling agents, humectants, lubricants, moisturizers, bufferants, pH control agents, plasticizers, retarding agents, stabilizers, suspending agents, sweeteners, disintegrants, thickening agents, surfactants, opacifiers, coloring agents, preservatives, antigellants, rheology control agents, tonicifiers etc.

The pharmaceutically acceptable excipients used in the composition of the present invention shall be compatible with Aprepitant.

Diluents may be selected from calcium carbonate, calcium phosphate dibasic, calcium phosphate tribasic, calcium sulfate, microcrystalline cellulose, microcrystalline silicified cellulose, powdered cellulose, dextrates, dextrose, fructose, lactitol, lactose anhydrous, lactose monohydrate, lactose dihydrate, lactose trihydrate, mannitol, sorbitol, starch, pregelatinized starch, sucrose, t alc, xylitol, maltose, isomalt, maltodextrin, maltitol and the like. Diluents may be in the range of 10-90 weight % of the total weight of the composition.

Binders may be selected from acacia, alginic acid, caromer, carboxymethylcellulose calcium, carboxymethylcellulose sodium, microcrystalline cellulose, powdered cellulose, ethyl cellulose, gelatin liquid glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, maltodextrin, methylcellulose, polydextrose, polyethylene oxide, povidone, sodium alginate, starch paste, pregelatinized starch, sucrose, tragacanth, low-substituted hydroxypropyl cellulose, glucose, sorbitol. Suitable fillers are preferably selected from at least one of starch derivatives, such as corn starch, potato starch, maize starch maize or rice starch. Polysaccharides such as dextrins, maltodextrins, dextrates, microcrystalline cellulose, powdered cellulose, mixture of microcrystalline cellulose and guar gum, coprocessed blends of microcrystalline cellulose; and polyhydric alcohols, such as xylitol, sorbitol and the like. Binders may be in the range of 1-40 weight % of the total weight of the composition.

Disintegrants may be selected from alginic acid, carbon dioxide, carboxymethylcellulose calcium, carboxymethylcellulose sodium, microcrystalline cellulose, powdered cellulose, croscarmelose sodium, crospovidone, sodium docusate, gaur gum, hydroxypropyl cellulose, methylcellulose, polacrilin potassium, poloxamer, povidone, sodium alginate, sodium glycine carbonate, sodium lauryl sulfate, sodium starch glycolate, starch, pregelatinized starch, low-substituted hydroxypropyl cellulose and the like. Disintegrants may be in the range of 5 - 25 weight % of the total weight of the composition.

Glidants may be selected from calcium silicate, powdered cellulose, starch, talc, colloidal silicon dioxide and the like. Glidants may be in the range of 0.01-2 weight % of the total weight of the composition.
Lubricants may be selected from magnesium stearate, stearic acid, sodium stearyl fumarate, magnesium lauryl sulphate, talc, polyethylene glycol, glyceryl behenate and the like. Lubricants may be in the range of 0.010-2 weight % of the total weight of the composition.

Suitable sweeteners may be selected from sugars such as sucrose, lactose and glucose; cyclamate and salts thereof; saccharin and salts thereof; aspartame and the like.

Flavouring agents may be selected from natural or synthetic flavours such as strawberry flavour, wild cherry flavour, green apple flavour, spearmint flavor, peppermint flavor and the like.

Solubilizers may be selected from complex forming agents such as cyclodextrins, ion exchange resins, crown ethers and the like.

According to the present invention the formulations with said lipid/surfactant-based drug delivery system improve the bioavailability and pharmacokinetic profile of Aprepitant or pharmaceutical acceptable salt, prodrug or derivative thereof, after oral, parenteral, intramuscular, transdermal, nasal, sublingual, buccal and/or subcutaneous administration and/or improve patient compliance through an easily followed dosing regimen.

According to another embodiment of the present invention, the Aprepitant composition of the present invention forms an oil/water nanoemulsion instantaneously when brought into contact with the aqueous medium of the GI tract with mild agitation provided by gastric mobility in the tract region. The formation of nanoemulsion leads to a superior absorption and enhanced bioavailability of the aprepitant enabling consistent profiles of drug absorption and protection of drug from the hostile environment in gut.

The composition of the present invention, by virtue of its choice of surfactants, does not lead to any precipitation of the active ingredient, and subsequently also does away with the use of any polymeric molecular aggression inhibitors, thus providing a composition that is effective and stable over a wide period of time.

The pharmaceutical compositions of the present invention may be prepared by mixing Aprepitant or pharmaceutical acceptable salt, pro-drug, derivative or metabolite thereof, with the LSBDDS excipients. Preferably, one or more lipids, surfactants, co-surfactants, co-solvents, antioxidants, active ingredient and several selected excipients are mixed to obtain a homogeneous solution/suspension.

The aprepitant compositions of the present invention are ideal for oral delivery systems, since they are homogeneous, thermodynamically stable, and have uniform droplet sizes. The aprepitant LSBDDS composition of the present invention may be processed in the form of liquid by filling appropriate capsule shells or "transformed" into solid dosage form.

When the composition of the present invention is in the form of a soft gelatin capsule, the plasticizer comprised may be selected from a group consisting of glycerine, sorbitol, hexanetriol propylene carbonate, hexane glycol, sorbitans, tetrahydrofuryl alcohol ether, diethylene glycol monoethyl ether, 1,3-trimethyl-2-imidazolidone, and dimethylsorbide.

Comparison of soft and hard gelatin capsules indicate that soft gelatin capsule contains a significant amount of plasticizer, usually glycerol or sorbitol, while the gelatin used in hard
capsules contain no plasticizer. Plasticizers impact elasticity to the gelatin shell and allow it to accommodate a wide range of hydrophilic excipients, but their presence raises issues of component migration. However, capsule makers recently introduced a hard gelatin capsule with a small amount of plasticizer in order to compensate these drawbacks. Furthermore, soft gelatin capsules may expose the fill material to more oxygen compared to hard gelatin capsule shells, leading to potential oxidation. On the contrary, when the LSBDDS is in liquid form in room temperature, liquid hard gelatin capsules may require an extra process step for sealing in order to avoid any risks of leakage.

In the case of hard capsule shells (gelatin, gelatin plus plasticizer, HPMC, PVA etc.) the LSBDDS should not exceed the 90% of the total capsule fill volume capacity in order to avoid product leakage during production. The selection of appropriate materials (excipients, reagents etc.) should be done carefully in order to avoid any incompatibility issues with the capsule shell. Especially in the case of hard gelatin capsule shells, gelatin crosslinking may occur by the formation of an insoluble pellicle. Internal crosslinking describes the situation where the inner surface of the dissolving capsule shell appears to be less soluble than outer surface, suggesting incompatibility between gelatin and formulation. External crosslinking may suggest that environmental factors, such as heat, humidity and packaging components, are responsible for the incompatibility. In addition to the above incompatibility issues, the water content of the hard gelatin capsule shell should be carefully monitored in order to avoid capsule swelling, shrinkage, turned edges, or accumulation of static charge. It is important to note that many of these incompatibilities may be counterbalanced in the case of other types of shells (such as HPMC, PVA, gelatin plus plasticizer etc.) although these solutions are not a panacea, as issues regarding oxidation, solubility in low pH values (for HPMC based shells) and increased costs, should be taken into consideration before making a decision.

In the case where the liquid LSBDDS is "transformed" into a solid dosage form, a free flowing, dry, stable and compactable powder mixture is obtained. The solid free flowing powder may be further processed as is filled into capsule/sachet etc, or may be compressed into tablets/mini-tablets etc. Conversion into solid state can be achieved by different means including the methods given below:

- The LSBDDS comprising the surfactant, co-surfactant, oil, co-solvent and optionally water is adsorbed onto a solid support. The solid support is chosen from the different solid pharmaceutical excipients, such as: colloidal silicon dioxide, talc, microcrystalline cellulose, magnesium oxide, magnesium hydroxide, titanium dioxide, lactose, polyvinylpyrrolidone (PVP), magnesium aluminum silicate, calcium carbonate, calcium phosphate dibasic anhydrous, calcium phosphate tribasic, calcium stearate, calcium sulfate, crossPVP, polycarbophil, calcium silicate, magnesium carbonate. The LSBDDS is slowly added to the selected excipient system during continuous and vigorous mixing in order to obtain a free flowing powder.

- The LSBDDS is converted into a solid by stabilization of individual emulsion phases with hydrophilic and hydrophobic solid supports. Preferably a hydrophobic and a hydrophilic excipients are used (e.g. colloidal silicon dioxide). The water phase of the dispersion is adsorbed on a hydrophilic while the oil phase is adsorbed on a hydrophobic
solid excipients also by vigorous mixing. Then, solid state water phase, solid state oil phase and emulsifier mixture were mixed to obtain a free flowing powder.

- The LSBDDS is incorporated in a melting excipient such as polyethylene glycol. The obtained mixture is rapidly solidified and the composition is pulverized and sieved to form a free flowing granule.
- The LSBDDS is spray dried on a solid carrier such as MCC or sugar spheres, sugars lactose, maltose, fructose, dextran, glucose; sugar alcohols such as sorbitol, maltitol; PVP, polyvinyl alcohol (PVA), low viscosity grades of cellulose derivatives, colloidal silicon dioxide etc.

The prepared "transformed" free flowing solid can be a formulation into powder for reconstitution in a suspension, granules, tablet, mini-tablet, soluble tablet, rapidly disintegrating tablet, orally disintegrating tablet, rapidly disintegrating film, capsule, sachet, effervescent tablet, a chewable tablet, water dispersible tablet, a chewing gum and suspension, pellets etc.

The granules or tablets may be coated with functional or non-functional coating.

The composition of the present invention may be prepared using conventional techniques employed in the art for mixing/lubrication, compaction/slugging, wet and dry granulation, milling, drying, sizing, compressing, filling in capsules, sachets and the like.

The steps in the wet granulation technique may be as follows: (a) Weighing and mixing ingredients; (b) Adding binder solution or an adhesive /kneading; (c) Screening the damp mass into pellets or granules; (d) Drying and screening/sizing; (e) Mixing/Lubricating; And (f) Tableting or filling in capsules/sachet.

In dry granulation there is no addition of binder solution, but the powdered drug mixture is compressed into large masses called slugs, sized into smaller granules, mixed, lubricated and compressed in tablets or filled in capsules or sachet.

The composition optionally may be prepared by direct compression of the ingredients into tablets or mini-tablets, which may be filled in capsules or by dry mixing the ingredients, which may be filled in capsules/sachets.

Accordingly, the present invention provided a drug delivery system for aprepitant based on a lipid/surfactant pharmaceutical composition.

In contrary to all previous attempts where the bioavailability of Aprepitant is being enhanced by increasing the active ingredient dissolution rate in aqueous media, in the present invention the enhancement of Aprepitant bioavailability, or pharmaceutical acceptable salt, prodrug or derivative thereof, is achieved by active ingredient partitioning through the gastric digestion process, using a lipid/surfactant based drug delivery system that is safe, easy to produce and efficient.

While the present invention has been described with respect to the particular embodiments, it will be apparent to those skilled in the art that various changes and modifications may be made in the invention without departing from the spirit and scope thereof, as defined in the appended claims.
1. A pharmaceutical composition for oral administration comprising a therapeutically effective quantity of a non-lipophilic hydrophobic active ingredient, such as aprepitant or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and a lipid/surfactant based drug delivery system in order to enhance the solubility/bioavailability of said active ingredient.

2. The pharmaceutical composition according to claim 1, wherein said system comprises an oil phase, a surfactant and/or co-surfactant and/or a co-solvent.

3. The pharmaceutical composition according to claim 1, wherein said active ingredient is aprepitant or a pharmaceutically acceptable salt, prodrug, or derivative thereof.

4. The pharmaceutical composition according to claim 1, wherein the amount of aprepitant in said composition is in the range of 3-50 weight % of the total weight of the composition.

5. The pharmaceutical composition according to claim 1, wherein said pharmaceutical composition spontaneously forms a micro/nano emulsion when brought in contact with an aqueous fluid of human gastro-intestinal tract.

6. The pharmaceutical composition according to claim 1, wherein the aprepitant is present in the range of 3-50 %, said oil phase is present in the range 0-99 %, said surfactant/co-surfactant is present in the range of 0-99 %, and said co-solvent is present in the range of 0-99 % by weight in said composition.

7. The pharmaceutical composition according to claim 1, wherein said pharmaceutical composition further comprises pharmaceutically acceptable additives selected from a group comprising of absorbents, acids, adjuvants, anticaking agents, glidants, antitacking agents, antifoamers, anticoagulants, antimicrobials, antiplatelets, diluents, binders, chelating agents, sequestrants, coating agents, colorants, detergents, pigments, complexing agents, softeners, crystal growth regulators, denaturants, desiccants, dehydrating agents, dispersants, solubilizers, emollients, emulsifiers, fillers, flavor masking agents, gelling agents, humectants, lubricants, moisturizers, bufferants, pH control agents, plasticizers, retarding agents, stabilizers, suspending agents, sweeteners, disintegrants, thickening agents, surfactants, opacifiers, coloring agents, preservatives, antigellants, rheology control agents, tonicifiers and their combinations thereof.

8. A process for the preparation of a pharmaceutical composition for oral administration comprising a therapeutically effective quantity of a non-lipophilic hydrophobic active ingredient, such as aprepitant or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and a lipid/surfactant based drug delivery system in order to increase the solubility/bioavailability of the active ingredient, wherein said active ingredient is mixed or suspended or dissolved with the lipid/surfactant based drug delivery system.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/107 A61K31/5377
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"A" document member of the same patent family

Date of the actual completion of the international search: 21 July 2015

Date of mailing of the international search report: 28/07/2015

Name and mailing address of the ISA:
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer: Palma, Vera

Form PCT/ISA210 (second sheet) (April 2005)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>CN 102 379 845 A (NANJING YOKO BIOLOG LTD) 21 March 2012 (2012-03-21). The whole document example 1-8.</td>
<td>1-8</td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-----------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>CN 102379845 A</td>
<td>21-03-2012</td>
<td>NONE</td>
</tr>
<tr>
<td>WO 2009108828 A2</td>
<td>03-09-2009</td>
<td>EP 2254555 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2011009362 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2009108828 A2</td>
</tr>
</tbody>
</table>