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SELF EMULSIFYING DRUG DELIVERY SYSTEM: AN EMERGING PARADIGM

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Abstract: One of the primary challenges to any oral formulation development is maintaining drug solubility within the gastrointestinal tract and, in particular, maximizing drug solubility within the prime absorptive site of the gut. For lipophilic drug compounds that exhibit dissolution-rate-limited absorption, Self Emulsifying Drug Delivery System (SEDDS) can offer an improvement in rate and extent of absorption, resulting in reproducible blood time profiles. SEDDS are isotropic mixtures of drug, lipids and surfactants and usually with one or more hydrophilic co-solvents or co-surfactants. Upon mild agitation followed by dilution with aqueous media, these systems can form fine (oil in water) emulsion instantaneously, and hence when administered orally get self emulsify in gastro-intestinal fluids with the help of GI motility. The drug, therefore, remains in solution in the gut, avoiding the dissolution step that frequently limits the absorption rate of hydrophobic drugs from the crystalline state. The drug is absorbed by lymphatic pathways, and thus reduces the hepatic first-pass effect.

Keywords: Self-emulsifying drug delivery system, Biopharmaceutical Classification system, Self-micro-emulsifying drug delivery systems, Bioavailability

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INTRODUCTION

Drug absorption, sufficient and reproducible bioavailability and/or pharmacokinetic profile in humans are recognized today as one of the major challenges in oral delivery of new drug substances. The advent of high-throughput screening technologies, combinatorial chemistry, computational modeling, and proteomics has resulted in many more targets and compounds during drug discovery stage, however many of these compounds are highly lipophilic and with high molecular weight. This is because compounds with these properties tend to have more potency (in vitro binding activity) due to additional hydrophobic interactions with enzyme or receptor surface. These compounds are usually not drug-like because of their low water solubility, a major cause for poor pharmacokinetics and oral bioavailability. As a result, they may falter in further development, resulting in a higher attrition rate and lost productivities [1].

Solubility in different solvents is an intrinsic material characteristic for a defined molecule. To achieve a pharmacological activity, the molecules must in general exhibit certain solubility in physiological intestinal fluids to be present in the dissolved state at the site of absorption. The aqueous solubility is a major indicator for the solubility in the intestinal fluids and its potential contribution to bioavailability issues. Today, about 35–40% of the lead substances are known to have an aqueous solubility of less than 10µM or 5 mg/ml at pH 7 and it is not expected that this figure will change in the future. The solubility or dissolution of the drug substance can be mainly altered on two levels, through material engineering of the drug substance or through formulation approaches [2].

Major formulation strategies for poorly soluble substances [2, 3]:

I. Physical modifications

Particle size

a. Micronization

b. Nanosuspensions

Modifications of the crystal habit

Polymorphs

Pseudopolymorphs (including solvates)

Complexation

a. Use of cyclodextrines

Drug dispersion in carriers

a. Eutectic mixtures

b. Solid dispersions (non-molecular)

c. Solid solutions

Microemulsion

Liposomes

Lyophilisation

Co solvent

II. Chemical modification

Soluble prodrugs

Salts

Self emulsifying drug delivery system:

To overcome the solubility problems, recently much attention has been paid to lipid-based formulations with particular emphasis on self-emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of lipophilic drugs. SEDDS or self-emulsifying oil formulations (SEOF) are isotropic mixtures of drug, lipids and surfactants, usually with one or more hydrophilic co-solvents or co-surfactants [4, 5]. Upon mild agitation followed by dilution with aqueous media, these systems can form fine (oil in water) emulsion instantaneously. 'SEDDS' is a broad term, typically producing emulsions with a droplet size ranging from a few nano-meters to several microns. 'Self-micro-emulsifying drug delivery systems' (SMEDDS) indicates the formulations forming transparent micro-emulsions with oil droplets ranging between 100 and 250 nm. 'Self-nano-emulsifying drug delivery systems' is a recent term construing the globule size range less than 100 nm [6].

The drug, therefore, remains in solution in the gut, avoiding the dissolution step that frequently limits the absorption rate of hydrophobic drugs from the crystalline state. The drug is absorbed by lymphatic pathways, and thus bypasses the hepatic first-pass effect. When compared with emulsions, which are sensitive and metastable dispersed forms, SEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate–limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood–time profiles [7].

Advantages:

Dispersion leads to rapid absorption and reduced variability thereby enhanced oral bioavailability enabling reduction in dose. These lipid formulations give selective targeting of drug(s) toward specific absorption window in GIT and also protect drug(s) from the hostile environment in gut. Could be prepared as a free flowing powder or compressed into tablet form or can be given as such liquid in hard or soft gelatin capsules [8, 9].

Disadvantages:

Surfactant used may be poorly tolerated in chronic use. Soft gelatin or hard gelatin capsule can be used in principle but seal must be effective. Physical stability of product is questionable as drug or polymer may crystallize [8].

Lipid formulation classification system:

The Lipid Formulation Classification System (LFCS) was introduced as a working model in 2000, and an extra 'type' of formulation was added in 2006. The main purpose of the Lipid Formulation Classification System is to enable in vivo studies to be interpreted more readily and, subsequently, to facilitate the identification of the most appropriate formulations for specific drugs (i.e. with reference to their physicochemical properties).Table 1 and 2 shows the fundamental differences and their composition between types I, II, III and IV formulations [6].

Mechanism of self emulsification:

The process by which self-emulsification takes place is not yet understood. Nevertheless, it has been suggested that self-emulsification takes place when the entropy change favoring dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of a conventional emulsion formulation is a direct function of the energy required to create a new surface between the oil and water phases, hence

$$\Delta G = \Sigma N_i 4\pi r_i^2 \sigma \quad \text{.....(1)}$$

Where, ΔG is the free energy associated with the process (ignoring the free energy of mixing), N denotes the number of droplets of radius r and σ is the interfacial energy. The two phases will tend to separate over a period of time in order to reduce the interfacial area between the two phases and hence to reduce the free energy of the system. Conventional emulsifying agents such as surfactants form a layer around the emulsion particles and hence reduce the interfacial energy, as well as providing a barrier to coalescence. In all these cases, however, the separation of the phases is merely being delayed, as thermodynamically these emulsions are still unstable.

In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low or positive or actually negative (i.e., the formation is thermodynamically spontaneous). The interface between the oil and aqueous continuous phases is formed upon addition of a binary mixture (oil/surfactant) to water. This is followed by the solubilization of water within the oil phase as a result of aqueous penetration through the interface. This will occur until the solubilization limit is reached close to the interface. Further aqueous penetration will lead to the formation of the dispersed liquid crystallization (LC) phase. In the end, everything that is in close proximity with the interface will be LC, the actual amount of which depends on the surfactant concentration in the binary mixture. Thus, following gentle agitation of the self-emulsifying system, water will rapidly penetrate into the aqueous cores and lead to interface disruption and droplet formation. As a consequence of the LC interface formation surrounding the oil droplets, SEDDS become very stable to coalescence [5, 10].

Suitable drug candidate identification for SEDDS:

Logically speaking, however, use of SEDDS can be extended to all four categories of biopharmaceutical classification system (BCS) class drugs [6]. These systems can help in solving the under-mentioned problems of all the categories of BCS class drugs, as depicted in table 3.

Digestion and absorption of SEDDS:

While the inclusion of highly lipophilic compounds in self-emulsifying drug delivery systems (SEDDS) is often reported to result in strongly enhanced oral absorption, it is still controversial whether further lipolysis of the dispersed lipidic material is required for final transfer to the enterocyte membranes. P.C. de Smidt et al. [11] has prepared a series of three formulations consisting of penclomedine (Pcm), medium chain triglyceride (MCT), tocophersolan (TPGS) and varying in particle size (160–180; 710–730 nm and crude oil). In order to assess the influence of digestibility, each set was divided into a formulation with or without tetrahydrolipstatin (THL). THL is a known inhibitor of intestinal lipases and is reported to effectively protect triglyceride droplets when predissolved in oil. It was anticipated that when digestion of lipid is essential for uptake of Pcm, co-inclusion of THL would result in low or nonexistent bioavailability. The experimental data clearly indicate that the emulsified formulations containing THL all had similar *F* values as their analogous compositions without THL, providing no support for a critical role of lipid digestion for the absorptive pathway of Pcm in this study. Instead, the finest emulsions of below 200 nm had identical blood-time profiles for the preparations with and without THL, suggesting that interfacial partitioning dominated the absorptive process. The lipid particles of intermediate size (710–730 nm), appeared to have slightly lower bioavailabilities (*F* = 0.79). Furthermore, lower maximum blood concentration values were obtained as compared to formulations showing globule size below 200 nm. The data suggest that for lipid particles of

these dimensions, interfacial transfer can still result in substantial absorption. Administration of Pcm in crude MCT oil resulted in significantly lower *F*, and furthermore showed a quantitative (two-fold decreased absorption) effect of the inhibition of the lipid digestion pathway. For Pcm dissolved in crude oil, the diminution of particle size attained by mechanical forces in the GI tract, such as the passage through the pylorus is not sufficient for the generation of an absorptional surface that can yield efficient interfacial transfer. In this case, the lipid digestion pathway substantially aids the absorptive process. Excipients used in the SEDDS not only aid in solubilization of drug but also facilitates the permeation through the gut wall. Zhaopeng Hu et al. [12] have studied the intestinal permeability of gentamicin in rats, in their study they found that Labrasol(PEG-8 Caprylic/Capric glycerides) have both enhanced gentamicin absorption from the GI lumen into the systemic circulation and inhibition of efflux of gentamicin from the enterocytes to the GI lumen.

Excipients used in SEDDS:

Self-emulsification has been shown to be specific to the nature of the oil/surfactant pair; the surfactant concentration and oil/surfactant ratio; and the temperature at which self-emulsification occurs. In support of these facts, it has also been demonstrated that only very specific pharmaceutical excipient combinations could lead to efficient self-emulsifying systems.

Factors affecting the choice of excipients for lipid-based formulations [13]

1. Regulatory issues—irritancy, toxicity, knowledge and experience
2. Solvent capacity
3. Miscibility
4. Morphology at room temperature (i.e. melting point)
5. Self-dispersibility and role in promoting self-dispersion of the formulation
6. Digestibility, and fate of digested products
7. Capsule compatibility
8. Purity, chemical stability
9. Cost of goods

Oils:

The oil represents one of the most important excipients in the SEDDS formulation not only because it can solubilise marked amounts of the lipophilic drug or facilitate self-emulsification but also and mainly because it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride. Both long and medium chain triglyceride oils with different degrees of saturation have been used for the design of self-emulsifying formulations. Many lipids are used in oral lipid-based formulations as shown in table 4. Furthermore, edible oils which could represent the logical and preferred lipid excipient choice for the development of SEDDS are not frequently selected due to their poor ability to dissolve large amounts of lipophilic drugs. Modified or hydrolyzed vegetable oils have been widely used since these excipients form good emulsification systems with a large number of surfactants approved for oral administration and exhibit better drug solubility properties. They offer formulative and physiological advantages and their degradation products resemble the natural end products of intestinal digestion. Novel semi-synthetic medium chain derivatives, which can be defined as amphiphilic compounds with surfactant properties, are progressively and effectively replacing the regular medium chain triglyceride oils in the SEOFs [5].

Surfactants:

A surfactant is obligatory to provide the essential emulsifying characteristics to SEDDS. Surfactants, being amphiphilic in nature, invariably dissolve (or solubilise) high amounts of hydrophobic drug compounds. The two issues that govern the selection of a surfactant encompass its hydrophilic–lipophilic balance (HLB) and safety. The HLB of a surfactant provides vital information on its potential utility in formulation of SEDDS. For attaining high emulsifying performance, the emulsifier involved in formulation of SEDDS should have high HLB and high hydrophilicity for immediate formation of o/w droplets and rapid spreading of formulation in aqueous media in this context. It would keep drug solubilised for a prolonged period of time at the site of absorption for effective absorption, so precipitation of drug compound within GI lumen is prevented. Non-ionic surfactants with a relatively high hydrophilic–lipophilic balance (HLB) are most widely used in SEDDS. The commonly used emulsifiers are various solid or liquid ethoxylated polyglycolyzed glycerides and polyoxyethylene 20 oleate (Tween 80). Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactants. However, these excipients have a limited self-emulsification capacity. Non-ionic surfactants are less toxic than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen. Usually the surfactant concentration ranges between 30 and 60% w/w in order to form stable SEDDS. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SMEDDS. There is a relationship between the droplet size and

the concentration of the surfactant being used. In some cases, increasing the surfactant concentration could lead to droplets with smaller mean droplet size such as in the case of a mixture of saturated C_8–C_{10} polyglycolized glycerides (Labrafac CM–10). This could be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil–water interface. On the other hand, in some cases the mean droplet size may increase with increasing surfactant concentrations. This phenomenon could be attributed to the interfacial disruption elicited by enhanced water penetration into the oil droplets mediated by the increased surfactant concentration and leading to ejection of oil droplets into the aqueous phase. [5, 6]

Some of the commonly used surfactants are listed below:-

- Polysorbate 20 (Tween 20)
- Polysorbate 80 (Tween 80)
- Sorbitan monooleate (Span 80)
- Polyoxy-35-castor oil (Cremophor EL)
- Polyoxy-40- hydrogenated castor oil (Cremophor RH40)
- PEG-8 Caprylic/Capric glycerides(Labrasol® 14)
- PEG-8 Caprylic/Capric glycerides (Labrafac®CM10)

Co-surfactants:

The production of an optimum SEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants. Organic solvents such as, ethanol, propylene glycol (PG) and polyethylene glycol (PEG) are suitable for oral delivery, and they enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in the lipid base. These solvents can even act as co-surfactants in micro-emulsion systems. On the other hand, alcohols and other volatile co-solvents have the disadvantage of evaporating into the shells of the soft gelatin, or hard, sealed gelatin capsules in conventional SEDDS leading to drug precipitation. [5]

Characterization of SEDDS:

Visual Observations:

The tendency to emulsify spontaneously and also the progress of emulsion droplets are observed by introducing unit dose formulation into approximately 300 ml of water. The tendency to form an emulsion is judged as 'good' when droplets spread easily in water and formed a fine milky emulsion, and it was judged 'bad' when there was poor or no emulsion formation with immediate coalescence of oil droplets, especially when stirring was stopped [15].

Turbidity measurement:

This identifies efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time [6].

Droplet Size Analysis:

Dynamic light scattering like photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zetasizer able to measure sizes between 10 and 5000 nm [9, 16].

Zeta potential determination:

The difference in potential between the surface of the electro-neutral region of the solution and the surface of tightly bound layer of ions on the particle is the zeta potential.The emulsion stability is directly related to the magnitude of the surface charge. The zeta potential of the diluted SEDDS formulations is measured using a Zeta Meter System. [17, 18]

Transmission electron microscopy (TEM):

The morphology of SEDDS can be observed by TEM. In this the sample is diluted with water and placed on a copper grid. The excess is drawn off with a filter paper. Then the samples are subsequently stained with uranyl acetate solution for 30 s. [19]

Emulsification Time:

Patil P et al have used turbidimeter to determine the emulsification time. SES (0.5mL) was added to 0.1N hydrochloric acid (150 mL) under continuous stirring (50 rpm) on a magnetic plate at ambient temperature, and the increase in turbidity. Time required to disperse the system completely and uniformly was determined by observing change in turbidity as a function of time. Time point beyond which there was no increase in the turbidity was recorded as emulsification time. [20]

Viscosity Determination:

Patil P et al have measured the viscosities of the systems as such and after dilution with 5% vol/vol water were determined using Brookfield DV III programmable rheometer. [21]

Small-angle neutron scattering:

Small-angle neutron scattering can be used to obtain information on the size and shape of the droplets. The term 'droplet' is used to describe micelles, mixed micelles and oil-swollen micelles throughout the present work. Small-angle neutron scattering experiments use the interference effect of wavelets scattered from different materials in a sample (different scattering-length densities) [6].

Drug encapsulation efficiency:

The quantities of the drugs theoretically contained in the SEDDS are compared with the quantity actually obtained from the drug content studies i.e. the quantity loaded into the SEDDS formulated, to get the drug encapsulation efficiency. Following equation is used for the calculation:

$$EE\ (\%) = \frac{ADC}{TDC} \times 100 \quad \ldots\ldots (2)$$

Where ADC is the actual drug content and TDC is the theoretical drug content. [22]

Dissolution studies:

Palamakula A et al have carried out dissolution study using an Erleynmeyer flask at 25^{0}C. Capsules containing 30 mg of CoQ were introduced into 250 mL of prewarmed distilled water for initial screening. Screened formulations were then subjected to dissolution testing in a USP2 rotating-paddle apparatus, at 37±0.5^{0}C, with a rotating speed of 50 rpm in 900 mL of water. Capsules were held to the bottom of the vessel with aluminum sinkers. [17]

Permeability studies:

Transport of drug across Caco-2 cell monolayer's can be studied to correlate it with the in vivo absorption. [23]

In addition to these tools, others such as nuclear magnetic resonance and differential scanning colorimetry have also been exploited to characterize these self-emulsifying systems for a better insight.

Applications of SEDDS:

SEDDSs present drugs in a small droplet size and well-proportioned distribution and increase the dissolution and permeability. Furthermore, because drugs can be loaded in the inner phase and delivered by lymphatic bypass share, SEDDSs protect drugs against hydrolysis by enzymes in the GI tract and reduce the presystemic clearance in the GI mucosa and hepatic first-pass metabolism.

Conventional SEDDS, however, are mostly prepared in a liquid form, which can produce some disadvantages. Hence now the focus is on developing the solid self emulsifying drug delivery system(S-SEDDS) with the techniques like capsule filling of liquid/semisolid SEDDS [24], adsorption on solid carriers [25], spray drying [26,27], melt granulation, Melt extrusion/extrusion spheronization. [7]

Oral solution:

Arunothayanun P et al have prepared self emulsifying ritonavir oral solution. In the SEDDS with equal alcohol content (43% v/v), polyoxyl hydrogenated 40 castor oil(PH40) allowed wider variation of water and propylene glycol content when comparing with those using polyoxyl 35 castor oil(P35) as a surfactant. With 10.5% w/v PH40, as a surfactant, a wider range of water content (11.8-23.8 %v/v) can be added to obtain clear ritonavir solutions while P35 allowed a narrow range of water content (18.8-21.8 %v/v). [28]

Semisolid SEDDS:

Viegas et al have carried out in-vitro studies to study the efficacy of mixed and self-emulsifying creams and hydrophobic ointment formulations in delivering peldesine into and across cryopreserved human cadaver skin. [29]

Solid SEDDS:

Solid SEDDS have been developed into variety of formulations from tablet to nanoparticles. Some examples of bioavailability enhancement achieved with various self emulsifying dosage forms are capsules [17], tablets [25, 30], pellets [31, 32, and 33], beads [20], self-emulsifying osmotic pump tablet [34], solid dispersion [35], nanoparticles, microspheres and implants. [7]

Spray formulation:

Cirri M et al have developed liquid spray formulation of xibornol. The final selected formulations, containing Labrafil M1944, Transcutol, Labrafac PG and a hydrophilic co-solvent (propylene glycol or PEG 200) allowed complete solubilization of the required xibornol

concentration (3%, w/v) and showed physical good stability up to 2 months at 25 and 4^0C, suitable viscosity and organoleptic properties. [36]

Table 5 shows some of the marketed formulations of SEDDSs available for oral delivery of various drugs.

Conclusion:

Self emulsifying drug delivery is becoming a key asset to overcome the bioavailability problems of poorly soluble drugs. Especially with the emergence of solid forms of SEDDS the market success of SEDDS will increase in the near future. With future development of this technology, SEDDS will continue to enable novel applications in drug delivery and solve deficiency associated with the delivery of poorly soluble drugs.

Table 1: The Lipid Formulation Classification System [6, 8]

LFCS Type	Characteristics	Advantages	Disadvantages
I	Oils without surfactants Non-dispersing; requires digestion	GRAS status; simple; excellent capsule compatibility	Formulation has poor solvent capacity unless drug is highly lipophilic
II	SEDDS without water-soluble components	Unlikely to lose solvent capacity on dispersion	Turbid o/w dispersion (particle size 0.25–2 µm)
IIIA	SEDDS/SMEDDS with water-soluble components	Clear or almost clear dispersion; absorption without digestion	Possible loss of solvent capacity on dispersion; less easily digested
IIIB	SMEDDS with water-soluble components and low oil content	Clear dispersion; drug absorption without digestion	Likely loss of solvent capacity on dispersion
IV	Oil-free formulation based on surfactants and cosolvents	Good solvent capacity for many drugs; disperses to micellar solution	Loss of solvent capacity on dispersion; may not be digestible

Table 2: The lipid formulation classification system (LFCS) showing typical composition of various types of lipid formulations [8]

Sr. No	Excipients in formulation	Content of formulation (%, w/w)				
		Type I	Type II	Type IIIA	Type IIIB	Type IV
1.	Oils: triglycerides or mixed mono and diglycerides	100	40-80	40-80	<20	-
2.	Water-insoluble surfactants (HLB < 12)	-	20-60	-	-	0-20
3.	Water-soluble surfactants (HLB > 12)	-	-	20-40	20-50	30-80
4.	Hydrophilic co-solvents (e.g. PEG, propylene glycol, transcutol)	-	-	0-40	20-50	0-50

Table 3: Application of SEDDS in various BCS category drugs

BCS class	Problems
Class I	Enzymatic degradation, gut wall efflux
Class II	Solubilisation and bioavailability
Class III	Enzymatic degradation, gut wall efflux and bioavailability
Class IV	Solubilisation, enzymatic degradation, gut wall efflux and bioavailability

Table 4: Lipids Used in Oral Lipid-Based Formulations [14]

Class	Chemical Name	Trade or Common Name (Examples)
LCTs	Various	Corn oil, Soyabean oil Safflower oil, Olive oil
MCTs	Glyceryl tricaprylate/caprate	Fractionated coconut oil, Captex®300 Miglyol®810 Miglyol®812 Neobee®M-5
Propylene glycol esters	Propylene glycol monocaprylate, Propylene glycol monolaurate	Capmul®PG-8 Capmul® PG-12 Lauroglycol®
Fatty acids	cis-9 Octadecenoic acid Hexadecanoic acid Octadecanoic acid Z,Z-9, 12 Octadecadienoic acid	Oleic acid, Palmitic acid Stearic acid and Linoleic acid
Monoglycerides/ Diglycerides	Glyceryl caprylate/caprate Glycerol monocaprylate, Glycerol monooleate	Capmul®MCM; Imwitor®742 Imwitor®308 Capmul®GMO
Unsaturated polyglycolized glycerides	Linoleoyl macrogol-6 glycerides	Labrafil ®M 2125 CS, Labrafil® M 1944 CS
Lipid mixtures	SaturatedC8 –C18 triglycerides	Gelucire®33/01

Table 5: Marketed formulations of SEDDS [6]

Active moiety	Trade name	Dosage forms
Tretinoin	Vesanoid (Roche)	Soft gelatin capsule, 10 mg
Isotretinoin	Accutane (Roche)	Soft gelatin capsule, 10, 20 and 40 mg
Cyclosporine	Panimum bioral (Panacea Biotec)	Capsule, 50 and 100 mg
Cyclosporin A	Gengraf (Abbott)	Hard gelatin capsule, 25 and 100 mg
Cyclosporin A	Sandimmune (Novartis)	Soft gelatin capsule, 25, 50 and 100 mg
Lopinavir and Ritonavir	Kaletra (Abbott)	Soft gelatin capsule, Lopinavir 133.33 mg and Ritonavir 33.3 mg
Sanquinavir	Fortovase (Roche)	Soft gelatin capsule, 200 mg
Tipranavir	Aptivus (Boehringer Ingelheim)	Soft gelatin capsule, 250 mg
Amprenavir	Agenerase (GSK)	Soft gelatin capsule

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