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Review article

SELF-EMULSIFYING DRUG DELIVERY SYSTEMS AS AN APPROACH TO IMPROVE THERAPEUTIC EFFECTIVENESS OF ORALLY ADMINISTRATED DRUGS

Ivaylo Pehlivanov
Department of Pharmaceutical Technologies, Faculty of Pharmacy, Medical University, Varna, Bulgaria.

ABSTRACT

There is no doubt that the improvement of oral bioavailability is a challenge for a significant number of the novel active pharmaceutical ingredients (API). Many of the novel APIs fall into class II, III or IV of Biopharmaceutical Classification System (BCS). There are different approaches to improve oral bioavailability. One that is gaining much popularity is including such molecules into lipid-based drug delivery systems (LBDDS) that leads to an improved dissolution and mucosal permeability profiles and greater oral bioavailability. The LBDDS are promising vehicles for many APIs and can be classified as lipid solutions, lipid suspensions, emulsions, and self-emulsifying systems. Among the entire LBDDS, self-emulsifying drug delivery systems (SEDDS) are gaining much popularity. We can find coarse emulsions (SEDDS), microemulsions (SMEDDS), and nanoemulsions (SNEDDS). They are defined as isotropic mixtures of one or more lipids, hydrophilic solvents, and emulsifier/co-emulsifier that form fine emulsions oil-in-water (O/W) and water-in-oil-in-water (W/O/W) by a slight agitation such as gastrointestinal (GI) peristaltic and dilution in the hydrophilic fluids.

The article presents a detailed overview of the SEDDS' formulation and outlines the advantages of these over conventional dosage forms on the improvement of oral bioavailability.

Keywords: lipid-based drug delivery systems, SEDDS, SMEDDS, SNEDDS,

BACKGROUND

It is well known that the oral administration of drugs is one of the most effective and of wide use. Despite the high therapeutic effectiveness, low production costs and very high patient compliance, the orally administered drugs suffer from some drawbacks. On the one hand, about 40% of the new drug molecules have lipophilic physicochemical properties [1], high molecule weight, and low water solubility.

On the other hand, the high hydrophilicity of others is a reason for the limited permeability through the enterocyte membranes, and hence, it is a limiting factor for their absorption [2]. Other important factors that influence the drug bioavailability are the low dissolution rate, first-pass metabolism, pre-absorption metabolism, and the cellular excretion. These molecules show low bioavailability and although their high pharmacological value, they fall of the later development stages. A big challenge for the technology pharmacists is to include these drug molecules into dosage forms capable of ensuring high oral bioavailability.

An already established approach for the pharmaceutical development of a given drug molecule is the biopharmaceutical classification system (BCS). BCS is a scientific frame for categorization of the drugs based on their solubility and membrane permeability along with some in-vitro characteristics such as dissolution rate. Solubility, dissolution rate and intestinal permeability are taken into account as significant factors regulating the absorption rate and quantity of a given drug from oral dosage forms [3]. According to these criteria, drugs can be located in four BCS classes. For every given BCS class, there are critical drug characteristics, *in-vitro-in-vivo* (IVIV) correlations, and some guidelines to solve problems related to bioavailability improvement [4].

Some of the widely used technological approaches can overcome these challenges to a certain extent. Different techniques are being used, such as chemical modifications, absorption enhancers, cyclodextrin complexes, micronization, and surfactants [4, 5]. One of the popular solutions is the inclusion of the drug into LBDDS that leads to improved oral bioavailability. These include lipid solutions and suspensions, emulsions and emulsifying systems, vesicles, and lipid particles [6]. Of these, SEDDS are gaining much interest and can be divided into to three major groups: (i) SEDDS, self-emulsifying to coarse emulsions; (ii) SMEDDS, self-emulsifying to micro-emulsions; and (iii) SNEDSS, self-emulsifying to nano-emulsions.

Patel et al. [7] have reported an optimized oral SEDDS formulation for Telmisartan. This system has significantly improved dissolution rate during *in-vitro* testing compared to a conventional suspension. *In-vivo* results showed nearly 7.5 times increased bioavailability. In another research, A. A. Kassema et al. [8] have reported an optimized oral SEDDS containing Nystatin. Compared to the conventional dosage form, the selected formulation showed higher antimycotic activity during *in-vitro* studies confirmed with the *in-vivo*

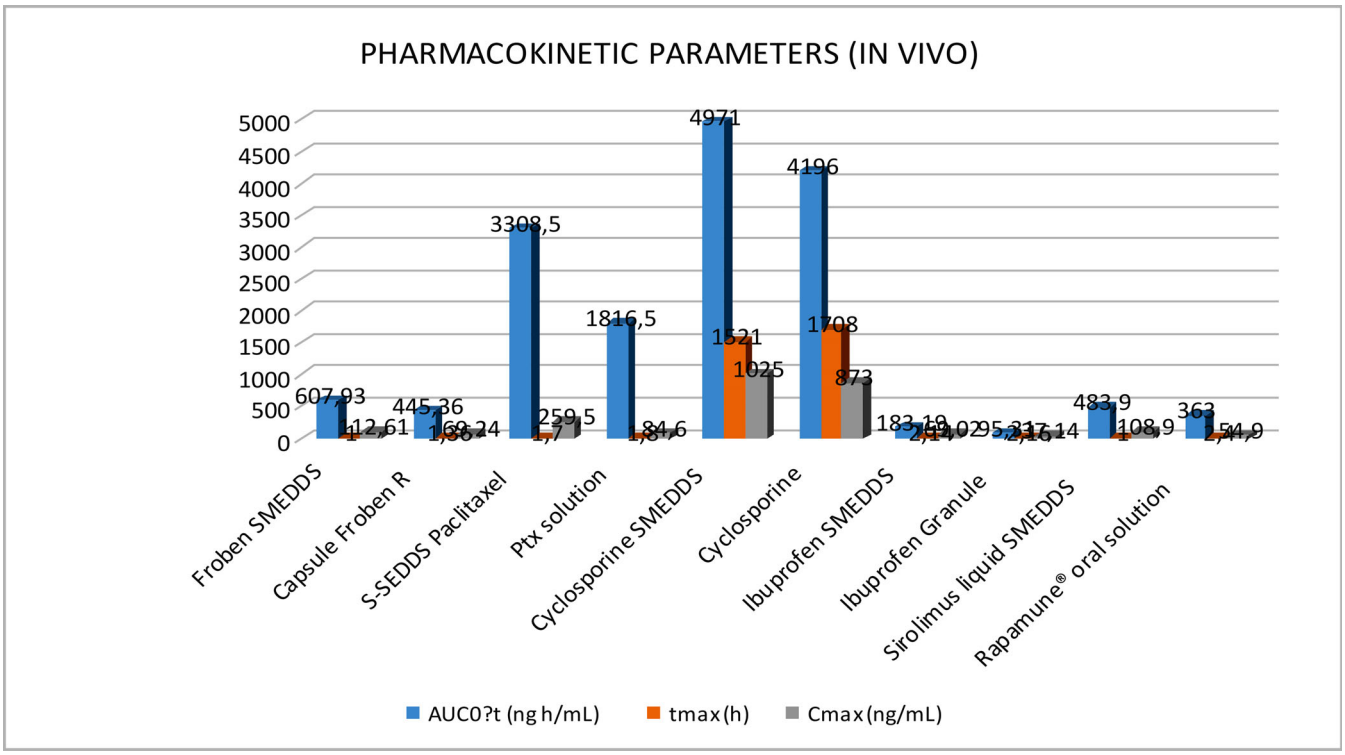
testing on immunosuppressed mice with induced Candidiasis. The studies showed that Nystatin- SEDDS oral activity on the reduction of *C. Albicans* colonies is significantly higher (P< 0.05) compared to a commercial Nystatin-containing product. Hea-Young Cho et al. [9] have studied the inclusion of Paclitaxel in saturated SEDDS (S-SEDDS). *In-vitro* tests showed significantly better dissolution profile compared to the conventional dosage form and higher dissolution rate at pH= 6.8 than at pH=1.2 having 70-75% of the dose in solution within the first 30-60 min. The authors suppose that this phenomenon is due to the characteristics of the gelatin capsules because Paclitaxel is usually better soluble in acidic medium. *In-vivo* testing showed values of AUC and C_{max} 1.8 and 3 times higher related to the conventional dosage form, respectively.

Table 1 shows drugs with improved oral bioavailability trough different lipid-based drug delivery systems [10, 11].

Table 1. Drugs with improved oral bioavailability through different LBDDS [10, 11]

No	DRUG MOLECULE	THERAPEUTIC CLASS	DRUG DELIVERY SYSTEM
1	Paclitaxel	Anticancer	SMEDDS
2	Fenofibrate, Fluvastatin	Antihyperlipidemic	SMEDDS
3	Rapamycin, Cyclosporine	Immunosuppressive	SMEDDS
4	Nifedipine	Antihypertensive	SMEDDS
5	Ibuprofen, Naproxen	Analgesic	SMEDDS
6	Tipranavir	Anti- HIV	SMEDDS
7	Progesterone, Testosterone	Hormones	SMEDDS
8	Vitamins (A, D, E, K)	Nutrition supplement	SMEDDS
9	Acyclovir	Antiviral	SMEDDS
10	Melatonin	Immunomodulatory	SMEDDS
11	Sirolimus	Immunosuppressive	SMEDDS
12	Ritonavir	Antiviral/ Anti- HIV	SMEDDS
13	Dutasteride	5-á-reductase inhibitor, BPH	LBDDS
14	Topotecan	Antineoplastic	LBDDS
15	Nintedanib	IPF treatment	SEDDS

Graphic 1. Pharmacokinetic parameters comparison (in vivo) of some drugs with improved oral bioavailability through SMEDDS



The mechanisms through which LBDDS increase drug absorption are not entirely understood. Increased intestinal diffusion, lymphatic transport, increased membrane permeability, and limited cellular clearance are some of them. The emulsion obtained from SEDDS promotes increased membrane absorption and lymphatic diffusion due to the presence of emulsifiers and lipids. The reduced droplet size of the dispersed phase is a favorable factor too [11].

The stability of LBDDS is of high importance in order to be introduced in practice. The emulsions are systems of unstable nature because of thermodynamics, dependent on emulsifiers' nature and concentration, droplet size, viscosity, conductivity, and phase ratio [5**,** 13].

Self-emulsifying systems find application not only in the pharmaceutical but the food and the cosmetic industries as well. Multiple emulsions (w/o/w) can be used to mask unpleasant organoleptic characteristics, to increase dermal penetration, etc. Due to their structure, they have potential application in vaccine and peptide drug delivery. These can provide modified drug delivery due to the diffusion processes that the drug molecules have to undergo if they are located in the inner phase of such emulsions. This release profile is dependent on the physicochemical characteristics of the API, type of lipids, emulsifiers, other used excipients and preparation technique [5].

The article presents a detailed overview of the SEDDS' formulation and outlines the advantages of these over conventional dosage forms on the improvement of oral bioavailability.

REVIEW RESULTS

1. Self-emulsifying drug delivery systems as carriers

SEDDS are defined as isotropic mixtures of emulsifiers, co-emulsifiers (second emulsifier or solvent), usually but not always including one or more lipids and a drug substance. In aqueous medium SEDDS spontaneously form O/W or W/O/W emulsions. The formed emulsions are classified according to the droplet size (between 10 nm to 150 nm) as SEDDS, SMEDDS, and SNEDDS. Oral SEDDS are usually formulated in gelatin capsules.

Entirely new kind of SEDDS is S-SEDDS. These are formulated using lower emulsifiers' concentrations and including crystal growth inhibitors such as HPMC, other cellulose derivatives, etc. The drug molecule delivered by S-SEDDS is supersaturated after dispersion in the intestinal fluids, and its bioavailability can be improved, leading to shorter T_{max} and greater $C_{max.}$ Another advantage of these systems is its potential to reduce some emulsifier side effects such as diarrhea and colitis [14].

2. Mechanism of self-emulsification

A critical point during the formulation of a stable emulsion is finding the most suitable emulsifier for a given combination of substances. Emulsification is a process going along with significant absorption of mechanical energy. The newly formed larger surface possesses free surface energy that is dependent on the surface area and interphase tension:

$$\varepsilon = \sigma \times S$$

Where **ε** is the free surface energy (**N/m**), **S** is the total interphase surface (**m^2**), **σ** is the surface tension (**N/m**).

The equation shows that the droplet sizes of the dispersed phase have to remain constant in order for the physical state to be stable. Lowering σ – values and hence minimizing the values of ε is the way to obtain stable dispersions. In practice, this is possible to be achieved with the aid of substances that are absorbed on the interphase surface and are capable of lowering the surface energy, emulsifiers [15].

Historically there are three theories used to explain the formation and the stability of micro-emulsions: *(i) Interfacial mixed film theory, Schulman et al. 1959; (ii) Solubilization theory, Gillberg et al. 1970; (iii) Òhermodynamic theory, Paul and Moulik 1997* [16, 17, 18, 19].

It is agreeable that the free forming energy of a microemulsion depends on the extent to which the emulsifiers lower the water/oil interphase tension and change the system entropy [20].

The formation of new or the extension of the existing contact phase surfaces between water and oil is a process that requires a certain amount of energy. According to *Reiss,* self-emulsification occurs when the Entropy change (**S**) that favors the dispersing process is greater than the energy required for the increase of the surface area of a given dispersion. The free energy incrementation in the emulsification process is directly proportional to the work done for the forming of a new contact surface between the two phases. If the free energy of mixing is ignored, the next equation can be written:

$$\Delta G = \sum_i N_i \pi r_i^2 \sigma$$

Where **ΔG** is the free energy of the process, N_i is the number of droplets, r_i is the droplet radius, **σ** is the interphase tension.

In the self-emulsification, the free forming energy of an emulsion is either minimal and positive or negative for the process to be spontaneous. In most cases, a small amount of energy is required for the destabilization of some interphase regions, their shrinking and hence self-emulsification to occur [21].

3. Mechanisms of gastrointestinal transport of drugs from SEDDS

In recent years, lipids are subject of great interest as vehicles for poorly water-soluble drugs. The development of new lipid excipients having acceptable regulations and safety profile led to the formulation of new LBDDS. Some factors, such as droplets' dimensions, emulsification level, dispersion rate, drug precipitation after dispersion, have a significant influence on drug absorption. These have to be taken into account for the formulation to be successful.

These systems increase intestinal absorption trough accelerated solubilization, which is facilitated due to phase solubilization by size reduction to the molecule level. This process leads to a solid-state solution in the carrier and

changes the drug absorption, efflux and location by enterocyte-based transport and increased drug transport to the circulatory system through lymphatic system [22].

The lymphatic system plays a vital role in drug transport, taking into account the extent of the draining network that presents. Using the lymphatic path, the first-pass metabolism is being by-passed as well as some types of lymphoma or HIV infections can be targeted, for instance. Promising mechanisms for drug absorption could be: (i) increased membrane fluidity that leads to increased cellular transport; (ii) paracellular transport through tight junctions opening; and (iii) increased intracellular concentration and idle time in consequence of P-gp and CYP450 inhibition and lipoprotein/chylomicron production prompting.

After oral administration of SEDDS, digestion of exogenous triglycerides is taking place. In this process, an active role has the pancreatic lipase and biliary acids salts, which degrade the triglycerides to di- and monoglycerides and form a primary coarse emulsion. The peristaltic motion favors these processes. The primary digestion products are further included in different structures such as micelles, uni- and multilamellar vesicles. This is the reason why foods with high lipid content to have a positive effect on hydrophobic drugs absorption, including the long intestinal residence time [23]. Further triglycerides favor the contact between drugs and lipoproteins. Food influence on the absorption of some drugs can be troubleshooting factor on reaching subtherapeutic blood levels when taken on the fasted state.

SEDDS have the potential significantly to reduce the differences in the plasma concentrations between fed and fasted states. Another significant advantage is dose reduction because of improved bioavailability.

4. SEDDS – structure and excipients selection

There is a large variety of excipients with lipid nature. Since lipids influence the absorption processes, it is necessary to know their characteristics when used as excipients. The factors which determine their selection for preparation of SEDDS with desired features are solubility; solubilization capacity; self-dispersibility and ability to promote the formulation self-dispersion; digestibility and destiny of the digested substances; regulatory issues such as purity, chemical stability, toxicity, irritation; capsule compatibility; melting temperature; and price.

Lipids usually present in the everyday diet, mainly built-up by long- and medium-chain triglycerides, are used for LBDDS. Different emulsifiers and co-solvents are included as well. Many lipids are of amphiphilic nature since they are built of fatty acids esters and a hydrophilic portion. The melt temperature is higher as fatty acid chains become more extended, and it is lower as the number of unsaturated bonds in the chains increases. The higher number of unsaturated bonds can lead to increased risk of oxidative instability [22].

The type and concentration of emulsifiers and co-emulsifiers influenced the thermodynamic stability of SELDS formulation. Correct selection of these excipients can only be made after in-depth experimental and literature research because in different cases there is a possibility to increase drug absorption or to decrease it as well [24, 25, 26].

5. Lipids

Oils represent basic excipients for the formulation of SEDDS. They can solubilize large quantities of hydrophobic drugs and aid the self-emulsification process. Oils mostly assist the lymphatic transport of drugs and thus augment their absorption according to their triglyceride composition. Vegetable oils are mostly used in SEDDS formulation since they are GRAS- approved, wholly digested, and absorbed.

There is no exact classification of lipids. Different criteria can be used for this purpose: natural or semisynthetic lipids; tri-, di- and mono-glycerides; long-, medium- and short-chain glycerides; homo-, hetero- and complex lipids. As already mentioned, according to their chemical structure, lipids can exhibit different properties. Medium chain triglycerides (MCTs) have better solubilization capacity than the long chain triglycerides (LCTs), for example. This quality can be forecasted by the number of active esther groups present in the structure [22, 30, 31].

Table 2. Schematic classification of different lipids

Homolipids	Heterolipids	Complex lipids	Simple lipids	Neutral lipids	Miscellaneous lipids
Cerides Glycerides Stérides	Phospholipids Glycolipids Sulfolipids Amino lipids Sphingophospholipids	Chylomicrons Lipoproteins	Oils fats	Mono-, di-triglycerides Cholesterol Cholesteryl esters	Carotenoids Squalene Terpenes

Table 3. A short list of lipids used in SEDDS formulations [1,24, 34]

CLASS	EXAMPLES
1) Vegetable oils' triglycerides:	
LCTs	Soy oil; maize oil; peanut oil; sunflower oil; corn oil; olive oil; sesame oil
MCTs	Coconut oil; Castor oil; Myglyol 812; Captex 355; Captex 200; Labrafac; Viscoleo

2) Vegetable oil derivatives:	
Hydrogenated oils	Hydrogenated cottonseed oil
Mixed partially etherified glycerides	Capmul MCM
Polyoxyl glycerides/ Macrogol glycerides	Labrafil 1944 CS; Labrafil M2125 CS; Labrasol; Gelucire 44/14
Ethoxylated glycerides	Cremophor EL; Cremophor RH40; Cremophor RH60;
Polyalcohol esters of fatty acids	Plurol Oleique CC497; Caproyl 90; Mirj;
Fatty acids	Oleic acid; Palmitic acid; Myristic acid; Caprylic acid; Caproni acid;
Ethyl Esters	Ethyl oleate
3) Miscellaneous	Bee wax; D-α-Tocopherol acetate

6. Emulsifiers

The emulsifiers are substances of amphiphilic nature and their molecules present hydrophilic and lipophilic portion. Because of their structural characteristics, they are compatible with a different extent with other ingredients used in SEDDS formulations and determine some important characteristics: self-emulsification rate, droplet size, stability, etc. There is a large variety of emulsifiers of natural or semisynthetic nature in order to satisfy the formulation needs.

Different groups of emulsifiers can be applied for the micro-emulsion stability and formulating of SEDDS: (i) ionic; (ii) cationic; (iii) anionic; (iv) zwitterionic; and (v) nonionic. Nonionic emulsifiers are the largest group in use due to their low toxicity. Usually, different combinations between nonionic and ionic emulsifiers are used because of the synergic effect on emulsion stability. Schmidts et al. reported that adding 0.2% lecithin to a SPAN80/TWEEN80 system had a synergic effect on w/o/w double emulsion stability. Synergism is achieved usually when critical micellar concentration (CMC) is reached. Chemical similarity between hydrophilic and lipophilic emulsifiers is an essential factor to be considered. The couple SPAN80/TWEEN80 is mostly used because of the chemical similarity (oleates) between the two emulsifiers and produce much more stable double emulsions compared to SPAN80/TWEEN20 couple (oleate and laurate).

Some emulsifiers have irritating effects, and thus their concentration in formulations is limited. In cases of SEDDS, the concentration range of emulsifiers can vary between 30% and 60% [32].

Table 4. A short list of some mostly used emulsifiers in SEDDS formulations [33]

COMMERCIAL NAME	CHEMICAL STRUCTURE	HLB
Arlacel 170	PEG-100 stearate	18.8
Myrj S40	PEG-40 stearate	17.0
Brij 35	Laureth-20/23	16.9
Tween 20	Polyethylene glycol sorbitan monolaurate	16.7
Cremophor RH40	Polyoxy-40- hydrogenated castor oil	14-16
Tween 80	Polyethylene glycol sorbitan monooleate	15.0
Cremophor EL	Polyoxy-35-castor oil	12-14
TPGS	D-alpha Tocopheryl polyethylene glycol 1000 succinate	13
Labrafil M 2125 Cs	Polyoxyethylated glycerides	9
Labrafil M 1944 Cs	Polyoxyethlated oleic glycerides	9
Span 60	Sorbitan monostearate	4.7
Span 80	Sorbitan monooleate	4.3
PGPR	Polyglycerol polyricinoleate	3.0
Span 65	Sorbitan tristearate	2.1
Span 85	Sorbitan trioleate	1.8

7 Co-emulsifiers and co-solvents

Excipients grouped into these two categories aid or modulate emulsifiers and increase systems' solubilization capacity. Short chain hydroxyl derivatives such as ethanol, glycerol, propylene glycol, PEG400 are used as co-solvents. Nonionic emulsifiers such as Lauroglycol FCC (propylene glycol monolaurate) or Transcutol P (diethylene glycol monoethyl ether) are found in the co-emulsifiers category.

These substances are used for different purposes in SEDDS formulations. These can (i) increase the solvent capacity of the system; (ii) increase interphase film flexibility; (iii) prevent formation of liquid crystal or gel phases that eventually can block or delay emulsion forming; and (iv) aid fine HLB regulation of emulsifying system and promote

spontaneous flexing of interphase film by changing the distribution of emulsifiers.

Like other excipients, co-emulsifiers and co-solvents are used within certain limits because of future incompatibilities or because of solubility issues. For example, ethanol is incompatible with the capsule shell or can cause drug precipitation [1].

Table 5. A short list of some of the most used co-emulsifiers and co-solvents

CO-EMULSIFIERS	CO-SOLVENTS
Lauroglycol FCC	Propylene glycol
Lutrol E400	Glycerol
Lauromacrogol 300	Ethanol
Plurol Oleique	Transcutol P
Plurol stearic	PEG 200,400,600
Triacetin	benzyl alcohol
Phospholipon 90	PhytoSolve

8. Other excipients

SEDDS formulations include excipients that ensure system stability such as viscosity and gelling agents, antioxidants, pH regulators, and aromatizing agents.

Viscosity and gelling agents increase the physical stability of the system and can be incorporated in both aqueous and lipid phases. In multiple emulsions as w/o/w, these can be added in both internal and external phases if needed, in quantities up to 20% of each phase. Gelatin, methylcellulose, and tragacanth are typical hydrophilic viscosity agents; cetyl alcohol, stearic acid, aluminum monostearate, and beeswax are used as lipophilic viscosity and gelling agents.

Lipid peroxides are an important issue regarding the stability of these drug delivery systems and can result after auto-oxidation. As the number of unsaturated bonds in lipid structure increases; thus, there is an increased risk of peroxides forming. Antioxidants used in the formulation for this purpose are α-tocopherol, β-carotene, propyl gallate, ascorbyl palmitate, BHT, and BHA.

CONCLUSIONS

SEDDS represent a relatively new technique to increase oral bioavailability. Evidence about this is the increasing number of publications on this topic. There is an increasing number of commercialized drugs, formulated or reformulated as different SEDDS. (Table 6.)

For successful promoting of SEDDS formulation, a careful excipient selection is needed along with exhaustive stability studies. In addition to increased oral bioavailability of many drugs, the other advantages of these systems are simple production technology, easy to scale-up and low production costs.

Table 6. List of some SEDDS-drugs authorized for commercialization

COMMERCIAL NAME	DRUG	DOSAGE FORM	OWNER OF AUTHORIZATION	INDICATIONS
Neoral®	Cyclosporine A/I	softgells	Novartis	Immunî suppressant
Norvir®	Ritonavir	softgells	Abbott Laboratories	HIV antiviral
Fortovase®	Saquinavir	softgells	Hoffmann-LaRoche Inc.	HIV antiviral
Agenerase®	Amprenavir	softgells	Glaxo SmithKline	HIV antiviral
Convulex®	Valproic acid	softgells	Pharmacia	Antiepileptic
Lipirex®	Fenofibrate	Hard gelatin caps	Genus	Antihyperlipoproteinemic
Sandimmune®	Cyclosporine A/II	softgells	Novartis	Immuno Suppressant
Targretin®	Bexarotene	softgells	Ligand	Antineoplastic
Rocaltrol®	Calcitriol	softgells	Roche	Calcium regulator
Gengraf®	Cyclosporine A/III	Hard gelatin caps	Abbott Laboratories	Immunosuppressant
Marinol®	Dronabinol	softgells	Solvay Pharmaceuticals	Antianorexissant / antiemetic
Vesanoid®	Tretinoin	softgells	Roche	Treatment of acute promyelocytic leukemia.
Avodart®	Dutasteride	softgells	Glaxo SmithKline	Anti BPH
Lipofen®	Fenofibrate	Hard gelatin caps	Galephar Pharmaceutical Research Inc	Antihyperlipoproteinemic
Kaletra®	Ritonavir/lopinavir	film-coated tablets	AbbVie Ltd	HIV antiviral

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Address for correspondence:
Ivaylo Pehlivanov
Department of Pharmaceutical Technologies, Faculty of Pharmacy, Medical University of Varna
84, Tzar Osvoboditel Blvd., Medical College building, room 314 B. Varna, Bulgaria.
E-mail: Ivaylo.Pehlivanov@mu-varna.bg