REVIEW ARTICLE

An Emerging Technique For Poorly Soluble Drugs: Self Emulsifying Drug Delivery System


Department of Pharmaceutics and Pharmaceutical Technology, K. B. Institute of Pharmaceutical Education and Research, Sector-23, GH-6, Gandhinagar. 382023 (Gujarat).

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ABSTRACT
Up to 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which leads to poor oral bioavailability. Currently a number of technologies are available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs. Recently much attention has been paid to lipid based formulations with particular emphasis on self emulsifying drug delivery system (SEDDS), to improve the oral bioavailability of lipophilic drugs. Self-micro emulsifying formulations are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsion when introduced into aqueous phase under conditions of gentle agitation. The digestive motility of the stomach and intestine provide the agitation necessary for self-emulsification in vivo. The present review describes various formulation components, mechanism of self emulsification, biopharmaceutical aspects, characterization methods and applications of self emulsifying drug delivery system.

Key Words: Poor solubility, Oral Bioavailability, Lipophillic drugs, Self-Micro Emulsifying Drug delivery system.

INTRODUCTION
In recent years, the formulation of poorly soluble compounds presented interesting challenges for formulation scientists in the pharmaceutical industry. Up to 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which lead to poor oral bioavailability, high intra and inter subject variability and lack of dose proportionality. Currently a number of technologies are available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs. Various formulation strategies reported in the literature includes, incorporation of drug in oils, solid dispersions, emulsions, liposomes, use of cyclodextrins, coprecipitates, micronization, nanoparticles, permeation enhancers and lipid solutions.

Figure 1: Some of the formulation approaches to improve the oral bioavailability of poorly water soluble drugs.
The Self-Dispersing Lipid Formulations (SDLFs) is one of the promising approaches to overcome the formulation difficulties of various hydrophobic/lipophilic drugs and to improve the oral bioavailability of poorly absorbed drugs. Recently much attention has been paid to lipid based formulations with particular emphasis on self emulsifying drug delivery system (SEDDS), to improve the oral bioavailability of lipophilic drugs [1].

The self-emulsification process is specific to the particular pair of oil and surfactant, surfactant concentration, oil/surfactant ratio, and the temperature at which self-emulsification occurs [2, 3, 4]. After self dispersion, the drug is rapidly distributed throughout the gastrointestinal tract as fine droplets. Bioavailability enhancement results from the finely dispersed state of the drug containing lipid globules. The emulsion globules are further solubilised in the gastrointestinal tract by bile fluids. The presence of surfactant causes enhanced absorption due to membrane induced permeation changes. As the mucosal lining is negatively charged it was observed that positively charged particles penetrated deeper into the ileum. A cationic emulsion has greater bioavailability than an anionic emulsion concentration, oil/surfactant ratio, and the temperature at which self-emulsification occurs [6, 7].

Self Emulsifying Drug Delivery Systems (SEDDS) formed using surfactants of HLB < 12 and Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) formed with surfactants of HLB > 12. Both SEDDS and SMEDDS are stable preparations and improve the dissolution of the drug due to increased surface area on dispersion. Therefore, they are not dependent on bile secretion for absorption. The emulsified form itself is readily absorbable. This ensures a rapid transport of poorly soluble drugs into the blood. Potential advantages of these systems include enhanced oral bioavailability (enabling dose reduction), more consistent temporal profiles of drug absorption, selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment in the gut [8, 9].

For selecting a suitable self-emulsifying vehicle, drug solubility in various components, identification of emulsifying regions and resultant droplet size distribution need careful monitoring, since these are drug-specific systems [10]. Microemulsions (drop size 10-100nm) have received considerable attention for their potential as drug delivery vehicle due to advantages like excellent thermodynamic stability, longer shelf life, high drug solubilisation capacity, improvement in oral bioavailability and protection against enzymatic hydrolysis [11].

However, poor palatability due to lipidic composition leads to poor patient compliance and acceptability, and due to their water content, micro emulsions cannot be encapsulated in soft gelatin and hard gelatin capsules [12]. A feasible substitute is Self-Micro Emulsifying Drug Delivery System (SMEDDS), an anhydrous system of microemulsion. Self-micro emulsifying formulations are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsion when introduced into aqueous phase under conditions of gentle agitation. The digestive motility of the stomach and intestine provide the agitation necessary for self emulsification in vivo [13]. These systems advantageously present the drug in dissolved form and the small droplet size provides a large interfacial area for drug absorption [14, 15].

Advantages of SEDDS over Conventional DDS:

• Upon mild agitation followed by dilution in aqueous media, such as gastrointestinal (GI) fluids, these system can form fine oil in water (o/w) emulsion or microemulsion (S(M)EDDS). Fine oil droplets would pass rapidly and promote wide distribution of the drug throughout the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall.

• Emulsion are sensitive and metastable dispersed forms while S(M)EDDS are physically stable formulation that are easy to manufacture.

• As compared with oily solutions, they provide a large interfacial area for partitioning of the drug between oil and water. Thus for lipophilic drug compounds that exhibit dissolution rate limited absorption, this system may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles.
Drawback of SEDDS:
One of the obstacles for the development of self emulsifying drug delivery systems (SEDDS) and other lipid-based formulations is the lack of good predicative in vitro models for assessment of the formulations. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug. To mimic this, an in vitro model simulating the digestive processes of the duodenum has been developed. This in vitro model needs further development and validation before its strength can be evaluated. Further development will be based on in vitro- in vivo correlations and therefore different prototype lipid based formulations needs to be developed and tested in vivo in a suitable animal model. Future studies will address the development of the in vitro model.

BIOPHARMACEUTICAL ASPECTS
The ability of lipids and/or food to enhance the bioavailability of poorly water-soluble drugs has been comprehensively reviewed [17, 18]. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms, including:

- **Alterations (reduction) in gastric transit:** Thereby slowing delivery to the absorption site and increasing the time available for dissolution.

- **Increases in effective luminal drug solubility:** The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipids (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilisation capacity of the GI tract. However, intercalation of administered (exogenous) lipids into these BS structures either directly (if sufficiently polar), or secondary to digestion, leads to swelling of the micellar structures and a further increase in solubilisation capacity [19].

- **Stimulation of intestinal lymphatic transport:** For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly via a reduction in first-pass metabolism [20, 21, 22].

- **Changes in the biochemical barrier function of the GI tract:** It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p-glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism [23, 24, 25].

- **Changes in the physical barrier function of the GI tract:** Various combinations of lipids, lipid digestion products and surfactants have been shown to have permeability enhancing properties. For the most part, however, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water-soluble, and in particular, lipophilic drugs [26, 27].

FORMULATION CONSIDERATION
Studies have revealed that the self-micro emulsification process is specific to the nature of the oil/surfactant pair; the surfactant concentration and oil/surfactant ratio; the concentration and nature of co-surfactant and surfactant/co-surfactant ratio and the temperature at which self-micro emulsification occurs [2, 3, 4]. These important discoveries were further supported by the fact that only very specific combinations of pharmaceutical excipients led to efficient self-micro emulsifying systems. The formulated Self-Micro Emulsifying Drug Delivery Systems is specific to that particular drug only. Various major components of SMEDDS are:

Oils:
Long chain triglyceride and medium chain triglyceride oils with different degree of saturation have been used in the design of SMEDDS. Unmodified edible oils provide the most natural basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-micro emulsification markedly reduces their use in SMEDDS. Modified or hydrolyzed vegetable oils have contributed widely to the success of SMEDDS owing to their biocompatibility [28].

Recently medium chain triglycerides are replaced by novel semi synthetic medium chain triglycerides containing compound such as GELUCIRE (Gattefosse Corporation, Westwood, N.J.). These excipients form good emulsification systems because of higher fluidity, better solubilising potential and self-micro emulsification ability. Other suitable oil phases are digestible or non-digestible oils and fats such as olive oil, corn oil, soyabean oil, palm oil and animal fats [29].
Following are some frequently used oil ingredients for SEDDS formulation:

- Corn oil
- Mono, di, tri-glycerides
- DL-alpha-Tocopherol
- Fractionated triglyceride of coconut oil
- Fractionated triglyceride of palm seed oil
- Mixture of mono-and di-glycerides of caprylic/capric acid
- Medium chain mono-and di-glycerides
- Corn oil
- Olive oil
- Oleic acid
- Sesame oil
- Hydrogenated soyabean oil
- Hydrogenated vegetable oils
- Soyabean oil
- Peanut oil
- Beeswax

**Surfactant:**
The choice of surfactants is limited as very few surfactants are orally acceptable. Non-ionic surfactants with high HLB value are used in formulation of SMEDDS including: Ethoxylated polyglycolysed glycerides, Tween 80, LABRAFAC CM1O-a mixture of saturated compounds containing 8 carbon polyglycolysed glycosides (HLB =10, Gattefosse Corporation, Westwood, N.J.) and other long chain alkyl sulfonate sulfate surfactants, such as sodium dodecyl benzene sulfonate, sodium lauryl sulfate and dialkyl sulfo succinate and quaternary ammonium salts, fatty alcohols such as lauryl, cetyl and stearyl, glyceryl esters, fatty acid esters and polyoxyethylene derivatives are also employed.

Emulsifiers derived from natural sources are expected to be safer than synthetic ones and are recommended for SMEDDS use despite their limited ability to self emulsify. Non-ionic surfactants are known to be less toxic compared to ionic surface-active agents. The high HLB and subsequent hydrophility of surfactants is necessary for the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous environment, providing a good dispersing/self-micro emulsifying performance. The usual surfactant concentration in SMEDDS required forming and maintaining a microemulsion state in the GI tract ranged from 30 to 60 % w/w of the formulation [29].

The surfactants used in these formulations are known to improve the bioavailability by various mechanisms including: improved drug dissolution, increased intestinal epithelial permeability, increased tight junction permeability and decreased / inhibited p-glycoprotein drug efflux [30]. However, the large quantity of surfactant may cause moderate reversible changes in intestinal wall permeability or may irritate the GI tract. The effect of formulation and surfactant concentration on gastrointestinal mucosa should ideally be investigated in each case.

**Co-surfactant:**
In SMEDDS, generally co-surfactant of HLB value 10-14 is used. Hydrophilic co-surfactants are preferably alcohols of intermediate chain length such as hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formulation of microemulsion [29, 31]. Examples of co-surfactants are as mentioned below:

- Polyoxyethylated glycerides (Labrafil M2125 Cs)
- Polyoxyethlated oleic glycerides (Labrafil M1944 Cs)
- D-alpha Tocopheryl polyethylene glycol 1000 succinate (TPGS)

**Co-solvent:**
Organic solvents are suitable for oral administration. Examples are ethanol, propylene glycol, and polyethylene glycol, which may help to dissolve large amounts of hydrophilic surfactant or drug in liquid base [32]. Addition of an aqueous solvent such as Triacetin, (an acetylated derivative of glycerol) for example glyceryl triacetate or other suitable solvents act as co-solvents. Triacetin is suitable since it is miscible in the oil lipid phases and it can be used to solubilize a hydrophobic drug [29].

Examples of co-solvents are:

- Ethanol
- Glycerin
- Polypylene glycol
- Polyethylene glycol

**Consistency builder:**
Additional material can be added to alter the consistency of the emulsions; such materials include tragacanth, cetyl alcohol, stearic acids and/or beeswax [33].

**Polymers:**
Inert polymer matrix representing from 5 to 40% of composition relative to the weight, which is not ionizable at physiological pH and being capable of
forming matrix are used. Examples are hydroxy propyl methyl cellulose, ethyl cellulose, etc.\textsuperscript{[34]}

**Formulation of SEDDSS:**

With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants, to watersoluble cosolvents, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures which disperse to give fine colloidal emulsions\textsuperscript{[35, 36, 37]}

The following should be considered in the formulation of a SEDDS:

- The solubility of the drug in different oil, surfactants and co-solvents.
- The selection of oil, surfactant and co-solvent based on the solubility of the drug and the preparation of the phase diagram\textsuperscript{35}.
- The preparation of SEDDS formulation by dissolving the drug in a mixture of oil, surfactant and co-solvent.

The addition of a drug to a SEDDS is critical because the drug interferes with the self emulsification process to a certain extent, which leads to a change in the optimal oil–surfactant ratio. So, the design of an optimal SEDDS requires preformulation-solubility and phase-diagram studies. In the case of prolonged SEDDS, formulation is made by adding the polymer or gelling agent\textsuperscript{[36]}.

**MECHANISM OF SMEDDS**

Different approaches have been reported in the literature. No single theory explains all aspects of microemulsion formation. Schulman et al.\textsuperscript{38} considered that the spontaneous formation of microemulsion droplets was due to the formation of a complex film at the oil-water interface by the surfactant and co-surfactant. Thermodynamic theory of formation of microemulsion explains that emulsification occurs, when the entropy change that favour dispersion is greater than the energy required to increase the surface area of the dispersion\textsuperscript{39} and the free energy ($\Delta G$) is negative. The free energy in the microemulsion formation, is a direct function of the energy required to create a new surface between the two phases and can be described by the equation:

$$\Delta G = \sum N \pi r^2 \sigma$$

where, $\Delta G$ is the free energy associated with the process (ignoring the free energy of the mixing), $N$ is the num of droplets of radius $r$ and $\sigma$ represents the interfacial energy. With time, the two phases of the emulsion tend to separate to reduce the interfacial area, and subsequently, the free energy of the system decreases. Therefore, the emulsion resulting from aqueous dilution are stabilized by conventional emulsifying agents, which forms a mono layer around the emulsion droplets, and hence, reduce the interfacial energy, as well as providing a barrier to prevent coalescence.

**EVALUATION**

**Thermodynamic stability studies:**\textsuperscript{40}

The physical stability of a lipid –based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipient matrix. In addition, poor formulation physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well. In addition, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug.

- **Heating cooling cycle:** Six cycles between refrigerator temperature (4°C) and 45°C with storage at each temperature of not less than 48 h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

- **Centrifugation:** Passed formulations are centrifuged thaw cycles between 21°C and +25°C with storage at each temperature for not less than 48 h is done at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.

- **Freeze thaw cycle:** Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

**Dispersibility test:**\textsuperscript{[40]}

The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus 2. One millilitre of each formulation was added to 500 ml of water at 37 ± 0.5°C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in vitro performance of the formulations is visually assessed using the following grading system:
Grade A: Rapidly forming (within 1 min) nano-emulsion, having a clear or bluish appearance.
Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.
Grade C: Fine milky emulsion that formed within 2 min.
Grade D: Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).
Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface. Grade A and Grade B formulation will remain as nano-emulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation.

Turbidimetric Evaluation:
Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of Self emulsifying system is added to fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter. However, since the time required for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity (rate of emulsification) [41, 42].

Viscosity Determination:
The SEDDS system is generally administered in soft gelatin or hard gelatin capsules. so, it can be easily pourable into capsules and such system should not too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination conform whether the system is w/o or o/w. If system has low viscosity then it is o/w type of the system and if high viscosities then it is w/o type of the system [41, 42].

Droplet Size Analysis Particle Size Measurements:
The droplet size of the emulsions is determined by 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. Light scattering is monitored at 25°C at a 90° angle, after external standardization with spherical polystyrene beads. The nanometric size range of the particle is retained even after 100 times dilution with water which proves the system’s compatibility with excess water [41, 42].

Refractive Index and Percent Transmittance:
Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it compare with water (1.333). The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance > 99 percent, then formulation have transparent nature.

Electro conductivity Study:
The SEDD system contains ionic or non-ionic surfactant, oil, and water. so, this test is used to measure the electroconductive nature of system. The electro conductivity of resultant system is measured by electroconductometer.

In Vitro Diffusion Study:
In vitro diffusion studies are performed to study the release behaviour of formulation from liquid crystalline phase around the droplet using dialysis technique [41].

Drug content:
Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution of drug.

FACTORS AFFECTING SMEDDS
- Drugs which are administered at very high dose are not suitable for SMEDDS, unless they exhibit extremely good solubility in at least one of the components of SMEDDS, preferably lipophilic phase. The drugs exhibit limited solubility in water and lipids are most difficult to deliver by SMEDDS.
- The ability of SMEDDS to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in oily phase. If the surfactant or co-surfactant is contributing to a greater extent for drug solubilization, then there could be a risk of precipitation, as dilution of SMEDDS will lead to lowering of solvent capacity of surfactant or co-surfactant.
- Equilibrium solubility measurement can be carried out to anticipate potential cases of precipitation in the gut. However, crystallization could be slow in solubilizing and colloidal stabilizing environment of the gut. Studies reveals that such formulations can
take up to 5 days to reach equilibrium and that the drug can remain in a super saturated state up to 24 hours after the initial emulsification event.

- The polarity of lipid phase is one of the factors that govern the release from the micro-emulsion. HLB, chain length and degree or unsaturation of the fatty acid, molecular weight of the hydrophilic portion and concentration of the emulsifier govern polarity of the droplets. In fact, the polarity reflects the affinity of the drug for oil and/or water, and the type of forces involved. The high polarity will promote rapid rate of release of the drug into the aqueous phase. Sang-Cheol Chi et al. observed that the rate of release of idebenone from SMEDDS is dependent upon the polarity of the oil phase used. The highest release was obtained with the formulation that had oily phase with highest polarity.

APPLICATION OF SEDDS
Supersaturable SEDDS (S-SEDDS):
The high surfactant level typically present in SEDDS formulations can lead to GI side-effects and a new class of supersaturable formulations, including supersaturable SEDDS (S-SEDDS) formulations, have been designed and developed to reduce the surfactant side-effects and achieve rapid absorption of poorly soluble drugs.

The S-SEDDS approach is to generate a protracted supersaturated solution of the drug when the formulation is released from an appropriate dosage form into an aqueous medium. Surpersaturation is intended to increase the thermodynamic activity to the drug beyond its solubility limit and, therefore, to result in an increased driving force for transit into and across the biological barrier.

Solid SEDDS:
SEDDS are normally prepared as liquid dosage forms that can be administered in soft gelatine capsules, which have some disadvantages especially in the manufacturing process. An alternative method is the incorporation of liquid self-emulsifying ingredients into a powder in order to create a solid dosage form (tablets, capsules).

Improvement in Solubility and Bioavailability:
If drug is formulated in SEDDS, then it increases the solubility because it circumvents the dissolution step in case of Class-II drug (Low solubility/high permeability). In SEDDS, the lipid matrix interacts readily with water, forming a fine particulate oil-in-water (o/w) emulsion. The emulsion droplets will deliver the drug to the gastrointestinal mucosa in the dissolved state readily accessible for absorption. Therefore, increase in AUC i.e. bioavailability and Cmax is observed with many drugs when presented in SEDDS.

Protection against Biodegradation:
The ability of self emulsifying drug delivery system to reduce degradation as well as improve absorption may be especially useful for drugs, for which both low solubility and degradation in the GI tract contribute to a low oral bioavailability. Many drugs are degraded in physiological system, may be because of acidic PH in stomach, hydrolytic degradation, or enzymatic degradation etc. Such drugs when presented in the form of SEDDS can be well protected against these degradation processes as liquid crystalline phase in SEDDS might be an act as barrier between degradating environment and the drug.

Table 1: List of the available marketed Self Emulsifying Product

<table>
<thead>
<tr>
<th>Brand</th>
<th>Drug</th>
<th>Dosage form</th>
<th>Dose</th>
<th>Company</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoral®</td>
<td>Cyclosporin</td>
<td>Soft gelatin capsule</td>
<td>25mg, 100 mg</td>
<td>Novartis</td>
<td>Immunosuppressant</td>
</tr>
<tr>
<td>Norvir®</td>
<td>Ritonavir</td>
<td>Soft gelatin capsule</td>
<td>100mg</td>
<td>Abbott Laboratories</td>
<td>HIV antiviral</td>
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<tr>
<td>Fortovase®</td>
<td>Saquinavir</td>
<td>Soft gelatin capsule</td>
<td>200 mg</td>
<td>Hoffmann-La Roche</td>
<td>HIV antiviral</td>
</tr>
<tr>
<td>Agenerase®</td>
<td>Amprenavir</td>
<td>Soft gelatin capsule</td>
<td>50mg, 150 mg</td>
<td>Glaxo Smithkline</td>
<td>HIV antiviral</td>
</tr>
<tr>
<td>Convulex®</td>
<td>Valproic</td>
<td>Soft gelatin capsule</td>
<td>100mg, 200 mg</td>
<td>Pharmacia</td>
<td>Antiepileptic</td>
</tr>
<tr>
<td>Lipirex®</td>
<td>Fenofibrate</td>
<td>Hard gelatin capsule</td>
<td>200 mg</td>
<td>Genus</td>
<td>Antihiperlipoprotei-</td>
</tr>
<tr>
<td>Targetin®</td>
<td>Bexarotene</td>
<td>Soft gelatin capsule</td>
<td>75 mg</td>
<td>Ligand</td>
<td>Antineoplastic</td>
</tr>
<tr>
<td>Rocaltrol®</td>
<td>Calcitriol</td>
<td>Soft gelatin capsule</td>
<td>0.25 µg, 0.5 µg</td>
<td>Roche</td>
<td>Calcium regulator</td>
</tr>
<tr>
<td>Gengraf®</td>
<td>Cyclosporin</td>
<td>Hard gelatin capsule</td>
<td>25mg, 100 mg</td>
<td>Abbott Laboratories</td>
<td>Immunosuppressant</td>
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</table>

REFERENCES


