A PROMISING APPROACH TO ENHANCE SOLUBILITY AND BIOAVAILABILITY BY SELF EMULSIFYING DRUG DELIVERY SYSTEM: A BRIEF REVIEW

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INTRODUCTION

Drawbacks to intravenous administration, together with extravasations of the drug or blood, tube infections, and occlusion may be prevented by administering the drug orally, creating the oral delivery the foremost well-liked route of administration [1]. However, oral administration is restricted by issues relating to physical-chemical properties of the drug, together with poor solubility, low permeability, instability, and speedy metabolism all of that decrease oral bioavailability [2]. With the appearance of drug style, numerous molecules are created that have a possible for therapeutic action. However, most of the freshly discovered chemical entities are of high mass and belong to biopharmaceutical system (BCS) – II, with poor binary compound solubility and high membrane permeability. Hence, these two characteristics limit the bioavailability of orally- administered drugs [3]. These drugs have low solubility, which results in low dissolution and limits absorption. This poor solubility not solely provides slow oral bioavailability, however conjointly results in high inter- and intra-subject variability and lack of dose proportionality [4]. Also, a number of these drugs have increased bioavailability once co-administered in conjunction with food, e.g., haloftantrine [5]. The evident increase in bioavailability of poorly water soluble drug with a fatty meal is that the baseline within the style of lipid based mostly formulations [6-8]. Oral delivery of poorly water soluble medicine victimization lipid because the vehicle could be a new and up to date approach to beat the same issues. Formulation excipients like surfactants employed in the lipid based mostly formulations can aid in achieving the goal. Stimulation of body secretions that facilitate in digestion of lipids: administration of lipid will stimulate the biliary and duct glan secretions that are useful within the digestion of lipids. The enzymes gift within the secretions is water soluble and act at water/lipid interface. Fatty acids liberated from the lipids digestion method move with the gall salts and lead to the formation of mixed micelles and micelles during which the drug gets solubilized. Prolongation of GI residence time: administration of lipids in conjunction with the drug permits the drug to be a gift for the prolonged period of the amount within the rat that facilitates the absorption of the drug [9,10]. Lipid-based drug delivery (LBDD) systems have gained a lot of importance within the recent years because of their ability to boost the solubility and bioavailability of medicine with poor water solubility [11]. The absorption of the drug from lipid based mostly formulation depends on various factors, together with particle size, the degree of emulsification, the speed of dispersion and precipitation of the drug upon dispersion [10,12]. Lipid based formulations might embrace oil answer or suspensions, emulsions, self-micro, self nano emulsifying drug delivery systems (SMEDDS/SNEDDS) [1,2,13]. Among numerous lipids based mostly formulations (liposomes, solid lipid nanoparticles, self-dispersing tablets, and solid solutions), self-micro emulsifying formulations are receiving additional attention by formulation scientists as these are advantageous within the facet of their stability, self-dispersing nature, easy preparation, and scale-up. SMEDDS are the isotropic, clear mixtures of oils and surfactants and generally embrace co solvents/co surfactants. These are designed to make O/W micro emulsions with gentle agitation made by the motility of rat followed by solubilization and absorption of the drug. SMEDDS sometimes turn out micro emulsions of drop size below 100nm upon dilution [14]. SMEDDS OFFER THE FOLLOWING ADVANTAGES

- Irritation caused by prolonged contact between the drug and also the wall of the rat may be head by the formulation of SMEDDS because the microscopic droplets shaped facilitate within the wide distribution of the drug on the rat and these are transported quickly from the stomach[15].
- Upon dispersion in water, these formulations turn out fine droplets with huge surface space because of that the simple partition of the drug from the oil section into the binary compound section is feasible that can’t be expected just in case of oily solutions of lipophilic drugs[15].
- Poor water soluble medicine that has dissolution rate restricted absorption may be absorbed expeditiously by the formulation of SMEDDS with sequent stable plasma-time profile[14].
- Drugs that have a propensity to be degraded by the chemical and protein suggests that in rate may be protected by the formulation of SMEDDS because the drug is transferred to the body in oil droplets [14].
- Micro emulsion pre concentrate is advantageous over micro emulsion to dispense within the type of liquid stuffed soft gelatine capsules [16].
- SMEDDS are advantageous over SEDDS because the former is a smaller amount obsessed with gall salts for the formation of
drops by that higher absorption of the drug is predicted compared to SEDDS [17].

- The Surfactants of high HLB like Tween 80 are used to extend the permeability of the drug once administered in conjunction with the formulation because of the loosening impact of those on tight junctions [18].

**COMPOSITION OF SEDDS**

**Lipid based excipients**

The lipid based excipients encompass vegetable oils and their derivatives.

- Vegetable oils: Vegetable oils contain a mixture of triglycerides (90-95% w/w) and also free fatty acids, phospholipids and non-saponifiable products such as pigments and steroids or fat soluble vitamins like tocopherol and carotenoids that act as natural antioxidants [19].
- Oil derivatives: the most oil derivatives are alter oil, partial animal oil, polyoxyglyceride, ethoxylated animal oil and esters of edible fatty acids and numerous alcohols normally used oil phases within the lipid based mostly drug delivery system were shown in Table No. 1.

### Table 1: Commonly Used oily phases [20,21]

<table>
<thead>
<tr>
<th>General class</th>
<th>Examples</th>
<th>Commercial name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium chain triglyceride</td>
<td>Triglycerides of capric/caprylic acids</td>
<td>Miglyol 810, 812, Labrafac CC</td>
</tr>
<tr>
<td>Medium-chain mono- and di-glycerides</td>
<td>Mono- and diglycerides of capric/caprylic acids</td>
<td>Capmul 300, 355, CapteX 500</td>
</tr>
<tr>
<td>Long-chain mono-glycerides</td>
<td>Glycerol monooleate</td>
<td>Capmul MCM</td>
</tr>
<tr>
<td>Propylene fatty acid esters</td>
<td>Glyceryl monostearate, dilaurate</td>
<td>Capryol 90, Capmul PG-8, Seslo 218</td>
</tr>
<tr>
<td></td>
<td>PG dicaprylate, caprate</td>
<td>Miglyol 840, CapteX 200</td>
</tr>
<tr>
<td><strong>Surfactants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Several compounds exhibiting surfactant properties may be employed for the design of self-emulsifying systems, however, the selection is restricted, as only a few surfactants are acceptable orally [22, 23]. The most widely recommended ones are the non-ionic surfactants with a relatively high HLB 34. Safety could be a major determinant considering selecting a wetting agent. The four main teams of surfactants are outlined as follows</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 1. Anionic surfactants wherever the deliquescent cluster carries a charge cherish carboxyl, salt or salt. Examples are potassium laurate and sodium lauryl salt.

#### 2. Cationic surfactants wherever the deliquescent cluster carry a charge, the instance is quaternary ammonia salt.

#### 3. Ampholytic surfactants (Also referred to as zwitterionic surfactants) contain each a negative and a charge the instance is sulfobetaines.

#### 4. Non-ionic surfactants where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene. Examples are sorbitan esters (Spans) and poly sorbates (Tweens). Some of the surfactants were shown in the following Table No.2.

### Table 2: Commonly Used Surfactants [21, 24]

<table>
<thead>
<tr>
<th>General class</th>
<th>Examples</th>
<th>Commercial name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysorbates</td>
<td>Polyoxethylene-20-sorbitan monooleate</td>
<td>Tween® 80, Crill 4</td>
</tr>
<tr>
<td></td>
<td>Polyoxylene-20-sorbitan monolaurate</td>
<td>Tween 20, Crill 1</td>
</tr>
<tr>
<td>Sorbitan esters</td>
<td>Sorbitan monoleate</td>
<td>Span® 60, Crill 4</td>
</tr>
<tr>
<td></td>
<td>Sorbitan monostearate</td>
<td>Span 20, Crill 1</td>
</tr>
<tr>
<td></td>
<td>Sorbitan monolaurate</td>
<td>Span 60, Crill 3</td>
</tr>
<tr>
<td></td>
<td>Polyoxylene castor oil</td>
<td>Cremphor® 35 HV</td>
</tr>
<tr>
<td>Polyoxylene-stearate</td>
<td>Polyethylene glycol-660-12-hydroxy stearate</td>
<td>Soluplus HS 150</td>
</tr>
<tr>
<td>Polyglycolized glycodies</td>
<td>Linoleyl macrogol glycerides</td>
<td>Labrafil® 2125 CS</td>
</tr>
<tr>
<td></td>
<td>Oleyl macrogol glycerides</td>
<td>Labrafil 1944 CS</td>
</tr>
<tr>
<td></td>
<td>Polyglyceryl oleate</td>
<td>Pluronic® 680</td>
</tr>
<tr>
<td></td>
<td>Lauryl macrogol glycerides</td>
<td>Gelucire® 44/14</td>
</tr>
<tr>
<td><strong>Co solvents</strong></td>
<td></td>
<td>The free energy of the emulsion can be described by the Following equation $ΔG = \Sigma r^2σ$</td>
</tr>
</tbody>
</table>

$ΔG$ is the free energy, $N$ is the number of droplets, $r$ is the radius of droplets, and $σ$ is the interfacial energy. From this equation, it’s evident that the lower the surface energy the lower the free energy. Self-emulsionification happens once the energy concerned within the dispersion is larger than the energy needed for the formation of droplets [26]. The free energy of typical emulsion is incredibly high as high energy is needed to make a brand new surface between two unmixable phases like oil and water. Because of high free energy, the emulsion might not be stable and also the two phases tend to separate. However just in case of SMEDDS, emulsion formation happens outright as a result of the free energy of the system is incredibly low and generally negative because of the presence of a versatile interface. On combining oil and wetting agent/co surfactant mixture with water, upon gentle agitation, An interface is made between two phases. Then, binary compound section penetrates through the interface and gets solubilized inside the oil section up to the solubilization limit. Redoubled water penetration causes the formation of the spread liquid crystalline section. The quantity of liquid crystalline section depends on the wetting agent concentration. Upon gentle agitation of SMEDDS, water penetration

### Table 3: List of Commonly Used Co solvents.

<table>
<thead>
<tr>
<th>General class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-chain alcohols</td>
<td>Ethanol, benzyl alcohol</td>
</tr>
<tr>
<td>Alkane diols and triols</td>
<td>Propylene glycol Glycerol</td>
</tr>
<tr>
<td>Polyethylene glycols</td>
<td>Polyethylene glycol 400</td>
</tr>
<tr>
<td>Glycol ethers</td>
<td>Diethylene glycol monoethyl ether (Transcutol®)</td>
</tr>
</tbody>
</table>

**MECHANISM OF SELF EMULSIFICATION**
happens apace and results in the disruption of the interface and droplets are formed [14].

PREPARATION OF SEDDS
Choice of oils, co solvent, and wetting agent supported the solubility of the drug. The preparation of the SEDDS formulation by dissolving the drug during a mixture of oil, wetting agent and co solvents. The addition of the drug to SEDDS is essential as a result of the drug interferes with the self-emulsifying method to a particular extent, that results in an amendment in best oil – wetting agent ratio; thus, the planning of best SEDDS needs pre formulation solubility and section diagram studies. Due to their low binary compound solubility and low permeability, dissolution rate from the delivery system forms the speed limiting step in their absorption and general availability [27]. In some cases, the drug is dissolved in any one of the excipients and also the remaining excipients are more to the drug solution [28]. Then, the answer ought to be properly mixed and tested for the signs of muddiness. Once stabilization at close temperature for 48 hours ought to be heated for the formation of the clear solution if needed. Reckoning on the ultimate volume, the formulation ought to keep in capsules of appropriate size [29].

CHARACTERIZATION OF SEDDS

Ternary phase diagram
Pseudo ternary diagrams are usually created for the event of SEDDS that facilitate in determinant the optimum concentration of various excipients necessary to get homogenous pre concentrates, self-emulsification ability, and drug loading in this technique, water is incorporated into the SMEDDS (Self micro emulsifying Drug Delivery System) pre concentrate in a drop wise manner, with a mild stirring to permit stabilization. Addition of water results in the formation of a fancy system starting from gels to a system containing lamellar, polygon phases to micro emulsions. The mixture is visually examined for transparency [30]. At totally different compositions, totally different structures could also be shaped like emulsions, micro emulsions, micelles, inverted micellar forms, then forth and also the extent of formation of those structures may be far-famed with the development of the section diagram. This section diagram helps within the determination of diluteness and in obtaining info concerning the various compositions that form monophasic clear solutions [31]. Then pseudo ternary diagram ought to be planned with the assistance of appropriate software package. The samples that shaped clear answer ought to be denoted by appropriate symbols within the section diagram [32].

Droplet size analysis and particle size measurements
The drop size of the emulsions is set by gauge boson correlation spectrometry (which analyses the fluctuations in light-weight scattering because of the Brownian movement of the particles) employing a Zetasizer able to live sizes between 10 and 5000nm. Light-weight scattering is monitored at 25°C at a 90°-angle. The nano size varies of the particle is maintained even once one hundred times dilution with water, that proves the system’s compatibility with excess water [33,34].

Zeta potential
This is often wont to establish the charge on the droplets. The charge on the oil droplets is because of in typical SMEDDS, and is negative because of the presence of free fatty acids, but, incorporation of an ion lipid cherish oleyamine at a level vary of 1-3% can yield ion SMEDDS. Later potential helps to predict the soundness and also the activity impact in emulsion systems. If the letter potential falls below a particular level, the mixture cans combination because of enticing forces. Conversely, a high letter potential maintains a stable system [35]. Zeta potential is usually measured by letter potential analyzer [34] or letter meter system thirty seven; price of letter potential indicates the soundness of emulsion once acceptable dilution. Higher letter potential indicates the great stability of formulation [37].

Emulsification rate
The speed of self-emulsification is typically determined by adding a dose of the SMEDDS pre concentrates, ideally during a capsule, to a relevant quantity of water or bio relevant media. The speed of dispersion is set by visual observation. The time required for self-emulsification for various formulations may be assessed typically victimization dissolution apparatus USP II during which the formulation is more drop wise to the basket containing water and observant the formation of the clear answer below agitation provided by a paddle at 50 rpm[36,27]. A speedy rate of emulsification is discovered with higher wetting agent concentration thanks to the speedy ejection of oil droplets by penetration of water into the interface. The emulsification time also can be determined by visual analysis once inserting the formulation in 0.1N HCl below stirring at the vital sign by that the Gastro intestinal conditions may be simulated [38].

Visual evaluation
The assessment of self-emulsification is feasible by visual analysis. Once dilution of SMEDDS with water, the opaque and opaque white look indicates the formation of macro emulsion whereas the clear, isotropic, clear answer indicates the formation of micro emulsion [14, 39, 40]. Assessment of precipitation of the drug in diluted SMEDDS is also possible by visual evaluation. The formulations can be considered as stable when drug precipitation is not evident. Precipitation is common if the formulation contains water soluble co solvents and can be avoided by increasing the concentration of surfactant [41].

Thermodynamic stability studies [42]
The physical stability of a lipid based formulation is additionally crucial to its performance, which may be adversely laid low with precipitation of the drug within the excipient matrix. Additionally, poor formulation, physical stability will result in section separation of the excipient, poignent not solely formulation performance, however visual look similarly. Additionally, incompatibilities between the formulation and also the gelatin capsule shell will result in crispness or deformation, delayed disintegration, or incomplete unharness of the drug.

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

2. Centrifugation
Passed formulations are centrifuged thaw cycles between 21°C and +25°C with storage at each temperature for not less than 4h is done at 3500 rpm for 30 min. Those formulations that do not show any phase separation are taken for the freeze thaw stress test.

3. Freeze thaw cycle
Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

Dispersibility test
Take a look at the potancy of self-emulsification of oral nano emulsion is assessed employing a commonplace USP XXII dissolution II. One ml of every formulation added to 500 ml of water at 37.5°C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in vtro 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 minutes
Grade D: Dull, greyish white emulsion having a 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 recommended for SNEDDS formulation [43].

Refractive index

Refractive index is the property by which the isotropic nature of the diluted SMEDDS that is micro emulsion can be determined. Karamustafa and Celebi performed refractive index measurements of the optimized formulation at 4°C and 25°C up to 6 h at different time intervals and concluded that there is no significant change in a refractive index indicating the constant micro emulsion structure [44]. The constant refractive index also indicates the thermodynamic stability of the formulation [45]. Usually, the refractive index measurements are carried out using refractometers[46].

In vitro dissolution profile

Drug release from formulation can be evaluated after filling the formulation in a hard gelatin capsule using USP XXIII apparatus II at 50 rpm[28,36] or with dialysis method[47]at 37± 0.5°C. Samples at regular intervals should be withdrawn from the medium and drug content is estimated and compared with the control. The polarity of oil droplet has an impact on drug release from the diluted SMEDDS. The higher the polarity, the faster the drug release from the oil droplet into the aqueous phase. Polarity is mainly dependent on the HLB of surfactant, the molecular weight of the hydrophilic part of the surfactant, and its concentration along with the degree of saturation of fatty acid lipid phase[44,48].

In vitro diffusion study

In vitro diffusion studies were performed for all the formulations developed, using a dialysis technique. The dialysing medium was phosphate buffer pH 6.8. One end of pretreated cellulose dialysis tubing (7 cm in length) was tied with thread, and then 1 ml of self-nano emulsifying formulation was placed in it along with 0.5 ml of dialyzing medium. The other end of the tubing was also secured with thread and was allowed to rotate freely in 200 ml of dialyzing medium and stirred continuously at 100 rpm with a magnetic bead on the magnetic plate at 37°C. Aliquots of 1 ml were removed at different time intervals and diluted further. The volume of the aliquots was replaced with fresh dialyzing medium each time. These samples were analyzed quantitatively for drug dialyzed across the membrane at the corresponding time by using UV Visible spectrophotometer [42].

In vivo studies

The impact of excipients on the bioavailability and the pharmacokinetic profile of drugs can be estimated by designing appropriate in vivo studies. A detailed study of intestinal lymphatic absorption is required since lipid-based formulations enhance bioavailability by improving the intestinal uptake of the drug. Due to insufficient clinical data and differences in methods and animal models used, studies related to the drug transport by the lymphatic system have become difficult [51]. Hence, further work has to be carried out to establish an in vivo method and model to predict lymphatic drug transport. A lipid-based formulation of saquinavir mesylate (For- tovases) enhanced the bioavailability of the drug up to threefold when compared to Invirase (saquinavir in hard gelatin capsules)[52]. Lipid-based drug delivery system a report on bioavailability enhancement using self-emulsifying formulation by different workers is presented in [53] Table No. 4.

Table 4: Enhancement of bio availability of drugs by Lipid based drug delivery system.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Enhancement</th>
<th>With reference to</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>3.5 fold</td>
<td>Pure drug solution</td>
<td>Tablets</td>
</tr>
<tr>
<td>Anethole trithione</td>
<td>2.5 fold</td>
<td></td>
<td>Male albino rats</td>
</tr>
<tr>
<td>Bicalutamide</td>
<td>2 fold</td>
<td>Suspension</td>
<td>Rats</td>
</tr>
<tr>
<td>Mitotane</td>
<td>3.4 fold</td>
<td>Lysodren</td>
<td>2 fold</td>
</tr>
<tr>
<td>Carvediolol</td>
<td>4.13 fold</td>
<td>Commercial tablet</td>
<td>Rabbits</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>2.6-6.6 fold</td>
<td>Conventional tablet</td>
<td>Beagle dogs</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>1.5 fold</td>
<td>Zocor tablets</td>
<td>New Zealand</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>1.13 fold</td>
<td>Pure drug</td>
<td>Humans</td>
</tr>
</tbody>
</table>

STABILITY ASSESSMENT

Stability studies are performed as per the ICH guidelines on the formulation which is filled in Stability studies are performed as per the ICH guidelines on the formulation which is filled in gelatin capsules. At regular intervals, the samples should be collected and tested for appearance, color, drug content, pH of the diluted formulation, and dissolution profile. If there is no change in all these properties during storage conditions, the formulation can be concluded as stable formulation [49,28,37,50].

CONCLUSION

Self-emulsifying drug delivery systems are a promising approach for the formulation of drugs with poor water solubility. SEDDS also an effective formulation for drugs having poor solubility in the GI fluids resulting from less drug exposure to GIT. SEDDS are a novel technology for formulating lipophilic compounds and represent an alternative for improving the oral absorption of lipophilic drugs. SEDDS are usually explored to improve the bioavailability of hydrophobic drugs. Currently, several formulations have been developed to produce modified emulsified formulations as alternatives to conventional SEDDS. Table No.5 indicates the list of commercially available marketed products In this review, we focused on the patents reviewed showing an assortment of the SEDDS and their delivery based on the less aqueous solubility of the drug compounds were shown in Table No.6. It is well demonstrated that SEDDS promotes lymphatic delivery of highly hydrophobic drugs (with high octanol: water partition coefficient) with good solubility in triglycerides. The present review highlighted the developmental steps (solubility studies, construction of pseudo ternary phase diagrams, and various evaluation tests) involved in obtaining a robust and stable dosage form.

Table 5: Commerciably Available SEDDS Formulations in Market[63]

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Year of Approval</th>
<th>Drug</th>
<th>composition</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vesnoid</td>
<td>1995</td>
<td>Tretinoin</td>
<td>beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oil, soybean oil, glycerin, yellow iron oxide, red iron oxide, sodium dodecyl ethylparaben, and propylparaben</td>
<td>Hoffmann La Roche</td>
</tr>
<tr>
<td>Norvir</td>
<td>1996</td>
<td>Ritonavir</td>
<td>butylated hydroxytoluene, ethanol, gelatin, iron oxide, oleic acid, polyoxy 35 castor oil, and titanium dioxide</td>
<td>Abbott</td>
</tr>
<tr>
<td>Fortovase</td>
<td>1997</td>
<td>Saquinavir</td>
<td>medium chain mono- and diglycerides, povidone, dl-alpha tocopherol, gelatin, glycerol, red iron oxide, yellow iron oxide, and titanium dioxide</td>
<td>Hoffmann La Roche</td>
</tr>
<tr>
<td>Gengraf</td>
<td>2000</td>
<td>Cyclosporine A</td>
<td>alcohol USP absolute, FD&amp;C Blue No. 2, gelatin NF, polyethylene</td>
<td>Abbott</td>
</tr>
</tbody>
</table>
Table 6: Patents of SEDDS Formulation [63]

<table>
<thead>
<tr>
<th>Title</th>
<th>Patent number</th>
<th>Published year</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods of forming a self-supporting film for delivery of therapeutic agents</td>
<td>US86.23.36B2</td>
<td>2014</td>
<td>54</td>
</tr>
<tr>
<td>Rhizoma corydalis total alkaloids self-emulsifying drug delivery system</td>
<td>CN10191.247B</td>
<td>2013</td>
<td>56</td>
</tr>
<tr>
<td>and preparation method and application thereof</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-emulsifying pharmaceutical composition with enhanced bioavailability</td>
<td>EP2062.371B1</td>
<td>2012</td>
<td>57</td>
</tr>
<tr>
<td>Oil-in-water emulsion and its use for the delivery of functionality</td>
<td>AU2006.31650.7B2</td>
<td>2012</td>
<td>58</td>
</tr>
<tr>
<td>Coated capsules and tablets of a fatty acid oil mixture</td>
<td>CAS2781.25A1</td>
<td>2011</td>
<td>59</td>
</tr>
</tbody>
</table>

REFERENCES


