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Emulsion based drug delivery system

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ABSTRACT

Oral route continues to be the preferred route for most drug therapy. However, more than 40% of new chemical entities exhibit poor aqueous solubility, resulting in unsatisfactory oral drug delivery. Recently, much attention has been focused on Self emulsifying drug delivery systems and Self-Micro Emulsifying Drug Delivery System to improve the oral bioavailability of poorly aqueous soluble drugs. Self-micro emulsifying formulations and Self 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 agitation required for self-emulsification is provided by the digestive motility of the stomach and intestine in vivo. When dissolution rate-limited absorption is seen, as in case of lipophilic drugs, Self emulsifying drug delivery systems and Self-Micro Emulsifying Drug Delivery System may be a promising strategy to improve the rate and extent of oral absorption. This review describes Self emulsifying drug delivery systems and Self-Micro Emulsifying Drug Delivery Systems used to formulate potent lipophilic drugs.

INTRODUCTION

The oral route is the preferred route for chronic drug therapy. Numerous potent lipophilic drugs exhibit low oral bioavailability due to their poor aqueous solubility properties. For this class of compounds, defined by Amidon et al. low solubility/high permeability class II, dissolution in the environmental lumen is the rate controlling step in absorption process [1]. Efforts are ongoing to enhance the oral bioavailability of such lipophilic drugs in order to increase their clinical efficacy. Hence, the loading of the active lipophilic component into various systems [2] , such as self-emulsifying formulations [3], emulsions [4,5] and liposome's [6,7].These self organizing systems often lead to improvement in the therapeutic index of the lipophilic drugs through increased solubilization and modification of their pharmacokinetic profiles [8,9]. One of the most popular approaches are the self-emulsifying drug delivery systems (SEDDS).

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Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils, cosolvents and surfactants, which is isotropic in nature and which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation[10-17]. 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 [18-20]. Upon per oral administration, these systems form fine emulsions (or micro-emulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility [21-22]. In these systems, the drug present is in dissolved form and the small droplet size, increases interfacial surface area for absorption of drug [23]. SEDDS has a droplet size between 100–300 nm whereas compared to SEDDS, self-microemulsifying drug delivery systems (SMEDDS) has droplet size of 50 nm which form transparent emulsion. SMEDDS are distinguished from SEDDS by the much smaller emulsion droplets produced on dilution, resulting in a transparent or translucent solution.

SMEDDS generally contain relatively high concentrations of surfactant (typically 40-60%

w/w), and regularly contain hydrophilic cosolvents (e.g. propylene glycol, polyethylene glycols) [24]. 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 [25]. Figure1 illustrates fate of SEDDS and SMEDDS following oral administration. Self emulsifying system (SES) can be formulated with little energy input and shelf life is longer than conventional emulsion, therefore SES can be efficient vehicle for class II to IV molecules of the bio pharmaceutical classification system (BCS) drugs [26]. The lipophilic (poorly water soluble) drugs such as Nifedipine, Griseofulvin, Cyclosporin, Digoxin, Itraconazole Carbamazepine, Piroxicam, Fluconazole, Indomethacin, Steroids, Ibuprofen, Diazepam, Finasteroids, Difunisal, etc. are formulated in SMEDDS to improve efficacy and safety [27]. Some marketed formulations are shown in Table1.

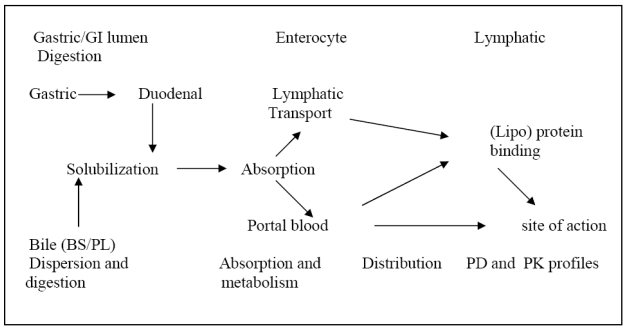

Figure1: Fate of SEDDS and SMEDDS following oral administration and mechanisms proposed for bioavailability enhancement of drugs.

Potential advantages of these systems include

1. Enhanced oral bioavailability enabling reduction in dose such as Ketoprofen [28]
2. More consistent temporal profiles of drug absorption e.g. Ontazolast [29]
3. Selective targeting of drug(s) toward specific absorption window in GIT [30]
4. Protection of drug(s) from the hostile environment in gut e.g. Acetylsalicylic acid [12]
5. Control of delivery profiles e.g. Paclitaxel [31]
6. Reduced variability including food effects e.g. Cyclosporine [32]
7. Protective of sensitive drug substances [30]
8. High drug payloads [30]
9. Liquid or solid dosage forms e.g. Progesterone [33]
10. Emulsion cannot be autoclaved as they have phase inversion temperature, while SMEDDS can be autoclaved [30]

TABLE 1: SEDDS and SMEDDS products available in the market

BRAND NAME	ACTIVE INGREDIENTS
3Vita-SEDDS	Multi-Vitamins
SEDDS CoQ10	Coenzyme Q10
Test 400	Pro testosterone
Knock out	IsoNox
C-4 Decanoate	Creatine Methyl Ester, Creatine Ethyl Ester, Creatine Gluconate, Creatine Decanoate.
Hyperdrine-OD	1-3Dimethylamine, AlphaYohimbinHCL, Caffeine, Hordenin, Phenyl ethylamine, Glucoronolactone, Metyl-Synepherine HCL, Salbutiamine.
Estro test	Resveratrol, Mucuna Puriens Stinging Nettle,3,17-dioxo etiochol-1,4,6-triene, Zinc Monomethionine aspartate Icariin,
Adrenaline-XR	Adrenaline

Disadvantages of these systems include

One of the disadvantages for 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. Further development will be based on *in vitro - in vivo* correlations and therefore different proto type lipid based formulations needs to be developed and tested in vivo in a suitable animal model [34].

Mechanism of Self-Emulsification

The theory of formation of microemulsion shows that emulsification occurs when the entropy change for dispersion, is greater than energy required to increase the surface area of the dispersion and the free energy (ΔG) is negative [35]. The free energy in the microemulsion formation, is directly proportional to the energy required to create new surface between the two desired phases and can be described by the equation (1)

$$\Delta G = \sum N \pi r^2 \sigma \quad \ldots\ldots\ldots (1)$$

Where, ΔG is the free energy associated with the process, N is the number of droplets of radius r and σ represents the interfacial energy.

After a certain time, the two phases of the

emulsion tend to separate to reduce the interfacial area, and subsequently, the free energy of the system decreases. To stabilize emulsions, emulsifying agents are added which reduces the interfacial energy, as well as provide a barrier to prevent coalescence.

General Formulation Approach

Preliminary studies are performed for selection of oil, which is an important and critical requisite for formulation of SEDDS and SMEDDS. It consists of oil, a surfactant and a co-surfactant. Solubility of drug is determined in various oils and surfactants. A series of SEDDS and SMEDDS system containing drug in various oil and surfactants are prepared. Then, in vitro self-emulsification properties and droplet size analysis of these formulations upon their addition to water under mild agitation conditions is studied. Pseudo-ternary phase diagram is constructed, identifying the efficient self-emulsification region. From these studies, an optimized formulation is selected and its bio-availability is compared with a reference formulation [22].

Composition of SEDDS and SMEDDS

Oils: Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDS owing to their formulation and physiological advantages. Novel semisynthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium- chain triglyceride [27, 36]. Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation are also valuable in designing of SEDDS.

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 glyceride, Tween 80, LABRFAC CM1O-a mixture of saturated compounds containing 8 carbon polyglycolysed glycosides 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 selfemulsify. Non-ionic surfactants are known to be less toxic compared to ionic surface-active agents. The high HLB and subsequent hydrophilicity 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 [25].

Co-surfactant: In SMEDDS, generally co-surfactant of HLB value [10-14] is used. Hydrophilic co-surfactants 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 micro emulsion [27], are used in formulation of SMEDDS.

Cosolvents: Cosolvents may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base which are as follows diethylene glycol, monoethyl ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, etc.[27].

Consistency builder: Materials such as tragacanth, cetyl alcohol, stearic acids and /or beeswax [37], are added to alter the consistency of emulsion.

Formulation

The method of making self microemulsion drug delivery system for increasing the bioavailability of a drug and/or pharmaceutical ingredient by emulsifying the drug with the self-microemulsifying excipient includes various steps as described below. [30]

1) Preparation of phase diagram [38].
2) Solubilizing a poorly water-soluble drug and/or pharmaceutical ingredient, in a mixture of surfactant, cosurfactant and solvent. Now mix the oil phase suitably prepared, if necessary, by heating or other preparatory means, to the solubilized drug formulation and thoroughly mixed.
3) The emulsion can then be added to a suitable dosage form such as soft or hard-filled gelatin capsules and allowed to cool.

Evaluation of SEDDS

1) Thermodynamic stability studies

- *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 [39].

2) Dispersibility test

The efficiency of self-emulsification of oral nano or microemulsion is assessed using a standard USP dissolution apparatus 2. One milliliter of each formulation is added to 500 ml of water at 37 ± 0.5˚C. A standard stainless steel dissolution paddle rotating at 50 rpm provides gentle agitation. The in vitro performance of the formulations is visually assessed using the following grading system:

Grade A: Rapidly forming (within 1 min) nanoemulsion, 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, grayish 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 nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation [39].

3) Turbidimetric Evaluation

Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of Selfemulsifying 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 [40].

4) Viscosity Determination

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 are w/o type of the system [39].

5) Droplet Size Analysis Particle Size Measurements

The droplet size of the emulsions is determined by photon correlation spectroscopy using a Zetasizer able to measure sizes between 10 and 5000 nm [40].

6) Refractive Index and Percent Transmittance

Refractive index and percent transmittance proved the transparency of formulation. The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank [34]

7) Drug content

Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract is analyzed by suitable analytical method against the standard solvent solution of drug [34].

Applications

Improvement in Solubility and bioavailability

If drug is incorporated in SEDDS, it increases the solubility because it circumvents the dissolution step in case of Class-Π drug (Low solubility/high permeability). Ketoprofen, a moderately hydrophobic (log P 0.979) Nonsteroidal anti-inflammatory drug (NSAID), is a drug of choice for sustained release formulation has high potential for gastric irritation during chronic therapy. Also because of its low solubility, ketoprofen shows incomplete release from sustained release formulations [28]. Different formulation approaches that have been sought to achieve sustained release, increase the bioavailability, and decrease the gastric irritation of ketoprofen include preparation of matrix pellets of nano-crystalline ketoprofen [28], sustained release ketoprofen microparticles and formulations [41], floating oral ketoprofen systems [42], and transdermal systems of ketoprofen [43]. Preparation and stabilization of nano-crystalline or improved solubility forms of drug may pose processing, stability, and economic problems. This problem can be successfully overcome when Ketoprofen is presented in SEDDS formulation. This formulation enhanced bioavailability due to increase the solubility of drug and minimizes the gastric irritation. Also incorporation of gelling agent in SEDDS sustained the release of Ketoprofen.

TABLE 2: Some Patented formulation of SEDDS and SMEDDS.

U.S. Patent No.	Date	Active ingredient	Information
7,749,540	July 6, 2010	Modafinil	Particle-forming compositions of modafinil compounds, and aqueous compositions of particles, wherein the particles comprise a modafinil compound, are disclosed, along with methods of their preparation, and their use in the treatment of diseases
7,736,666	June 15, 2010	Naproxen	The present invention claims and discloses a pharmaceutical composition suitable for oral administration, in form of an emulsion pre-concentrate, comprising a compound of formula one or more surfactants; optionally an oil or semi-solid fat; said composition forming an in-situ oil-in-water emulsion upon contact with aqueous media such as gastrointestinal fluids.
6,652,865	November 25, 2003	Simvastatin	A pharmaceutical composition for oral use is disclosed. The carrier includes: a therapeutically effective amount of the active principle; a lipophilic phase, which is a mixture of glycerol A method of decreasing the effect of intestinal metabolism on a drug using the composition is also disclosed.
6,555,558	April 29, 2003	Pyranone protease inhibitors	A microemulsion of pyranone protease inhibitor compounds that is substantially free of alcohol and propylene glycol comprising a pyranone protease inhibitor, one or more pharmaceutically acceptable surfactants, and a polyethylene glycol and di-glycerides, and optionally a basic amine.
6,309,665	October 30, 2001	Indomethacin	The invention concerns a composition comprising a microemulsion forming system by contact with a hydrophilic phase brought, after ingestion, comprising: at least an active principle; a lipophilic phase; a surfactant and a co-surfactant The invention further comprises an inert polymeric matrix being capable, after ingestion, of forming on contacting the physiological fluid, a gelled polymeric matrix enabling to release by diffusion, in continuous and prolonged manner the already micro-emulsified active principle.

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, enzymatic degradation or hydrolytic 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.

For water-soluble peptides typical bioavailability enhancements range from twenty to more than one hundred times. In an alternative application large proteins have been encapsulated for local activity in the gastrointestinal tract [12]. Some patents on SEDDS and SEDDS are shown in Table2.

CONCLUSION

The Self emulsifying drug delivery system and Self micro emulsifying drug delivery system appear to be unique and industrially feasible approach to overcome the problem of low oral bioavailability associated with the lipophilic drugs. Self emulsifying drug delivery system has improved solubility/dissolution, absorption and bioavailability for poorly water soluble drug. This is the method suited for lipophilic drugs where resulting emulsification gives faster dissolution rates and absorption. SEDDS is superior to other colloidal vehicle in reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance.

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