International Journal of Pharmacy and Pharmaceutical Sciences
Vol 2, Suppl 1, 2010

Review Article

NEWER APPROCHES TO SELF EMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT

Lipophilic drugs can be solublized to increase the bioavailability by using several methods as microemulsion, nanosuspension, liposome, solid lipid nanoparticles (SLN), self emulsifying drug delivery system (SEDDS), complexation with cyclodextrin etc.

SEDDS has received particular attention as a means of enhancing the oral bioavailability of poorly absorbed drugs. SEDDS are liquid to semisolid in nature, but it has drawbacks as formulation development, quality control, stability etc. These liquid SEDDS can be converted into solid dosage form without affecting drug release property. After administering the drug gets released and self emulsify in the GI tract.

Generally solid SEDDS are formed with mono, di or triglycrides of fatty acid, non ionic surfactants and solidifying agents with diluents such as microcrystalline cellulose, lactose etc.

Keywords: Self emulsification, biopharmaceutical classification, excipients, dosage form.

INTRODUCTION

The oral route is one of the preferred routes for chronic drug therapy. Approximately 35-40% of new drug candidates have poor water solubility. The oral delivery of such drugs is frequently associated with low bioavailability, high inter and intra subject variability and lack of dose proportionality. Efforts are going on to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy. To overcome these problems, new strategies were reported to increase solubility and bioavailability including complexation with cyclodextrins, solid dispersation (suspension), co-precipitation, micronisation, salt formation, emulsion, use of micelles, and cogrinding. [1-4]

Emulsions are used as vehicles for the administration of drugs, especially due to its potential of enhancing the oral bioavailability of poorly absorbed drugs. [5] Microemulsions has got advantage like excellent thermodynamic stability, high drug solubilization capacity, improvement in oral bioavailabity and protection against enzymatic hydrolysis. The only problem with microemulsion is poor palatability due to the lipid content leading to poor patient compliance, more over due to their water content, microemulsions cannot be encapsulated into soft gelatin or hard gelatin capsule. There is a need for converting it into an alternative formulation like anhydrous self emulsifying drug delivery system (SEDDS) etc., because of its low loading dose. [6]

SEDDS are solid dosage form with a unique property, that is they are able to self emulsify rapidly into fine O/W emulsion in the gastrointestinal fluids, under gentle agitation provided by the gastrointestinal tract. This fine O/W emulsion results in small droplets of oil dispersed in the gastrointestinal fluids that provide a large interfacial area enhancing the activity and minimizing the irritation due to contact of drug in the gut wall. [5, 7-10] Self Emulsifying System (SES) can be formulated with little energy input and the shelf life is longer than conventional emulsions. Therefore, an SES can be an efficient vehicle for class II to IV molecules of the Biopharmaceutical Classification System (BCS) drugs. [11]

Biopharmaceutical drug classification system

Biopharmaceutical drug classification is a fundamental guideline classifying drugs based on the solubility and permeability, as shown in Table 1. [12]

Table 1 : Biopharmaceutical drug classification

Class	Permeability	Solubility
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

Class I includes drugs that are water soluble and gastrointestinal tract permeable. This class does not suffer from absorption or permeation problems that may affect oral drug bioavailability. While classes II, III and IV contain drugs having problems in solubility and/or permeability that may reflect on their bioavailability in the blood after the drug is taken orally. Classes II, III and IV form approximately 80% of the drugs available in the market.

Purpose

1. Highly important consideration in the formulation of solid SES is effective incorporation of the drug, in

terms of both the solubilization within the oil-surfactant mix in order to allow a suitable solid dosage to form and once formed the effect that the drug may have on the emulsification properties.

Table 2: Summarizes examples of drugs related to II, III and IV classes

Class II	Class III	Class IV
Artemether	Abacavir,	Nelfinavir
Carbamazepine	Acetylsalicylic Acid,	Mesylate
Dapsone	Allopurinol.	Furosemide
Efavirenz	Atropine Sulfate	Albendazole
Folic Acid	Biperiden	Acetazolamide
Glibenclamide	Hydrochloride	Azathioprinei
Griseofulvin	Captopril.	Didancosine
Haloperidol	Chloramphenicol	Indinavir
Ibuprofen	Cimetidine	
Phenytoin Sodium	Colchicines	
	Ergometrine	
	Ethambulol	
	Hydrochloride	
	Hydralazine	
	Hydrochlorothaizide	
	Lamivudine	
	Levamisole	
	Metformin	
	Hydrochloride	
	Propyl thiouracil	

2. The advantage of solid SES is in its dose reduction, if an improvement in oral bioavailability is established.

3. SES are usually formulated in a liquid form, which has some disadvantages, especially during the manufacturing processes, leading to high production costs, tedious process control, and low stability. Furthermore, incompatibility problems as explained earlier with the capsule shell are common. [13, 14]

Mechanism of self emulsification

Self emulsifying process are related to the free energy, ΔG given by

$$\Delta G = \Sigma N \pi r^2 \sigma \qquad (i)$$

Here, N is the number of droplets with radius r and σ the interfacial energy. [15] It is apparent from the equation that the spontaneous formation of interface between the oil and water phase is energetically not favorable. The system commonly classified as SEDDS have not yet been shown to emulsify spontaneously in the thermodynamic sense.

Mustafa and Groves developed a method of quantitatively assessing the ease of emulsification by monitoring the turbidity of the oil-surfactant system in a water stream, using phosphated nonylphenoloxylate (PNE) and phosphated fatty alcohol ethoxylate (PFE) in n-hexane and suggested that the emulsification process may be associated with the ease with which water penetrates the oil-water interface, with formation of liquid crystalline phase resulting in swelling at the interface, thereby resulting in greater ease of emulsification.[16] Consequently, the authors were able to relate the phase behavior to the spontaneity of emulsification, with liquid crystals formation, tending to form emulsion more readily, as indicated by the lower equilibration times.[17] Pouton has argued that the emulsification properties of the surfactant may be related to phase inversion behaviour of the system.[18] For example, if one increases the temperature of the oil in the water system stabilized by using non-ionic surfactants, the cloud point of the surfactant will be reached followed by phase inversion.[19] The surfactant is highly mobile at the phase inversion temperature; hence the O/W interfacial energy is minimized, leading to a reduction in energy required to bring about emulsification. Pouton has suggested that the specificity of surfactant combination required to allow spontaneous emulsification is associated with a minimization of phase inversion temperature, there by increasing the ease of emulsification.[18]

Role of excipient used in solid self emulsification system

Self-emulsifying solid dosage form mainly contains oil, surfactant, cosurfactant, filler etc. A wide range of oils has been studied either as model system or as potential vehicles for the dosage forms, with many of the oils under study being medium chain fatty acid ester or a medium/long chain saturated, partially unsaturated or unsaturated hydrocarbon, in liquid, semisolid or solid form at room temperature. In SEDDS we can use different types of oil for examples mono, di, triglycerides of fatty acids, fatty alcohols, vegetable oils, mineral oils, refined animal oils etc [19]. Nature of oil is very important in the formation of SEDDS. Chemicals structure of the oil components and interactions of these components with the various enzymes, surfactants and proteins associated with digestion and absorption process, for example, fatty acid chain length is important factor for chylomicron formation. Short and medium chain acids are predominantly absorbed by portal blood system while longer chain fatty acid may be reesterified in the cell lining the small intestine and absorbed via the lymphatics. [20-21]

The absorption enhancement is greater when using unsaturated fatty acids. Figure 1 showed digestion of lipid and subsequent absorption via the portal blood and intestinal lymphatics.[22]

M. Cheema et al reported that a greater degree of unsaturation led to a more rapid onset of lipoprotein synthesis as a result of faster absorption or greater affinity of fatty acid binding to protein because unsaturated fatty acids have lower melting points as compared to saturated with increasing fluidity. [23] Liquid crystal formation from oil depends on oil polarity, which would influence the emulsification process. Very polar or non-polar oils tend to form poor

emulsions. Miglyol 812 and 840 both have intermediate polarity which shows favourable emulsification properties with Tween85. Solubility of the drug in the oil-surfactant mixture is very important whereas solubility of drug in vegetable oil is not a problem. The simplest and most desirable formulation may well be a simple oil solution which is self emulsified in the gut during digestion. [24]

For toxicity reason, these days research focuses on the use of non-ionic surfactant with relatively high hydrophile lipophile balance (HLB) value. Surfactants posses properties to inhibit the digestion of oils, so selection of surfactant is very important. Pouton and Wakerley et al have screened a range of surfactants, finding that in general molecules with unsaturated acyl chains were most efficient emulsifiers. [25-26]

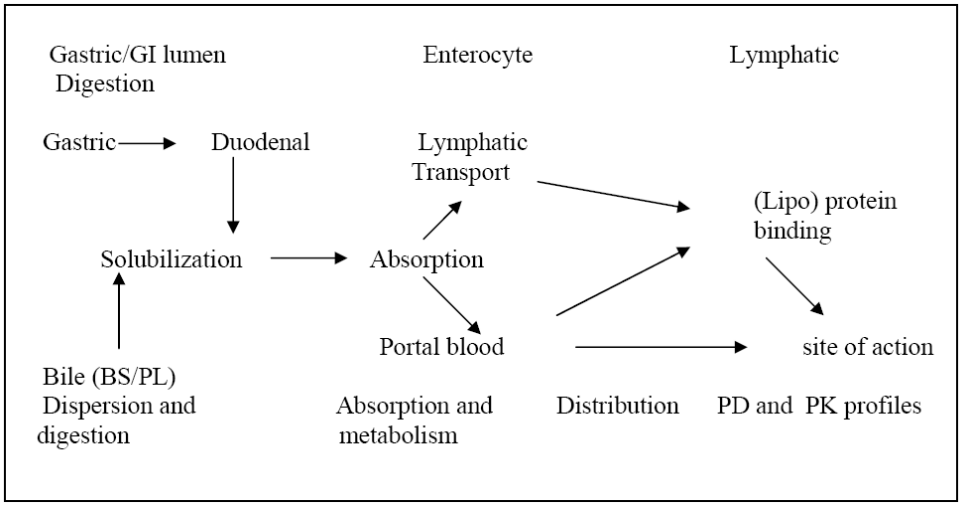

Fig. 1: Processing of lipid and co-administered Drug

Technique of solid SEDDS development

Solid SEDDS were developed mainly by adsorption of solid carriers, spray drying, melt extrusion, dry emulsion, solid dispersion etc. These solid SEDDS can be converted into pellets, tablets and capsules.

i) Solid carriers

These solid carriers have property to absorb liquid/semisolid formulation as self emulsifying system (SES). It is a simple procedure, where SES is incorporated into a free flowing powder material which has adsorption quality. The mixture is uniformly adsorbed by mixing in a blender. This solid mixture is filled into capsule or added to more excipient before compression into tablets.[27] The above mixture was solidified to powder forms using three kinds of adsorbents: microporous calcium silicate (FloriteTM RE); magnesium aluminum silicate (NeusilinTMUS2) and silicon dioxide (SylysiaTM 320).[28]

ii) Spray Drying

In this technique first the prepared formulation containing oil, surfactant, drug, solid carrier etc, is sprayed into a drying chamber through a nozzle. The volatile vehicles first evaporate leaving behind small solid particles. These particles are then filled into capsules or compressed into tablets.

iii) Melt extrusion

This formulation technique depends on the property of the plastic mass material which can be easily extruded and speronised with pressure. Here there is no need for addition of liquid form of excipient but a constant temperature and pressure need to be maintained. [29]

iv) Dry Emulsion

It is mainly O/W emulsion, which is then converted into solid form by spray drying/solid carrier/ freeze drying. [30-33]

Dosage forms from self emulsifying system:

Self emulsifying capsule: It is a capsules containing liquid or semisolid form of self emulsifying system. In the GIT, the capsules get dispersed to SES uniformly in the fluid to micron size, enhancing bioavailability. Second type of self emulsifying capsule is solid SES filled into capsule.

Self emulsifying tablets: S.Nazzal et al developed self-nanoemulsified tablet dosage form of Ubiquinone. The main objectives of this study were to study effect of formulation ingredients on the release rate of Ubiquinone and to evaluate an optimized self-nanoemulsified tablets formulation. The first prepared self nanoemulsion system containing Ubiquinone was prepared as nanoemulsion, this nanoemulsion was adsorbed by granular materials and then compressed to form tablets. The optimized formulation of coenzyme Q10 self-nanoemulsified tablet dissolution profile showed that 80-90% drug release took place in 45 minute. [34]

A.A. Attama et al formulated the solid self-emulsifying systems in the delivery of diclofenac. This solid self emulsifying system was developed using goat fat and tween 65. The fatty material and surfactant were heated together to melt and added to weighted quantity of drug and dissolved in the melt, this molten mass was then poured into plastic mould and cooled. This tablets will liquify at body temperature without agitation and at gastrointestinal conditions, agitation as peristaltic movement will lower the liquification time, resulting in faster emulsification with increased plasma concentration. Different formulation ratio shows varing dissolution profile at constant speed/agitation. These tablets showed good release profiles with acceptable tablet properties.[35]

Self emulsifying pellets: C. Tuleu et al presented comparative bioavailability study in dogs of a self – emulsifying formulation of progesterone presented as in pellets and the liquid form was compared with an aqueous suspension of progesterone. The in vitro dissolution tests showed that nearly 100% of progesterone dissolved within 30 min and within 5 min from capsules containing the progesterone dissolved in self emulsifying system. From the aqueous suspension, 50% of the dose was released within 60 min. They also showed that pellets administered orally to dogs were tested versus the same dose of progesterone dissolved in liquid SES in capsules or a suspension of micronized progesterone. In that SES pellets and SES solution had higher plasma levels of progesterone at each time point as compared to the aqueous suspension of progesterone.[36]

E. Franceschinis et al developed a method of producing self-emulsifying pellets by wet granulation. Here they first developed a binder solution containing an oil (mono and diglycerides), polysorbate 80 and model drug nimesulide in different proportion. This oil-surfactant mixture was stirred then added to water to form Self- emulsifying system. Second step was to prepare granules from microcrystalline cellulose and lactose in a granulator. These binder solutions were sprayed on to the granules and pellets were formed by increasing the speed of the granulator. Pellets were able to generate significantly smaller droplets with respect to corresponding emulsions.[37]

M. Serratoni et al presented controlled drug release from self-emulsifying pellets. The prepared self emulsifying system were formed by mixing oil-surfactant within solublised drug in appropriate concentrations, because higher quantity of drug incorporated into SES, could be precipitated when diluted with water. This SES was added into damp mass of microcrystalline cellulose and lactose monohydrate, water was then added to the prepared wet mass for extrusion-spheronization to form pellets. These pellets were coated by hydrophilic polymers namely ethyl cellulose then coated by aqueous solution of hydroxypropylmethyl cellulose in a fluid bed coater.

The ability of this formulation to enhance dissolution of the model drug, where dissolution results for the uncoated pellets containing methyl or propyl parabens with and without the addition of self emulsifying system were compared.[38]

Ahmed abdalla and Karsten Mader investigated preparation and characterization of self-emulsifying pellets formulation. They formulated three self emulsifying systems separately by melting Cithrol GMS (mono and diglycerides) and solutol HS 15, to this was added drug, dye and spin probe. Then added water to the molten lipid blend until creamy mass was formed, then added dry MCC into it to form suitable mass for extrusion.

The dye was added for assessment of self emulsification and spin probe was added for the release kinetics and microenvironment of pellets, during release process, which were assessed using electron spin resonance spectroscopy. The dissolution profile showed complete release of drug as diazepam from the non self emulsifying GMS/MCC pellets. It had a 3-fold duration of action. Nearly 90% of the drug was released after an hour while only 55% was released from the GMS/MCC pellets. Pellets composed of MCC/GMS were only capable of releasing diazepam until the saturation solubility reached.[39]

T. Iosio et al prepared bi-layered self emulsifying pellets, SEP was formed by co-extrusion-speronization with two cohesive layers, in that, type 1 pellets had formulation A (a matrix made of lactose and MCC loaded with a SES dispersion) in the inner part and formulation B (a inert matrix containing in lactose, MCC, and water) in the outer and type 2 having formulation B in the inner core and formulation A externally. SEP were formulated in two steps, first prepared oil-surfactant mixture then added to water to form self-emulsifying system and this mixture was then loaded into MCC and lactose to form suitable extrusion-speronization mass for pellets. Pellets of type I plus 2% of croscarmellose sodium released 90% of vinpocetine as a model drug within 30 min, pellets of type II were release in 20 min and from the physical mixture only 25% of drug was released after 60 min.[40]

Self emulsifying beads: Self emulsifying system can be formulated as a solid dosage form by using less excipient. Patil and Paradkar discovered that deposition of SES into microporous polystyrene beads was done by solvent evaporation. Porous polystyrene beads with complex internal void structures were typically produced by copolymerising styrene and divinyl benzene. It is inert and stable over a wide range of pH, temperature and humidity. Geometrical features, such as bead size and pore architecture of

PPB, were found to govern the loading efficiency and in vitro drug release from SES-loaded PPB.[41]

Self emulsifying microsphere: You et al. formulated solid SE sustained-release microspheres using the quasi-emulsion solvent diffusion method for the spherical crystallization technique. Zedoary turmeric oil release behavior could be controlled by the ratio of hydroxypropyl methylcellulose acetate succinate to Aerosil 200 in the formulation. The plasma concentration time profiles were achieved after oral administration of such microspheres into rabbits, with a bioavailability of 135.6% with respect to the conventional liquid SEDDS. [42]

Self-emulsifying nanoparticle: Nanoparticle technology can be applied to the formulation of self emulsifying nanoparticle. One of the solvent was injection, in this method the prepared molten lipid mass contained lipid, surfactant and drug. This lipid molten mass was injected drop wise into a non solvent system. This is filtered and dried to get nanoparticles. By this method 100 nm size particle with 70-75% drug loading efficiency was obtained.[43]

Second technique is sonication emulsion diffusion-evaporation; by this method co-load 5-flurouracil and antisense EGFR (epidermal growth factor receptor) plasmids into biodegradable PLGA/O-CMC nanoparticles. The mixture of PLGA (poly-lactide-co-glycolide) and O-CMC (O-carboxmethyl-chitosan) had a SE effect, with no additional surfactant required.[44]

Trickler et al. developed a novel nanoparticle drug delivery system consisting of chitosan and glyceryl monooleate (GMO) for the delivery of paclitaxel (PTX). These chitosan/ GMO nanoparticles, with bioadhesive properties increased cellular association and was prepared by multiple emulsion (o/w/o) solvent evaporation methods.[45]

CONCLUSION

Self emulsifying drug delivery system in solid dosage form 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. Solid SEDDS is superior to SEDDS in reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance. Solid SEDDS has the flexibility to develop into different solid dosage form for oral and parenteral administrations.

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