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SELF- MICRO EMULSIFYING DRUG DELIVERY SYSTEM: A NOVEL APPROACH FOR ENHANCEMENT OF ORAL BIOAVAILABILITY OF POORLY SOLUABLE DRUGS

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ABSTRACT

As a consequence of modern drug discovery techniques, there has been a steady increase in the number of new pharmacologically active lipophilic compounds that are poorly water-soluble. Approximately 40% of new drug candidates have poor water solubility and oral delivery of such drugs is frequently associated with implications of low bioavailability, high intra and inter subject variability, lack of dose proportionality and therapeutic failure. It is a great challenge for pharmaceutical scientists to convert those molecules into orally administered formulations with sufficient bioavailability. Among the approaches to improve the oral bioavailability of these molecules, the use of self-emulsified drug delivery systems (SEDDS) has been shown to be reasonably successful in improving the oral bioavailability of poorly water-soluble and lipophilic drugs. SEDDS is ideally an isotropic mixture of oils and surfactants and sometimes co-solvents. Hydrophobic drugs can be dissolved in these systems, enabling them to be administered as a unit dosage form for per-oral administration. When such a system is released in the lumen of the gastrointestinal tract, under conditions of gentle agitation provided by digestive motility of stomach and intestine, it spontaneously disperses to form a fine relatively stable o/w emulsion (micro/nano) with the aid of GI fluid. This leads to in situ solubilisation of drug that can subsequently be absorbed by lymphatic pathways, bypassing the hepatic first-pass effect.

Keywords: - Lipid based formulation, Self emulsifying drug delivery system, poorly water soluble drugs, surfactant and Bioavailability.

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INTRODUCTION

The oral route has been the major route of drug delivery for chronic treatment of many diseases. Oral drug delivery system is the most cost-effective and leads the world wide drug delivery market. However, in the present scenario, oral drug delivery is continuously looking into newer avenues as 40% of new drug candidates have poor water solubility and/or absorption, high intra- and inter-subject variability, rapid metabolism, high fluctuation in the drug plasma level, variability due to food effect, and lack of dose proportionality which are playing major role in disappointing *in vivo* results leading to failure of conventional drug delivery system¹. To overcome these problems, new strategies were reported to increase solubility and bioavailability including complexation with cyclodextrin, solid dispersion (suspension), co-precipitation, micronisation, salt formation, emulsion, use of micelles, and co grinding²⁻⁵. Recently much attention has been focused on lipid solutions, emulsions and emulsion pre-concentrates, which can be prepared as physically stable formulations suitable for encapsulation of such poorly soluble drugs. Emulsion systems are associated with their own set of complexities, including stability and manufacturing problems associated with their commercial production. Self-emulsification systems are one formulation technique that can be a fitting answer to such problems⁶.

Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of drug, lipids and surfactants, usually with one or more Hydrophilic co-solvents or coemulsifiers⁷. Upon mild agitation followed by dilution with aqueous media, these systems can form fine (oil in water) emulsion instantaneously. 'SEDDS' is abroad term, typically producing emulsions with a droplet size ranging from a few nano meters to several microns. 'Self-micro emulsifying Drug delivery systems' (SMEDDS) indicates the formulations forming transparent micro emulsions with oil droplets ranging between 100 and 250 nm. 'Self-nano-emulsifying drug delivery systems' is a recent term construing the globule size range less than 100 nm⁷.

Biopharmaceutical Classification System

There are number of formulation strategies that could be used to improve bioavailability of class II drugs, either by increasing the dissolution rate/ by presenting the drug in solution and maintaining the drug in solution in the intestinal lumen. As shown below in figure 1 bioavailability of class IV drugs can be improved by attention to the formulation. Formulation may improve bioavailability of class IV drugs but they are likely to be compromised by their poor membrane permeability. If a class II drug can be maintained in a solubilise state in the

lumen of the gut one can achieve an absorption profile more like that of a class I drug. Formulation strategies can do little to improve the absorption of class IV and III drugs which are limited by poor membrane Permeability.

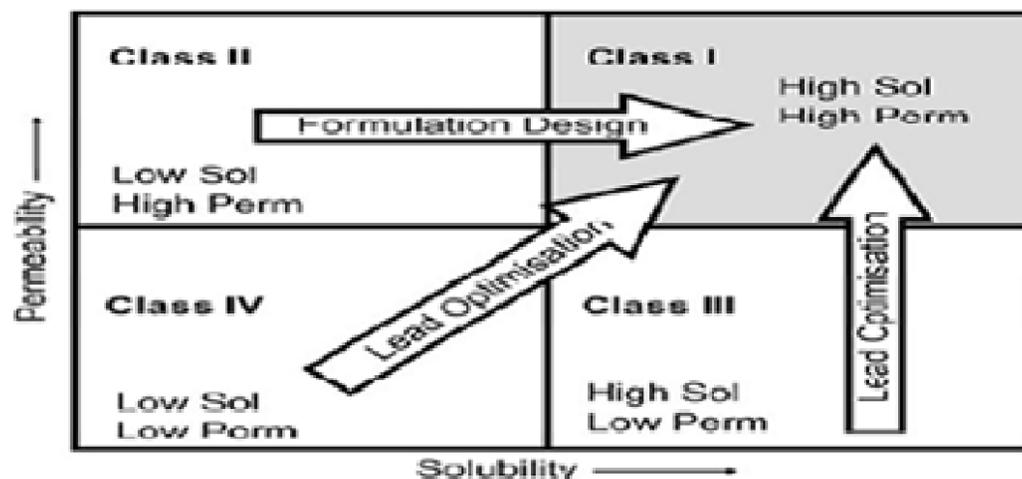


Figure 1: A typical representation of biopharmaceutical classification system

Table 1: Examples of drugs related to II, III and IV Class⁷

Class II	Class III	Class IV
Artemether	Abacavir	Albendazole
Dapsone	Allopurinol	Indinavir
Carbamazepine	Ethambutol	Acetazolamide
Folic acid	Biperiden	Furosemide
Gresiofulvin	Captopril	Mesylate
Ibuprofen	Metformin Hydrochloride	Nelfinavir
Phenytoin Sodium	Cimetidine	
Itraconazole	Atropine Sulphate	

Advantages

Potential advantages of these systems (SEDDS) include

1. Enhanced oral bioavailability enabling reduction in dose.
2. More consistent temporal profiles of drug absorption.
3. Selective targeting of drug(s) toward specific absorption window in GIT
4. Protection of drug(s) from the hostile environment in gut.
5. Control of delivery profiles.
6. Reduced variability including food effects.
7. Protection of sensitive drug substances.
8. High drug payloads.
9. Liquid or solid dosage forms.
10. Ease of manufacture and scale up.

Advantages of SMEDDS over Emulsion:

1) SMEDDS not only offer the same advantages of emulsions of facilitating the solubility of hydrophobic drugs, but also overcomes the drawback of the layering of emulsions after sitting for a long time. SMEDDS can be easily stored since it belongs to a thermodynamics stable system.

2) Micro emulsions formed by the SMEDDS exhibit good thermodynamics stability and optical transparency. The major difference between the above micro emulsions and common emulsions lies in the particle size of droplets. The size of the droplets of common emulsion ranges between 0.2 and 10 μm , and that of the droplets of micro emulsion formed by the SMEDDS generally ranges between 2 and 100 nm (such droplets are called droplets of nano particles). Since the particle size is small, the total surface area for absorption and dispersion is significantly larger than that of Solid dosage form and it can easily penetrate the gastrointestinal tract and be absorbed. The bioavailability of the drug is therefore improved⁸.

Suitable Drug candidate identification for SEDDS

One of the primary challenges to any oral formulation design Program is maintaining drug solubility within the gastrointestinal tract and, in particular, maximizing drug solubility within the prime absorptive site of the gut⁹. For lipophilic drug compounds that exhibit dissolution rate-limited absorption, SEDDS can offer an improvement in rate and extent of absorption, resulting in reproducible blood time profiles. Logically speaking, however, use of SEDDS can be extended to all four categories of biopharmaceutical classification system (BCS) class drugs⁷. These systems can help in solving the under-mentioned problems of all the categories of BCS class drugs, as depicted in Table 2.

Table 2: SEDDS as a solution to various problems to different classes of drugs

BCS class	Problems
Class I	Enzymatic degradation, gut wall efflux
Class II	Solubilization and bioavailability
Class III	Enzymatic degradation, gut wall efflux and bioavailability
Class IV	Solubilization, Enzymatic degradation, gut wall efflux and bioavailability

Lipinski's rule of five has been widely proposed as a qualitative predictive model for oral absorption trends. In the discovery setting, the 'rule of five' predicts that poor absorption or poor permeation is more likely when there are more than five H-bond donors, there are more than ten H-bond acceptors, the molecular weight >500 and the calculated $\log P > 5$. The question arising is whether solubility and $\log P$ are sufficient to identify potential drug candidates for such

formulations. Although classification systems such as the BCS and Lipinski's rule of five are useful, particularly at the initial screening stage, they have limitations. It is considered that the rule of five only holds for compounds that are not substrates for active transporters and with increasing evidence suggesting that most drugs are substrates for some efflux or uptake transporters, this limitation might be notable. Aqueous solubility and/or log P alone are unlikely to be sufficient for identifying the suitability of a lipid-based formulation approach because they do not adequately predict potential *in vivo* (i.e. physiological) effects. It has been found that individually, these poorly water-soluble compounds, which are generally classier as 'lipophilic', behave differently in similar vehicles, thus highlighting the need to assess candidate compounds on an individual basis^{7,9}.

Lipid formulation classification system (LFCS)

LFCS was established by Pouton in 2000 and recently updated in 2006 to help stratify formulations into those with similar component parts¹⁰. The LFCS briefly classifies lipid-based formulations into four types according to their composition and the possible effect of dilution and digestion on their ability to prevent drug precipitation and they are shown in Table 3

Regulatory aspects of lipid excipients

Initially excipients were considered inert substances that would be used mainly as diluents, filter, binders, lubricants, coatings, solvents and dyes in the manufacture of drug products. Over the years, however, advances in pharmaceutical science and technology have facilitated the availability of a wide range of novel excipients. It is now recognized that not all excipients are inert substances and some might be potential toxicants¹¹. In the United States, the Food and Drug Administration (FDA) has Published listings in the Code of Federal Regulations for Generally Recommended as Safe (GRAS) substances that are generally recognized as safe (<http://www.fda.gov/Food/foodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/default.htm>). Over the years, the agency has also maintained a list entitled 'Inactive Ingredient Guide' for excipients that have been approved and Incorporated in marketed products (<http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>). This guide is helpful in that it provides the database of allowed excipients with the maximum dosage level by route of administration or dosage form for each excipients¹².

Table 3: Lipid formulation classification system (LFCS) as described by Pouton showing typical compositions and properties of lipid-based^{13, 14}

Increasing Hydrophilic Typical composition (%)	Content				
	Type I	Type II	Type IIIA	Type IIIA	Type IV
Triglycerides or mixed glycerines	100	40-80	40-80	<20	-
Water-insoluble surfactants (HLB < 12)	-	20-60	-	-	0-20
Water-soluble surfactants (HLB > 12) Hydrophilic co solvents	-	-	20-40	20-50	30-80
Hydrophilic co solvents	-	-	0-40	20-50	0-50
Significance of aqueous Dilution	Limited Importance	Solvent capacity unaffected	Some loss of solvent capacity	Phase changes	Phase changes
Significance of digestibility	Crucial Requirement	Not crucial but likely to occur	Not crucial but may be inhibited	Not required	Not required
Advantages	GRAS status; simple; excellent capsule compatibility	Unlikely to lose solvent capacity on dispersion	Clear or almost clear dispersion; drug absorption without digestion	Clear dispersion; drug absorption without digestion	Formulation has good solvent capacity for many drugs
Disadvantages	Poor solvent capacity unless drug is highly lipophilic	Turbid o/w dispersion (particle size 0.25-2 μ m)	Possible loss of solvent capacity on dispersion; less easily digested	likely loss of solvent capacity on dispersion	Likely loss of solvent capacity on dispersion; may not be digestible

Mechanism of Self-Emulsification

In emulsification process the free energy (ΔG) associated is given by the equation¹⁵

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

In which “N” is number of droplets with radius “r” and “ σ ” is interfacial energy. It is apparent from equation that the spontaneous formation of the interface between the oil and water phase is energetically not favoured. The system commonly classified as SEDDS have not yet been shown to emulsify spontaneously in the thermodynamic sense. The process of self-emulsification was observed using light microscopy. The emulsification process may be associated with the ease with water penetrates the oil-water interface with the formation of liquid crystalline phases resulting in swelling at the interface thereby resulting in greater ease of emulsification.

Composition of SEDDS¹⁶

The self emulsifying process depends on:

- The nature of the oil–surfactant pair
- The surfactant concentration
- The temperature at which self-emulsification occurs.

1. Oils:

Oils can solubilize the lipophilic drug in a specific amount. It is the most important excipient because it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract.

Table 4: Examples of oils, surfactant and co-surfactant

Oils	Surfactants	Co-surfactants/Co solvent
Cotton seed oil	Polysorbate 20 (Tween 20)	Span 20
Soybean oil	Polysorbate 80 (Tween 80)	Span 80
Corn oil	D-alpha Tocopheryl polyethylene glycol 1000 succinate (TPGS)	Capryol 90
Sunflower oil	Polyoxy-35-castor oil(Cremophor RH40)	Lauroglycol
Castor oil	Polyoxy-40- hydrogenated castor oil(Cremophor RH40)	Transcutol
Sesame oil	Labrasol	Isopropyl alcohol
Peanut oil		Ethanol
Labrafac		Polyethylene glycol

Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDSs. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDSs owing to their formulation and physiological advantages. Novel semi synthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium-chain triglyceride.

2. Surfactant: Nonionic surfactants with high hydrophilic/lipophilic balance (HLB) values are used in formulation of SEDDSs (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore etc.). The usual surfactant strength ranges between 30–60% w/w of the formulation in order to form a stable SEDDS. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature they can dissolve or solubilise relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules.

3. Co-surfactants/Cosolvents: Formulation of effective SEDDSs requires high concentration of surfactants, co-surfactant/Cosolvents like span, capryol 90, capmul, lauroglycol, diethylene glycol

CHARACTERIZATION OF SEDDS

The primary means of self emulsification assessment is visual evaluation^{17, 18}. The various ways to characterize SEDDS are compiled below.

Equilibrium phase diagram

Although self-emulsification is a dynamic non-equilibrium process involving interfacial phenomena, information can be obtained about self-emulsification using equilibrium phase behaviour. There seems to be a correlation between emulsification efficiency and region of enhanced water solubilisation and phase inversion region, formation of lamellar liquid crystalline dispersion phase on further incorporation of water. An equilibrium phase diagram enables comparison of different surfactants and their synergy with co-solvent or co-surfactant¹⁹. The boundaries of one phase region can easily be assessed visually. The phase behaviour of a three-component system can be represented by a ternary phase diagram.

Thermodynamic stability studies

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.

1. 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.

2. Centrifugation: Passed formulations are centrifuged thaw cycles between 21 C and +25 0C 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.

3. Freeze thaw cycle: Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking²⁰.

Dispersibility test

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 0C. 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) 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 formulation²⁰.

Turbidity measurement

This identifies efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in are producible time²¹. These measurements are carried out on turbidity meters, most commonly the Hach turbidity meter and the Orbeco-Helle turbidity meter^{22, 23}. This apparatus is connected to a dissolution apparatus and optical clarity of formulation is taken every 15s to determine clarity of nano or micro emulsion formed and emulsification time. Turbidity can also be observed in terms of spectroscopic characterization of optical clarity (i.e. absorbance of suitably diluted aqueous dispersion at 400 nm)²⁴.

Droplet size

This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release, as well as the stability of the emulsion. Photon correlation spectroscopy,

microscopic techniques or a Coulter Nanosizer are mainly used for the determination of the emulsion droplet size^{25,26}.

Electron microscopic studies

Freeze-fracture electron microscopy has been used to study surface characteristics of such dispersed systems²⁷. Because of the high lability of the samples and the possibility of artifacts, electron microscopy is considered as somewhat misleading technique. Particle size analysis and low-frequency dielectric spectroscopy have been used to examine the self-emulsifying properties of Imwitor 742 (a mixture of mono- and diglycerides of capric and caprylic acids) and Tween 80 systems²⁸.

Zeta potential measurement

This is used to identify the charge of the droplets. In conventional SEDDS, the charge on an oil droplet is negative because of the presence of free fatty acids²⁹.

Determination of emulsification time

Pouton *et al.*³⁰ quantified the efficiency of emulsification of various compositions of the Tween85 and medium-chain triglyceride systems using a rotating paddle to promote emulsification in a crude nephelometer. This enabled an estimation of the time taken for emulsification. Once emulsification was complete, samples were taken for particle sizing by photon correlation spectroscopy, and self-emulsified systems were compared with homogenized systems. The process of self-emulsification was observed using light microscopy. It was clear that the mechanism of emulsification involved erosion of a fine cloud of small particles from the surface of large droplets, rather than a progressive reduction in droplet size.

Viscosity Determination

The SMEDDS system is generally administered in soft gelatin or hard gelatin capsules. Therefore, it should be easily pourable into capsules and such system should not be too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield Viscometer. This viscosity determination confirms 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 viscosity then it is w/o type of the system³¹.

Cryo-TEM studies

For Cryo-Transmission Electron Microscopy (TEM), samples were prepared in a controlled environment verification system. A small amount of sample is put on carbon film supported by a copper grid and blotted by filter paper to obtain thin liquid film on the grid. The grid is quenched

in liquid ethane at -180°C and transferred to liquid nitrogen at -196°C. The samples were characterized with a TEM microscope.

Liquefaction time

This test is designed to estimate the time required by solid SEDDS to melt *in vivo* in the absence of agitation to simulated GI conditions. One dosage form is covered in a transparent polyethylene film and tied to the bulb of a thermometer by means of a thread. The thermometer with attached tablets is placed in a round bottom flask containing 250 ml of simulated gastric fluid without pepsin maintained at $37 \pm 18^\circ\text{C}$. The time taken for liquefaction is subsequently noted.

Small-angle neutron scattering

Small angle neutron scattering can be used to obtain information on the size and shape of the droplets. The term ‘droplet’ is used to describe micelles, mixed micelles and oil-swollen micelles throughout the present work. Small-angle neutron scattering experiments use the interference effect of wavelets scattered from different materials in a sample (different scattering-length densities).

Small-angle X-ray scattering

This is a small-angle scattering technique in which the elastic scattering of X-rays by a sample that has inhomogeneities in the nm range is recorded at very low angles (typically 0.1–108). This angular range contains information about the shape and size of macromolecules, characteristic distances of partially ordered materials, pore sizes and other data. Small-angle X-ray scattering is capable of delivering structural information of macromolecules between 5 and 25nm, of repeat distances in partially ordered systems of up to 150nm. Small-angle X-ray scattering is used for the determination of the micro scale or nanoscale structure of particle systems in terms of such parameters as averaged particle sizes, shapes, distribution and surface-to-volume ratio. The materials can be solid or liquid and they can contain solid, liquid or gaseous domains (so-called ‘particles’) of the same or another material in any combination. In addition to these tools, others—such as nuclear magnetic resonance and differential scanning Colorimetry have also been exploited to characterize these self-emulsifying systems for a better insight.

APPLICATION

Super-saturable SEDDS

One of the most promising approaches for enhancing the oral bioavailability of poorly soluble drugs is the use of the principle of super saturation in the development of super-saturable

formulations. It should be clearly recognized that super-saturable formulations differ from supersaturated formulations. Supersaturated formulations are not thermodynamically stable and drugs in supersaturated formulations can crystallize on storage. Therefore, the physical stability of such formulations is fundamentally challenging and this limits their practical utility. In contrast, super-saturable formulations are thermodynamically stable dosage forms; they yield a supersaturated state only after administration *in vivo*. Reducing the amount of surfactant in a SEDDS formulation in order to generate a supersaturated state on dilution of the formulation with an aqueous medium can result in rapid precipitation of the poorly soluble drug, incorporation of hydroxyl propyl methyl cellulose (HPMC) or other cellulosic polymeric excipients in the SEDDS formulations can sustain the supersaturated state by preventing precipitation of the drug. These formulations are termed “super-saturable SEDDS or S-SEDDS”.

Solid-SEDDS

SEDDS are generally encapsulated either in hard or soft gelatin capsules. Lipid formulations however may interact with the capsule resulting in either brittleness or softness of the shell. To address this limitation, liquid lipid formulations could be transformed into free flowing powder by loading the formulation on a suitable solid carrier. Liquid lipid loading onto solid carriers combines the features of a lipid based drug delivery system and solid dosage form. In the 1990s, solid-self emulsifying drug delivery systems (S-SEDDS) were usually in the form of self emulsifying capsules, self emulsifying solid dispersions and dry emulsions, but other solid self emulsifying dosage forms have emerged in recent years, such as self emulsifying pellets/tablets, self emulsifying microspheres/nanoparticles and self emulsifying suppositories/implants.

Solidification Techniques for Converting Liquid/Semisolid SEDDS to Solid-SEDDS

Capsule filling with liquid and semisolid self-emulsifying formulations:

Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid self emulsifying formulations for the oral route. For semisolid formulations, it is a four-step process: i) heating of the semisolid excipient to at least 20°C above its melting point ii) incorporation of the active substance with continuous stirring iii) capsule filling with the molten mixture and iv) cool at room temperature. For liquid formulations it involves a two-step process: i) filling of the formulation into the capsules ii) sealing of the body and cap of the capsule, either by banding or by micro spray sealing.

Spray cooling

Spray cooling, also referred to as spray congealing, is a process whereby the molten formula is sprayed into a cooling chamber and, upon contact with the cooling air, the molten droplets congeal and re-crystallize into spherical solid particles that fall to the bottom of the chamber and can subsequently be collected as fine powder. The fine powder may then be used for development of solid dosage forms such as tablets or capsules. Equipment like rotary, pressure, two-fluid or ultrasonic atomizers are available to atomize the liquid mixture and to generate droplets³³. Most of the recent research conducted on spray cooling with lipid-based excipients used ultrasonic atomizers. The main class of excipient used with this technique are polyoxyl glycerides and, more specifically, stearyl polyoxyl glycerides Gelucire® 50/13 facilitating the production of microparticles with a narrow size distribution that exhibit significantly enhanced drug release profiles for poorly soluble drugs such as diclofenac or praziquantel^{34,35}.

Spray drying

Essentially, this technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilisation of the mixture before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets which are introduced into a drying chamber; the volatile phase (water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further processed into tablets or capsules. The atomizer, the temperature, the most suitable airflow pattern and the drying chamber design are selected according to the drying characteristics of the product and powder specifications. Spray drying has been employed to prepare dry emulsions by removing water from an ordinary emulsion containing a water-soluble solid carrier. The solid SMEDDS was prepared by spray drying the liquid SMEDDS in a laboratory spray dryer, using dextran as a solid carrier for nimodipine³⁶.

Adsorption to solid carriers

The adsorption process is simple and just involves addition of the liquid formulation onto carriers by mixing in a blender. The resultant powder may then be filled directly into capsule or alternatively, mixed with suitable excipients before compression into tablets. The major advantage of using this technique is good content uniformity. SEDDS can be adsorbed at higher levels (up to 70% w/w) onto suitable carriers. Solid carrier can be microporous substances, high surface area colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticle adsorbent, for example, silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, crospovidone.

Melt granulation

Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures. As a one-step operation, melt granulation offers several advantages compared with conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted. A wide range of solid and semisolid lipids can be applied as meltable binders. The melt granulation process was usually used for adsorbing self emulsifying system (lipids, surfactants and drugs) onto solid neutral carriers mainly silica and magnesium aluminometa silicate.

Melt extrusion

Melt extrusion is a solvent-free process that allows high drug loading approximately 60%. Extrusion is a procedure of converting a raw material with plastic properties into a product of uniform shape and density, by forcing through a die under controlled temperature, product flow, and pressure conditions.

Table 5: Considerations to be taken in selection of formulation techniques for bioavailability enhancement with lipid based excipients^{34,35}

Formulation techniques for solids And semisolid formulations	Physical properties of the lipid Excipients applied		Formulations advantages and limits	
	Liquid to solid	semi-solids	Maximum lipid Lip exposure*(%w/w)	Maximum drug loading(%w/w)
Capsule filling	X	X	99	50
Spray-cooling	X		99	30
Spray-drying	X	X	60	50
Adsorption on solid carrier	X		80	10
Melt granulation	X		50	80
Melt extrusion	X		50	60
Super critical fluid based methods	X		99	20
Solid lipid nanoparticles	X	X	99	50

Extrusion spheronization

The extrusion spheronization process is commonly used in the pharmaceutical industry to make uniformly sized pellets. This process requires the following steps: Mix dry active ingredients and excipients to form a homogeneous powder; wet massing with binder; extrusion into a spaghetti-like extrudate; spheronization from the extrudate to spheroids uniform size; drying; sifting to

achieve the desired size distribution. Applying this technique, self emulsifying pellets of diazepam and progesterone has been prepared to provide a good in vitro drug release (100% within 30 min, T50% at 13 min) and bi-layered cohesive self emulsifying pellets have also been prepared.

As shown in Table 5 following considerations should be taken in selection of formulation techniques for bioavailability enhancement with lipid based excipients.

Dosage Form Development of SSEDDS

1. Dry emulsions:

Dry emulsions are powders from which emulsion spontaneously occurs in vivo or when exposed to an aqueous solution. Dry emulsions can be useful for further preparation of tablets and capsules. Dry emulsion formulations are typically prepared from oil/ water (O/W) emulsions containing a solid carrier (lactose, maltodextrin, and so on) in the aqueous phase by rotary evaporation³⁷, freeze-drying³⁸ or spray drying. Myers and Shively obtained solid state glass emulsions in the form of dry 'foam' by rotary evaporation, with heavy mineral oil and sucrose. Such emulsifiable glasses have the advantage of not requiring surfactant. In freeze-drying, a slow cooling rate and the addition of amorphous cryoprotectants have the best stabilizing effects, while heat treatment before thawing decreases the stabilizing effects. The technique of spray drying is more frequently used in preparation of dry emulsions. The O/W emulsion was formulated and then spray dried to remove the aqueous phase. The most exciting finding in this field ought to be the newly developed enteric-coated dry emulsion formulation, which is potentially applicable for the oral delivery of peptide and protein drugs. This formulation consisted of a surfactant, a vegetable oil, and a pH-responsive polymer, with lyophilization used³⁹. Recently, Cui et al. prepared dry emulsions by spreading liquid O/W emulsions on a flat glass, then dried and triturated to powders⁴⁰.

2. Self emulsifying capsules:

After administration of capsules containing conventional liquid SE formulations, microemulsion droplets form and subsequently disperse in the GI tract to reach sites of absorption. However, if irreversible phase separation of the microemulsion occurs, an improvement of drug absorption cannot be expected. For handling this problem, sodium dodecyl sulfate was added into the SE formulation⁴¹. With the similar purpose, the super-saturatable SEDDS was designed, using a small quantity of HPMC (or other polymers) in the formulation to prevent precipitation of the drug by generating and maintaining a supersaturated state in vivo. This system contains a

reduced amount of a surfactant, thereby minimizing GI side effects^{42, 43}. Besides liquid filling, liquid SE ingredients also can be filled into capsules in a solid or semisolid state obtained by adding solid carriers (adsorbents, polymers, and so on). As an example, a solid PEG matrix can be chosen. The presence of solid PEG neither interfered with the solubility of the drug, nor did it interfere with the process of self micro emulsification upon mixing with water^{44, 45}. Oral administration of SE capsules has been found to enhance patient compliance compared with the previously used parenteral route. For instance, low molecular weight heparin (LMWH) used for the treatment of venous thrombo-embolism was clinically available only via the parenteral route. So, oral LMWH therapy was investigated by formulating it in hard capsules. LMWH was dispersed in SMEDDS and thereafter the mixture was solidified to powders using three kinds of adsorbents: micro porous calcium silicate (Florite™ RE); magnesium aluminum silicate (Neusilin™ US2) and silicon dioxide (Sylysia™ 320). Eventually these solids were filled into hard capsules⁴⁶. In another study, such adsorbents were also applied to prepare SE tablets of gentamicin that, in clinical use, was limited to administration as injectable or topical dosage forms⁴⁷.

3. Self emulsifying sustained/controlled release tablets:

Combinations of lipids and surfactants have presented great potential of preparing SE tablets that have been widely researched. Nazzal and Khan evaluated the effect of some processing parameters (colloidal silicates—X1, magnesium stearate mixing time— X2, and compression force—X3) on hardness and coenzyme Q10 (CoQ10) dissolution from tablets of eutectic-based SMEDDS. The optimized conditions (X1 = 1.06%, X2 = 2 min, X3 = 1670 kg) were achieved by a face-centered cubic design⁴⁸. In order to reduce significantly the amount of solidifying excipients required for transformation of SEDDS into solid dosage forms, a gelled SEDDS has been developed by Patil et al. In their study, colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems, which served the dual purpose of reducing the amount of required solidifying excipients and aiding in slowing down of the drug release⁴⁹. SE tablets are of great utility in obviating adverse effect, as disclosed by Schwarz in a patent. Inclusion of indomethacin (or other hydrophobic NSAID), for example, into SE tablets may increase its penetration efficacy through the GI mucosal membranes, potentially reducing GI bleeding. In these studies, the SES was composed of glycerol monolaurate and Tyloxapol™ (a copolymer of alkyl phenol and formaldehyde).

4. Self emulsifying sustained/controlled release pellets:

Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage forms, such as flexibility of manufacture, reducing intrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability⁴⁹. Thus, it is very appealing to combine the advantages of pellets with those of SEDDS by SE pellets. Serratori et al. prepared SE controlled release pellets by incorporating drugs into SES that enhanced their rate of release, and then by coating pellets with a water-insoluble polymer that reduced the rate of drug release. Pellets were prepared by extrusion/ spheronization and contained two water-insoluble model drugs (methyl and propyl parabens); SES contained monodiglycerides and Polysorbate 80. There is another report that SE sustained-release matrix pellets could be successfully formulated with glyceryl palmito-stearate (Gelucire 54/02) and glyceryl behenate (Gelucire 70/02)⁵⁰.

5. Self emulsifying solid dispersions:

Although solid dispersions could increase the dissolution rate and bioavailability of poorly water-soluble drugs, some manufacturing difficulties and stability problems existed. Serajuddin pointed out that these difficulties could be surmounted by the use of SE excipients^{51, 52}. These excipients have the potential to increase further the absorption of poorly water-soluble drugs relative to previously used PEG solid dispersions and may also be filled directly into hard gelatin capsules in the molten state, thus obviating the former requirement for milling and blending before filling⁵¹. SE excipients like Gelucire 44/14, Gelucire 50/02, Labrasol 1, Transcutol and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely used in this field⁵⁴.

6. Self emulsifying beads:

In an attempt to transform SES into a solid form with minimum amounts of solidifying excipients, Patil and Paradkar investigated loading SES into the micro-channels of porous polystyrene beads (PPB) using the solvent evaporation method. PPB with complex internal void structures is typically produced by copolymerizing styrene and divinyl benzene. They are inert, stable over a wide pH range and to extreme conditions of temperature and humidity. This research concluded that PPB was potential carriers for solidification of SES, with sufficiently high SES to PPB ratios required to obtain solid form. 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 PPB⁵⁵.

7. Self emulsifying Sustained release microspheres:

Zedoary turmeric oil (ZTO; a traditional Chinese medicine) exhibits potent pharmacological actions including tumour suppressive, antibacterial, and antithrombotic activity. With ZTO as the oil phase, You et al. prepared solid SE sustained-release microspheres using the quasi emulsion solvent-diffusion method of the spherical crystallization technique. ZTO release behaviour 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 to rabbits, with a bioavailability of 135.6% with respect to the conventional liquid SEDDS ⁵⁶.

8. Self emulsifying Nanoparticles:

Nanoparticle techniques have been useful in the production of SE nanoparticles. Solvent injection is one of these techniques. In this method, the lipid, surfactant, and drugs were melted together, and injected drop wise into a stirred non-solvent. The resulting SE nanoparticles were thereafter filtered out and dried. These approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74% ⁵⁷.

9. Self emulsifying suppositories:

Some investigators proved that S-SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption ⁵⁸. Glycyrrhizin, which, by the oral route, barely achieves therapeutic plasma concentrations, can obtain satisfactory therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE suppositories. The formulation included glycyrrhizin and a mixture of a C6–C18 fatty acid glycerol ester and a C6–C18 fatty acid macrogol ester ⁵⁹.

10. Self emulsifying implants:

Research into SE implants has greatly enhanced the utility and application of S-SEDDS. As an example, 1, 3-bis (2-chloroethyl) -1- nitrosourea (carmustine, BCNU) is a chemotherapeutic agent used to treat malignant brain tumors. However, its effectiveness was hindered by its short half-life. Loomis invented copolymers having a bioresorbable region, a hydrophilic region and at least two cross-linkable functional groups per polymer chain. Such copolymers show SE property without the requirement of an emulsifying agent. These copolymers can be used as good sealants for implantable prostheses ⁶⁰.

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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