Academic Sciences

International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 5, Issue 4, 2013

Review Article

NOVEL APPROACHES FOR DEVELOPMENT AND CHARACTERIZATION OF SMEDDS: REVIEW

U. A. DEOKATE, NITA SHINDE*, UJJWALA BHINGARE

Department of Pharmaceutics,Government College of pharmacy, Osmanpura, Aurangabad-431005, Maharashtra, India.
Email:nitabshinde66@gmail.com

Received: 06 August 2013, Revised and Accepted: 20 August 2013

ABSTRACT

As development of modern drug discovery technique, there has been steady increase in number of new pharmacologicaly active lipophilic compounds that are poorly water soluble.It is great challenge for pharmaceutical scientist to convert those molecules into orally administered formulations with sufficient bioavailability. Self emulsified drug delivery system has shown successful approach for improving bioavailability of poorly water soluble and lipophilic drugs. This review examines recent advances in Self emulsified formulations,the various solidification technique, the development of solid SMEDDS dosage forms, their characterization and possible future research prospectives.

Keywords: Self micron emulsifying drug delivery system, Bioavailability, Lipophilic compound.

INTRODUCTION

In recent years,40-70% of all new chemical entities entering drug development programs possess insufficient aqueous solubility which leads to poor bioavailability, high intra and inter subject variability, lack of dose,gastric and enzymatic degradation of drug. To overcome these problems, various formulation strategies have been developed e.g (use of surfactants, lipids, permeation enhancers, micronization, salt formulation, cyclodextrins, nanoparticles and solid dispersion). One of the most popular and commercially viable formulation approaches for solving these problems is self emulsifying drug delivery system (SEDDS). These systems has shown to be reasonably successful in improving the oral bioavailbiliity of poorly water-soluble and lipophilic drugs[1][1,4,5].

(A) Self micro emulsifying drug delivery systems

SEDDS are physically stable, isotropic mixtures of natural/synthetic oil,solid/liquid surfactants, one/ more hydrophilic solvents, cosolvent /surfactant and solubilised drug substance that suitable for oral drug delivery. These system have unique property that they are stable to self emulsify rapidly in gastrointestinal fluids and under the gentle agitation provided by the motion of gastrointestinal tract, they form fine O/W emulsion or microemulsions (SMEDDS).[2,11]These fine O/W emulsion produce small droplets of oil dispersed in the gastrointestinal fluids that provide large interfacial area increasing activity of pancreatic lipase to hydrolyze triglycerides and thereby promote faster release of drug and formation of mixed micelles of bile salts containing drug. Surfactant used for such formulations increases bioavailability of the drug by activation of different mechanisms, maintaining the drug in solution and thus avoiding the dissolution step from the crystalline state and enhancing intestinal epithelial permeability at the same site. Oil droplets lead to faster and more uniform distribution of the drug in gastrointestinal tract, minimizing the irritation due to contact between drug and gut wall.In addition lipid affect oral bioavailability of drug by exerting their effect through several mechanism,including protection of the drug from enzymatic and chemical degradation in the oil droplets and activation of lipoproteins promoting lymphatic transport of lipophilic drugs. SEDDS(self emulsified drug delivery syatem) typically produce opaque emulsions with a droplet size between 100 and 300 nm while SMEDDS(self micron emulsified drug delivery system) form transparent micro emulsions with a droplet size of less than 50 nm also the concentration of oil in SMEDDS is less than 20 % as compared to 40-80% in SEDDS[3]. When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles.The key step is to find a suitable oil surfactant mixture that can dissolve the drug within the required therapeutic concentration. The SMEDDS mixture can be filled in either soft or hard gelatin capsules. A typical SMEDDS formulation contains oils, surfactants and if required an antioxidants.Co-surfactants and co-solvents are added to improve the formulation characteristics.Conventionally SE(self emulsified) formulations are normally prepared as liquids that produce some drawbacks such as high production cost, low stability and portability, low drug loading and few choices of dosage form and irreversible drug/excipient precipitation. High concentration of surfactants(30-60%)in the formulation can induce gastrointestinal(GI) irritation. In order to overcome these problems, S-SMEDDS have been investigated as alternative approach.These system require self micron emulsifying (SME) ingredients into powders/nanoparticles which can be converted to various solid dosage form (SME tablets, SME pellets and so on)[8,9].Thus S-SMEDDS will have combined advantages of SMEDDS such as enhanced solubility and bioavailability with those of solid dosage form such as low production cost,convenience of process control,high stability,reproducibility and patient compliance[6].To date there have been studies that mainly focused on preparation and characterization of S-SMEDDS yet relatively few that introduce S-SMEDDS in systematic way, especially with respect to dosage form development and preparation technique[3,7].

(B) Suitable drug candidate identification for SMEDDS

Generally high dose drug not suitable for the SMEDDS. The solubility of drug and polarity of the lipid phase is also important factor. The polarity depends on the HLB value,the chain length and unsaturation of the fatty acid. One of the challenges to any oral formulation is maintaining drug solubility within prime absorptive site of the gut. 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,use of SEDDS can be extended to all four categories of BCS(biopharmaceutical classification system) class drugs. These system can help in solving the under-mentioned problems of all the categories of BCS class drug as follows in table1.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-donors, there are more than ten H-bond acceptors, the molecular weight>500 and calculated log P>5.

Although classification systems such as the BCS and Lipinski's rule of five are useful,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 lipid based formulation approach because they do not

adequately predict potential in vivo effects. These poorly water soluble compounds, which are generally classified as "Lipophilic", behave differently in similar vehicles,thus it is important to assess candidate compound on individual basis[12].

Table 1: Application of SMEDDS in various BCS category drugs[25,26]

BCS class	Aqueous solubility	Membrane permeability	Hurdles overcome by smedds	Example
BCS class 1	High	High	Enzymatic degradation, gut wall efflux	Metoprolol, Paracetamol
BCS class 2	Low	High	Solubilisation and bioavailability	Nifedipine, Phenytoin
BCS class 3	High	Low	Enzymatic degradation, gut wall efflux and bioavailability	Atenolol, Cimetidine
BCS class 4	Low	Low	Solubilisation, enzymatic degradation, gut wall efflux, bioavailability	Ritonavir, Cyclosporin A

(C) Advantages [13,14]

1) Quick Onset of Action
2) Reduction in the Drug Dose
3) Ease of Manufacture & Scale-up
4) Improvement in oral bioavailability
5) Inter-subject and Intra-subject variability and food effects
6) Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT
7) No influence of lipid digestion process
8) Increased drug loading capacity

(D) Disadvantages [13,14,15]

1) Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
2) This in vitro model needs further development and validation before its strength can be evaluated.
3) Further development will be based on in vitro - in vivo correlations and therefore different prototype lipid based formulations needs to be developed and tested in vivo in a suitable animal model.
4) The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which GIT

(E) Lipid formulation classification system

drugs are available such as, microemulsion, lipid solution, lipid emulsion, dry emulsion, whose formulation involve large number of possible combination of excipient, so to understand these lipid based formulation a classification namely 'lipid formulation classification system have been introduced by Pouton in 2000 and recently updated (2006). According to the composition and the effect of dilution and digestion on the ability to prevent precipitation of drug, lipid based formulations are classified into four groups as discussed in following table No.2 [16,17,18].

(F) Mechanism of self emulsification

According to "Reiss" self emulsification occurs when the entropy changes that favor dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phase and can be described by the equation-

$$DG = SNPr^2$$

DG – free energy associated with the process (ignoring free energy in mixing)

N – Number of droplets of radius r and s represent the interfacial energy [3,25].

Composition	Type i Oil	Type ii SEDDS	Type iii a SEDDS	Type iii b SMEDDS	type iv Oil free
glycerides (TG,MG,DG)	100%	40-80%	40-80%	<20%	-
Surfactants(HLB<12)	-	20-60%	-	-	-
HLB>12	-	-	20-40%	20-50%	-
Hydrophilic cosolvents	-	-	0-40%	20-50%	-
Particle size of dispersion(nm)	Coarse	100-250	100-250	50-100	-
Significance of aqueous dilution	Ltd. importance	Solvent capacity unaffected	Some loss of solvent capacity	Significant phase changes and potential loss of solvent capacity	Significant phase changes and potential loss of solvent capacity
Significance of digestibility	Crucial need	Not crucial but likely to occur	May br crucial but not 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 digesion	Clear dispersion drug absorption without diugestion	Good solvent capacity for many drugs,disperses to micellar solution
Disadvantages	Poor solvent capacity unless the drug is highly lipophilic	Turbid o/w emulsion(0.25-2µm)	Possible loss of solvent capacity on dispersion,less easily digested	Likely loss of solvent capacity on dispersion	Loss of solvent capacity on dispersion,may not be digestible LCFS-lipid classification formulation system

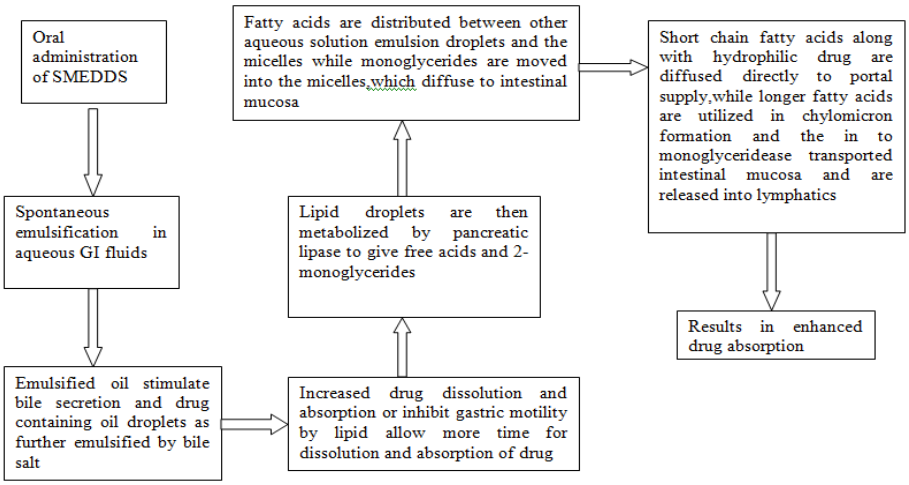

Fig. 1: Mechanisms proposed for bioavailability enhancement of drug[25]

Composition[3]

a) Active Pharmaceutical Ingredient(API)
b) Oil
c) Surfactant
d) Co-surfactant
e) Co-solvent
f) Consistency Builder
g) Enzyme Inhibitor
h) Polymer
i) Other Components

a) API

Active pharmaceutical agent should be soluble in oil phase as this influence the ability of SMEDDS to maintain the API in solubilised form. Drugs which have low solubility in water or lipids are difficult to deliver through SMEDDS. Drugs which are administered in very high dose are not suitable for formulation unless they have extremely good solubility in at least one of the components of SMEDDS, preferably oil phase. High melting point drugs with log P values of about 2 are poorly suitable for SMEDDS. While, lipophilic drugs having log P values greater than 5, are good candidate for SMEDDS[3,12].

b)Oils

Oil is one of the most important excipients because oil can solubilise the lipophilic drug in a specific amount and it can facilitate self emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, mainly the long chain and medium chain triglycerides are use. The concentration of oil present in SMEDDS is about the 40-80% the modified and hydrolyzed vegetable oils widely because they show the more solubility and good self emulsifying property. Solvent capacity for less hydrophobic drugs can be improved by bending triglycerides with mono- and di-glycerides[12].

c) Surfactant

Surfactant molecules consist of two part, polar head group region and non-polar tail region. They are classified into four categories according to the nature of hydrophilic group within the molecule :

a) Anionic surfactant
b) Cationic surfactant
c) Non-ionic surfactant
d) Ampholytic surfactant

Surfactant reduces the interfacial tension between two immiscible liquids and makes them miscible. When surfactants are incorporated in oil and water mixture then their polar heads is self associated towards water phase and non-polar tails towards oil phase or they can locate at the interface, which is thermodynamically stable.

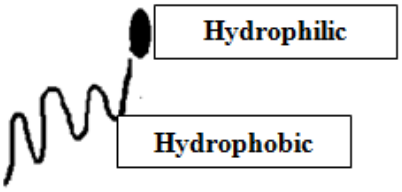

Fig. 2: Surfactant molecule containing hydrophilic head and hydrophobic tail

d) Co-surfactant

For the production of an optimum SMEDDS, high concentration of surfactant is required in order to reduce interfacial tension, which can be harmful, so co-surfactants are used to reduce the concentration of surfactants. Co-surfactants together with the surfactants provide the sufficient flexibility to interfacial film to take up different curvatures required to form micro-emulsion over a wide range of composition. Selection of proper surfactant and co-surfactant is necessary for the efficient design of SMEDDS and for the solubilization of drug in the SMEDDS. Generally co-surfactant of HLB value 10-14 is used. Organic solvents like ethanol, propylene glycol, polyethylene glycol are able to dissolve large amount of either drug or hydrophilic surfactant in lipid base and are suitable for oral delivery, so they can be used as co-surfactant for SMEDDS. Alcohols and other volatile co-solvents show a disadvantage that by evaporation they get entered into soft/hard gelatin capsule shells results in precipitation of drug. On the other hand formulations which are free from alcohols have limited lipophilic drug dissolution ability. Hence, proper choice of components has to be made for formulation of efficient SMEDDS[3].

e) Co-solvents

High concentration of surfactant (generally more than 30%) is required for optimum production of SMEDDS. Organic solvents enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in oil phase. Examples include ethanol, butanol, propylene glycol etc., esters such as ethyl propionate, tributyl citrate and amides as 2-pyrolidine, caprolactum and polyvinyl pyrollidine[25].

f) Consistency Builder

To alter consistency of emulsion, beeswax, cetyl alcohol can be added.

g) Enzyme Inhibitors:

If the active pharmaceutical agent is prone to enzymatic degradation, then enzyme inhibitors can be added to SMEDDS e.g. amino acids and modified amino acids- aminoborinine derivatives.[2]

Table 3: Examples of oils, surfactants, co-surfactant and co-solvents used [27]

Oils	Surfactants	Co-surfactant/Co-solvent
Cottonseed oil	Polysorbate 20 (Tween 20)	Span 20
Soya bean oil	Polysorbate 80 (Tween 80)	Span 80
Corn oil	D-alpha Tocopheryl polyethylene	Capryol 90
Sunflower oil	Glycol 1000 succinate (TPGS)	Lauroglycol
Castor oil	Polyoxy-35 castor oil	Transcutol
Sesame oil	Cremophor RH-40	Capmul
Peanut oil	Polyoxy-40- hydrogenated castor oil	Ethanol
Labrafac	Labrasol	Propylene glycol

Phase Diagrams

The micro emulsion region is usually characterized by constructing ternary-phase diagrams as shown in Fig.. Three components are the basic requirement to form a micro emulsion: an oil phase, an aqueous phase and a surfactant. If a cosurfactant is used, it may sometimes be represented at a fixed ratio to surfactant as a single component, and treated as a single "pseudo-component". The relative amounts of these three components can be represented in a ternary phase diagram. Gibbs phase diagrams can be used to show the influence of changes in the volume fractions of the different phases on the phase behaviour of the system. The three components composing the system are each found at an apex of the triangle, where their corresponding volume fraction is 100 %. Moving away from that corner reduces the volume fraction of that specific component and increases the volume fraction of one or both of the two other components. Each point within the triangle represents a possible composition of a mixture of the three components or pseudo-components, which may consist of one, two or three phases. These points combine to form regions with boundaries between them, which represent the "phase behaviour" of the system at constant temperature and pressure[20,21]. Phase diagrams were constructed to obtain the proportion of components that can result in maximum micro emulsion existence area. These diagrams were constructed with oil, surfactant/co-surfactant and water using water titration method at room temperature. The procedure consisted of preparing solutions of different ratio of surfactant to co-surfactant by weight such as: 1:1, 2:1, 3:1 etc, these solutions then vortexed for 5 min and placed at 50°C for 1 hr so that an isotropic mixture was obtained. Each of these solutions was then used for preparing a mixture containing oil and smix (mixture of surfactant and co-surfactant) in the following ratios by weight: 1:9, 2:8, 3:7, 4:6,5:5, 6:4, 7:3, 8:2, 9:1 and after preparation it is vortexed for 5 min followed by placing in oven at 50°C for 1 hr. All the mixtures were then placed at room temperature for 24hr. Water from 5% to 95% of the mixture was added at 10-15 min interval to each of the mixture under stirring on magnetic stirrer. After each addition the mixtures were observed for their appearance (turbid or clear).Turbidity of the samples would indicate formation of a coarse emulsion, whereas a clear isotropic solution would indicate the formation of a micro emulsion. Percentage of oil, smix and water at which clear mixture was formed were selected and the values were used to prepare ternary phase diagram[19,12].

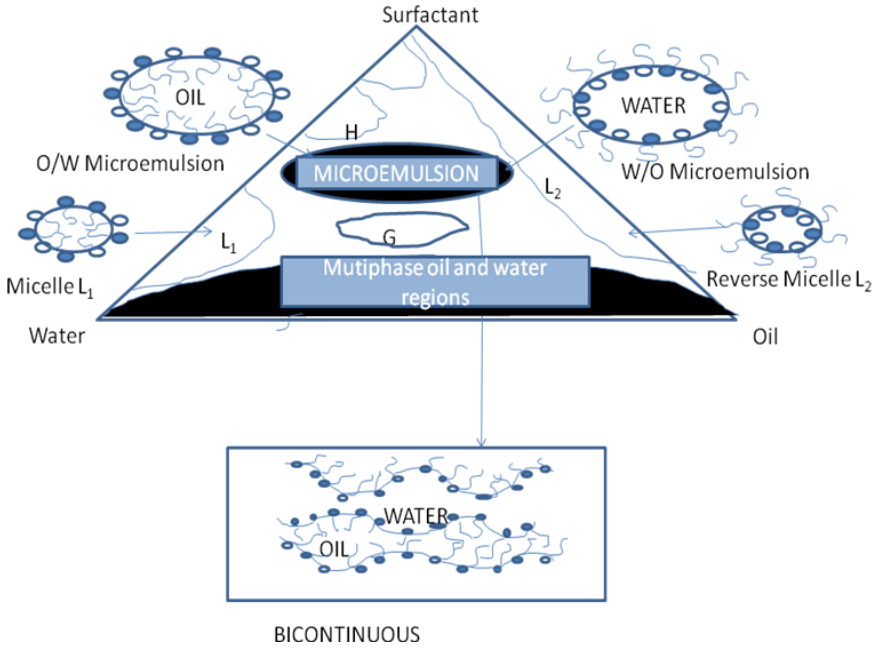

Fig. 3: Example of phase diagram[18,19]

Solidification Techniques for Transforming Liquid/Semisolid SMEDDS to S-SMEDDS

a) 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 SE 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 substances (with stirring); (iii) capsule filling with the molten mixture and (iv) cooling to room temperature. For liquid formulations, it involves a two-step process: filling of the formulation into the capsules followed by sealing of the body and cap of the capsule, either by banding or by micro spray sealing. In parallel with the advances in capsule technology proceeding, liquid-oros technology has been designed for controlled delivery of insoluble drug substances or peptides. This system is based on osmotic principles and is a liquid SME formulation system. It consists of an osmotic layer, which expands after coming into contact with water and pumps the drug formulation through an

orifice in the hard or soft capsule. A primary consideration in capsule filling is the compatibility of the excipients with the capsule shell. The advantages of capsule filling are simplicity of manufacturing, suitability for low-dose highly potent drugs and high drug loading (up to 50% (w/w)) potential[22,25].

b) Spray drying

Essentially, this technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared 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 specification[22,29].

(c) Adsorption to solid carriers:

Free flowing powders may be obtained from liquid SME formulations by 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 resulting powder may then be filled directly into capsules or mixed with suitable excipients before compression into tablets. A significant benefit of the adsorption technique is good content uniformity. SMEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers. Solid carriers can be micro porous inorganic substances, high surface-area colloidal inorganic adsorbent substances, cross-linked Polymers or Nanoparticle adsorbents, for example, silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, crospovidone, cross-linked sodium carboxymethyl cellulose and cross linked polymethyl methacrylate. Cross-linked polymers create a favorable environment to sustain drug dissolution and also assist in slowing down drug reprecipitation. Nanoparticle adsorbents comprise of porous silicon dioxide (Sylysia 550), carbon nanotubes, carbon nanohorns, fullerene, charcoal and bamboo charcoal[22,30].

(d) 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. The main parameters that control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder. A wide range of solid and semisolid lipids can be applied as meltable binders.Gelucire1, a family of vehicles derived from the mixtures of mono-/di-/tri-glycerides and polyethylene glycols (PEG) esters of fatty acids, is able to further increase the dissolution rate compared with PEG usually used before, probably owing to its SME property.Other lipid based excipients evaluated for melt granulation to create solid SMES include lecithin, partial glycerides, or polysorbates. The melt granulation process was usually used for adsorbing SMES (lipids, surfactants, and drugs) onto solid neutral carriers (mainly silica and magnesium alumina meta silicate)[30,31].

(e) Melt extrusion/extrusion Spheronization:

Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity. Extrusion is a procedure of converting a raw material with plastic properties into a product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions. The size of the extruder aperture will determine the approximate size of the resulting spheroids. The extrusion-spheronization process is commonly used in the pharmaceutical industry to make uniformly sized spheroids (pellets). The extrusion. Spheronization process requires the following steps: Dry mixing of the active ingredients and excipients to achieve a homogeneous powder; wet massing with binder; extrusion into a spaghetti-like extrudate; spheronization from the extrudate to spheroids of uniform size; drying; sifting to achieve the desired size distribution and coating. In the wet masses comprising SMES (Polysorbate 80 and mono-/di-glycerides), lactose, water and MCC, the relative quantities of SMES and water had a significant effect on the extrusion force, size spread, disintegration time, and surface roughness of pellets. Studies suggested that the maximum quantity of this SMES that can be solidified by extrusion spheronization occupies 42% of the dry pellet weight. Generally, the higher the water level, the longer the disintegration time. The rheological properties of wet masses may be measured by an extrusion capillary. It has been shown that SMES containing wet mass with a wide range of rheological characteristics can be processed, but a single rheological parameter cannot be used to provide complete characterization of how well it can be processed by extrusion-spheronization. Applying extrusion-spheronization, SME pellets of diazepam and progesterone and bi-layered cohesive SME pellets have been prepared[31].

Fig. 4: Liquid SMEDDS vs solid SMEDDS before and after diluted with water[22]

Dosage Form Development

(a) Self-emulsifying sustained/controlled-release tablets

Numerous potent drugs exhibit low oral bioavailability due to their poor aqueous solubilities or presystemic metabolism. Carvedilol one of those drug having low bioavailability, low solubility and having pre systemic metabolism. The novel self-emulsifying osmotic pump tablet (SEOPT) containing carvedilol has many advantages. It improves the bioavailability of carvedilol, controls the release rate and makes the plasma concentrations more stable. The results of dissolution experiment showed that the release of carvedilol from self-made SEOPT was controlled and complete and its profile was close to zero order release. 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[22,32].

(b) Self-emulsifying suppositories

Some investigators proved that Solid-SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption. 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[32].

(d) Self-nanoemulsifying drug delivery system (SNEDDS) /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 there after filtered out and dried[32].

(e) 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,reduction of intrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability. Thus, it seems very appealing to combine the advantages of pellets with those of SEDDS by SE pellets. Spherical pellets with low friability and self-emulsifying properties can be produced by the standard extrusion/spheronization technique. E.gLipid mixtures composed of Solutol® HS 15 and medium chain glycerides were optimized with respect to their self-emulsifying properties. The liquid SE lipid was mixed with microcrystalline cellulose and transformed into pellets by extrusion/spheronization. The pellets were characterized for size, shape, surface characteristics and friability. The combinations of coating and SES could control in vitro drug release by providing a range of release rates and the presence of the SEDDS did not influence the ability of the polymer film to control drug dissolution[25,32].

(f) Self-emulsifying solid dispersions

Gupta et al. prepared SE solid dispersion granules using the hot-melt granulation method for seven drugs, including four carboxylic acid containing drugs, a hydroxyl-containing drug, an amide containing drug (phenacetin) and a drug with no proton donating groups (progesterone) in which Gelucire 50/13 was used as the dispersion carrier, while Neusilin US2 was used as the surface adsorbent[22,32].

(g) Self-emulsifying beads

Solidification of liquid systems has been a challenge that has attracted wide attention due to handling difficulties and machinability and stability problems that are often encountered with liquids. One of the solidification is to transform into SES beds form with minimum amounts of solidifying excipients, investigated SES as microchannels of porous polystyrene beads (PPB) using the solvent evaporation method. PPB with complex internal void structure is typically produced by copolymerizing styrene and divinely benzene. Porous polymer structures such as macroporous high internal phase emulsion (HIPE) polymers were used as high-capacity reservoirs for included liquids and as carriers for active pharmaceuticals for sustained delivery.[25]

(h) Self-emulsifying sustained-release microspheres

Zedoary turmeric oil (ZTO) exhibits potent pharmacological actions including tumor suppression, and antibacterial, and antithrombotic activity. With ZTO as an oil phase, the solid SE sustained-release microspheres were prepared by the quasi-emulsion-solvent-diffusion method involving spherical crystallization. The ZTO release behaviour was controlled by the ratio of hydroxyl-propylmethylcellulose acetate succinate to Aerosil 200 in the formulation, and the plasma concentration time-profiles after oral administration to rabbits showed a bioavailability of 135.6%compared with the conventional liquid SEDDS[12].

(i) Positively charged self-emulsifying drug delivery system

One of the most persistent problems faced by the formulation scientists has been to find methods of improving the oral bioavailability of poorly water-soluble drugs. This positively charged SEDDS gives several fold increase in the bioavailability than the negatively charge done. Cationic lipids are use in this type of system. E.g. positively charged Meloxicam SEDDS were prepared using oil components (ethyl oleate, sunflower oil and arachis oil), cationic lipid (oleylamine) and surfactants (combination of Tween 80 and Span 80)[22,12].

(j) Self-double-emulsifying drug delivery system (SDEDDS) SDEDDS

can spontaneously emulsify to water-in-oil in-water (w/o/w) double emulsions in the mixed aqueous gastrointestinal environment, with drugs encapsulated in the internal water phase of the double emulsions. We employed SDEDDS to improve the oral absorption of pidotimod, a peptide-like drug with high solubility and low permeability[22,25].

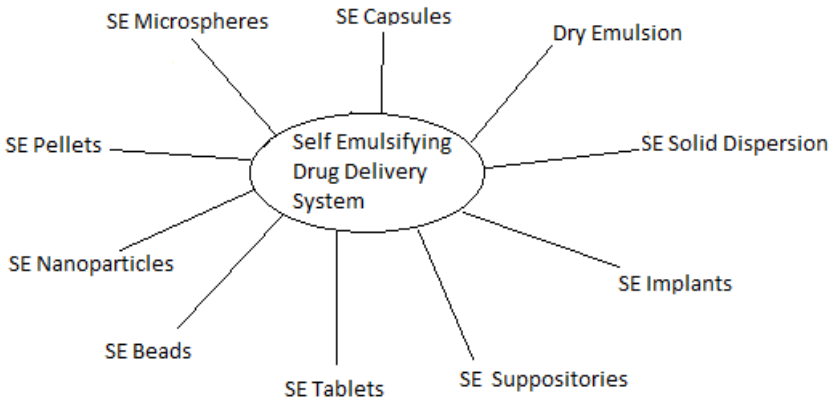

Fig. 5: Types of solid SMEDDS[28]

Table 4: Some examples of marketed pharmaceutical smedds formulations are as shown below[25]

Brand	Drug	Dose	Company	Dosage form
Neoral	Cyclosporin A	25,100mg	Novartis	Soft gelatin capsule
Norvir	Ritonavir	100mg	Abbott laboratories	Soft gelatin capsule
Fortovase	Saquinavir	200mg	Hoffmann-La- Roche	Soft gelatin capsule
Avodart	Dutasteride	0.4,0.5mg	GlaxoSmithKline	Soft gelatin capsule
Rapamune	sirolimus	0.5,1,2mg	Wyeth-Ayerst	Oral solution
Zemplar	Paricalcitol	1,2 and 4mcg	Abbott laboratories	Soft gelatin capsule
Lipirex	Fenofibrate	200mg	Genus	Hard gelatin capsule

Characterization of SMEDDS

a) Differential scanning calorimetry

Differential scanning calorimetry for SMEDDS can be determined using DSC 60. Liquid sample and Solid sample should be placed in the aluminum pan and result can be recorded. Any type of chemical interaction should be determined using DSC[21]. DSC allows study of the thermal behavior of excipients melting, crystallization, solid to solid transition temperatures and determination of solid fat content of the excipient verses temperature[11].

b) Fourier transform-infrared spectroscopy

Fourier transform-infrared for SMEDDS can be determined using FT-IR. Liquid sample should be placed in the liquid sample holder and result can be recorded. Any type of chemical interaction should be determined using FT-IR[21].

c) Macroscopic evaluation

Macroscopic analysis was carried out in order to observe the homogeneity of microemulsion formulations. Any change in color and transparency or phase separation occurred during normal storage condition (37±2ºC) was observed in optimized microemulsion formulation.

d)Visual assessment

To assess the self-emulsification properties, formulation (60 mg) was introduced into 100 ml of water in a glass Erlenmeyer flask at 25°C and the contents were gently stirred manually. The tendency to spontaneously form a transparent emulsion was judged as good and it was judged bad when there was poor or no emulsion formation. Phase diagram was constructed identifying the good self-emulsifying region[12].

e) Determination of Self emulsification time

The emulsification time of SMEDDS was determined according to USP 22, dissolution apparatus 2. 300 mg of each formulation added drop wise to 500ml purified water at 37ºC. Gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 50rpm. Emulsification time was assessed visually.

f) Solubility studies

Unknown amount of selected vehicles was added to each cap vial containing an excess of drug. After sealing, the mixture was heated at 40ºC in a water bath to facilitate the solubilization. Mixing of the systems was performed using a vortex mixer. Formed suspensions were then shaken with a shaker at 25ºC for 48 hours. After reaching equilibrium, each vial was centrifuged at 3000 rpm for 5 minutes, and excess insoluble LOV was discarded by filtration using a membrane filter (0.45 µm, 13 mm, Whatman, India). The concentration of drug was then quantified by U.V. Spectrophotometer.[13]

g) Transmittance Test

Stability of optimized microemulsion formulation with respect to dilution was checked by measuring Transmittance through U.V. Spectrophotometer (UV-1700 SHIMADZU). Transmittance of samples was measured at 650nm and for each sample three replicate assays were performed.

h) Droplet size determination

Photon correlation Spectroscopy (PCS) or dynamic light scattering (DLS) or Laser Diffraction Techniques are used to determine droplet size of emulsion. A number of equipments are available for measurement of particle size viz. Particle Size Analyzer, Mastersizer, Zetasizer etc which are able to measure sizes between 10 and 5000 nm. In many instances nanometric size range of particle is retained even after 100 times dilution with water which indicates the system's compatibility with excess water[28].

i) Zeta potential measurement

Zeta potential for microemulsion was determined using Zetasizer HSA 3000 (Malvern Instrument Ltd., UK). Samples were placed in clear disposable zeta cells and results were recorded. Before putting the fresh sample, cuvettes were washed with the methanol and rinsed using the sample to be measured before each experiment[21,28].

j) Temperature Stability

Shelf life as a function of time and storage temperature was evaluated by visual inspection of the SMEDDS system at different time period. SMEDDS was diluted with purified distilled water and to check the temperature stability of samples, they were kept at three different temperature range (2-8°C (refrigerator), Room temperature) and observed for any evidences of phase separation, flocculation or precipitation[21].

h) Centrifugation

In order to estimate metastable systems, the optimized SMEDDS formulation was diluted with purified distilled water. Then microemulsion was centrifuged at 1000 rpm for 15 minute at 0°C and observed for any change in homogeneity of microemulsions[21].

i) In vitro release

The quantitative *in vitro* release test was performed in 900 ml purified distilled water, which was based on USP 24 method. SMEDDS was placed in dialysis bag during the release period to compare the release profile with conventional tablet. 10 ml of sample solution was withdrawn at predetermined time intervals, filtered through a 0.45 µ membrane filter, dilute suitably and analyzed spectrophotometrically. Equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percent drug dissolved at different time intervals was calculated using the Beer Lambert's equation[21].

CONCLUSION

Self emulsifying drug delivery systems are promising approach for formulation of drug compounds with poor aqueous solubility, having high molecular weight, pre systemic first pass effect, enzymatic degradation, gastric irritation, limited dissolution rate and low bioavailability. This method is suitable for all BCS class drugs where resulting emulsification gives faster dissolution rate and absorption. As improvement of conventional liquid SMEDDS, Solid SMEDDS are superior in reducing production cost, simplifying industrial manufacture, improving stability and patient compliance. Most importantly, S-SMEDDS are very flexible to develop various solid dosage forms for oral and parenteral administration.GI irritation is avoidable and controlled/sustained release of drug is achievable.SE Capsules are only available in the market. Because there exist some

fields of S-SMEDDS to be further exploited, such as studies related human bioavailability and correlation in vitro/vivo.

ACKNOWLEDGEMENT

The author and coauthors are highly thankfull to Government college of Pharmacy Aurangabad.

REFERENCES

1. Vishvajit A. Kambe, "Self Micro Emulsifying Drug Delivery System", International Journal of Pharma and Bio Sciences, 2010,Vol.1(2),pg.no.1-9
2. Shah NH, Carvagal MT, Patel CI, "Self-emulsifying drug delivery system (sedds)with polyglycolyzed glycerides for improving in vitro dissolution and oral absorption of lipophilic drugs" Int J pharma,1994,vol.106,pg.no.15-23.
3. M.Nirosha, "Recent advances in self emulsifying drug delivery system",International Journal of Review in Life Sciences,2011, vol.1(14),pg,no.206-214.
4. Pouton C.W., "Lipid formulations for oral administration of drugs:nonemulsifying,self-emulsifying and self microemulsifying drug delivery systems",European Journal of pharmaceutical science,2000,vol.11,pg.no.593-598.
5. Gursoy R.N.,Benita S. "Self Emulsifying Drug Delivery System for improved oral delivery of lipophilic drug", Biomed. Pharmacother,2004,vol.58,pg.no.173-182.
6. Prajapati B.G., Patel M.M. "Conventional and alternative pharmaceutical methods to improve oral bioavailability of lipophilic drugs, Asian Journal pharm.,2007,vol.1,pg.no.1-8.
7. Preethi Sudheer, "Approaches to development of solid- self micron emulsifying drug delivery system: formulation techniques and dosage forms – a review", Asian Journal of Pharmacy and Life Science, April-June2012,Vol.2(2), pg.no. 214-225
8. Attama A.A.,"The use of solid self-emulsifying systems in the delivery of diclofenac", Int.J.Pharm,2003,vol.262,pg.no.23-28.
9. Abdalla A. and Mader K.,"Preparation and characterization of a self emulsifying pellet formulation",Eur.J.Pharm.Biopharm, 2007,vol.66,2007,pg.no.220-226.
10. Ito Y. et al.,"Oral solid gentamicin preparation using emulsifier and adsorbent",J Control Release,2005,vol.105,pg.no.23-31.
11. Rakesh kumar Sharma, "Solubility Enhancement of Lipophilic Drug-Solid Self Emulsified Drug Delivery Systems", International Journal of Research in Pharmaceutical and Biomedical Siences, Jan-Mar 2013,vol.4(1),pg.no.255-265.
12. Latika M. Ingle, "New Approaches for Development and Characterization of SMEDDS", International Journal of Pharmacy and Pharmaceutical Science Research,2013, 3(1), pg.no.7-14.
13. Pallavi M. Nigade, "SELF EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS): A Review", International Journal of Pharmacy and Biological Sciences,April-June 2012,vol.2,issue 2,. pg.no.42-52.
14. Patel P.A.,Chaulang G.M..,"Self Emulsifying Drug Delivery System: A Review. Research", J Pharm and Tech,2008,vol.1(4) ,pg.no.313-323.
15. Hauss D.J,Fogal S.E.,"Lipid-based delivery systems for improving the bioavailability and lymphatic transport of poorly water soluble LTB inhibitors",J Pharm Sci,1998, vol.87, pg.no.164-169.
16. Anand U. Kyatanwar," Self micro-emulsifying drug delivery system (SMEDDS): Review" Journal of Pharmacy Research, 2010,vol.3(1),pg.no.75-83.
17. Pouton C.W.,"Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system", European Journal of Pharmaceutical Science,2006,vol.29,pg.no.278-87.
18. Suman Katteboina, "Approaches for the development of solid self-emulsifying drug delivery systems and dosage forms", Asian Journal of Pharmaceutical Sciences,2009,vol.4 (4), pg.no.240-253.
19. Turner S.R, Siano,D.B and Bock J.,A, "Microemulsion Process for Producing Acrylamide-Alkyl Acrylamide Copolymers.",U. S. Patent,1985,vol.4,pg.no.521-580.
20. Urvashi Goyal, "self microemulsifying drug delivery system: a method for enhancement of bioavailability",International Journal of Pharmaceutical Sciences and Research, 2012, vol.3,issue 1,pg.no.66-79.
21. Maulik J. Patel, "A SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS)", International Journal of Pharmaceutical Sciences Review and Research, Sept.-Oct. 2010,vol.4,issue 3,pg.no.29-35.
22. Bo Tang,Gang Cheng,Jian-Chu, "Development of Solid Self-Emulsifying Drug Delivery System:Preparation techniques and dosage forms", Drug Discovery Today,July2008,vol.13, pg.no.606-612
23. M. P. Khinchi, Akanksha Gupta, "Self Emulsifying Drug Delivery System: A Review",Asian Journal of Biochemical and Pharmaceutical Research,2011,vol.1,issue 2,pg.no.359-367.
24. H. Reiss., *J. Colloids interface Sci*.,1975,53, 61.
25. Sarita Agrawal, "A Review on Novel Therapeutic Strategies for the Enhancement of Solubility for Hydrophobic Drugs through Lipid and Surfactant Based Self Micro Emulsifying Drug Delivery System:A Novel Approach",American Journal of Drug Discovery and Development,2012,vol.2(4),pg.no.143-183.
26. Chakraborty S.,D.Shukla,and et al,"Lipid:An Emerging platform for oral delivery of drugs with poor bioavailability",European J. Pharm.Biopharm.,2009,vol.73,pg.no.1-15.
27. D.S.Rajput, "Novel Integrated Approach for the Strategic Delivery of Hydrop[hobic Drugs by the Use Of Self Emulsifying Drug Delivery System",Journal of Applied Sciences,2012, vol.12(6),pg.no.502-517.
28. Kavita Sapra, "Self Emulsifying Drug Delivery System: A Tool in Solubility Enhancement of Poorly Soluble Drugs", Indo Global Journal of Pharmaceutical Sciences,2012,vol. 2(3), pg.no. 313-332.
29. Jannin, V. et al.,"Approaches for the development of solid and semi-solid lipid-based formulations", Adv. Drug. Deliv.Rev, 2008,vol.60,pg.no.734–746
30. Dong, L.et al.," A novel osmotic delivery system: L-OROS SOFTCAP. Proceedings of the International Symposium on Controlled Release of Bioactive Materials", July, Paris (CD ROM),2000,
31. Dong, L. et al.,L-OROS HARDCAP: a new osmotic delivery system for controlled release of liquid formulation. Proceedings of the International Symposium on Controlled Release of Bioactive Materials, June, San Diego (CD-ROM),2001
32. Cui, F.D. et al.," Preparation of redispersible dry emulsion using Eudragit E100 as both solid carrier and unique emulsifier. Colloid. Surf. A: Physicochem. Eng. Asp.,2007,vol.307, pg.no.137–141.