Contemporary Strategies in Emulsified Drug Delivery Systems: A Retrospective Overview

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ABSTRACT

Oral bioavailability of drugs can be augmented by self-emulsifying systems. Different self-emulsifying systems such as self-emulsifying drug delivery systems (SEDDS), self-microemulsifying drug delivery systems (SMEDDS), and self-nanoemulsifying drug delivery systems (SNEDDS) offerstrategic drug delivery systems to improve the solubility, permeability and bioavailability of both hydrophilic andhydrophobic drug moieties. The success of commercial formulations such as Sandimmune Neoral brand of cyclosporine A and Fortovase of Saquinavir escalated interest in lipid based formulations. Self-micro-emulsifying drug delivery systems (SMEDDS) are isotropic mixtures of lipids (oils), surfactant and co-surfactant with unique property of producing oil-in-water (o/w) microemulsion upon gentle agitation. Current research is focused on self-double emulsifying drug delivery systems (SDEDDS) for effective administration of hydrophilic active moieties, proteins and peptide drugs. The SDEDDS comprises double emulsions of larger oil droplets incorporating an aqueous internal phase existing in a dispersed phase in an aqueous dispersion medium. The solid forms of lipid based drug delivery systems have been developed to overcome their stability problems. This article provides an overview on novel emulsions, physico-chemical factors of SMEDDS, excipients used for self emulsification, aspects on formulation and the mechanism of drug transport through SDEDDS. This review specially emphasizes on the techniques which are employed in converting the liquid/semi solid self-microemulsifying systems into solid-self microemulsifying formulations. Encapsulation process, spray drying, adsorption onto inert vehicles, melt granulation and melt extrusion techniques were evidenced retrospectively in this article. Solid SEDDS are suitable for lipophilic drugs while solid SDEDDS are most suited for hydrophilic moieties.

Keywords: Adsorption, Melt granulation, Extrusion-spheronization, Polarity of lipids, Solidification.

1. INTRODUCTION

Improving oral bioavailability by enhancing the solubility of drug has been a challenging task in drug product design. Different techniques have been adopted to enhance the solubility of hydrophobic compounds using micronization, solid dispersions, surfactants, salt formation and complexation with cyclodextrins (CD's) among others[1]. In the past, solutions, and dispersion systems like emulsions and suspensions were utilized to prop up bioavailability. SEDDS/ SMEDDS/SNEDDS are closely related lipid dosage forms designed for oral delivery, comprising of a mixture of oils, surfactants and possibly co-solvents capable of forming a fine oil in water (*o/w*) emulsion or microemulsion or nanoemulsion. These are subjected to mild agitation followed by dilution with anaqueous dispersion phase. This promotes SEDDS/ SMEDDS/ SNEDDS as better candidates for administering hydrophobic drugs in oil or oil/surfactant

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blends orally while providing satisfactory solubility[2,3]. Upon dilution, SEDDS typically produce emulsion with droplet size beyond 200 nm, but SMEDDS can form microemulsions of 50 nm or less size[4]. Like microemulsions, nanoemulsions are also dispersions of oil and water, kinetically stabilized with the incorporation of surfactant but not thermodynamically stable owing to the nontendency of nanoemulsion droplets to coarsen overtime. Microemulsions like nanoemulsions have also generated high interest as drug delivery vehicles[5]. When compared with many other delivery systems, these systems can boost the apparent solubility of hydrophobic drugs, lessen the level of efflux and reduces the pre-systemic metabolism providing a platform to enhance the bioavailability while ensuring the attainment of desired and reproducible pharmacokinetic profile upon oral administration of drugs.

Recently antiviral drugs like ritonavir and saquinavir have been formulated as SMEDDS to test their therapeutic efficacy against AIDS. However their clinical benefit was not significant. After the accomplishment of Sandimmune NeoralTM (cyclosporine A)[6], Fortovase (Saquinavir) and Norvir (Ritonavir)[7], the lipid based formulations have gained promise in the treatment of many disorders. But recently in 2015, ritonavir SMEDDS (soft capsules) have been reported with toxic epidermal necrolysis and hence their sale was restricted in European countries. Cyclosporin was the first drug marketed as a SMEDDS with significant improvement of bioavailability compared to that of its solution form[8]. As shown in Table 1, the SMEDDS can help in solving many problems of all drugs in the categories of biopharmaceutical classification system.

The liquid SMEDDS are prone to problems with stability, manufacturing, filled formulation and capsule shell interaction and storage temperature maintenance[9,10]. The solid-SMEDDS were evolved to handle the above concerns. Solidification of the liquid self-microemulsifying (SME) systems into powders or nanoparticles which can be converted into different solid dosage forms like SME capsules, SME tablets, SME pellets among others are the possible S-SMEDDS formulations. Solid-SMEDDS will thus have the advantages of improved solubility and consequent good bioavailability, in a solid dosage form ensuring better patient compliance, economy in production, higher stability and reproducibility[11,12].

Table 1. Problems addressed by SMEDDS

BCS class	Properties		Drugs	Problems overcome by SMEDDS
	Solubility	Permeability		
Class I	↑	↑	Ketoprofen, Verapamil, Diltiazem	Enzymatic degradation, gut wall efflux
Class II	↓	↑	Phenytoin, Nifedipine, Danazol	Solubility and bioavailability
Class III	↑	↓	Cimetidine, Atenolol, Acyclovir, Captopril	Enzymatic degradation, gut wall efflux and bioavailability
Class IV	↓	↓	Hydrochlorthiazide, Taxol, Furosemide, Allopurinol	Solubility, Enzymatic degradation, gut wall efflux and bioavailability

↑= High ↓ = Low

2. Stability aspects of emulsions

Though it is difficult to obtain stable *w/o* systems, stabilizers and sometimes absorption bases are utilized to achieve it. Absorption bases are pre-mixtures with the ability to bind relatively higher amounts of water. Mineral oil mixed with decyloleate or lanolin alcohols are typical absorption bases and the emulsions (*w/o* type) can be stabilized by using either sodium chloride or magnesium sulfate. Addition of glycols like propylene glycol or glycerin helps in obtaining the stabile systems. But, the

combination of salts and high levels of glycols may destabilize the emulsion. Addition of some copolymers like PEG-45 dodecyl glycol polymer can also be used for stabilization[13,14].

3. Novel types of emulsions

3.1. Self emulsifying drug delivery systems (SEDDS)

In 1982, Pouton first reported the use of SEDDS for the enhancement of oral bioavailability of poorly aqueous soluble moieties. In his work, he identified that an effective self-emulsifying system formed with the composition of Miglyol 812 (M812, medium chain triglyceride (MCT)) and Tween 85 (T85, polyoxyethelene-sorbitantrioleate). Since then, a number of attempts have been made by researchers on various SEDDS formulations. In recent times SEDDS are formulated with mixtures of lipid vehicles and non-ionic surfactants without addition of water, and are assumed to exist as transparent isotropic mixtures. They have a unique property of self-emulsification in gastrointestinal fluids, forming fine oil-in-water (o/w) emulsions under mild agitation provided by gastro-intestinal motility, thus enabling oral delivery when incorporated in soft and hard gelatin or hard hydroxyl propyl methyl cellulose (HPMC) capsules[15].

SEDDS can be formulated by the incorporation of surfactants with hydrophilic lipophilic balance (HLB) <12 in the formulation[16]. The self emulsification progression is specific to the definite pair of oil and surfactant, concentration of surfactant, ratio of oil/surfactant and the temperature in which self-emulsification takes place[17-19].

3.1.1. Selection of excipients for SEDDS

Oils/lipids:

Oil/lipid vehicles are important to solubilize specified quantities of lipophilic drugs and to promote self-emulsification thereby encouraging the lymphatic transport of drug absorbed in GIT[20]. Long-chain as well as medium- chain triglyceride oils were shown to be effective in self-emulsifying formulations. Hydrolyzed vegetable or edible oils were successfully used in designing high soluble lipophilic drugs due to their formulation and physiological characteristics[21].

Surfactants:

High HLB non-ionic surfactants were widely employed in self emulsifying formulations (e.g. Tween, cremophore, labrasol, etc.). In self emulsifying formulations, the strength of a surfactant varies between 30 to 60% w/w. The higher quantities of surfactants present in self emulsifying preparations causes GIT irritation, leading to preference for non-ionic surfactants compared to ionic surfactants. Amphiphilic surfactant dissolves relatively high amounts of hydrophobic drugs thereby preventing the precipitation of drugs within the GI lumen[22].

Co-solvents:

The co-solvents facilitate the dissolution of large quantities of hydrophilic surfactants or hydrophobic drugs in oil phase. Besides co-solvents also exhibit co-surfactant nature in microemulsion systems (eg: polyethylene glycol (PEG), propylene glycol (PG) and ethanol)[22].

3.2. Self microemulsifying drug delivery systems (SMEDDS)

Currently SMEDDS are becoming more popular drug delivery systems in research arenas for their potential in improving oral bioavailability of poorly soluble therapeutic agents. Microemulsions were first introduced in 1943, by Hoar and Schulman, of Cambridge University[23]. The microemulsions are often termed transparent emulsions, swollen micelles, micellar solutions and solubilized oils. The SMEDDS are defined as transparent systems containing oil, surfactant and co-surfactant. When contacting aqueous environment they rapidly form o/w microemulsion upon gently agitation or as a result of the agitation induced by GI motility during peristalsis. The SMEDDS are formed with surfactants of HLB > 12[16]. Microemulsions are formed when the interfacial tension are reduced to a low level with formation of a flexible interfacial layer between oil and water phases. To achieve this, components of formulations have to be selected in specific proportions. Co-surfactants bring flexibility at interface and provide a thermodynamically optimized structure to microemulsion.

Particle size of microemulsion is lesser than the wavelength of visible light making them transparent. Thus, the formation of microemulsion is difficult to observe through an optical microscope[23]. SMEDDS presents the drug in nano-sized droplets and offers large interfacial area for drug molecule permeation. Additionally, SMEDDS offer advantages such as reduction in inter-and intra-subject pharmacokinetic variability, improvement in lymphatic transport, GI permeability and reversal of P-glyco protein (P-gp) efflux. Concurrent results were portrayed in improving the bioavailability of hydrophobic drugs like entacapone, atorvastatin etc with SMEDDS[24,25]. Various research findings on SMEDDS to improve solubility, dissolution rate and bioavailability have been listed in Table 2.

Table 2. Research outcomes from SMEDDS drug delivery systems

Drug	Lipid phase	Surfactant	Cosolvents/ co-surfactants	Significance of study	Reference
Valproic acid	Castor oil and Corn oil	Tween 20. Tween 80 and Span 20	PEG 200, Polypropylene glycol 200 and 400	Dissolution profile was improved	26
Simvastatin	Capryol 90, Lauroglycol 90, Labrafil M 1944 CS and M2125	Cremophor EL and Tween 80	Carbitol, PEG 400 and Polypropylene glycol	Oral bioavailability was enhanced in animal study	27
Tacrolimus	Lauroglycol FCC, Maisine 35-1, Gelurice 50/13 and Labrafil M2130	Tween 20 and Cremophor RH	PEG 400	Exhibited superior *in- vitro* dissolution profile as compared to pure drug	28
β-Artemether	Capryol 90 and Natural lipophile (N-LCT)	Cremophor EL and Tween 80	Gelucire 44/14	Excellent self-micro emulsification efficiency and released >98% of the drug in just 15 min	29
Sorafenib	Ethyl oleate	Cremophor EL	PEG-400 and Ethanol	Oral bio-availability was Increased about 25 times	30
Exemestane	Capryol 90	Cremophor ELP	Transcutol HP	Enhancement of dissolution rate was observed	31
Carbamazepine	Caprylic/ Capric triglycerides	Polysorbate 80, Poly-oxyethylene 20 and sorbitan monooleate	Cremophor RH 40, PEG-40 and hydrogenated castor oil	Improved dissolution rate and bioavailability	32
Fenofibrate	Oleic acid, Captex oil, Olive oil and Capyol capmul	Tween 20, Span 20, Lebrasol and Tween 80	Cremophor EL, PEG 400 and Propylene glycol	Improved solubility, dissolution rate and bioavailability	33
Sirolimus	Oleic acid and Castor oil	Glycerol triacetate	Propylene glycol mono caprylate	Improved bioavailability of sirolimus	34
Flurbiprofen	Labrasol, Labrafil M 1944 CS, Transcutol HP	Tween 80	Poly glycolized glycerols	Improved dissolution rate and bioavailability	35
Itraconazole	Transcutol HP	Tween 20 and Span 20	Poly glycolized glycerols	Enhanced solubility and bioavailability	36

3.2.1. Physico-chemical factors influencing the design of SMEDDS

Formulation of SMEDDS is influenced by the following factors:

Surfactant HLB: Surfactant with HLB of 10 was found to be optimal for emulsification and can be obtained by combining polar and non-polar surfactants at predetermined levels[37,38]. The surfactants with approximate HLB values[39] are given in Table 3. Recently, patent cooperation treaty (PCT) granted a patent for self-emulsifying water/oil microemulsion of a therapeutic peptide drug with high HLB surfactant, which comprises medium-chain alkyl/dialkyl sulfate, sulfonate, or sulfosuccinate salt that showed improved delivery characteristics[40].

Table 3. Approximate surfactant HLB values

Surfactant	HLB value
Oleic acid	1
Sorbitan tristearate (Span 65)	2
Sorbitan monooleate (Span 80)	4
Diethylene glycol monolaurate	6
Sorbitan monolaurate (Span 20)	9
Glycerol monostearate	11
Polyoxyethylene (10) cetyl ether (Brij 56)	13
Polyoxyethylene sorbitan monooleate (Tween 80)	15
Sodium octadecanoate	18
Sodium dodecanoate	21
Sodium octanoate	23
Dioctyl sodium sulfosuccinate	32
Sodium heptadecyl sulfate	38
Sodium dodecyl sulfate	40
Sodium octyl sulfate	42

Melting point: Drugs with low and moderate melting point in the range of 70-180°C are optimal for the development of lipid based systems. Drugs with high melting point are not appropriate for the development of SMEDDS[9].

Oil phase polarity: Lipid phase polarity is a factor which governs the release of drug from SMEDDS. The high polarity enhances the rate of drug release into water layer. Precise amounts of drug can be obtained from formulation which contains oil phase of the highest polarity[9].

3.3. Self nano-emulsifying drug delivery systems (SNEDDS)

In current times, SNEDDS has emerged as very effective delivery systems due to their commendable properties. The advantages of SNEDDS include bypassing hepatic metabolism, and inhibition of action of cytochrome P450 enzymes in enterocytes and hepatocytes, resulting in the reduced metabolism of drugs, enhanced lymphatic lipophilic drug transport, and P-glycoprotein efflux reduction[41,42]. These advantages might be due to the nano sized globule formation attributed to the usage of specific lipids and emulgents as formulation components[43]. S-SNEDDS offer potential benefits such as good portability, enhanced loading of drug in formulation, better stability accompanied by high shelf-life, with a simple method of production resulting in reduced financial burden[44-46]. The S-SNEDDS can be formulated by various methodologies such as spray drying, extrusion-spheronization and adsorption technique in which liquid SNEDDS are incorporated on to the surface of inert carriers viz., colloidal silicon dioxide and magnesium aluminometasilicate[44]. Such specialized machination techniques are mixed with robustness, optimization of process variables, ease of scale-up and reduced cost of production, implementation of appropriate

formulation approaches and additional excipients. Solid-SNEDDS of carvedilol with inert porous carrier such as Nikkol HCO50 as emulgent has displayed pronounced absorptivity parameters of lymphatic delivery with reduced P-gp efflux[47].

Differences between microemulsion, SEDDS, SMEDDS and SNEDDS

Microemulsions are thermodynamically stable systems whereas in SMEDDS, microemulsion formed spontaneously upon gastric agitation may not be thermodynamically stable. SEDDS and SMEDDS differ in their droplet size. Droplet size of SEDDS and SMEDDS is <300 nm and < 100 nm respectively. The dispersion of type IIIB formulation forms nanoemulsion rather than microemulsion spontaneously, which is thermodynamically unstable. Hence those formulations are referred to as SNEDDS rather than SMEDDS.

3.4. Supersaturable self microemulsifying drug delivery systems (supersaturable SMEDDS)

When SMEDDS formulations enterthe gastrointestinal region, drug precipitation may occur, which leads to the failure of intestinal absorption. The supersaturable SMEDDS represents a novel thermodynamically stable formulation approach and it is designed to contain small amounts of surfactant and hydrophilic polymers like polyvinylpyrrolidone (PVP) as precipitation inhibitors or supersaturated promoters to inhibit drug precipitation by the generation and maintenance of an *in-vivo* supersaturated state.

Carbamazepine (CBZ) supersaturable SMEDDS with tween 80 and PVP as precipitation inhibitor at lower levels produced sustained supersaturated state by retarding kinetics of precipitation. The bioavailability of CBZ was improved by 5-folds with the SMEDDS formulations[48-52].

3.5. Self double emulsifying drug delivery system (SDEDDS)

Seifritz, first described the SDEDDS as multiple emulsions that have the spontaneous formation of a continuous phase which possess emulsion droplets as internal phase, in which the continuous phase exists as dispersed phase[53-55]. Water-in-oil-in-water (*w/o/w*) type of multiple emulsions is gaining great interest. They are widely exploited in the areas of drug delivery, cosmetics and food items[56,57]. The *w/o/w* double emulsions are depicted in Figure 1. The hydrophilic drugs present in internal aqueous phase exist as internal phase in the oil membrane which acts as a storage chamber and thereby it protects the drug and improves its oral bioavailability despite of its poor permeability[58]. However industrial applicability of double emulsions is meager because of instability to solvents, pH fluctuations and heat. Despite a lot of effort, no pharmaceutical double emulsion is available in the market and remains at research levels[59,60].

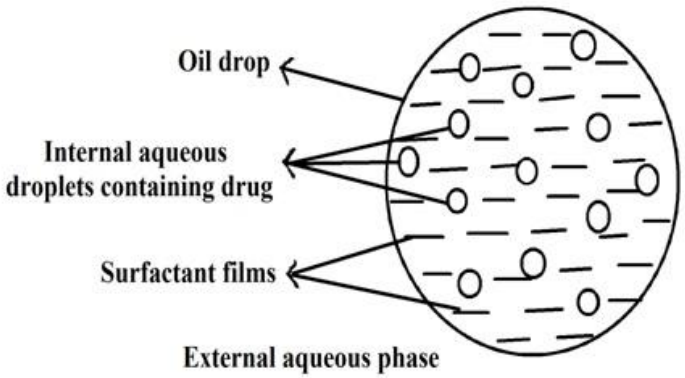

Figure (1): w/o/w double emulsion

Methods of formulation of *w/o/w* emulsions: so far, two methods have been adopted to prepare double

emulsions viz: single-step emulsification and two step emulsification processes.

Single-step emulsification process: In one step emulsification process, hydrophilic surfactant is dissolved in aqueous phase, hydrophobic emulsifier is incorporated in oil phase and both the phases are subjected to strong mechanical agitation. Water in oil emulsion is formed which is converted to w/o/w double emulsion[61]. Besides this, the other method to produce double emulsions is formation of w/o emulsion using hydrophobic surfactant and a little amount of hydrophilic emulsifier with subsequent heat treatment of the formed emulsion till it gets invert. At specific temperature and HLB emulsifiers, w/o/w emulsion can be formed. However, these accidental preparations are not reproducible, as their production results in the mutual incidence of catastrophic and transitional inversion of the phases. Hence these systems are referred as transitory or temporary systems. The w/o/w emulsions can be exclusively stabilized using a synthetic diblock copolymer. Contrasting the usage of normal small molecule, combination of surfactants is widely used. Multiple emulsions alleviated by block copolymers like polyurethanes, are more stable and have shown the capacity to individually encapsulate both polar and non-polar moieties[62].

Two-step emulsification process: Both the hydrophilic and hydrophobic surfactants are used to produce the multiple emulsions in this process. Initially, *w/o* type emulsion was developed by one-step technique and then the prepared *w/o* emulsions were added to hydrophilic surfactant (tween 80) under continuous stirring until multiple emulsions are obtained[63] as represented in Figure. 2. Pidotimod, a peptide molecule posing low permeability was formulated as SDEDDS to address the low bioavailability issues along with oleic acid, span 80, tween 80 and MCT (glycerin). The pidotimod SDEDDS exhibited good absorption devoid of major local damage. Thus SDEDDS can be an alternative method to deliver protein, peptide and peptidomimetic drugs[63].

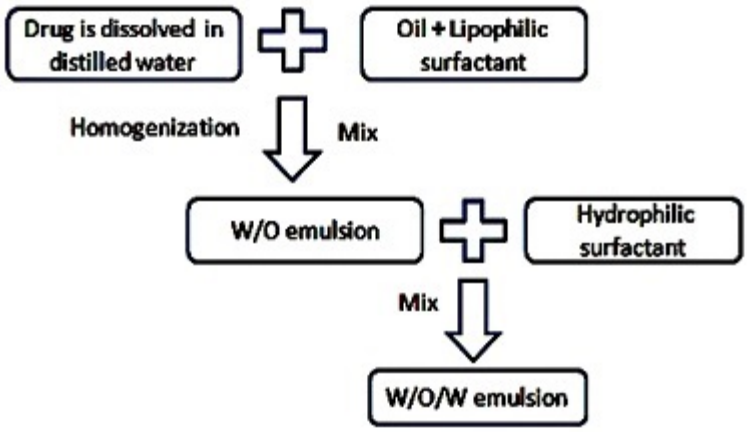

Figure (2): Scheme of double emulsion preparation

3.5.1. Mechanism of drug transport through SDEDDS[61]

Diffusion: For ionized lipid soluble drugs, the diffusion depends on the type of lipid, the nature and dissociation constant of the entrapped drug, and the pH of the aqueous phase. Similar transport mechanism was demonstrated in the treatment of over dosing of barbiturates. At low pH, barbiturate is in unionized state and gets solubilized in oil phase. Thereby the drug can easily pass through the lipid membrane to internal water media with basic buffer that ionizes the supplement, which, in turn become insoluble in a lipid medium and is entrapped in an internal aqueous portion. Then the emulsion carries the drug and is emptied from the gastrointestinal tract, showing first-order kinetics, in accordance with Fick's law.

Micellar transport: Inverse micelles containing non-polar tails of a surfactant faces outside with the hydrophilic polar head residing inside, encapsulate the hydrophilic active moiety inside the core. They permeate the lipid layer owing to the lipophilic nature outside. They possess the ability to entrap ionized as well as unionized drugs. Tetradecane release patterns from tetradecane/water/hexadecane multiple emulsion portrayed micellar transport mechanism predominantly than diffusion.

Rupture of oil phase: In *w/o/w* emulsion systems, rupture of lipid layer that exists between two aqueous phase's results in their union and thus drug might be released simply. It was attributed that the permeation of water and aqueous soluble drugs through lipid layer occurs by two mechanisms i.e., reverse micellar transport and diffusion through surfactant lamellae.

3.5.2. Applications of multiple emulsions

The areas where multiple emulsions are widely exploited include food science, drug delivery and separation sciences[56].

Some of the applications are comprehensively summarized below:

(a) Influenza virus surface antigen hemagglutinin was developed as a w/o/w emulsion and it was proved that the usage of w/o/w emulsion as an alternative antigen adjuvant with enhanced immune response compared to antigen alone[64].

(b) Various multiple *w/o/w* emulsion systems containing cytarabine, methotrexate, vinblastine sulphate and some other anticancer drugs delivered successfully in cancer chemotherapy, because many of anti-cancer drugs are water soluble[64,65].

(c) Double emulsion technique was employed to treat the barbiturate overdose toxicity by pH differential. The double emulsion has an inner aqueous basic buffer phase of emulsion. Upon oral administration, gastric fluid acts as external aqueous acidic buffer phase. At acidic pH, the barbiturate remains unionized transferring through lipid layer into the internal water phase, where they are ionized. Once ionized, they are entrapped inside due to low affinity for the lipid layer. Over dosage is mitigated as excess drug gets entrapped in double emulsion[66].

(d) s*/o/w* (solid-oil-water) emulsion containing insulin was developed for oral administration. In which, the surfactant- coated insulin was dispersed in oil and then the dispersion was again dispersed in the external aqueous phase. Peroral administration of insulin s*/o/w* emulsion displayed prolonged hypoglycemic action in rodents[67].

(e) The double emulsions are effective in masking the bitter taste of chloroquine and chlorpromazine[68].

f) Herbal oils such as camptothecin, bruceajavanica, coixenolide and zedoary oils were also suitable for multiple emulsions[69].

(g) Apart from healthcare applications, food industries also utilize the concept of *w/o/w* emulsions by encapsulating sensitive food materials and flavors. There exists a notable taste difference between *w/o/w* multiple emulsions and *o/w* emulsions having the same component. Additionally flavor release was delayed in double emulsions[70].

Instability in the systems prompted by either partial or induced polarity in selected oily phases, which is a prime concern in development of liquid self emulsifying drug delivery systems. In order to address such stability issues in liquid systems, solid-SMEDDS were evolved. The solid-SMEDDS have both the advantages of SMEDDS such as improved solubility, oral bioavailability and solid dosage forms. S-SMEDDS are achieved with low production cost and ensured patient compliance, high stability and reproducibility[11,12]. The techniques that are widely employed for developing solid-SMEDDS were enlisted below.

4. Methods to convert liquid/semi solid SMEDDS into solid-SMEDDS

4.1. Encapsulation of liquid or semi solid SME formulation

Capsule filling is the widely used technique to encapsulate liquid/ semi solid SME formulations meant for oral administration. Conversion of semi solid SME into

solid-SMEDDS is performed in four steps: (a) heating of semi solid excipients to at least 20°C above their melting point, (b) inclusion of API into molten semi solid excipient mass by stirring, (c) encapsulation of the above molten mixture and (d) cooling to room temperature[71]. In case of liquids, a two-step process is involved to convert liquid SME formulation to solid-SMEDDS through filling of liquid SME into capsules and sealing the body and cap of capsule, by banding / microscopic sealing[72]. In capsule technology, the first consideration is the compatibility between excipients and capsule shell. The major advantages of this technique are manufacture of SME capsules is simple, suitable for highly potent drugs, with higher drug loading potentials.

4.2. Spray drying

In the spray drying process, solubilization of liquid SME mixture has to be carried out prior to spray drying. Subsequently the solubilized liquid SME is sprayed through an atomizer to obtain micro droplets. The droplets are introduced into a drying chamber, where the relatively volatile liquid (water) evaporates, leaving the dry product under controlled temperature. These dry particles are further processed or formulated into tablets or capsules. This technique was successfully applied for telmisartan systems along with acrysol EL 135, tween 80, carbitol and water soluble maltodextrin[71].

4.3. Adsorption

Liquid SME can be converted to free flowing powders by adsorption onto the surface of suitable solid carriers. It is a simple process with good content uniformity in which liquid SME formulation is combined with a solid carrier to obtain a free flowing product. The mixture may be either directly encapsulated or compressed appropriately[73]. The solid carriers are usually porous with highly specific surface of inorganic colloids, nanoparticle adsorbents and cross-linked polymers. The examples for microporous inorganic substances include silica, silicates, magnesium hydroxide and magnesium trisilicate[74]. Cross-linked polymers like cross-povidone, cross-linked sodium carboxymethylcellulose (NaCMC) and cross-linked polymethylmethacrylate (PMMA) generate a positive milieu to maintain the dissolution of drug and slow down the drug reprecipitation[75]. Examples for nanoparticle adsorbents include porous silicondioxide (sylysia 550), carbon nanohorns, carbon nanotubes, charcoal, fullerene and bamboo charcoal[76]. This technique proved to be successful with atorvastatin S-SMEDDS. Aerosil 200 was used as an inert carrier adsorbent[77].

4.4. Melt granulation

In this technique, powder agglomeration is obtained by adding binders that soften/ melt at relatively lower temperature. This method offers many advantages over conventional wet granulation method, including the avoidance of liquid addition followed by the avoidance of drying and solvent usage. A large variety of solid and semisolid lipids are used as meltable binders. Especially Gelucire® and PEG fatty acids esters with SME property can improve the rate of dissolution against PEG[78]. On other hand lecithin, partial glycerides or polysorbates were also proven as good lipid based excipients whereas silica and magnesium aluminometasilicate were used as solid neutral carriers[79,80]. This technique was proven to be effective with atorvastatin S-SMEDDS which contain PEG2000 as hydrophilic carrier[77].

4.5. Melt extrusion/ extrusion spheronization

Extrusion is a method in which a raw matter is converted into uniform shape and density product, by passing through a die in a set of controlled conditions of temperature, pressure and outflow of product[81]. The pellet size of spheroids formed is dependent on the extruders' aperture size. Small size pellets can be obtained with small extruder aperture and vice-versa. High drug loading percent[72], content uniformity and solvent free process are the merits of this technique. The extrusion spheronization is involved with steps of (i) dry mixing of the drug and excipients to get a homogenous powder, (ii) wet massing of the above powder with binder, (iii) extrusion, (iv) spheronization of the extrudate to uniform sized pellets, (v) drying and (vi) straining to get the preferred size distribution and permit discretionary coating. The

spherical SME pellets of diazepam were obtained by extrusion/spheronization technique. Diazepam spherical pellets have less friability value and good self-emulsion formation which allow the transfer of the hydrophobic drug into an aqueous phase, enhancing its oral bioavailability[82]. A pellet formulation of progesterone in a self-emulsifying system had more pronounced bioavailability parameters[83]. Bi-layered vinpocetine pellets contain one layer with inert layer of microcrystalline cellulose (MCC), lactose and water; and a second layer of the self-emulsifying system. The bi-layered pellets demonstrated adequate morphological and technological characteristics with improved therapeutic efficacy[84].

4.6. Lyophilization

Lyophilization or freeze-drying is the technique which involves the transfer of heat and mass to and from the product during production due to freezing/sublimation. Freeze drying of an *o/w* emulsion can be an alternative technique to produce pilot dry emulsions. In lyophilization, molecular dispersion is obtained by dissolving meloxicam, glyburide and amylobarbitone/hydroxyl propyl-β-cyclodextrin in a common solvent and followed by freezing and sublimation[85-87]. Suitable conditions during freeze drying of *o/w* emulsions are deliberate cooling rate and incorporation of cryo-protectants[88]. Maltodextrins DE38 are one of the useful matrix forming agents in the formulation of freeze-dried hydrochlorthiazide compressed tablets[89].

5. The future

Researchers should focus on understanding the role of key components such as lipids, surfactants and cosurfactant utilized in SEDDS design in terms of dispersion mechanism, size and the structure of emulsion droplets formed in the process and solubilization of drug in GI fluids. The rationale selection of excipients play pivotal role in the formulation and development of S-SEDDS. In consequence, the selection criterion of the excipients must be projected as a chief focusing arena in the development of S-SEDDS.

Conclusion

Self emulsifying drug delivery systems are one of the potential approaches to formulate active moieties with less water solubility and poor biomembrane permeation. SEDDS/ SMEDDS/SNEDDS/supersaturable-SMEDDS, have shown a substantial improvement in the bioavailability upon oral administration of hydrophobic active moieties. The bioavailability of hydrophilic drugs is confluence by formulating the SDEDDS. The solid forms of self emulsifying formulations were well successful to enhance the stability of liquid self emulsifying formulations. In comparison to liquid SEDDS, S-SEDDS are advantageous for the portability, reduced economical burden due to its ease of manufacturing, lowering production cost, improved stability and ensured patient compliance. Most importantly sustained /controlled drug release from the formulation can be attained devoid of gastrointestinal irritability.

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الاستراتيجيات المعاصرة في المستحلب المخدرات أنظمة التسليم: لمحة استعادية

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ملخص

يعد التوافر الحيوي عن طريق الفم من الأدوية التي يمكن زيادتها من قبل أنظمة الاستحلاب الذاتي .نظم الاستحلاب الذاتي مختلفة مثل: نظم تسليم الاستحلاب الذاتي المخدرات (SEDDS)، نظم تسليم المخدرات microemulsifying النفس (SMEDDS)، وأنظمة تسليم nanoemulsifying الذاتي المخدرات (SNEDDS). توفر أنظمة توصيل الدواء الإستراتيجية لتحسين القابلية للذوبان والنفاذية والتوافر البيولوجي لكل أنصاف المخدرات المائية والكارهة للماء .نجاح المستحضرات التجارية مثل: العلامة التجارية Sandimmune نيورال من السيكلوسبورين ألف و Fortovase من ساكوينافير أدى إلى تصاعد الاهتمام في التركيبات القائمة على الدهون. نظم ايصال المخدرات الذاتي الصغرى الاستحلاب (SMEDDS) هي مزيج الخواص من الدهون والزيوت، السطحي، ويتشارك مع خاصية فريدة من إنتاج النفط في المياه) س/ ث microemulsion (على الإثارة لطيف .وتركز الأبحاث الحالية على أنظمة توصيل الدواء الذاتي الاستحلاب المزدوج (SDEDDS) للإدارة الفاعلة للأنصاف النشطة ماء والبروتينات والعقاقير الببتيد .تضم SDEDDS المستحلبات مزدوجة من قطرات النفط أكبر دمج مرحلة داخلية المائية الموجودة في مرحلة متفرقة في المتوسط تشتت مائي. وقد وضعت أشكال صلبة من أنظمة توصيل الدواء الدهون استنادا للتغلب على مشاكل استقرارها. توفر هذه المقالة لمحة عامة عن المستحلبات جديدة، والعوامل الفيزيائية والكيميائية للSMEDDS، سواء أكانت تستخدم لاستحلاب الذاتي، أو للجوانب المتعلقة بصياغة وآلية نقل المخدرات من خلال SDEDDS، هذا الاستعراض يركز بشكل خاص على التقنيات التي تستخدم في تحويل/ شبه أنظمة microemulsifying الذاتي الصلبة السائلة في تركيبات microemulsifyingالصلبة الذاتي. عملية التغليف والتجفيف بالرش، والامتزاز على مركبات خاملة، تذويب التحبيب والتذويب يدل على تقنيات البثق بأثر رجعي في هذه المقابلة SEDDS الصلبة هي مناسبة للمخدرات محبة للدهون، بينما SDEDDS الصلبة هي الأكثر ملاءمة لأنصاف ماء.

الكلمات الدالة: الاستراتيجيات المعاصرة، المستحلب، المخدرات، أنظمة التسليم، لمحة استعادية.

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