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Self-Micro Emulsifying Drug Delivery Systems: A Strategy to Improve Oral Bioavailability

Sistema de administración de fármacos autoemulsionante: una estrategia para mejorar la biodisponibilidad oral

Vijay K. Sharma[1], Aishwarya Koka[2], Jyoti Yadav[3], Anil K. Sharma[3], Raj K. Keservani[4]

1. School of Pharmaceutical Sciences, Jaipur National University, Jaipur-302025, India

2. Mallareddy Institute of Pharmaceutical Sciences, Secunderabad, Andhra Pradesh-500014, India

3. Delhi Institute of Pharmaceutical Sciences and Research, Formerly College of Pharmacy, University of Delhi, Pushp Vihar, Sector III, New Delhi-110017, India

4. School of Pharmaceutical Sciences, Rajiv Gandhi Proudyogiki Vishwavidyalaya, Bhopal, 462036, India

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Correspondencia
Correspondence

Raj K. Keservani
School of Pharmaceutical Sciences,
Rajiv Gandhi Proudyogiki Vishwavidyalaya, Bhopal, 462036, India,
+917897803904
rajksops@gmail.com

RESUMEN

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Objetivo: La vía oral siempre ha sido la ruta preferida de administración de fármacos en muchas enfermedades y hasta hoy es la primera forma investigada en el desarrollo de nuevas formas de dosificación. El principal problema en las formulaciones de fármacos orales es la baja y errática biodisponibilidad, lo que resulta fundamentalmente por la escasa solubilidad en agua, con lo que plantean problemas en su formulación. Para la administración terapéutica de los grupos activos lipófilos (BCS clase II drogas), las formulaciones a base de lípidos están teniendo cada vez más atención.

Métodos: Con ese objetivo, a partir de los sitios web de PubMed, HCAplus, Thomson, y sus registros se utilizaron como fuentes principales para llevar a cabo la búsqueda de los artículos de investigación más importantes publicados sobre el tema. A continuación, la información fue analizada cuidadosamente, poniendo de relieve los resultados más importantes en la formulación y desarrollo de sistemas de administración de fármacos auto-emulsionante micro, así como su actividad terapéutica.

Resultados: El sistema de administración de fármacos autoemulsionante (SMEDDS) ha ganado más atención debido a la mejorada que permite la reducción de la biodisponibilidad oral en dosis, los perfiles temporales más consistentes de la absorción del fármaco, la orientación selectiva de fármaco (s) hacia la ventana de absorción específica en el tracto gastrointestinal, y la protección del fármaco (s) desde el entorno poco receptivo en el intestino.

Conclusiones: Este artículo proporciona una visión completa de SMEDDS como un enfoque prometedor para abordar eficazmente el problema de moléculas poco solubles.

Palabras clave: SMEDDS; tensioactivo; aceite; cosurfactante; biodisponibilidad.

ABSTRACT

Aim: Oral route has always been the favorite route of drug administration in many diseases and till today it is the first way investigated in the development of new dosage forms. The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility, thereby pose problems in their formulation. For the therapeutic delivery of lipophilic active moieties (BCS class II drugs), lipid based formulations are inviting increasing attention.

Methods: To that aim, from the web sites of PubMed, HCAplus, Thomson, and Registry were used as the main sources to perform the search for the most significant research articles published on the subject. The information was then carefully analyzed, highlighting the most important results in the formulation and development of self-micro emulsifying drug delivery systems as well as its therapeutic activity.

Results: Self-emulsifying drug delivery system (SMEDDS) has gained more attention due to enhanced oral bio-availability enabling reduction in dose, more consistent temporal profiles of drug absorption, selective targeting of drug(s) toward specific absorption window in GIT, and protection of drug(s) from the unreceptive environment in gut.

Conclusions: This article gives a complete overview of SMEDDS as a promising approach to effectively deal with the problem of poorly soluble molecules.

Keywords: SMEDDS; surfactant; oil; co-surfactant; bioavailability.

Vijay K. Sharma, Aishwarya Koka, Jyoti Yadav, Anil K. Sharma, Raj K. Keservani

INTRODUCTION TO LIPID-BASED FORMULATIONS

Successful oral delivery of drugs has always remained a challenge to the drug delivery field, since approximately 40% of the new drug candidates have poor water solubility, and thus oral delivery is frequently associated with implications of low bioavailability. Many approaches have been meticulously explored to improve the oral bioavailability of such drugs including particle size reduction (micronization or nanosizing), complexation with cyclodextrins, salt formation, solubilization based on cosolvents, surfactants, etc. Modification of the physicochemical properties, such as by salt formation and particle size reduction of the drug may improve the dissolution rate of the drug but these methods are not always practical, for example, salt formation of neutral compounds is not feasible. Moreover, the salts of weak acid and weak base may convert back to their original acid or base forms and lead to aggregation in the gastrointestinal tract. Particle size reduction may lead to build up of static charges, present handling difficulties and is not desirable where poor wettability are experienced for very fine powders. To overcome these limitations, various other formulation strategies have been attempted such as use of cyclodextrins, nanoparticles, solid dispersions and permeation enhancers. Indeed, in some selected cases, these approaches have been successful.[1] Of late lipid-based formulations have attracted great deal of attention to improve the oral bioavailability of poorly water soluble drugs. In fact, the most favored approach is to incorporate lipophilic drugs into inert lipid vehicles such as oils, surfactant dispersions, micro emulsions, self-emulsifying formulations, self-micro emulsifying formulations, and liposomes. This could lead to increased solubilisation with concomitant modification of their pharmacokinetic profiles, leading to increase in therapeutic efficacy.[1]

Lipid based formulations offer a wide variety of formulations like solutions, suspensions, solid dispersions and self-micro emulsifying drug delivery systems (SMEDDS).[2] The SMEDDS have attracted considerable interest after commercial success of immunosuppressive agent cyclosporine A (Neoral®) and the two HIV protease inhibitor ritonavir (Norvir®) and saquinavir (Fortovase®). Self- emulsifying formulations comprise isotropic mixtures of natural or synthetic oils with lipophilic or hydrophilic surfactants and co-solvents which spontaneously emulsify when exposed to the fluids of the gastrointestinal tract (GIT) to form oil-in-water emulsion or micro emulsion. The SMEDDS offer following advantages:

– Thermodynamic steadiness.[3]

– Enhanced solubilization of bioactive substances.[3]

– Improvement in oral bioavailability by increasing solubility and efficient drug transport.[3]

– Improved patient compliance.

– Reduced dosing frequency.

– Ease of manufacture and scale-up as compare to other lipid dosage forms.[4]

– Reduction in inter-subject and intra-subject variability and food effects.[3,4]

– Ability to deliver active biomolecules including peptides that are sensitive towards enzymatic hydrolysis in GIT.[3]

– No influence of lipid digestion process unlike the other lipid-based drug delivery systems.[5,6]

– When polymer is incorporated in composition of SMEDDS it gives prolonged release of medicament.

The lipidic systems provide the abovementioned merits, however, this suffers from pit falls as under:[3,4]

1. Lack of good predicative in vitro models for assessment of the formulations.

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. Another is chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which irritate GIT.

Classification System for Lipid Formulations

The lipid formulation classification system was first introduced in 2000 and the extra 'type' of formulation was added in 2006.[7]

Type I - These systems shows poor initial aqueous dispersion and require digestion by pancreatic lipase/co-lipase in GIT to produce more amphiphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase. These are a good option for drugs having sufficient solubility in oils. Valproic acid has been formulated in soft gelatine capsules containing corn oil as lipidic component.[7]

Type II - Type II lipid formulations constitute SEDDS. Self-emulsification is generally obtained at surfactant content above 25% (w/w). These formulations provide the advantage of overcoming the slow dissolution step typically observed with solid dosage forms and as described above generate large interfacial areas which in turn allows efficient partitioning of drug between oil droplets and the aqueous phase from where absorption occurs.[7,8]

Type III - Type III lipid based formulations, commonly referred to as self-micro emulsifying drug delivery systems (SMEDDS), are defined by inclusion of hydrophilic surfactant (HLB > 12) and co-solvent such as ethanol, poly ethylene glycol and propylene glycol. Type III formulation can be further segregated into type IIIA and type IIIB formulations in order to identify more hydrophilic systems (type IIIB) where the content of hydrophilic surfactant and co-surfactant increases and the lipid content reduces. Type IIIB formulations typically achieve greater dispersion rates when compared to type IIIA although the drug precipitation risk on dispersion of the formulation is higher given the lower lipid content. [7]

Type IV- These formulations commonly offer increased drug payloads when compared to the formulations containing simple glycerides lipids and also produce very fine dispersion when introduce in aqueous An example of type IV formulation is the current capsule formulation of the HIV protease inhibitor Amprenavir (Agenerase®) which contains TGPS as a surfactant and PEG 400 and PG as a cosolvent. [7]

MECHANISM OF SELF-MICRON EMULSIFICATION

According to Reiss, the energy required to increase the surface area of the dispersion for self-emulsification process bear less importance when compared to the entropy change that favours dispersion. Self- micron emulsifying process is related to the free energy. [9] That is free energy of the conventional emulsion is a direct function of the energy essential to create a new surface between the oil and water phases and can be described by the equation:

DG=S N p r 2s

Where, DG is the free energy related to the process, N is the number of droplets of radius r and s represents the interfacial energy. The emulsion is stabilized by emulsifying agents only after the two phases of emulsion is separated with respect to time to reduce the interfacial area. The emulsifying agent forms a monolayer of emulsion droplets, and hence reduces the interfacial energy, and providing a barrier to avoid coalescence. In the case of self–micron emulsifying systems, the free energy required to form the emulsion is either very low or positive, or negative.[10] Emulsification requires very little input energy involves destabilization through contraction of local interfacial region.

Phase Diagrams

The microemulsion region is usually characterized by constructing ternary-phase diagrams. Three components are the basic requirement to form a microemulsion: an oil phase, an aqueous phase and a surfactant. If a co-surfactant 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 (ideally, according to the Gibbs' phase rule) 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.

The Gibbs phase diagram, however, is an empirical visual observation of the state of the system and may, or may not express the true number of phases within a given composition. Apparently clear single phase formulations can still consist of multiple iso-tropic phases (e.g. the apparently clear heptane/ Sodium bis (2-ethylhexyl) sulfosuccinate (AOT)/water microemulsions consists of multiple phases). Since these systems can be in equilibrium with other phases, many systems, especially those with high volume fractions of both the two immiscible phases, can be easily destabilised by anything that changes this equilibrium e.g. high or low temperature or addition of surface tension modifying agents. However, examples of relatively stable microemulsions can be found. It is believed that the mechanism for removing acid build up in car engine oils involves low water phase volume, water-in-oil (w/o) microemulsions. Theoretically, transport of the aqueous acid droplets through the engine oil to microdispersed calcium carbonate particles in the oil should be most efficient when the droplets are small enough to transport a single hydrogen ion (the smaller the droplets, the greater the number of droplets, the faster the neutralisation). Such microemulsions are probably very stable across a reasonably wide range of elevated temperature. [11]

FORMULATION OF SMEDDS

Upon dilution, the SMEDDS formulation immediately forms a clear dispersion and remains stable (Fig.1). The hydrophobic drug dispersed in the SMEDDS formulation remains solubilized it is absorbed. Efficient release of the drug from the formulation mainly depends on two factors, globule size and polarity of the droplets. In case of oil-in-

water microemulsions, the polarities of oil droplets are not considerable, since the drug incorporated in the oil globules reach the capillaries. [12,13]

The following parameters must be considered during the formulation of SMEDDS:

1. Solubility of the drug in different oil, surfactants and co-solvents.
2. Selection of oil, surfactant and cosolvent based on the solubility of the drug, and preparation of the phase diagram.
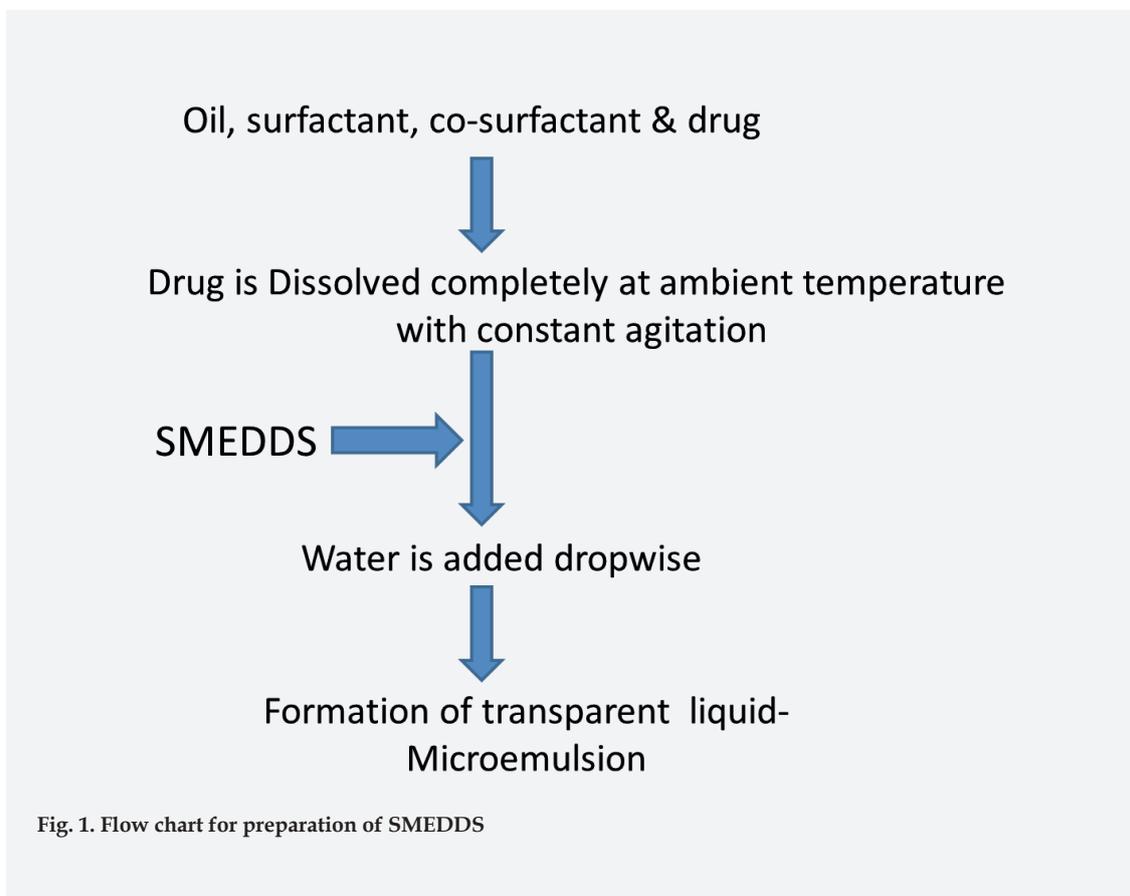
Oil, surfactant, co-surfactant & drug

Drug is Dissolved completely at ambient temperature with constant agitation

SMEDDS

Water is added dropwise

Formation of transparent liquid-Microemulsion

Fig. 1. Flow chart for preparation of SMEDDS

Selection of suitable drug candidate

Lipid based formulations offer a potential platform for improving oral bioavailability of drugs specially those belonging to Biopharmaceutical Classification System (BCS) class II and class IV. A primary indication of the potential utility of lipid based formulation can be obtained by assessing the drug lipophilicity (log P) and its solubility in pharmaceutically-acceptable lipid excipients, which should be sufficient to allow the entire dose of the drug to be administered in a single dosage unit. Another indicator of the potential for success of lipid based formulation is the observance of a strong positive food effect when the drug is administered with a fatty meal as opposed to dosing in the fasted.[14] For lipophilic drug compounds that exhibit

dissolution dissolution-rate-limited absorption, SMEDDS can offer an improvement in rate and extent of absorption resulting in reproducible blood time profile. The systems SMEDDS usually provide advantage of increased drug loading capacity when compared with lipid solutions as the solubility of poorly water soluble drugs with intermediate partition coefficient (2<log P<4) are typically low in natural lipids and much greater in amphiphilic surfactants, co-surfactants and co-solvents.[2] The partition coefficient (log P) is the prime criterion of designing lipid based systems. High log P (greater than 4) is desirable for lipidic systems. Next physicochemical criteria that play an important role are melting point and dose. Low melting point and low dose are desirable for development of lipidic systems (Table 1).

Table 1. Applications of SMEDDS relevant to BCS Classification

BCS class	Aqueous solubility	Membrane permeability	Hurdles overcome by SMEDDS
I	High	High	Enzymatic degradation, Gut wall efflux
II	Low	High	Solubilization, Bioavailability
III	High	Low	Enzymatic degradation, Gut wall efflux, Bioavailability
IV	Low	Low	Solubilization Enzymatic degradation, Gut wall efflux Bioavailability

Composition of SMEDDS

SMEDDS formulations mainly comprise of the following substances:

a) Lipids (Oils)

Lipids are the important component of SMEDDS, as solubilization and access of the drug to the lymphatic circulation of poor water soluble drugs depend on the type and concentration of oil used in the formulation. Digestive lipids such as triglycerides, diglycerides, fatty acids, phospholipids, cholesterol and other lipids based on synthetic origin offer improvement in bioavailability of the drug in contrast to the non-digestible lipids with which reduced bioavailability may occur due to impairment in absorption caused by retention of the fraction of administered drug in the formulation itself. Lipids are generally insoluble in water and are often identified by their fatty acid composition, melting point, Hydrophilic-Lipophilic Balance (HLB), and solubility in non-polar organic solvents.[15,16] Lipids with low HLB and high melting point are suitable for sustained release. Semi-solid excipients and those with high HLB serve as immediate release and bioavailability enhancement excipients. Lipid based excipients include dietary oils composed of medium (palm seed oil or coconut oil) or long chain triglycerides (corn, olive, peanut, sesame oil).

b) Surfactants

Selection of a surfactant is mainly governed by the following two factors: HLB and safety. In order to achieve high emulsifying property, the emulsifier used in SMEDDS formulation should have high HLB and high hydrophilicity. This ensures immediate formation of oil-in-water droplets and rapid dispersion of formulation in aqueous media (e.g. gastrointestinal fluid). The drug dispersed in the SMEDDS formulation would remain solubilized for a prolonged period of time at site of absorption for efficient absorption, thus preventing precipitation of drug compound within GI lumen.[17] Non-ionic surfactants are most widely recommended as they possess relatively high HLB value. Concentration of surfactant ranging in between 30% and 60% w/w form stable SMEDDS. Pharmaceutically acceptable surfactants include Cremophor® EL, Cremophor® RH40, Cremophor® RH60, polysorbate 80, various grades of gelucires, etc.

c) Co-surfactants

Pharmaceutically acceptable co-surfactants include polyethylene glycol 400, ethanol, propylene glycol. Lipid soluble solvents are used in the formulation of SMEDDS as they enable dissolution of large quantities of hydrophilic surfactants (Table 2). The lipid mixture with higher surfactant and co-surfactant: oil ratios lead to the formation of stable SMEDDS.[18]

Table 2. Examples of typical excipients used in SMEDDS formulations

Trade Name	Chemical Name	HLB	Regulatory Status
LIPIDS			
Vegetable oil	Long-chain TAG	-	Oral products, GRAS,FDA IIG
Miglyol 812	Medium- chain TAG caprylic/ capric TAG	-	Oral products, GRAS,FDA IIG
Tricaprylin	Medium-chain TAG	-	-
Labrafac CC	Caprylic/capric TG	-	-
Ethyl oleate	Ethyl ester of 18:1 FA	-	FDA IIG
Captex 355	Glycerol caprylate caprate	-	GRAS,FDA IIG
Isopropyl mysistate	FA ester	-	FDA IIG
Labrafac PG	PG dicaprylocaprate	-	USFA,JSFA,EP
Peceol	Glyceryl mono-oleate	3.3	GRAS,E47,1EP,USP-NF,FDA IIG
Maisine 35-1	Glyceryl mono-linoleate	4	Oral products,GRAS,EP,USP-NF,E471
Imwitor 988	Caprylic/capric glycerides	3.8	USP,Ph.Eur
Akoline MCM	Caprylic/capric glycerides	5-6	-
Surfactants HLB<12			
Tween 85	Polyoxyethylene (20) sorbitan trioleate	11	UK
Labrafil M1944CS	Oleoyl macrogolglycerdies	4	EP,FDA IIG,USP- NF
Labrafil M2125CS	Linoleoyl macrogolglycerides	4	EP,FDA IIG,USP- NF
Lauroglycol 90	PG monolaurate	5	USFA,FCC,EFA,USP-NF
Surfactants HLB>12			
Vitamin E TPGS	D-alpha-tocopheryl PEG 1000 succinate	13	Oral products
Cremophor EL	Polyoxyl 35 castor oil	12-14	Oral products,USP-NF,FDA IIG
Cremophor RH 40	Polyoxyl 40 hydrogenated castor oil	14-16	Oral products,USP-NF,FDA IIG
Gelucire 44/14	Lauroyl macrogolglycerides	14	EP,USP-NF,FDA IIG
Labrasol	Caprylocaproyl macrogol glycerides	14	EP,USP-NF,FDA IIG
Polysorbate 80/Tween 80	Polyoxyethylene (20) sorbitan monooleate	15	Oral products,GRAS,EP,USP-NF,FD A IIG
Polysorbate 20/Tween 20	Polyoxyethylene (20) sorbitan monolaurate	16.7	Oral products,GRAS,EP,USP-NF,FDA IIG
Co-solvents			
Ethanol	-	-	Oral products,EP,USP-NF
PEG	PEG 300 and PEG 400	-	Oral products,EP,USP-NF
Transcutol P	Diethyl glycol monoethyl ether	-	EP,FDA IIG

CHARACTERISATION OF SMEDDS

Differential Scanning Calorimetry

Differential scanning calorimetry for SMEDDS can be determined using DSC 60.Liquid sample and solid sample should be placed in aluminium pan and result can be recorded. The deviation from established thermal behavior could be determined by using DSC. This might be helpful to provide an idea about possible drug-excipient interactions.

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. This technique enables the researchers to find out presence of newly formed bonds between functional groups present in drug as well as selected excipients.

Macroscopic evaluation

Macroscopic evaluation analysis is carried out in order to observe the homogeneity of micro emulsion formulations. Any change in color and transparency or phase separation occurring during normal storage condition (37±2°C) is observed in optimized micro emulsion formulation. The uniformity of globule size ensures adequate drug distribution in the formulation.

Visual assessment

To assess the self-emulsification properties, formulation is 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 is judged as good and it is judged bad when there is poor or no emulsion formation. Phase diagram is constructed identifying the good self-emulsifying region. The formation of transparent product may be taken as end point to declare accomplishment of preparation.

Determination of self-emulsification time

The emulsification time of SMEDDS is determined according to USP 22; dissolution apparatus about 2 mg of each formulation are added drop wise to 500 ml purified water at 37°C. Gentle agitation is provided by a standard stainless steel dissolution paddle rotating at 50 rpm. Emulsification time is assessed visually. This gives the formulator information regarding time lapsed during formulation.

Solubility studies

Unknown amount of selected vehicle is added to each cap vial containing an excess of drug, after sealing, the mixture is heated at 40°C in a water bath to facilitate the solubilization. Mixing of the system is performed using a vortex mixer. Formed suspensions are then shaken with a shaker at 25°C for 48 hours. After reaching equilibrium, each vial is centrifuged at 3000 rpm for 5 minutes, and excess insoluble drug is discarded by filtration using a membrane filter. The concentration of drug is quantified by U.V. spectrophotometer. The solubility is an important aspect while selection of excipients. Only the optimized selection of excipients may yield a transparent product.

Transmittance test

Stability of optimized micro emulsion formulation with respect to dilution is checked by measuring Transmittance through U.V. spectrophotometer (UV-1700 SHIMADZU), Transmittance of samples is measured at suitable wavelengths and for each sample three replicates assays were performed. This is done to see the impact of dilution on the prepared formulation.

Droplet size determination

It is a precise method for evaluation of stability the size of droplets is measured by photon-correlation spectroscopy (PSC) with Zetasizer. All measurements are carried out at scattering angle of 90°C and 25°C temperatures. Prior to measurement, microemulsion is diluted into two steps with pure water then it is filtered through a 0.22µm filter just before it is added to cuvette. At first it is diluted with equal amount of water. In second step the mixture if further diluted to appropriate concentration for the measurement. That depends on droplet size (usually diluted 100-200 times). The globule size measurement helps to maintain the size distribution in desired range. Any deviations from this call for further trials.

Zeta potential measurement

Zeta potential for micro emulsion is determined using Zetasizer HAS 3000. Samples are placed in clear disposable zeta cells and results are recorded. Before putting the fresh sample cuvettes are washed with the methanol and rinsed using the sample to be measured before each experiment. The zeta potential values represent the surface charge of the dispersed globules. The higher the value of zeta potential more the stability is. This may be because of repulsion caused by individual globules during random movements in the continuous medium.

Stability

Temperature Stability

Shelf life is a function of time and storage temperature is evaluated by visual inspection of the SMEDDS system at different time period. SMEDDS is diluted with purified water and to check the temperature stability of samples, they are kept at three different temperature range [2-8°C

(refrigerator), room temperature etc.] and observe for any evidence of phase separation, flocculation or precipitation so that an appropriate storage condition may be prescribed for the developed product.

Centrifugation

In order to estimate metastable system, the optimized SMEDDS formulation is diluted with purified distilled water. Then micro emulsion is centrifuged at 1000 rpm for 15 minute at 0°C and observed for any change in homogeneity of micro emulsions. This indicates the stability of product upon dilution.

In vitro drug release

The quantitative in vitro release test is performed in 900 ml purified distilled water, which is based on USP 24 method. SMEDDS is placed in dialysis bag during the release period to compare the release profile with other pharmaceutical dosage forms.10 ml of sample solution is withdrawn at predetermined time intervals, filtered through 0.45 µ membrane filter, dilute suitably and analyzed spectrophotometrically. Equal amount of fresh dissolution medium is replaced immediately after withdrawal of test sample. Percent drug dissolved at different time interval is calculated. The drug release studies are performed to assess the dissolution pattern of the formulation in selected medium. The drug release data are further subjected to various kinetic models such as zero order, first order, Korsemeyer, Higuchi's equation etc. in order to determine mechanism of drug release.

SOLID SELF-MICRON EMULSIFYING DRUG DELIVERY SYSTEMS (S-SMEDDS)

SMEDDS can exist in either liquid or solid states. SMEDDS are usually, however, limited to liquid dosage forms, because many excipients used in SMEDDS are not solids at room temperature. Given the advantages of solid dosage forms, S-SMEDDS have been extensively exploited in recent years, as they frequently represent more effective alternatives to conventional liquid SMEDDS. From the perspective of dosage forms, S-SMEDDS mean solid dosage forms with self-emulsification properties. S-SMEDDS focus on the incorporation of liquid/semisolid SME ingredients into powders/nanoparticles by different solidification techniques (e.g. adsorptions to solid carriers, spray drying, melt extrusion, nanoparticles technology, and so on). Such powders/nanoparticles, which refer to SE nanoparticles[19] dry emulsions/solid dispersions, are usually further processed into other solid SE dosage forms, or, alternatively, filled into capsules (i.e. SME capsules). SME capsules also include those capsules into which liquid/semisolid SMEDDS are directly filled without any solidifying excipients. To some extent, S-SMEDDS are combinations of SMEDDS and solid dosage forms, so many properties of S-SMEDDS (e.g. excipients selection, specificity, and characterization) are the sum of the corresponding properties of both SMEDDS and solid dosage forms. For instance, the characterizations of SME pellets contain not only the assessment of self-emulsification, but also friability, surface roughness, and so on. In the 1990s, S-SMEDDS were usually in the form of SME capsules, SME solid dispersions and dry emulsions, but other solid SME dosage forms have emerged in recent years, such as SME pellets/tablets, SME microspheres/nanoparticles and SME suppositories/implants. The merits of S-SMEDDS are as follows:

– Spontaneous formation

– Ease of manufacture

– Thermodynamic stability and

– Improved solubilization of bioactive materials

– More consistent temporal profiles of drug absorption

– Greater bioavailability

– less drug need to be used

– For many drugs taken by mouth

– Faster release rates and it improve the drug acceptance by consumers

– Selective drug targeting toward a specific absorption window in the GI tract and

– Drug protection from the hostile environment in the gut

– 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

– This may lower cost

Solidification techniques for transforming liquid/semisolid SMEDDS to S-SMEDDS

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 200°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 microspray sealing.[20] 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.[21] 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.

a) 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]

b) 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, alternatively, mixed with suitable excipients before compression into tablets. A significant benefit of the adsorption technique is good content uniformity. A formulation of Liquid SMEDDS which is converted to Solid SMEDDS using maltodextrin as a solid carrier is represented in Fig. 2. SMEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers.[23] 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 porous silicon dioxide, carbon nanotubes, carbon nanohorns, fullerene, charcoal and bamboo charcoal.[24]

Fig. 2. Liquid SMEDDS versus Solid SMEDDS before and After Dilution with Water

c) 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. Moreover, it is also a good alternative to the use of solvent. 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 semi-solid lipids can be applied as meltable binders. There into, 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.[25] 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 metasilicate).[26, 27]

d) 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.[28] 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 (optional). 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.[29] Generally, the higher the water level, the longer the disintegration time.[30] 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.[31] Applying extrusion-spheronization, SME pellets of diazepam and progesterone and bi-layered cohesive SME pellets have been prepared.[32, 33]

Dosage form development of S-SMEDDS

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 evaporation[34], freeze-drying[35] or spray drying.[36, 37] 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.[38] 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 lyophilisation used.

Self-micron emulsifying capsules

After administration of capsules containing conventional liquid SME 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 SME formulation.[39] With the similar purpose, the supersaturable SMEDDS 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.[40, 41] 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.[42, 43] Oral administration of SME 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 thromboembolism 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; magnesium aluminium silicate and silicon dioxide. Eventually these solids were filled into hard capsules.[44] In another study, such adsorbents were also applied to prepare SME tablets of gentamicin that, in clinical use, was limited to administration as injectable or topical dosage forms.

Self- micron emulsifying sustained/controlled-release tablets

Combinations of lipids and surfactants have presented great potential of preparing SME tablets that have been widely researched. In order to reduce significantly the amount of solidifying excipients required for transformation of SEDDS into solid dosage forms, a gelled SMEDDS has been developed, 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 release. SE tablets are of great utility in obviat-

ing adverse effect for example; SE tablets may increase its penetration efficacy through the GI mucosal membranes, potentially reducing GI bleeding. The resultant SME tablets consistently maintained a higher active ingredient concentration in blood plasma over the same time frame compared with a non-emulsifying tablet.[45] The newest advance in the research field of SME tablet is the SME osmotic pump tablet, where the elementary osmotic pump system was chosen as the carrier of SMES. This system has outstanding features such as stable plasma concentrations and controllable drug release rate, allowing a bioavailability of 156.78% relative to commercial carvedilol tablets.[46]

Self- micro 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 bioavailability.[47] Thus, it is very appealing to combine the advantages of pellets with those of SMEDDS by SME pellets.

Self- micron 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. 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 filling. SME excipients like Gelucire1 44/14, Gelucire150/02, Labrasol1, Transcutol1 and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely used in this field.[48-51]

Self- micron emulsifying suppositories

Some investigators proved that S-SMEDDS could increase not only GI adsorption but also rectal/vaginal adsorption.[52] For example Glycyrrhizin, which is given by the oral route, barely achieves therapeutic plasma concentrations, can obtain satisfactory therapeutic levels for chronic hepatic diseases by either vaginal or rectal SME suppositories.

Self- micron emulsifying implants

Research into SME implants has greatly enhanced the utility and application of S-SMEDDS. As an example, 1,3bis (2-chloroethyl)-1- nitrosourea is a chemotherapeutic agent used to treat malignant brain tumours. However, its effectiveness was hindered by its short half-life. In order to enhance its stability compared with that released from poly (d, l-lactide-co-glycolide) (PLGA) wafer implants, SMES was formulated. Such wafers had higher in vitro antitumor activity and were less susceptible to hydrolysis.[53]

Table 3. Bioavailability enhancement of some drugs using micron emulsion technology

S. No.	Drug	Category	System
1	Paclitaxel	Anticancer	SMEDDS
2	Fenofibrate, Fluvastatin	Antihyperlipidemic	SMEDDS
3	Rapamycin, Cyclosporin	Immunosuppresive	SMEDDS
4	Nifedipine	Antihypertensive	SMEDDS
5	Ibuprofen, Naproxen	Analgesic	SMEDDS
6	Tipranavir	Anti- HIV	SMEDDS
7	Progesterone,	Hormones	SMEDDS
8	Vitamins (A,D,E,K)	Nutritional supplement	SMEDDS
9	Acyclovir	Antiviral	SMEDDS
10	Melatonin	Immunomodulatory	SMEDDS

CONCLUSIONS

SMEDDS are a promising approach for the formulation of drugs with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SMEDDS, which have been shown to substantially improve oral Bioavailability. As mentioned above, numerous studies have confirmed that SMEDDS substantially improved solubility/dissolution, absorption and bioavailability of poorly water-soluble drugs; some of such drugs are listed in Table 3. As improvements or alternatives of conventional liquid SMEDDS, S-SMEDDS are superior in reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance. Most importantly, S-SMEDDS are very flexible to develop various solid dosage forms for oral and parenteral administration. Moreover, GI irritation is avoidable and controlled/sustained release of drug is achievable. There is still a long way to go, however, before more solid SME dosage forms (except for SME capsules) appear on the market. Because there exist some fields of S-SMEDDS to be further exploited, such as studies about human bioavailability and correlation of in vitro/in vivo.

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