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Review Article

Review on self micro emulsifying drug delivery systems

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ABSTRACT

In modern drug discovery techniques, there has been a consistent increase in the number of poor water soluble drug candidate compounds, and currently more than 50% of new pharmacologically active chemical entities are lipophilic and exhibit poor water solubility. Self-micro emulsifying drug delivery (SMEDDS) is the one of the method for the improvement of oral bioavailability. SMEDDS are the isotropic mixtures of oils, surfactants, solvents and co-solvents. This review article tries to describe the formulation of SMEDDS and also talks about the construction of the phase diagram for SMEDDS. It describes the mechanism involved in self emulsification and the biopharmaceutical aspects involved. The advantages of SMEDDS over conventional emulsions are listed. Some of the marketed preparations of SMEDDS are listed in detail. A few drug delivery systems which show the scope for usage of the SMEDDS are also described.

Keywords: self-micro emulsifying; oral delivery; targeted delivery; lipophilic drugs.

INTRODUCTION

Self-micro emulsifying drug delivery system(SMEDDS) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids (Kawakami, 2002). SMEDDS spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification (Attwood, 1994).

The basic difference between self emulsifying drug delivery systems (SEDDS) also called as self emulsifying oil formulation (SEOF) and SMEDDS is, SEDDS typically produce opaque emulsions with a droplet size between 100 and 300 nm while SMEDDS 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. When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. There are also many differences between the conventional emulsions and the SMEDDS, some of which are listed in Table 1.

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. SMEDDS formulation is in theory, comparatively simple. 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. Often co-surfactants and co-solvents are added to improve the formulation characteristics.

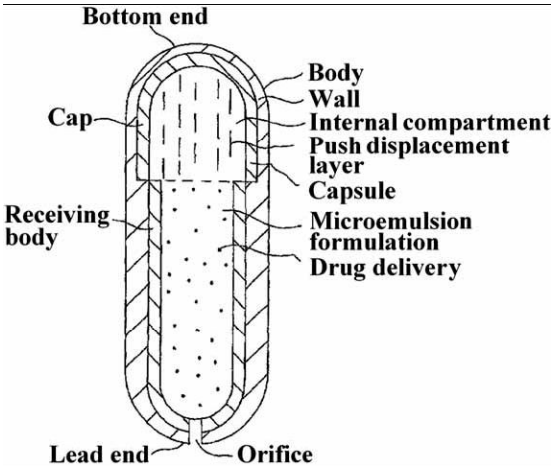

Figure 1: Capsule dosage form containing micro emulsion

FORMULATION OF SMEDDS

A large number of oils and surfactants are available which can be used as components of microemulsion systems but their toxicity, irritation potential and unclear mechanism of action limit their use. One must choose materials that are biocompatible, non-toxic, clinically acceptable, and use emulsifiers in an appro-

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Table 1: Comparison of Micro emulsion with Conventional Emulsion

S. No	Property	Microemulsion	Emulsion
1	Appearance	Transparent (or translucent)	Cloudy
2	Optical Isotropy	Isotropic	Anisotropic
3	Interfacial tension	Ultra low	High
4	Microstructure	Dynamic (interface is continuously and spontaneously fluctuating)	Static
5	Droplet size	20-200 nm	> 500 nm
6	Stability	Thermodynamically stable, long shelf-life	Thermodynamically unstable (kinetically stable), will eventually phase separate
7	Phases	Monophasic	Biphasic
8	Preparation	Facile preparation, relatively lower cost for commercial production	Require a large input of energy, higher cost
9	Viscosity	Low viscosity with Newtonian behaviour	Higher viscosity

priate concentration range that will result in mild and non-aggressive microemulsions. Early studies revealed that the self-microemulsification process is specific to the nature of the oil/surfactant pair, the surfactant concentration and oil/surfactant ratio, the concentration and nature of co-surfactant and surfactant/co-surfactant ratio and the temperature at which self-microemulsification occurs. These important discoveries were further supported by the fact that only very specific combinations of pharmaceutical excipients led to efficient self- microemulsifying systems.

SMEDDS formulation contains following components:

1. Oil phase
2. Surfactant
3. Secondary surfactant (co-surfactant)
4. Co-Solvent

1. Oils

The oil represents one of the most important excipients in the SMEDDS formulation not only because it can solubilize the required dose of the lipophilic drug or facilitate self emulsification but also and mainly because it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride. Both long and medium chain triglyceride (LCT and MCT) oils with different degrees of saturation have been used for the design of self-emulsifying formulations.

Edible oils are not frequently selected due to their poor ability to dissolve large amounts of lipophilic drugs. Modified or hydrolyzed vegetable oils have been widely used since these excipients form good emulsification systems with a large number of surfactants approved for oral administration and exhibit better drug solubility properties (Shah, 1994).

Novel semi synthetic medium chain derivatives, which can be defined as amphiphilic compounds with surfactant properties, are progressively and effectively replacing the regular medium chain triglyceride oils in the SMEDDS. This is in accordance with findings of Deckelbaum (1990) showing that MCT is more soluble and have a higher mobility in the lipid/water interfaces associated with a more rapid hydrolysis of MCT than LCT. In general, when using LCT, a higher concentration of cremophor RH40 was required to form microemulsions compared with MCT.

2. Surfactants

Surfactant molecules may be classified based on the nature of the hydrophilic group within the molecule. The four main groups of surfactants are defined as follows (Khoo, 1998)

i. Anionic surfactants
ii. Cationic surfactants
iii. Ampholytic surfactants
iv. Nonionic surfactants

i. Anionic Surfactants: where the hydrophilic group carries a negative charge such as carboxyl (RCOO-), sulphonate (RSO3-) or sulphate (ROSO3-). Examples: Potassium laurate, sodium lauryl sulphate.

ii. Cationic surfactants: where the hydrophilic group carries a positive charge. Example: quaternary ammonium halide.

iii. Ampholytic surfactants (also called zwitterionic surfactants) contain both a negative and positive charge. Example: sulfobetaines.

iv. Nonionic surfactants, where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene (OCH2CH2O). Examples:

Sorbitan esters (Spans), polysorbates (Tweens) (Kamble, 2010)

Nonionic surfactants with high hydrophilic lipophilic balance (HLB) values are used in formulation of SMEDDS. The usual surfactant strength ranges between 30-60% w/w of the formulation in order to form a stable SMEDDS. Surfactants having a high HLB and hydrophilicity assist the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amount of hydrophobic drug compounds.

3. Co surfactants and Co solvents

The production of an optimum SMEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants, thus the concentration of surfactant can be reduced by incorporation of co-surfactant. Role of the co-surfactant together with the surfactant is to lower the interfacial tension to a very small even transient negative value (Georgakopoulos, 1992). At this value the interface would expand to form fine dispersed droplets, and subsequently adsorb more surfactant and surfactant/co-surfactant until their bulk condition is depleted enough to make interfacial tension positive again. This process known as 'spontaneous emulsification' forms the microemulsion.

However, the use of co-surfactant in self emulsifying systems is not mandatory for many non-ionic surfactants. The selection of surfactant and co-surfactant is crucial not only to the formation of SMEDDS, but also to solubilization of the drug in the SMEDDS (Georgakopoulos, 1992).

Organic solvents, suitable for oral administration (ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base and can act as co-surfactant in the self emulsifying drug delivery systems (Craig, 1995).

On the other hand, alcohol- free self-emulsifying microemulsions have also been described in the literature. Indeed, such systems may exhibit some advantages over the previous formulations when incorporated in capsule dosage forms, since alcohol and other volatile co-solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft gelatin or hard sealed gelatin capsules resulting in the precipitation of the lipophilic drug. But, the lipophilic drug dissolution ability of the alcohol free formulation may be limited. Hence, proper choice has to be made during selection of components.

CONSTRUCTION OF A PHASE DIAGRAM

Micro emulsions are prepared by the spontaneous emulsification method (phase titration method) and can be depicted with the help of phase diagrams. Construction of phase diagram is a useful approach to study the complex series of interactions that can occur when different components are mixed.

Microemulsions are formed along with various association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion) depending on the chemical composition and concentration of each component. The understanding of their phase equilibriums and demarcation of the phase boundaries are essential aspects of the study.

As quaternary phase diagram (four component system) is time consuming and difficult to interpret, pseudo ternary phase diagram is often constructed to find the different zones including microemulsion zone, in which each corner of the diagram represents 100% of the particular component. In the case where four or more components are investigated, pseudo-ternary phase diagrams are used where a corner will typically represent a binary mixture of two components such as surfactant / Co-surfactant, water /drug or oil / drug. The number of different phases present for a particular mixture can be visually assessed. A highly schematic (pseudo) ternary phase diagram illustrating these features is presented in figure below (Fig. 2) (Patel, 2010).

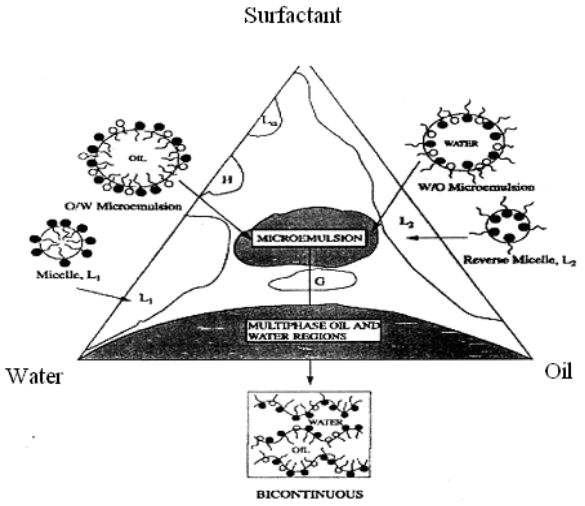

Figure 2: Phase diagram

It should be noted that not every combination of components produce microemulsions over the whole range of possible compositions, in some instances the extent of microemulsion formation may be very limited.

A Titration method is employed to construct phase diagram. Mixture of oil with surfactant is prepared at different ratios (e.g. 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, 0:10) into different vials. A small amount of water in 5 % (w /w) increments is added into the vials. Following each water addition the mixture in vials is centrifuged for 2 to 3 minute and is incubated at 25°c for 48 hrs with gentle shaking. The resulting mixture is evaluated by visual and microscopic observation. For phase diagram the micro emulsion is the region of clear and isotropic solution. Coarse emulsion is the region of cloudy dispersion (Constantinides, 1995).

MECHANISAM OF SELF EMULSIFICATION

According to Reiss, self emulsification occurs when the entropy change that favors 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 phases and can be described by the equation:

$DG = S N \pi r^2 s$ ---- (Shah, 1994)

Where,

DG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius r and S represents the interfacial energy (Kamble, 2010). The two phases of emulsion tend to separate with time to reduce the interfacial area. The emulsion is stabilized by emulsifying agents who form a monolayer on emulsion droplets and hence reduce the interfacial energy as well as provide a barrier to prevent coalescence. In the case of self emulsifying systems the free energy required to form the emulsion is either very low or positive or negative (then the emulsification process occurs spontaneously). Emulsification requiring very little input energy involves destabilization through contraction of local interfacial regions (Shukla et al, 2010).

GENERAL PREPARATION METHOD OF SMEDDS

The appropriate quantity of lipid and surfactant are melted together in a crucible at 40°C to 60°C. The drug is added and stirred thoroughly. The mixture is injected drop wise into a stirred solvent using a syringe fitted with an 18G needle at a stirring speed approx of 1000 rpm. The SMEDDS is filtered out from the solvent with aid of a filter paper (Whatman no.1) and then dried for 72 hrs in desiccator.

Drug incorporation into SMEDDS

Drugs with low aqueous solubility present a major challenge during formulation as their high hydrophobicity prevents them from being dissolved in most approved solvents. The novel synthetic hydrophilic oils and surfactants usually dissolve hydrophobic drugs to a greater extent than conventional vegetable oils. The addition of solvents including ethanol, PG and PEG, may also contribute to the improvement of drug solubility in the lipid vehicle. The efficiency of drug incorporation into a SMEDDS is generally specific to each case depending on the physicochemical compatibility of the drug/system. In most cases, there is an interference of the drug with the self emulsification process up to a certain extent leading to a change in the optimal oil/surfactant ratio. The efficiency of a SMEDDS can be altered either by halting charge movement through the system by direct complexation of the drug compound with some of the components in the mixture through its interaction with the LC phase, or by penetration into the surfactant interfacial monolayer. The interference of the drug compound with the self-emulsification process may result in a change in droplet size distribution that can vary as a function of drug concentration. It should be pointed out that emulsions with smaller oil droplets in more complex formulations are more prone to changes caused by addition of the drug compound. Hence, the design of an optimal SEDDS requires preformulation solubility and phase diagram studies to be conducted (Attwood, 1994).

CHARACTERIZATION 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 the aluminum pan and result can be recorded. Any type of chemical interaction should be determined using DSC.

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.

Macroscopic evaluation

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

Visual assessment (Rajesh, 2010)

To assess the self-emulsification properties, formulation 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.

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.

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

Table 2: Bioavailability enhancement of some drugs using micro emulsion technology

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

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.

Transmittance Test

Stability of optimized micro emulsion formulation with respect to dilution was checked by measuring Transmittance through U.V. Spectrophotometer (UV-1700 SHIMADZU) (Constantinides, 1995). Transmittance of samples was measured at suitable wavelengths and for each sample three replicate assays were performed (Attwood, 1994)**.**

Droplet size determination (Tojo, 2002)

It is a precise method for evaluation of stability. Size of droplet is measured by photon-correlation spectroscopy (PSC) with Zetasizer (Craig, 1995). All measurements are carried out at scattering angle of 90° and 25°C temperatures. Prior to measurement, micro emulsion is diluted in two-steps with pure water then it is filtered through a 0.22um filter just before it is added to cuvette. In first step it is diluted with equal amount of water. In second step the mixture is further diluted to appropriate concentration for the measurement. That depends on droplet size (usually diluted 100-200 times).

Zeta potential measurement

Zeta potential for micro emulsion was determined using Zetasizer HSA 3000 (Malvern Instrument Ltd., UK) (Craig, 1995). 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.

Stability

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, etc] (Kumar, 1999) and observed for any evidences of phase separation, flocculation or precipitation (Attwood, 1994).

Centrifugation

In order to estimate metastable systems, the optimized SMEDDS formulation was diluted with purified distilled water. Then micro emulsion was centrifuged (Remi Laboratories, Mumbai, India) at 1000 rpm for 15 minute at 0°C and observed for any change in homogeneity of micro emulsions (Attwood, 1994).

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 (Kang, 2004).

BIOPHARMACEUTICAL ASPECTS

The ability of lipids and/or food to enhance the bioavailability of poorly watersoluble drugs is well known. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms, including (Khoo, 1998).

a) Alterations (reduction) in gastric transit, thereby slowing delivery to the absorption site and increasing the time available for dissolution (Kommuru, 2001).

b) Increases in effective luminal drug solubility. The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipids (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilization capacity of the GI tract. However, intercalation of ad-

Table 3: Some examples of SEDDS designed for oral delivery of lipophilic drugs

Type of delivery system	Oil	Surfactant(s)	%w/w	Solvent(s)	Drug compound	Drug Content %
SEDDS	A mixture of mono-and diglycerides of oleic acid	Solid, polyglycolyzed mono-di and triglycerides, Tween 80	80 or 20		Ontazolast	7.5
SEDDS (Sandimmune)	Olive oil	Polyglycolyzed glycerides	30	ethanol	csA	10
SEDDS	Medium chain saturated fatty acids, peanut oil	Medium chain mono-and diglycerides, Tween 80,PEG25 glyceryl trioleate, polyglycolyzed glycerides	5-60	--	A napthalene derivative	5
SEDDS	Medium chain saturated fatty acids	Peg25 glyceryl trioleate	25		- 5-(5-(2,6-dichloro-4-(dihydro-2-oxazolyl)phenoxy)pentyl)-30methylisoxazole	35
SEDDS (positively charged)	Ethyl oleate	Tween 80	25	Ethanol	CsA	10
SEDDS (positively charged)	Ethyl oleate	Tween 80	25	Ethanol	Progesterone	2.5
SEDDS	Myvacet 9-45 or captex 200	Labrasol or Labrafac CM10	5-30 0-25	--	CoQ10	5.66
SEDDS (Norvir)	Oleic acid	Polyoxyl 35 castor oil	NA	Ethanol	Ritonavir	8
SEDDS (Fortovase)	dl-alpha tocopherol	Medium chain mono-and diglycerides	NA	-	Saquinavir	16

ministered (exogenous) lipids into these BS structures either directly (if sufficiently polar), or secondary to digestion, leads to swelling of the micellar structures and a further increase in solubilization capacity (Kommuru, 2001).

c) Stimulation of intestinal lymphatic transport. For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly via a reduction in first-pass metabolism. A hydrophilic drug is less likely to be absorbed through the lymphatic (chylomicron) and instead may diffuse directly in to the portal supply. Hence in this case, increased dissolution from the large surface area afforded by emulsion may be a contributing factor to enhanced absorption of drugs (Porter, 2001).

d) Changes in the biochemical barrier function of the GI tract. It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p glycoprotein efflux pump, and thus reduce the extent of enterocytebased metabolism (Porter, 2001).

e) Changes in the physical barrier function of the GI tract. Various combinations of lipids, lipid digestion products and surfactants have been shown to have permeability enhancing properties. For the most part, however, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water-soluble, and in particular, lipophilic drugs.

ADVANTAGES OF SMEDDS

Improvement in oral bioavailability

Dissolution rate dependant absorption is a major factor that limits the bioavailability of numerous poorly water

soluble drugs. The ability of SMEDDS to present the drug to GIT in solubilised and micro emulsified form (globule size between 1- 100 nm) and subsequent increase in specific surface area enable more efficient drug transport through the intestinal aqueous boundary layer and through the absorptive brush border membrane leading to improved bioavailability.

Example: In case of halofantrine approximately 6-8 fold increase in bioavailability of drug was reported in comparison to tablet formulation, increase the 3 fold bioavailability from SEDDS which is composed of the Tween 80 and palm oil (Julianto, 2000).

Ease of manufacture and scale-up

Ease of manufacture and scale- up is one of the most important advantages that make SMEDDS unique when compared to other drug delivery systems like solid dispersions, liposomes, nanoparticles, etc., dealing with improvement of bio-availability. SMEDDS require very simple and economical manufacturing facilities like simple mixer with agitator and volumetric liquid filling equipment for large-scale manufacturing. This explains the interest of industry in the SMEDDS.

Reduction in inter-subject and intra-subject variability and food effects

There are several drugs which show large inter-subject and intra-subject variation in absorption leading to decreased performance of drug and patient non-compliance. Food is a major factor affecting the therapeutic performance of the drug in the body. SMEDDS are a boon for such drugs. Several research papers specifying that, the performance of SMEDDS is independent of food and, SMEDDS offer reproducibility of plasma profile are available.

Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT

One unique property that makes SMEDDS superior as compared to the other drug delivery systems is their ability to deliver macromolecules like peptides, hormones, enzyme substrates and inhibitors and their ability to offer protection from enzymatic hydrolysis. The intestinal hydrolysis of prodrug by cholinesterase can be protected if Polysorbate 20 is emulsifier in micro emulsion formulation. These systems are formed spontaneously without aid of energy or heating thus suitable for thermo labile drugs such as peptides.

No influence of lipid digestion process

Unlike the other lipid-based drug delivery systems, the performance of SMEDDS is not influenced by the lipolysis, emulsification by the bile salts, action of pancreatic lipases and mixed micelle formation. SMEDDS are not necessarily digested before the drug is absorbed as they present the drug in micro-emulsified form which can easily penetrate the mucin and water unstirred layer.

Increased drug loading capacity

SMEDDS also provide the advantage of increased drug loading capacity when compared with conventional lipid solution 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 amphilic surfactants, co surfactants and co-solvents. When polymer is incorporated in composition of SMEDDS it gives prolonged release of medicament.

ADVANTAGES OF SMEDDS OVER EMULSION

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

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

c. SMEDDS offer numerous delivery options like filled hard gelatin capsules or soft gelatin capsules or can be formulated in to tablets whereas emulsions can only be given as an oral solutions.

DISADVANTAGES OF SMEDDS

i. One of the obstacles for the development of SMEDDS and other lipid-based formulations is the lack of good predicative *in vitro* models for assessment of the formulations.

ii. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.

iii. This *in vitro* model needs further development and validation before its strength can be evaluated.

iv. 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.

v. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which irritate GIT. Moreover, volatile co solvents in the conventional self-microemulsifying formula-

tions are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.

and in the SEDDS liquid formulation resulted in similar AUC, C max and T max values (Bo, 2008).

Table 4: Examples of marketed SMEDDS formulations

Drug Name	Compound	Dosage form	Company	Indication
Neoral®	Cyclosporine A/I	Soft gelatin capsule	Novartis	Immune suppressant
Norvir®	Ritonavir	Soft gelatin capsule	Abbott Laboratories	HIV antiviral
Fortovase®	Saquinavir	Soft gelatin capsule	Hoffmann-La Roche inc.	HIV antiviral
Agenerase®	Amprenavir	Soft gelatin capsule	Glaxo Smithkline	HIV antiviral
Convulex®	Valproic acid	Soft gelatin capsule	Pharmacia	Antiepileptic
Lipirex®	Fenofibrate	Hard gelatin Capsule	Genus	Antihyperlipoproteinemic
Sandimmune®	Cyclosporine A/II	Soft gelatin capsule	Novartis	Immuno Suppressant
Targretin®	Bexarotene	Soft gelatin capsule	Ligand	Antineoplastic
Rocaltrol®	Calcitriol	Soft gelatin capsule	Roche	Calcium regulator
Gengraf®	Cyclosporine A/III	Hard gelatin Capsule	Abbott Laboratories	Immuno suppressant

vi. The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.

vii. Formulations containing several components become more challenging to validate.

APPLICATIONS

1. Super Saturable SMEDDS (SS-SMEDDS) (Rajesh, 2010)

The high surfactant level typically present in SMEDDS formulation can lead to GI side effects and a new class of supersaturable formulations including supersaturable SMEDDS. (S-SMEDDS) formulations have been designed and developed to reduce the surfactant side effects and achieve rapid absorption of poorly soluble drugs.

2. Solid SMEDDS (Rajesh, 2010)

SMEDDS are normally prepared as liquid dosage forms that can be administrated in soft gelatin capsules, which have some disadvantages especially in the manufacturing process. An alternative method is the incorporation of liquid self emulsifying ingredients into a powder in order to create a solid dosage form (tablets, capsules). A pellet formulation of progesterone in SMEDDS has been prepared by the process of extrusion / spheronization (Jannin, 2008) to provide a good in vitro drug release (100% within 30 min, T50% at 13 min). The same dose of progesterone (16 mg) in pellets

3. Solubilization in SMEDDS

Owing to their frequently high content oil, as well as of surfactant, SMEDDS are usually efficient solubilizers of substances of a wide range of lipophilicity. Thus, the solubilizing capacity of a w/o micro emulsion for water soluble drugs is typically higher than that of an o/w micro emulsion, while the reverse is true for oil soluble drugs. Furthermore, the solubilization depends on the SMEDDS composition.

4. Sustain release from SMEDDS (Porter, 2001)

Due to the wide range of structures occurring in them, SMEDDS display a rich behavior regarding the release of solubilized material. Thus in case of O/W micro emulsion, hydrophobic drugs solubilized mainly in the oil droplets, experience hindered diffusion and are therefore released rather slowly (depending on the oil/water partitioning of the substance). Water soluble drugs, on the other hand, diffuse essentially without obstruction (depending on the volume fraction of the dispersed phase) and are release fast. For balanced micro emulsions, relatively fast diffusion and release occur for both water soluble and oil soluble drugs due to the bicontinuous nature of micro emulsion "structure". Apart from the micro emulsion structure, the micro emulsion composition is important for the drug release rate (Gursoy, 2004).

SOME DRUG DELIVERY SYSTEMS USING SMEDDS

1. Oral Delivery

It takes into account contributions of three major factors, dissolution, solubility, and intestinal permeability, which affect oral drug absorption. Microemulsions have the potential to enhance the solubilization of the poorly soluble drugs and overcome the dissolution related bioavailability problems (Stegemanna, 2007). This is particularly important for the BCS class II or class IV drugs. The successful formulation of such drugs is highly dependent on the performance of the formulated product. Microemulsions act as super solvent of these drugs and can be optimized to ensure consistent bioavailability. In addition, they can be used for the delivery of hydrophilic drugs including macromolecules such as proteins and peptides. This is due to the existence of polar, nonpolar and interfacial domains which allow encapsulation of drugs with varying solubility. Moreover, these systems have been reported to protect the incorporated drugs against oxidation, enzymatic degradation and enhance the membrane permeability. Presently, Sandimmune Neoral® (Cyclosporine A), Fortovase® (Saquinavir), Norvir® (Ritonavir), etc. are the commercially available SMEDDS formulations.

2. Parenteral Delivery

The formulation of lipophilic and hydrophobic drugs into parenteral dosage forms has proven to be difficult. O/W microemulsions are beneficial in the parenteral delivery of sparingly soluble drugs where the administration of suspension is not desirable. They provide a means of obtaining relatively high concentration of these drugs which usually requires frequent administration. Other advantages are that they exhibit a higher physical stability in plasma than liposomes or other vesicles and the internal oil phase is more resistant against drug leaching. Several sparingly soluble drugs have been formulated into o/w microemulsion for parenteral delivery. Microemulsions can also be used as intravenous delivery systems for the fat soluble vitamins and lipids in parenteral nutrition.

3. Topical Delivery

Microemulsion systems are now being investigated zealously for topical delivery which is evident from the numerous publications coming up every year. They have been reported to enhance the transdermal permeation of drugs significantly compared to conventional formulations such as solutions, gels or creams. They are able to incorporate both hydrophilic (5-fluorouracil, apomorphine hydrochloride, diphenhydramine hydrochloride, tetracaine hydrochloride, methotrexate) and lipophilic drugs (estradiol, finasteride, ketoprofen, meloxicam, felodipine, triptolide) and enhance their permeation. Since the microemulsion is a multicomponent system and its formation requires high surfactant concentration, the skin irritation aspect must be considered especially when they are intended to be applied for a longer period.

4. Opthalmic Delivery

In conventional ophthalmic dosage forms, water soluble drugs are delivered in aqueous solution while water insoluble drugs are formulated as suspensions or ointments. Low corneal bioavailability and lack of efficiency in the posterior segment of ocular tissue are some of the serious drawbacks of these systems. Recent research efforts have therefore focused on the development of new and more effective delivery systems. Microemulsions have emerged as a promising dosage form for ocular use.

5. Nasal Delivery

Microemulsions are now being studied as a delivery system to enhance uptake across nasal mucosa. Addition of a mucoadhesive polymer helps in prolonging the residence time on the mucosa. Nasal route for administration of diazepam might be a useful approach for the rapid onset of action during the emergency treatment of status epilepticus.

6. Periodontal Delivery

Periodontal disease is a collective term for a number of progressive oral pathological afflictions like inflammation and degeneration of the gums, periodontal ligaments, cementum and its supporting bone. It is a major cause of tooth loss. The invention of Brodin et al. included a novel pharmaceutical composition comprising local anaesthetic in oil form, surfactant, water and optionally a taste masking agent. The composition was in the form of an emulsion or microemulsion and had thermoreversible gelling properties ie it was less viscous at room temperature than after introduction onto a mucous membrane of a patient. The composition could be used as a local anaesthetic for pain relief within the oral cavity in conjunction with periodontal scaling and root planning and overcame the problem with the existing topical products (jelly, ointment or spray) such as lack of efficacy due to inadequate depth of penetration, too short duration and difficulties in administration due to spread, taste etc.

7. Drug Targeting

Drug targeting to diseased cells can be achieved by exploiting the presence of various receptors, antigens/proteins on the cell membrane which may be uniquely expressed or over expressed in these cells as compared to the normal cells. Specific antibodies to the surface proteins and ligands for the receptors can be used to target specific cells. Submicron size range of these systems confers excellent opportunities to overcome the physiological barriers and enables efficient cellular uptake followed by intracellular internalization (Talegaonkar, 2008).

FUTURE TREND

In relation to formulation development of poorly soluble drugs in the future there are now techniques being used to convert liquid/semi-solid SEDDS and SMEDDS formulations into powders and granules which can then be further processed into conventional 'powder-fill' Capsules or even compressed into tablets. Hot melt granulation is a technique for producing granules or pellets and by using a waxy solubilizing agent as a binding agent, up to 25% solubilizing agent can be incorporated in a formulation. There is also increasing interest in using inert adsorbents products for converting liquids into powders which can then be processed into powder fill capsules or tablets. However, to obtain solids with suitable processing properties the ratio of SMEDDS to solidifying excipients must be very high which seems to be practically non-feasible for drugs having limited solubility in oil phase. In this regard, it was hypothesized that the amount of solidifying excipients required for transformation of SMEDDS in solid dosage forms will be significantly reduced if SMEDDS is gelled. Colloidal silicon dioxide (Aerosol 200) is selected as a gelling agent for the oil based systems which may serve the dual purpose of reducing the amount of solidifying excipients required and aiding in slowing drug release.

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