Review Article **CODEX: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

SELF MICROEMULSIFYING DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT

Microemulsions are excellent candidates as potential drug delivery systems because of their improved drug solubilization, long shelf life, and ease of preparation and administration. Self micro emulsifying drug delivery systems are isotropic mixtures of oil, surfactant, co-surfactant and drug with a unique ability to form fine oil in water microemulsion upon mild agitation following dilution with aqueous phase. The hypothesis behind dissolution rate enhancement with SMEDDS is the spontaneous formation of the emulsion in the gastrointestinal tract which presents the drug in solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption. SMEDDS is evaluated by various methods like visual assessment, droplet polarity and droplet size, size of emulsion droplet, dissolution test, charge of oil droplets, viscosity determination, *in vitro* diffusion study. With future development of this technology, SMEDDS will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

KEYWORDS

Self-micro emulsifying drug delivery system, Oral bioavailability, Surfactant, Oil and Co-surfactant.

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INTRODUCTION

The oral route has been the major route of drug delivery for chronic treatment of many diseases. Oral drug delivery system is the most cost-effective and leads the world wide drug delivery market. However, in the present scenario, oral drug delivery is continuously looking into newer avenues as 40% of new drug candidates have poor water solubility and/or absorption, high intra-and inter-subject

variability, rapid metabolism, high fluctuation in the drug plasma level, variability due to food effect, and lack of dose proportionality which are playing major role in disappointing in vivo results leading to failure of conventional drug delivery system. To overcome these problems, new strategies were reported to increase solubility and bioavailability including complexation with cyclodextrin, solid dispersion (suspension), co-precipitation, micronsation, salt formation, emulsion, use of micelles, and co grinding. Recently much attention has been focused on lipid solutions, emulsions and emulsion pre-concentrates, which can be prepared as physically stable formulations suitable for encapsulation of such poorly soluble drugs. Emulsion systems are associated with their own set of complexities, including stability and manufacturing problems associated with their commercial production. Self-emulsification systems are one formulation technique that can be a fitting answer to such problems[1].

Self microemulsifying drug delivery system (SMEDDS) (Figure No.1) 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[1]. SMEDDS spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. 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 (Figure No.2) 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. 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[2].

ADVANTAGES OF SMEDDS[1-5]

Potential advantages of these systems (SMEDDS) include

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

DISADVANTAGES OF SMEDDS[1-5]

1. One of the obstacles for the development of SMEDDS and other lipid-based formulations is the lack of good predicative *invitro* models for assessment of the formulations.
2. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
3. This *invitro* model needs further development and validation before its strength can be evaluated.
4. Further development will be based on *invitro* - *invivo* correlations and therefore different prototype lipid based formulations needs to be

developed and tested *invivo* in a suitable animal model.

5. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which irritate GIT.
6. Moreover, volatile co solvents in the conventional self-microemulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.
7. The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.
8. Formulations containing several components become more challenging to validate.

EXCIPIENTS USED IN SMEDDS[1-8]

Pharmaceutical acceptability of excipients and the toxicity issues of the components used makes the selection of excipients really critical. There is a great restriction as which excipients to be used. Early studies revealed that the self-micro emulsification 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-micro emulsification occurs. These important discoveries were further supported by the fact that only very specific combinations of pharmaceutical excipients led to efficient self- microemulsifying systems.

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. Furthermore, edible oils which could represent the logical and preferred lipid excipients choice for the development of SMEDDS 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. They offer formulative and physiological advantages and their degradation products resemble the natural end products of intestinal digestion. Novel semisynthetic 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 than LCT associated with a more rapid hydrolysis of MCT. In general, when using LCT, a higher concentration of cremophor RH40 was required to form microemulsions compared with MCT.

E.g: Cotton seed oil, Soybean oil, Corn oil, Sunflower oil, Castor oil etc.

SURFACTANTS

Several compounds exhibiting surfactant properties may be employed for the design of self-emulsifying systems, but the choice is limited as very few surfactants are orally acceptable. The most widely recommended ones being the non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB). The commonly used emulsifiers are various solid or liquid ethoxylated polyglycolyzed glycerides and polyoxyethylene oleate. Safety is a major determining factor in choosing a surfactant. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactants. However, these surfactants have a limited self-emulsification capacity. Non-ionic surfactants are less toxic than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SMEDDS.

There is a relationship between the droplet size and the concentration of the surfactant being used. In some cases, increasing the surfactant concentration could lead to droplets with smaller mean droplet size, this could be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface. On the other hand, in some cases the mean droplet size may increase with increasing surfactant concentrations. This phenomenon could be attributed to the interfacial disruption elicited by enhanced water penetration into the oil droplets mediated by the increased surfactant concentration and leading to ejection of oil droplets into the aqueous phase. The surfactants used in these formulations are known to improve the bioavailability by various mechanisms including: improved drug dissolution, increased intestinal epithelial permeability, increased tight junction permeability and decreased/inhibited p-glycoprotein drug efflux. However, the large quantity of surfactant may cause moderate reversible changes in intestinal wall permeability or may irritate the GI tract. Formulation effect and surfactant concentration on gastrointestinal mucosa should ideally be investigated in each case.

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,

1. Anionic surfactants
2. Cationic surfactants
3. Ampholytic surfactants
4. Nonionic surfactants

Anionic Surfactants: where the hydrophilic group carries a negative charge such as carboxyl ($RCOO^-$), sulphonate (RSO_3^-) or sulphate ($ROSO_3^-$). Examples: Potassium laurate, sodium lauryl sulphate.

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

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

Nonionic surfactants: where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene (OCH_2CH_2O). Examples: Sorbitan esters (Spans), polysorbates (Tweens).

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. 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. 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, although 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. On the other hand, the lipophilic drug dissolution ability of the alcohol free formulation may be limited. Hence, proper choice has to be made during selection of components.

CO-SURFACTANT[3]

In SMEDDS, generally co-surfactant of HLB value 10-14 is used. Hydrophilic co-surfactants are preferably alcohols of intermediate chain length such

as hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formulation of micro emulsion.
E.g. span, capyrol 90, capmul.

CONSISTENCY BUILDER[3]

Additional material can be added to alter the consistency of the emulsions; such materials include tragacanth, cetyl alcohol, stearic acids and /or beeswax.

POLYMERS[3]

Inert polymer matrix representing from 5 to 40% of composition relative to the weight, which is not ionizable at physiological pH and being capable of forming matrix are used. Examples are hydroxy propyl methyl cellulose, ethyl cellulose, etc.

MECHANISM OF SMEDDS[3]

Different approaches have been reported in the literature. No single theory explains all aspects of micro emulsion formation. Schulman et al. considered that the spontaneous formation of micro emulsion droplets was due to the formation of a complex film at the oil-water interface by the surfactant and co-surfactant. Thermodynamic theory of formation of micro emulsion explains that emulsification occurs, when the entropy change that favour dispersion is greater than the energy required to increase the surface area of the dispersion and the free energy (ΔG) is negative. The free energy in the micro emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by the equation:

$\Delta G = \Sigma N_л r^2 \sigma$

Where,

ΔG is the free energy associated with the process (ignoring the free energy of the mixing).

N is the number of droplets of radius r and

σ are presents the interfacial energy.

With time, the two phases of the emulsion tend to separate to reduce the interfacial area, and subsequently, the free energy of the system decreases. Therefore, the emulsion resulting from aqueous dilution are stabilized by conventional emulsifying agents, which forms a mono layer around the emulsion droplets, and hence, reduce the interfacial energy, as well as providing a barrier to prevent coalescence.

RECENT DOSAGE FORM DEVELOPMENT IN SEDDS[1-5]

1. Dry emulsions
2. Self- emulsifying capsules
3. Self- emulsifying sustained/controlled-release tablets
4. Self- emulsifying sustained/controlled-release pellets
5. Self-emulsifying solid dispersions
6. Self-emulsifying beads
7. Self-emulsifying Sustained release microspheres
8. Self-emulsifying nanoparticles
9. Self-emulsifying suppositories
10. Self-emulsifying implants.

DRUG PROPERTIES SUITABLE FOR SMEDDS[6]

1. Dose should not be so high
2. Drug should be oil soluble
3. High melting point drug is poorly suited to seeds
4. Log P Value should be high.

PREPARATION OF SMEDDS[9-15]

Preparation involves determination of solubility in various oils, surfactants, co-surfactants/co-solvents and the excipients showing good solubility are then chosen for preparing the formulation.

1. Solubility study

The solubility of drug in various oils, surfactants, and co-surfactants needs to be determined by adding excess amount of drug into each selected vehicle, and the mixture have to be continuously stirred for 72 h at 300C. After equilibrium is achieved, the mixture is centrifuged at 2500×g for 20 min, and the supernatant is filtered through a membrane filter. The concentration of drug can be determined by high-performance liquid chromatography (HPLC)/ spectrophotometry. After performing the solubility study surfactant, cosurfactant and oil showing maximum solubility of drug are selected for preparing the formulation.

2. Titration method

Titration method is most commonly employed approach as the titration techniques are rapid reasonably accurate and precise and economical as

large number of observations can be made using limited excipients and drugs. In titration method, a series of pseudo binary component systems are formed which are titrated using the third component, evaluating the mixture after each addition. Most commonly the third component is the aqueous phase however,

Surfactants mixture or oil phase can also be employed. Titrating binary phase with the third component will yield an optically clear system (indicating formation of microemulsion) from which usually the ratio and concentrations of individual components are derived by back calculation method. By this method the amount of water that can be incorporated in the microemulsion can be determined by finding turbidity/clarity ratio. Heat and sonication are often employed tools to speed up the process. The method is also useful in accurately delineate the phase boundaries (i.e. formation of bilayer emulsion, O/W emulsion, W/O emulsion). The major disadvantage with titration technique is that it can provide true picture of the phase boundaries but the systems existing within the periphery can't be taken in isolated manner for further studies such as characterization.

3. Pseudo ternary phase diagram method

Pseudo-ternary phase diagram is a very useful and important tool to study the phase behavior. Pseudo ternary phase diagram can be represented in a triangular format (triangle) which has three coordinates. Each coordinate represents one component of microemulsion system. A typical pseudo-ternary phase diagram illustrating the different phases on respective coordinates is shown in Figure No.1. As seen from the Figure No.1, each coordinate is representing one phase present in the ME system viz. (1) Oil phase (O component), (2) Surfactant: Co-surfactant phase (S: CoS component) and (3) Aqueous phase (AQ component). Each coordinate also represents 0 to 100% concentration of each of the phases in the increment of 10%. In case where four or more components are investigated to formulate ME system, pseudo-ternary phase diagram is used wherein one of the corners typically represents binary mixture of two components such as surfactant/ co-surfactant, water/drug, or oil/drug. Phase diagram is an imperative tool to comprehensively study the ME system and its phase behavior although construction phase diagram is highly time consuming exercise. In addition to that, phase diagram represents 36 ME points hence, for each ratio or a ME system, a number of experiments including excipients and drug are required to expansively study the phase behavior. Various software's such as chemix® (Arne Standnes), sigma plot ® (Systat Software Inc), Design expert® (state-ease), chemdraw® (Cambridge Soft Corporation) can be used to plot the phase diagram.

SOLID SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM (S-SMEDDS) [1]

SMEDDS can exist in either liquid or solid states. SMEDDS are usually, 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 SE 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/dry emulsions/solid dispersions are usually further processed into other solid SE dosage forms, or, alternatively, filled into capsules (i.e. SE capsules). SE capsules also include those capsules into which liquid/semisolid SEDDS are directly filled without any solidifying excipient.

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 SE pellets contain not only the assessment of self-

emulsification, but also friability, surface roughness, and so on.

In the 1990s, S-SEDDS were usually in the form of SE capsules, SE solid dispersions and dry emulsions, but other solid SE dosage forms have emerged in recent years, such as SE pellets/tablets, SE microspheres /nanoparticles and SE suppositories /implants.

SOLIDIFICATION TECHNIQUES FOR TRANSFORMING LIQUID/ SEMISOLID SMEDDS TO S-SMEDDS [1-10]

Capsule filling with liquid and semisolid self-emulsifying formulations

Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid self-emulsifying formulations for the oral route. For semisolid formulations, it is a four-step process

1. Heating of the semisolid excipient to at least 20^{o}C above its melting point
2. Incorporation of the active substance with continuous stirring
3. Capsule filling with the molten mixture and Cool at room temperature.

For liquid formulations it involves a two-step process

1. Filling of the formulation into the capsules
2. Sealing of the body and cap of the capsule, either by banding or by micro spray sealing.

1. Spray cooling

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

2. Spray drying

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

3. Adsorption to solid carriers

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

4. Melt granulation

Melt granulation is a process in which powder agglomeration is obtained through the addition of a

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

5. Melt extrusion

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

6. Extrusion spheronization

The extrusion spheronization process is commonly used in the pharmaceutical industry to make uniformly sized pellets. This process requires the following steps: Mix dry active ingredients and excipients to form a homogeneous powder; wet massing with binder; extrusion into a spaghetti like extrudate; spheronization from the extrudate to spheroids uniform size; drying; sifting to achieve the desired size distribution. Applying this technique, self-emulsifying pellets of diazepam and progesterone has been prepared to provide a good in vitro drug release (100% within 30 min, T50% at 13 min) and bi-layered cohesive self-emulsifying pellets have also been prepared.

As shown in Table No.1: following considerations should be taken in selection of formulation techniques for bioavailability enhancement with lipid based excipients.

EVALUATION OF SMEDDS[11-20]

The SMEDDS can be evaluated in the following manner.

Dispersibility test

The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus 2. One milliliter of each formulation was added to 500 ml of water at 37 ± 0.5˚C. A standard stainless steel dissolution paddle rotating at 50 r/min provided gentle agitation. The in vitro performance of the formulations is visually assessed using the following grading system:

Grade A: Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

Grade C: Fine milky emulsion that is formed within 2 min.

Grade D: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface. Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT, while formulation falling in Grade C could be recommend for SMEDDS formulation.

Turbidimetric evaluation

Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of self-emulsifying system is added to fixed quantity of suitable medium (0.1 M hydrochloric acid) under continuous stirring (50r/min) on magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter. However, since the time required for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity.

Viscosity determination

The SMEDDS system is generally administered in soft gelatin or hard gelatin capsules. So, it should be easily pourable into capsules and such system should not be too thick. The viscosity of ME was measured using a Brookfield Viscometer (Brookfield Engineering LABS, Stoughton, MA) with spindle LV-III at 100 g using interval of 30 s. All aspects of testing were controlled using optional Rheocalc Software. The viscosity determinations confirm whether the system is W/O or O/W. If system has low viscosity then it is O/W type of the system and if high viscosity then it is W/O type of the system.

Droplet size analysis (globule size measurement)

The average droplet size and polydispersity index of ME was measured by photon correlation spectroscopy with inbuilt Zetasizer (Nano ZS, Malvern Instruments, UK) at 630 nm. Helium–neon gas laser having an intensity of 4 mW is the light source. The droplet size is calculated using Stokes–Einstein relationship by Zetasizer software. The ME formulations had the average particle size in the range of 28 to 96 nm. Particle size of plain ME and drug loaded ME should be determined and there should be no significant difference observed in average particle size after loading the drug. The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the globule) using a Zetasizer able to measure sizes between 10 and 5000 nm. Light scattering is monitored at 25˚C at a 90˚ angle, after external standardization with spherical polystyrene beads. The nanometric size range of the globule retained even after 100 times dilution with water should be maintained for the system's compatibility with excess water.

Polydispersitivity index (PI)

PI is a measure of particle homogeneity and it varies from 0.0 to 1.0. The closer to zero the PI value the more homogenous are the particles. The PI showed that ME formulation had narrow size distribution.

Refractive index and percent transmittance

Refractive index and percent transmittance prove the transparency of formulation. The refractive index of the system was measured by an Abbe refractometer (Bausch and Lomb Optical Company, Rochester, New York) by placing one drop of solution on the slide. The percent transmittance of the system was measured using a colorimeter (Digital Colorimeter, D-801, Photocon, Delhi) at 570–590 nm and it is compared with water (1.333). The percent transmittance of the system is measured at 630 nm using UV-spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water, formulation has percent transmittance > 99 percent and it has transparent nature.

Electric conductivity study

The electric conductivity of ME was measured with a conductivity meter (Equip-Tronics, EQ-664, Mumbai, India) equipped with in-built magnetic stirrer. This was done by using conductivity cell (with a cell constant of 1.0) consisting of two platinum plates separated by desired distance and having liquid between the platinum plate acting as a conductor. The SMEDDS contains ionic or non-ionic surfactant, oil, and water. This test is used to measure the electoconductive nature of system. The higher values indicate the O/W type of emulsion and lower value indicates W/O type of emulsion.

Dissolution study

The SMEDDS and the marketed formulation of the drug are added to dissolution vessels of United States Pharmacopeia (USP)-24 type 2 dissolution test apparatus. The dissolution medium used is 0.1 M hydrochloric acid (900 ml) maintained at 37.0˚C ± 0.5˚C and stirred at 100 r/min. A blank (placebo) is tested for dissolution, simultaneously, under identical conditions to check for interference, if any. Aliquots were collected periodically and replaced with fresh dissolution medium. Aliquots, after filtration through whatman filter paper are analyzed by spectrophotometer for drug content.

Thermodynamic stability studies

The physical stability of a lipid-based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipients matrix. Poor formulation physical stability can lead to phase separation of the excipient, affecting the formulation performance and visual appearance. In addition, incompatibilities between the formulation and gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug.

Heating cooling cycle

Six cycles between refrigerator temperature 4˚C and 45˚C with storage at each temperature of not less than 48 h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test. In which passed formulations are centrifuged (Remi Laboratories, Mumbai, India) keeping the temperature between 21˚C and 25˚C

with storage at each temperature for not less than 48 h is done at 3500 r/min for 30 min. The formulations that pass test are taken for the freeze thaw stress test. The formulations passed this test showed good stability with no phase separation, creaming, or cracking. Average particle size and conductivity of prepared microemulsion batches were measured at different time intervals and no significant difference was observed in these parameters up to 3 months.

***In vitro* diffusion study**

The dialysis bag method can be used along with USP paddle type of dissolution apparatus. It is filled with 500 ml of simulated gastric fluid used as dissolution medium at a temperature of 37˚C and a paddle speed of 100 r/min. Prior to the test, dialysis bag is kept in 3ml blank medium for 2 h. Subsequently, SMEDDS formulations were put directly into the release medium, one dialysis bag is then taken out at 30, 60, 120, 180 and 240 min and the drug concentration is determined. After 2 h, the pH of the medium is adjusted to 6.8 by the addition of trisodium phosphate. It can also performed by using rat intestine (intestinal permeability study) using pH 6.8 buffer solution as dissolution medium. Aliquots should be collected periodically and replaced with fresh dissolution medium. Aliquots, after filtration through whatman filter paper and analyzed by spectrophotometer for drug content.

Drug content

Drug from pre-weighed SMEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract can be analyzed by suitable validated analytical method.

***In vivo* study**

The prepared smedds can be evaluated by using rats, rabbits or dogs as animal model. The pure drug, suspension of drug and prepared formulations are given to the group of animals and the drug content can be analyzed by using HPLC plasma method. The parameters such as *C*max and AUC are determined for each of them and compared with the marketed formulation of the drug.

Thermodynamic Stability Studies

Freeze–thaw cycle

Freeze thawing was employed to evaluate the stability of formulations. The formulations were subjected to 3 to 4 freeze-thaw cycles, which included freezing at -4°C for 48 hours followed by thawing at 40°C for 48 hours. Centrifugation was performed at 3000 rpm for 5 minutes. The formulations were then observed for phase separation. Only formulations that were stable to phase separation were selected for further studies.

Stability Studies

The microemulsion formulations were put into empty hard gelatin capsules (size 0) and subjected to stability studies at 25°C/60% relative humidity (RH), 30°C/65% RH, and 40°C/75% RH. Samples were charged in stability chambers with humidity and temperature control. They were withdrawn at specified intervals for analysis over a period of 3 months for intermediate and accelerated conditions and 6 months for long-term conditions. Drug content of the capsules was analyzed using a previously developed and validated stability-indicating HPLC method.

APPLICATIONS OF SMEDDS

There has been a revolution in the last two decades in the utilization of microemulsion systems in a variety of pharmaceutical, chemical, industrial processes etc.

Self-Microemulsion in pharmaceutical

Liquid crystalline, miceller and emulsion forming systems are widely used in pharmaceutical preparations. The easy formation, remarkable environment independent stability, excellent solubilization capacity, etc. favour microemulsions to be a better proposition over other compartmentalized systems. The dispersed phase, lipophilic or hydrophilic (o/w or w/o type) can act as a potential reservoir of lipophilic or hydrophilic drugs that can be partitioned between the dispersed and the continuous phases. Coming in contact with a semipermeable membrane, such as skin or mucous membrane, the drug can be transported through the barrier. Both lipophilic and hydrophilic drugs can be administered together in the same preparation.

Low viscous formulations using microemulsions with suitable protein compatible surfactants can be used as injection solutions, for they are miscible with blood in any ratio. In contrast to emulsions, microemulsions cause minimum immuno reactions or fat embolism. Proteins are not denatured in microemulsions although they are unstable at high or low temperatures. The total dose of the drug can be reduced when applied through the microemulsion route and thus side effects can be minimized. Toxicity, bio-incompatibility of surfactants and cosurfactants, requirement of high concentrations for formulations and other relevant factors such as maintenance of thermodynamic stability in the temperature range between 0^0 C and 40^0 C, salinity, constant pressure during storage, low solubilizing capacity for high molecular weight drug (and oil), etc. limit the uses of microemulsions in the pharmaceutical and medicinal fields.

An application of o/w microemulsion in the pharmaceutical industry is the use of strongly hydrophobic fluorocarbons (as oils) to produce short-time blood plasma substitutes to maintain the supply of oxygen in the living systems. The components to be used must have low allergic potential, good physiological compatibility and high biocompatibility. The biocompatibility requirements of the amphiphiles are fulfilled by lecithins, non-ionic surfactants (Brijs, Arlacel 186, Spans and Tweens).

Garcia-Celma has reviewed microemulsions as drug delivery systems for different types of drugs, viz. antineoplastics/ antitumour agents (doxorubicin, idarubicin, tetrabenzamidine derivative), peptide drugs (cyclosporine, insulin, vassopressin), sympatholytics (bupranolol, timolol, levobunolol, propanolol), local anesthetics (lidocaine, benzocaine, tetracaine, heptacaine), steroids (testosterone, testosterone propionate, testosterone enanthate, progesterone, medroxyprogestorane acetate), anxiolytics(benzodiazepines), antiinfective drugs (cloitrimazole, ciclopirox olamine, econazole nitrate, tetracycline hydrochloride), vitamins (menadione, ascorbic acid), anti-inflammatory drugs (butibufen, indomethacin), and dermological products (tyrocine, azelaic acid, octyl dimethyl PABA, 2- ethyl hexyl _p-methoxy cinnamate).

Enzyme doped silica nanoparticles (ceramic drug carrier) in the aqueous core of reverse micelles and microencapsulation of diospyrin, a plant-derived bisnapthoquinol of potential chemotherapeutic activity have been very recently reported.

Self-Microemulsions in cosmetics

It is believed that microemulsion formulation will result in a faster uptake into the skin. Costs, safety, appropriate selection of ingredients are key factors in the formulation of microemulsions. Skin care microemulsions contain, sodium alkyl sulfate, tetraethylene glycol monododecyl ether, lecithin, dodecyl oligoglucoside, alkyl dimethyl amine oxide, propanol,hexadecane, isopropyl myristate have been used as surfactants, cosurfactants and oils respectively. Hair care microemulsions contain an amino-functional polyorganosiloxane (a nonionic surfactant) and an acid and/or a metal salt. A cosmetic microemulsion (transparent and translucent) of silicone oils was produced by emulsion polymerization tehnique. Ultrafine emulsions prepared by condensation method have some advantages in cosmetic and medical products, as they have excellent stability and safety and their droplet size can be readily controlled. Ultrafine emulsions can be regarded as thermodynamically unstable microemulsions, as they are o/w emulsions with droplet size similar to microemulsion. Tokuoka *et al.* studied the solubilization of several systems consisting of water, surfactant and synthetic perfumes (viz. d-limonene, a-ionone, benzyl accetate, linalol, eugenol and *a*-hexylcinnamaldehyde), clarifying (a) the influence of fragrance structure on the phase regions in a water/nonionic surfactant systems, (b) the distribution coefficient between micelles and the bulk phase, and (c) the partition between dissolved and solubilized perfume components on their volatility. In this, the phase equilibria in water, lecithin, soybean oil and vanillin have been studied.

Self-Microemulsions in analytical applications

Microemulsions are widely used in the field of analytical techniques such as chromatography, laser-

excited photoionization spectroscopy, etc. In microemulsion electrokinetic chromatography (MEEKC), characterization of solute hydrophobicity was carried out, which provides a quick and reproducible method to obtain hydrophobic parameters for solvents. Microemulsions are able to enhance analytical spectroscopic techniques by functioning as solubilized media, spectral shift reagents, intensity amplification agents, etc. The utilization of microemulsion media in analytical spectroscopy and the analytical sensitivities of the three systems o/w, w/o and bicontinuous microemulsion have been assessed. A series of studies have been reported on the determination of aluminium, zinc, copper, cadmium, manganese ions using both microemulsion and mixed microemulsion systems. These studies are mostly published in the journals published by the Chinese Chemical Society.

Self-Microemulsions in biotechnology

Recently, interest on microemulsions is being focused for various applications in biotechnology, viz, enzymatic reactions, immobilization of proteins and bioseparation. Microemulsions are advantageous over other multiphase equilibrium systems because of simultaneous solubilization of polar and nonpolar reactants in the same solution, shifting of the equilibrium position of the reaction and the separation of products by physical means. However, bio-incompatibility of the amphiphiles used poses a serious limitation in the advancement of this field. The prospects of biotechnological applications have also been reviewed. Enzyme reactions (catalysis) in microemulsion media have widely been studied. The use of microemulsion for enzyme catalysis is not arbitrary for enzymes under *in vivo* condition function in the cell as well as at the interface of hydrophobic and hydrophilic domains of cell and tissue containing lipids and other natural amphiphiles.

Enzymatic reactions in microemulsions

The potential advantages of employing enzymes in media of low water content, i.e. w/o microemulsions are: (i) increased solubility of nonpolar reactants; (ii) possibility of shifting thermodynamic equilibria in favour of condensation; (iii) improvement of thermal stability of the enzymes, enabling reactions to be carried out at higher temperature. Catalysis by a large number of enzymes in microemulsion media has been studied for a variety of reactions, such as synthesis of esters, peptides and sugar acetals; transesterifications; various hydrolysis reactions; glycerolysis; oxidation and reduction and steroid transformation. The conformation and activity of an enzyme depend on ([water]/ [surfactant]); the enzyme is thus sensitive to amount of surrounding water. Gomez-Puyon has carried the work on behaviour of enzymes in microemulsions.

Immobilization of protein in microemulsion

In the field of protein immobilization, microemulsion medium has been found to be a good proposition. Immobilization of a variety of proteins on suitable solid surfaces using microemulsion media has been successfully carried out.

Microemulsions for bioseparations

The possibility of microemulsions to extract biopolymers (proteins and enzymes) from an aqueous phase has been explored. Microemulsions are gentle solvents for extraction of proteins without altering their enzymatic or functional properties although the process can readily be scaled by conventional liquid-liquid extraction techniques. The pH, ionic strength, type of salt, concentration of solvent and temperature influence the partition of a protein.

Microemulsion as chemical sensor materials

Microemulsions as novel crystalline colloidal arrays (CCA) are new findings which act as novel chemical sensors. A intelligent photoionic crystalline colloidal array self-assemblies have been developed, which can have use in medicine, environmental chemistry, process control and remote sensing. These are mesoscopically periodic fluid materials that diffract light satisfying the Bragg condition. The crystalline colloidal array self-assemble into either face centered or body centered cubic form. Just as atomic crystals diffract X-rays that fulfill the Bragg condition, CCAs diffract ultraviolet, visible and near-infrared light, depending on the lattice spacing. Colloidal particles of inorganic materials, such as

silica or organic polymers, such as poly (N- have been synthesized having periodicity of the order of ~200 nm. Asher *et al.* and Holtz *et al* have developed a novel sensing material from a polymerized crystalline colloidal array (PCCA) which is a mesoscopically periodic crystalline colloidal array of spherical polystyrene colloids within a thin, intelligent polymer hydrogel film. They have fabricated a sensor, utilizing crown ether as the recognization agent that can detect Pb2+ in the 0.1 DM- 20 mM (~20 ppb - ~ 400 ppm) concentration range. The sensors for glucose and galactose utilising glucose oxidase or fe-D-isopropylacrylamide).
galactosidase as the recognization entities have been developed. Besides sensing glucose, this sensor can estimate dissolved oxygen concentration in the presence of constant glucose concentration. Development of thermally tunable photonic crystal of poly (N-isopropylacrylamide) (PNIPAM), a novel CCA photoionic crystals with variable sphere sizes and variable array periodicity and sensors that change volume in response to nonionic molecular recognition processes such as antibody/antigen interactions have been attempted.

Table No.1: Considerations to be taken in selection of formulation techniques for bioavailability enhancement with lipid based excipients

S.No	Formulation techniques for solid and semi-solid formulations	Physical properties of the lipid excipients applied		Formulations advantages and limits	
		Liquid to solids	Semi-solids	Maximum lipid LIP Exposure*(%w/w)	Maximum Drug Loading(%w/w)
1	**Capsule filling**	**X**	**X**	99	50
2	**Spray cooling**	**X**		99	30
3	**Spray drying**	**X**	**X**	60	50
4	**Adsorption to solid carriers**	**X**		80	10
5	**Melt granulation**	**X**		50	80
6	**Melt extrusion**	**X**		50	60
7	Super critical fluid based methods	**X**		99	20
8	Solid lipid nanoparticles	**X**	**X**	99	50

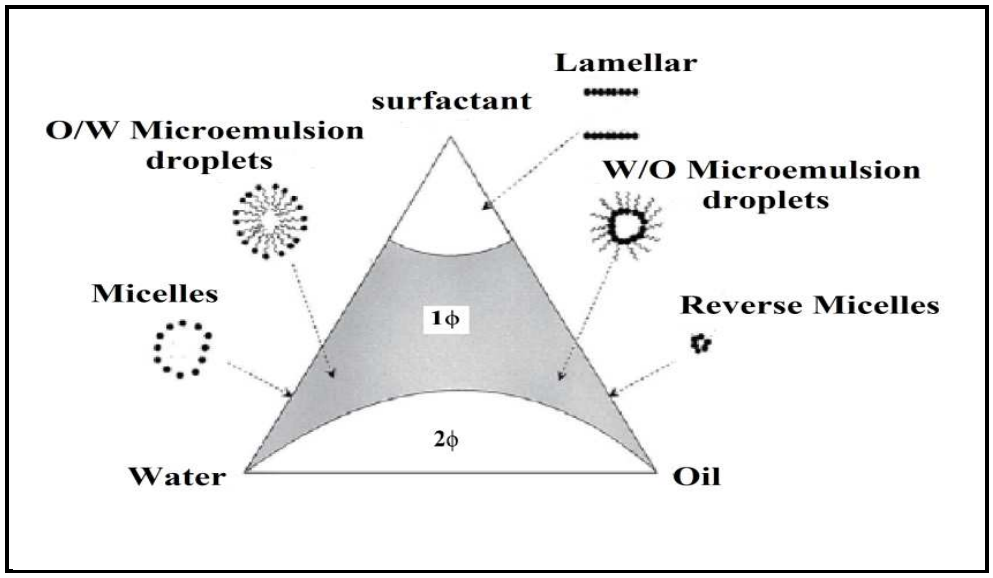

Figure No.1: Phase diagram showing various regions of microemulsion

CONCLUSION

The Microemulsions have been shown to be able to protect labile drug, control drug release, improve the drug solubility, improve the bioavailability, enhance the drug absorption and reduce patient variability. This review has captured much of the current activity surrounding the formation, physical properties, structure of Microemulsions and it has provided motivation for more research and applications. In future we predict that Microemulsions will become as good Novel dosage form in the field of Pharmaceuticals.

ACKNOWLEDGEMENT

The authors are sincerely thanks to A.M Reddy Memorial College of Pharmacy, Narasaraopet, Guntur, Andhra Pradesh, India for providing the facilities to complete this review work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

REFERENCES

1. Solans C, Garcia Celma M J. Surfactants for microemulsions, *Curr. Opin. Colloid Interf. Sci,* 2(5), 1997, 464-471.
2. Zana R, Microemulsions, *Heterogeneous Chem. Rev*, 1(2), 1994, 145-157.
3. Paul B K, Moulik S P. Microemulsions: an overview, *J. Disp. Sci. Technol*, 18(4), 1997, 301-367.
4. Samad A, Sultana Y and Aquil M. Liposomal drug delivery systems: an update review, *Curr. Drug Del*, 4(4), 2007, 297-305.
5. Uchegbu I F, Vyas S P. Non-ionic surfactant based vesicles (niosomes) in drug delivery, *Int. J. Pharm*, 172(1-3), 1998, 33-70.
6. Hamdan S, Lizana R, Laili C R. Aqueous and nonaqueous microemulsion systems with a palm oil-base emollient, *J. Am. Oil Chem. Soc*, 72(1), 1995, 151-155.
7. Garti N. Microemulsions as microreactors for food applications, *Curr. Opin. Colloid Interf. Sci*, 8(2), 2003, 197-211.
8. Yaghmur A, De Campo L, Sagalowicz L. Emulsified microemulsions and oil containing liquid crystalline phases, *Langmuir*, 21(2), 2005, 569-577.
9. Kunieda H, Umizu G, Yamaguchi Y. Mixing effect of polyoxyethylene-type nonionic surfactants on the liquid crystalline structures, *J. Colloid Interf. Sci*, 218(1), 1999, 88-96.

10. Lesser M E, Sagalovwicz L, Michel M, Watzke H. Self-assembly of polar food lipids, *Adv. colloid Interf. Sci,* 123(6), 2006, 125-136.
11. Gupta S, Moulik S P. Biocompatible microemulsions and their prospective uses in drug delivery, *J. Pharm. Sci,* 97(1), 2008, 22-43.
12. Hwang T L, Fang C L, Chen C H, Fang J Y. Permeation enhancer containing water-in-oil nanoemulsion as carriers for intravesical cisplantin delivery, *Pharm. Res*, 26(10), 2009, 2314-2323.
13. Gupta S, Sanyal S K, Datta S, Moulik S P. Preparation of prospective plant oil derived microemulsion vehicles for drug delivery, *Indian J. Biochem. Biophys*, 43(4), 2006, 254-257.
14. Gupta S, Moulik S P, Lala S, Basu M, Sanyal S K, Datta S. Designing and testing of an effective oil-in-water microemulsion drug delivery system for *in vivo* application, *Drug Del*, 12(5), 2005, 267-274.
15. Gupta S, Moulik S P, Hazra B, Ghosh R, Sanyal S K and Datta S. New pharmaceutical microemulsion system for encapsulation and delivery of a plant-derived bioactive quinonoid compound, diospyrin, *Drug Del*, 13(13), 2006, 193-199.
16. Lala S, Gupta S, Basu M K and Moulik S P. Critical evaluation of the therapeutic potential of basic acid entrapped in oil-in-water microemulsions and classical polylactide nanoparticles against Leishmaniasis, *J. Drug Target*, 4(12), 2006, 171-179.
17. Nazar M F, Khan A M and Shah S S. Microemulsion system with improved loading of piroxicam. A study of microstructure, *AAPS Pharm. Sci Technol*, 10(4), 2009, 1286-1294.
18. Mehta S K, Kaur G and Bhasin K K. Incorporation of antitubercular drug isoniazid in pharmaceutically accepted microemulsion: effect on microstructure and physical parameters, *Pharm. Res*, 25(1), 2008, 227-235.
19. Guo R, Qian S, Zhu J and Qian J. The release of cephanone in CTAB/n C5H11Oh/H2O system, *Colloid Polym. Sci,* 284(5), 2006, 468-474.
20. Nazar M F, Khan A M and Shah S S. Microemulsion system with improved loading of piroxicam A study of microstructure, *AAPS Pharm. Sci Technol*, 10(4), 2009, 1286-1294.

Please cite this article in press as: Uma Maheswara Reddy P. *et al*. Self-micro emulsifying drug delivery systems: a review, *International Journal of Research in Pharmaceutical and Nano Sciences*, 2(3), 2013, 317-331.