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Review Article

REVIEW ON: SELF DISPERSING FORMULATIONS & CHARACTERIZATION

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Abstract

Solubility is one of the most important parameter to achieve desired concentration of drug in systemic circulation for therapeutic response. As a consequence of modern drug discovery techniques, there has been a steady increase in the number of new pharmacologically active lipophilic compounds that are poorly water soluble. It is a great challenge for pharmaceutical scientist to convert those molecules into orally administered formulation with sufficient bioavailability. Among the several approaches to improve oral bioavailability of these molecules, Self- micron emulsifying drug delivery system (SMEDDS) is one of the approaches usually used to improve the bioavailability of hydrophobic drugs. SMEDDS, which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. Oral route continues to be the preferred route for most drug therapy. However, more than 40% of new chemical entities exhibit poor aqueous solubility, resulting in unsatisfactory oral drug delivery. When dissolution rate-limited absorption is seen, as in case of lipophilic drugs, Self emulsifying drug delivery systems and Self-Micro Emulsifying Drug Delivery System may be a promising strategy to improve the rate and extent of oral absorption.

Keywords: Solubility, Self Micron Emulsifying Drug Delivery System, Hydrophobic drugs.

Introduction

Oral drug delivery is by far the most preferable route of drug administration due to ease of administration, patient compliance, flexibility in formulation, etc. However in case of the oral route there are several challenges such as limited drug absorption resulting in poor bioavailability and poor pharmacological response resulting into inadequate and erratic oral absorption. (Jain 2004) Recently synthesized drug that are being discovered are lipophilic in nature and have poor aqueous solubility, thereby posing problems in their formulation into delivery systems. Because of their low aqueous solubility and low permeability, dissolution and/or release rate from the delivery system forms the rate-limiting step in their absorption and systemic availability. More than 60% of potential drug products suffer from poor water solubility. For the therapeutic delivery of lipophilic active moieties (BCS class II drugs), lipid based formulations are inviting increasing attention. Currently a number of technologies are

available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs. Nearly half of the new drug candidates that reach formulation have poor water solubility, and oral delivery of such drugs is frequently associated with low bioavailability. (Kohli, et al. 2010, Pouton 2000)

The Self-Dispersing Formulations (SDFs) is one of the promising approaches to overcome the formulation difficulties of various hydrophobic/ lipophilic drugs and to improve the oral bioavailability of poorly absorbed drugs. The SDFs contain oil and a surfactant mixture into which the drug is incorporated. They emulsify when mixed with aqueous environment. The self emulsification process is specific to the particular pair of oil and surfactant, surfactant concentration, oil/surfactant ratio, and the temperature at which self-emulsification occurs. After self dispersion, the drug is rapidly distributed throughout the gastrointestinal tract as fine droplets. Bioavailability

enhancement results from the finely dispersed state of the drug containing lipid globules. The large surface area enhances the dissolution. The emulsion globules are further solubilized in the gastrointestinal tract by bile fluids. The presence of surfactant causes enhanced absorption due to membrane induced permeation changes. The droplets formed are either positively charged or negatively charged. As the mucosal lining is negatively charged it was observed that positively charged particles penetrated deeper into the ileum. A cationic emulsion has greater bioavailability than an anionic emulsion. The SDFs are of two kinds namely, Self-Emulsifying Drug Delivery Systems (SEDDS) formed using surfactants of HLB < 12 and Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) formed with surfactants of HLB > 12. Both SEDDS and SMEDDS are stable preparations and improve the dissolution of the drug due to increased surface area on dispersion. Therefore, they are not dependent on bile secretion for absorption. The emulsified form itself is readily absorbable. This ensures a rapid transport of poorly soluble drugs into the blood. The SDF system is a liquid-based formulation rather than a semisolid formulation and, therefore, an alternative approach are required. The concept works by the adsorption/absorption of a liquid SDF onto a neutral carrier (i.e., neutral silicate). Although surprisingly straightforward, developing this solid dosage form technique has required extensive investigation of critical success parameters including:

Extensive screening of different neutral carriers to evaluate their ability to adsorb maximum levels of the liquid SELF.

Maximum loading value of the carrier and effect on tablet compression.

Absorption onto the carrier and effect on flow ability — an essential feature for tablet compression.

Evaluation of the integrity of the system with a poorly soluble API to examine the effect of transforming a liquid into a powder on drug solubility and dissolution rate.

Self emulsifying drug delivery systems (SEDDS) and self micro emulsifying drug delivery systems (SMEDDS) are defined as isotropic mixtures of natural 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. the basic difference between SEDDS and SMEDDS is that 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 to emulsions, which are

sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. (Kyatanwar 2010) 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 profile.

In the present topic focus will be on lipophilic drug based delivery systems. Emulsion particles can be of either micro or nano size depending on the composition of the system. These formulations circumvent the dissolution step in the gastrointestinal tract, but are still dependent on digestion. (S 2011)

NEED OF SDFs

Oral delivery of poorly water soluble compounds is to pre dissolve the compound in a suitable solvent and fills the formulation into capsules. (Patel 2008)The main benefit of this approach is that pre dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, Particularly if a hydrophilic solvent is used (e.g. polyethylene glycol).if the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favour the drug remaining in the lipid droplets.

Another strategy for poorly soluble drugs is to formulate in a solid solution using a water soluble polymer to aid solubility of the drug compound. For example polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG 6000) have been used for preparing solid solutions with poorly soluble drugs. One potential problem with this type of formulation is that the drug may favour a more thermodynamically stable state, which can result in the compound crystallizing in the polymer matrix. Therefore the physical stability of such formulations needs to be assessed using techniques such as differential scanning calorimetry or X-ray crystallography. In this type of case SEDD system is a good option.

ADVANTAGES OF SDFs:

Improvement in oral bioavailability

Dissolution rate dependant absorption is a major factor that limits the bioavailability of numerous poorly water soluble drugs. (Shukla 2010) 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. E.g. In case of halofantrine approximately 6-8 fold increase in bioavailability of drug was reported in comparison to tablet formulation. (Tang 2007)

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 bioavailability. 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 shows 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. (Khoo 1998) 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 (Cortesi 1997).

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 amphiphilic surfactants, co surfactants and co-solvents.

ADVANTAGES OF SDFs OVER EMULSION:

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. (Shukla 2010)

Micro emulsions formed by the SMEDDS exhibit good thermodynamics stability and optical transparency. The major difference between the above micro emulsions 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 micro emulsion 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.

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. (Kawakami 2002)

Emulsion cannot be autoclaved as they have phase inversion temperature, while SMEDDS can be autoclaved.

DRAWBACKS OF SDFs

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. (Wakerly 1986)

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

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

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.

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-micro emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs (Murdandea 2008).

The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent. Formulations containing several components become more challenging to validate.

FORMULATION OF SELF DISPERSING SYSTEMS:

A.COMPOSITION OF SDFs: Pouton revealed that the self-emulsification process depends on:

The nature of the oil–surfactant pair.

The surfactant concentration and oil/surfactant ratio.

The temperature at which self-emulsification occurs.

The types of oils used.

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 (Kimura 1994). 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 excipient 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 (Murdandea 2008). They offer formulative and physiological advantages and their degradation products resemble the natural end products of intestinal digestion. 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. (Lawrence 2000) 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 micro emulsions compared with MCT.

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 polyglycolized glycerides and polyoxyethylene 20 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 (Haus 1998). 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,

- a. 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. (Karim 1994)
- b. Cationic surfactants: where the hydrophilic group carries a positive charge. Example: quaternary ammonium halide.
- c. Ampholytic surfactants (also called zwitterionic surfactants): contain both a negative and a positive charge. Example: sulfobetaines.
- d. 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).

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 micro emulsion. 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 micro emulsions 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-SURFACTANTS:

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.

CONSISTENCY BUILDER

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

POLYMERS: 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 hydroxyl propyl methyl cellulose, ethyl cellulose, etc.

THE EMULSIFICATION PROCESS

Self-emulsification is a phenomenon which has been widely exploited commercially in formulations of emulsifiable concentrates of herbicides and pesticides. Concentrates of crop-sprays are to be diluted by the user, such as farmers or house-hold gardeners, allowing very hydrophobic compounds to be transported efficiently. In contrast, SMEDDS, using excipients acceptable for oral administration to humans, have not been widely exploited and knowledge about their physicochemical principles is therefore limited.

Mechanism of Self Emulsification:

In emulsification process the free energy (G) associated is given by the equation:

$$G = N \cdot 4 \pi r^2 \gamma \quad (1)$$

In which 'N' is Number of droplets with radius 'r' and 'γ' is interfacial energy.

It is apparent from equation that the spontaneous formation of the interface between the oil and water phases is energetically not favored. The system commonly classified as SEDDS have not yet been shown to emulsify spontaneously in the thermodynamic sense.

The process of self-emulsification was observed using light microscopy. Groves and Mustafa developed method of quantitatively assessing the ease of emulsification by monitoring the turbidity of the oil-surfactant in a water stream using phosphate nonylphenoxylate (PNE) and phosphated fatty alcohol ethoxlate (PFE) in n hexane (Swenson 1994). Pouton has argued that the emulsification properties of the surfactant may be related to phase inversion behavior of the system. For example, on increase the temperature of an oil in water system stabilized using nonionic surfactant, the cloud point of the surfactant will be reached followed by phase inversion. The surfactant is highly mobile at the phase inversion temperature; hence the o/w interfacial energy is minimized leading to a reduction in energy required to cause emulsification. The specificity of surfactant combination required to allow spontaneous emulsification may be associated with a minimization of the phase inversion temperature, thereby increasing the ease of emulsion. Phase studies are also necessary for liquid crystal formation in self emulsification. These indicate that good formulations are usually operating close to a phase inversion region and in a region of enhanced close to a phase inversion region and in a region of enhanced aqueous solubilization. In the phase diagram of the system (30 % w/w tween and 85/70 % w/w MCT oil) for dilution in water over a range of temperature shows that the phase inversion region is at approximately 40° C and the system works well at ambient temperature up to 60°C above which water in oil emulsion tend to form. The emulsification process may be associated with the ease with which water penetrates the oil-water interface with the formation of liquid crystalline phases resulting in swelling at the interface thereby resulting in greater ease of emulsification. However, for system containing co-surfactant, significant partitioning of components between the oil and aqueous phases may take place leading to a mechanism described as "diffusion and stranding", where by the oil is solubilized, leading to migration in to the aqueous phase.

Dilution phases

Upon dilution of a SMEDDS formulation, the spontaneous curvature of the surfactant layer changes via a number of possible liquid crystalline phases. The droplet structure can pass from a reversed spherical droplet to a reversed rod-shaped droplet, hexagonal phase, lamellar phase, cubic phase and various other structures until, after appropriate dilution, a spherical droplet will be formed again. Representation of the of commonly encountered phases upon addition of water to an oil-surfactant combination. (Gursoy 2004)

The lipids may enhance bioavailability of poorly soluble drugs via a number of potential mechanisms, including (Shah 1994):

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

Increase 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 administered (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

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.

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 may also reduce the extent of enterocyte-based metabolism. 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.

Effect of oils on the absorption: Such formulations form a fine oil-in-water emulsion with gentle agitation, which may be provided by gastrointestinal motility. A SES also improves the reproducibility of the plasma level-time profile. Various physiological mechanisms have been proposed to explain the effect of oils on the absorption of water-insoluble compounds, including altered gastrointestinal motility, increased bile flow and drug solubilization, increased mucosal permeability, enhanced mesenteric lymph flow, and increased lymphatic absorption of water insoluble drugs and bioavailability also increased of hydrophobic compound.

CHARACTERIZATION OF SDFs: The primary means of self-emulsification assessment is visual evaluation. The efficiency of self-emulsification could be estimated by determining the rate of emulsification, droplet-size

distribution and turbidity measurements (Stegemanna 2007).

1. **Visual assessment:** This may provide important information about the self emulsifying and micro emulsifying property of the mixture and about the resulting dispersion.
2. **Turbidity measurement:** This is to identify efficient self emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time.
3. **Droplet size:** This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as the stability of the emulsion. Photon correlation spectroscopy, microscopic techniques or a coulter nanosizer are mainly used for the determination of the emulsion droplet size. The reduction of the droplet size below 50 μm leads to the formation of SMEDDSs, which are stable, isotropic and clear o/w dispersions. (Kumar 2010)
4. **Zeta potential measurement:** This is used to identify the charge of the droplets. In conventional SEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids.
5. **Determination of emulsification time:** Self emulsification time, dispersibility, appearance and flow ability was observed and scored according to techniques described in H. Shen et al. used for the grading of formulations.
6. **Refractive Index and Percent Transmittance:** Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it compare with water (1.333). The percent transmittance of the system is measured at particular wavelength using UVs spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance > 99 percent.
7. **Viscosity Determination:** The SEDDS system is generally administered in soft gelatin or hard gelatin capsules. So, it can be easily pourable into capsules and such system should not too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination conform 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 a high viscosity then it is w/o type of the system.
8. **Droplet polarity and droplet size of emulsion:** Polarity of oil droplets is governed by the HLB value of oil, chain length and degree of unsaturation of the fatty acids, the molecular weight of the hydrophilic portion and concentration of the emulsifier. A combination of small droplets and their appropriate polarity (lower partition coefficient o/w of the drug) permit acceptable rate of release of the drug. Polarity of the oil droplets is also estimated by the oil/water partition coefficient of the lipophilic drug. Size of the emulsion droplet is very important factor in self emulsification / dispersion performance, since it determine the rate and extent of drug release and absorption. The Coulter nanosizer, which automatically performs photon correlation analysis on scattered light, can be used to provide comparative measure of mean particle size for such system. This instrument detects dynamic changes in laser light scattering intensity, which occurs when particle oscillates due to Brownian movement. This technique is used when particle size range is less than 3 μm ; a size range for a SMEDDS is 10 to 200 nm.
9. **Dissolution studies:** For sustained release characteristic, dissolution study is carried out for SEMDDS. Drugs known to be insoluble at acidic pH can be made fully available when it is incorporated in SMEDDS.
10. **Equilibrium phase diagram:** Although self-emulsification is a dynamic no equilibrium process involving interfacial phenomena, information can be obtained about self-emulsification using equilibrium phase behavior. There seems to be a correlation between emulsification efficiency and region of enhanced water solubilization and phase inversion region, formation of lamellar liquid crystalline dispersion phase on further incorporation of water. An equilibrium phase diagram enables comparison of different surfactants and their synergy with cosolvent or co surfactant. The boundaries of one phase region can easily be assessed visually. The phase behavior of a three-component system can be represented by a ternary phase diagram.
11. **Electron microscopic studies:** Freeze-fracture electron microscopy has been used to study surface characteristics of such dispersed systems. Because of the high liability of the samples and the possibility of artifacts, electron microscopy is considered a somewhat misleading technique. Particle size analysis and low-frequency dielectric spectroscopy have been used to examine the self emulsifying properties of Imwitor 742 (a mixture of mono- and diglycerides of capric and caprylic acids) and Tween 80 systems.
12. **Cryo-TEM studies:** For Cryo-Transmission Electron Microscopy (TEM), samples were prepared in a controlled environment verification system. A small amount of sample is put on carbon film supported by a copper grid and blotted by filter paper to obtain thin liquid film on the grid. The grid is quenched in liquid ethane at -180°C and transferred to liquid nitrogen at -196°C . The samples were characterized with a TEM microscope.

- 13. Liquefaction time:** This test is designed to estimate the time required by solid SEDDS to melt in vivo in the absence of agitation to simulated GI conditions. One dosage form is covered in a transparent polyethylene film and tied to the bulb of a thermometer by means of a thread. The thermometer with attached tablets is placed in a round bottom flask containing 250 ml of simulated gastric fluid without pepsin maintained at 37 ± 18C. The time taken for liquefaction is subsequently noted.
- 14. Small-angle neutron scattering:** Small-angle neutron scattering can be used to obtain information on the size and shape of the droplets. The term 'droplet' is used to describe micelles, mixed micelles and oil-swollen micelles throughout the present work. Small-angle neutron scattering experiments use the interference effect of wavelets scattered from different materials in a sample (different scattering-length densities). Small-angle X-ray scattering: This a small-angle scattering technique in which the elastic scattering of X-rays by a sample that has non homogeneities in the nm range is recorded at very low angles (typically 0.1–108). This angular range contains information about the shape and size of macromolecules, characteristic distances of partially ordered materials, pore sizes and other data. Smallangle X-ray scattering is capable of delivering structural information of macromolecules between 5 and 25 nm, of repeat distances in partially ordered systems of up to 150 nm. Small-angle X-ray scattering is used for the determination of the microscale or nanoscale structure of particle systems in terms of such parameters as averaged particle sizes, shapes, distribution and surface-to-volume ratio. The materials can be solid or liquid and they can contain solid, liquid or gaseous domains (socalled 'particles') of the same or another material in any combination. In addition to these tools, others such as nuclear magnetic resonance and differential scanning calorimetry – have also been exploited to characterize these self-emulsifying systems for a better insight.
- 15. 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 excipient matrix. In addition, poor formulation physical stability can lead to phase separation of the excipient, affecting not only the formulation performance, but visual appearance as well. In addition, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug.
- a. 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.
- b. Centrifugation:** Passed formulations are centrifuged thaw cycles between 21 C and +25 C with storage at each temperature for not less than 48 h is done at 3500 rpm for 30 min. those formulations that do not show any phase separation are taken for the freeze thaw stress test.
- c. Freeze thaw cycle:** Three freeze for the formulations. Those formulations that passed this test showed good stability with no phase separation, creaming, or cracking.
- 16. 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 rpm provided gentle agitation. The invitro performance of the formulations is visually assessd using the following grading system:
- Grade A:** Rapidly forming (within 1 min) nano emulsion, having a clear or bluish appearance.
- Grade B:** Rapidly forming, slightly less clear emulsion, having a blusih white appearance.
- Grade C:** Fine milky emulsion that 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.
- 17. Electro conductivity study:** The SEDD system contains ionic or non-ionic surfactant, oil, and water so this test is used to measure the electro conductive nature of system. The electro conductivity of resultant system is measured by electro conductometer.
- 18. In vitro diffusion study:** In vitro diffusion studies are performed to study the release behavior of formulation from liquid crystalline phase around the droplet using dialysis technique.
- 19. Drug content:** Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution of drug.

RECENT ADVANCES IN SDFS:

- I. Dry emulsion
- II. Self emulsifying capsules
- III. Self emulsifying sustained/controlled release tablets
- IV. Self emulsifying sustained/controlled release pellets.
- V. Self emulsifying solid dispersions
- VI. Self emulsifying sustained release microspheres
- VII. Self emulsifying nanoparticles
- VIII. Self emulsifying suppositories
- IX. Self emulsifying implants (Tatyana and Benita 2000)
- X. Micro emulsion drug delivery

Solid Self-Micro emulsifying Drug Delivery System

SMEDDS can exist in either liquid or solid states.1. SMEDDS are usually, limited to liquid dosage forms,2. 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, SSMEDDS mean solid dosage forms with self-emulsification properties. SSMEDDS focus on the incorporation of liquid/semisolid SE ingredients into3. 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. (al 2008)

Solidification Techniques For Transforming Liquid/Semisolid SMEDDS to SSMEDDS

Various solidification techniques are listed below:

1. Capsule filling with liquid and semisolid self emulsifying formulations
2. Spray drying
3. Adsorption to solid carriers
4. Melt granulation
5. Melt extrusion/ Extrusion spheronization (Bo 2008)

APPLICATIONS OF SDFs

Improvement in Solubility and bioavailability: If drug is incorporated in SEDDS, it increases the solubility because it circumvents the dissolution step in case of Class- drug (Low solubility/high permeability).

Ketoprofen, a moderately hydrophobic (log P 0.979) non steroidal anti-inflammatory drug (NSAID), is a drug of choice for sustained release formulation has high potential for gastric irritation during chronic therapy. Also because of its low solubility, ketoprofen shows incomplete release from sustained release formulations. Vergote et al. (2001) reported complete drug release from sustained release formulations containing ketoprofen in nano crystalline form Different formulation approaches that have been sought to achieve sustained release, increase the bioavailability, and decrease the gastric irritation of ketoprofen include preparation of matrix pellets of nano-crystalline ketoprofen, sustained release ketoprofen micro particles and formulations, floating oral ketoprofen systems, and transdermal systems of ketoprofen. (Pal 2011).

Protection against Biodegradation: The ability of self emulsifying drug delivery system to reduce degradation as well as improve absorption may be especially useful for drugs, for which both low solubility and degr (Kyatanwar 2010) adation in the GI tract contribute to a low oral bioavailability. Many drugs are degraded in physiological system, may be because of acidic pH in stomach, enzymatic degradation or hydrolytic degradation etc.

FUTURE TRENDS

In relation to formulation of poorly soluble drugs in the future, there are now techniques being use 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 solubilising agent as a binding agent, up to 25% solubilising agent can be incorporated in a formulation. There is also increasing interest in using inert adsorbents, such as the Neusilin (Fuji Chemicals) and Zeopharm (Huber) products for converting liquids into powders- which can be processed into powder fill capsules or tablets. But to obtain solids with suitable processing properties, the ratio of SEDDS 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 SEDDS in solid dosage forms will be significantly reduced if SEDDS is gelled. Colloidal silicon dioxide (Aerosil 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.

Table 1: Examples of marketed SEDDS formulations

Drug name	Compound	Dosage form	Company	Indication
Neoral®	Cyclosporine A/I	SGC	Novartis	Immuno suppressant
Fortovase®	Saquinavir	SGC	Hoffmann-La Roche Inc.	HIV antiviral
Convulex®	Valproic acid	SGC	Pharmacia	Antiepileptic
Targretin®	Bexarotene	SGC	Ligand	Antineoplastic
Gengraf®	Cyclosporine A/III	HGC	Abbott laboratories	Immune suppressant

SGC: Soft Gelatin Capsules, HGC: Hard Gelatin Capsules

Conclusion

More than 40% of the new chemical entities exhibit poor aqueous solubility and complex technical formulation problems. They represent a real challenge for the design of appropriate formulations aimed at enhancing oral bioavailability. This review outlined SDFs as one of the most promising approaches towards overcoming the formulation difficulties of these hydrophobic/lipophilic drugs. Bioavailability. As mentioned above, numerous studies have confirmed that SMEDDS substantially improved solubility/dissolution, absorption and bioavailability of poorly water soluble drugs. There are reduced the particle size up to nanometer range. So, increase the solubility of lipophilic drug. With future development of this technology, solid dispersions will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

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