Self Microemulsifying Nutraceutical and Drug Delivery Systems

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ABSTRACT
Many chemical entities and nutraceuticals are poor water soluble and show high lipophilicity. It’s difficult to formulate them into oral formulation because of its low aqueous solubility which ultimately affects bioavailability. To enhance the bioavailability of such drugs compounds, self microemulsifying drug delivery system is the reliable drug delivery system. In this system the drug is incorporated in the isotropic system and formulated as unit dosage form. Self microemulsifying drug delivery system is the novel emulsified system composed of anhydrous isotropic mixture of oils, surfactant, and co solvent and sometimes co surfactant. Drug is directly dispersed into the entire gastro intestinal tract with continuous peristaltic movement and drug is available in the solution form of microemulsion, absorbed through lymphatic system and bypasses the dissolution step. Hence they increase the patient compliance. The excipients are selected on basis of construction of ternary phase diagram. Self micro-emulsifying drug delivery system is very useful for drug in which drug dissolution is rate limiting step. This review describes the novel approaches and evaluation parameters of the self microemulsifying drug delivery system towards different classic drugs, proteins-peptides, and nutraceuticals in various oral microemulsion compositions and microstructures.

KEYWORDS: Nutraceuticals; Microstructure; Microemulsion; Ternary phase-diagram; Bioavailability.

Introduction
The oral route is the preferred route and has dominated over other routes of administrations for chronic drug delivery. This may not be possible for roughly 50% of currently marketed drug compounds that exhibit low oral bioavailability due to their poor aqueous solubility. According to biopharmaceutical classification system (BCS), for this class of compounds, defined by low solubility/high permeability class II and low solubility/low permeability class IV, dissolution in the GIT is the rate controlling step in the absorption process (Patel et al., 2010). One of the novel approach to address this problem include administration of drug components with lipid vehicle such as oils through formation of self-microemulsifying drug delivery system (SMEDDS) or self-emulsifying oil/lipid formulation (Carrier et al., 2010). Which are isotropic mixtures of surfactants, oils, solvents and co solvents/surfactants with a unique ability to form fine oil in water microemulsion, having droplets of size range is less than 50nm on dilution with physiological fluid. Self-micro-emulsifying drug delivery formulations are classified as class IIIA/IIIB according to lipid based drug delivery system. Lipid-based drug delivery systems (LBDDS) have the potential to increase the oral bioavailability of poorly water-soluble drugs.

Self-micro-emulsifying drug delivery system is regarded as an attractive approach for improvement in both rate and extent of absorption by the lymphatic system (Fig. 1). Ideally, these novel formulations allow the drug to remain in dissolved state throughout the transit in the gastrointestinal tract thereby enhancing the bioavailability of poorly water-soluble therapeutic agents with reproducible plasma profiles. For oral use, SMEDDS may be formulated as numerous liquids, solids or semisolid dosage form, the solids packaged in capsules or tablets. Various studies have compared the bioavailability of liquid SMEDDS and solid SMEDDS, which are supercilious to conventional tablets.

Fig. 1. Lipid digestion and drug solubilization process in the small intestine.

Self-emulsifying system offer several different mechanisms that include: (a) Bypassing the dissolution step via delivering the drug in a pre-dissolved form and avoidance of re-precipitation from this pre-dissolved state; (b) Increasing drug solubilisation in the intestinal
milieu directly through formulation components formed upon digestion of formulation excipient, enhancing intestinal drug permeability through inhibition of P-gp and other efflux transporters; and (c) Decreasing first-pass metabolism of the drug through recruitment of intestinal lymphatic processes.

Selection of Drug Candidates for SMEDDS

For lipophilic drug compounds that exhibit dissolution-rate-limited absorption, having log P value greater than 5 and low melting point drugs are good candidate for SMEDDS. At the other end of the spectrum SMEDDS can be formulated for all four categories of biopharmaceutical classification system (BCS) class drugs. These systems can help in outcome the under-mentioned problems of all the categories of BCS class drugs as shown in Table1.

TABLE 1

Biopharmaceuticals classification system.

<table>
<thead>
<tr>
<th>BCS class</th>
<th>Properties</th>
<th>Problems associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>High solubility and high permeability</td>
<td>Enzymatic degradation, gut wall efflux</td>
</tr>
<tr>
<td>Class II</td>
<td>Low solubility and high permeability</td>
<td>Solubilation and bioavailability</td>
</tr>
<tr>
<td>Class III</td>
<td>High solubility and low permeability</td>
<td>Enzymatic degradation, gut wall efflux and bioavailability</td>
</tr>
<tr>
<td>Class IV</td>
<td>Low solubility and low permeability</td>
<td>Solubilation, enzymatic degradation, gut wall efflux and bioavailability</td>
</tr>
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</table>

For further discovery, Lipinski’s rule of five has been widely proposed as a qualitative and predictive model for oral absorption trends, ‘rule of five’, predicts that poor absorption or poor permeation is commonly observed. The rule states as for reasonable absorption when there are more than five H-bond donors. Similarly there are more than ten H-bond acceptors, the molecular weight > 500 and the calculated log P > 5.

It is considered that the rule of five only holds for compounds that are not substrates for some efflux or uptake transporters, this limitation might be accounted (Kohli et al., 2010). It has been found that particularly, these poorly water-soluble compounds, which are generally classified as ‘lipophilic’ thus highlighting the need to assess candidate compounds.

Nutraceuticals

The term nutraceutical was coined from “nutrition” and “pharmaceutical” by Stephen Defelice MD, founder and the chairman of the foundation for innovation in medicine (FIM) Cranford, New Jersey, in 1989. According to Defelice “nutraceuticals are food or part of a food that provides medical or health benefits including the prevention and/or treatment of a disease”. According to HIPPOCRATES (known as father of medicines) Greekphysician said “let food is your medicine”. The philosophy behind is “focus on prevention” other words used in the, context are, multi-functional food as dietary supplements, functional food, etc. Functional foods are ordinary foods that have ingredients that incorporated into give them a specific medicinal or health benefit moreover nutritional effect.FDA regulated dietary supplements as foods to ensure that they were regarded as safe. In 2006, the Indian government passed Food Safety and Standard Act to regulate the nutraceutical industry (Chauhan et al., 2013).

Nutraceuticals are products derived from food sources that were provided extra health benefits, in order to the basic nutritional value. Depending on the jurisdiction and regulation, products may claim to prevent chronic diseases, improve health, even delay the aging process, increase life expectancy, and support the function of the body. The term is applied to nutrients, dietary supplements and natural product, specific diets and processed foods such as cereals, soups, vitamins, proteins, carbohydrates, lipids, minerals and beverages. Vitamins are further categorised into fat soluble vitamins and water soluble vitamins. In case of fat soluble vitamins such as vitamins A, D, E, K due to their lipophilic solubility these cannot be formulated as aqueous formulation which possess the bioavailability problems and hence reduces the patient compliance. The appreciable formulations for this type of compounds are self-emulsified drug delivery systems are particularly suitable for this type of application.

Excipients used in SMEDDS

Three types of excipients are generally used in SMEDDS including oils, surfactants, and co-surfactants. They are described below.

Oils

Oils are preferred vehicle because it can solubilize the lipophilic drug in a specific amount. It is the prime most important excipient because it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, ultimately increasing absorption from the GI tract. Both long- and medium-chain triglyceride (MCT) oils with different degrees of saturation have been used for the design of self-dispersing formulations. Use of unmodified edible oils provide the most ‘natural’ basis for lipid vehicles, but their poor capacity to dissolve large amounts of hydrophobic drugs so in contrast modified or hydrolyzed vegetable oilse have contributed widely to the success of SMEDDSs. MCTs were selected in the earlier because of higher fluidity, better solubility properties and self-emulsification ability, but evidently, they are not enough attractive compared to the novel semi-synthetic medium chain derivatives which can be defined rather as amphiphilic compounds. Solvent capacity for poor hydrophobic drugs can be improved by blending triglycerides with mono- and di-glycerides.

Surfactants

Emulsifiers absorb to the oil-water interface, which leads to a reduction in the interfacial tension thereby facilitating further droplet disruption. Once they have adsorbed to the droplet surface the emulsifiers should prevent the droplets from coalescing with each other,
which means they must for a protective coating around the oil droplets.

There are four main groups of surfactants are defined as following:

(a) Anionic surfactants- In which the hydrophilic group carries a negative charge.
(b) Cationic surfactant - Where the hydrophilic group carries a positive charge.
(c) Ampholytic surfactants- Contain both a negative and a positive charge called zwitterionic surfactants.
(d) Non-ionic surfactants- In which the hydrophilic group carries no charge but derives its water solubility from highly polar groups.

Non-ionic surfactants with a relatively high hydrophilic lipophilic balance (HLB) were ideal for the design of self-dispersing systems because the high HLB and subsequent hydrophilicity of surfactants is necessary for the instantaneous formation of o/w droplets and/or rapid spreading of the formulation in the aqueous environment.

In nutraceutical formulation proteins are also employed as surfactant/emulsifier, the incorporation of proteins at the oil–water interface has allowed scientists to utilize them to form emulsions (O/W or W/O), may be used in food formulations, drug and nutrient delivery. The use of polysaccharides to complex with proteins will also be explored in relation to enhancing emulsion stability, commonly used proteins used by the food industry for their emulsifying abilities include: whey protein isolate, casein, ovalbumin, soy, and bovine serum albumin. Polysaccharides based emulsifier: Gum Arabic, Modified Starch (Lam and Nickerson, 2013). Also a natural food-grade surfactant (Q-Naturale) isolated from the bark of the Quillaja saponaria Molina tree used in nutraceutical formulation.

**Co-solvent**

Use of high surfactant concentrations usually more than 30% w/w is needed in order to produce an effective self-micro emulsifying system. Organic solvents, preferred for oral administration these solvents many times, play the role of the co-surfactant in the micro emulsion systems which may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base but dissolution ability by using co-solvent may depend upon drug monograph (Nekati and Kalepu, 2012). The most widely used excipients are described below.

**Carriers:** Carriers are largely used to enhance therapy efficiency via the encapsulation of active drug molecules. The encapsulation enhances the stability of drug molecules, improves the specific properties such as targeting and prolongs pharmacological activity via continuous local release of active molecules (Paudel et al., 2013).

**Consistency builder:** In some formulation additional material can be added to alter the consistency of the emulsions; such materials include tragacanth, cetyl alcohol, stearic acids and/or beeswax.

**Alkalinising agent:** for accelerating the solubility of the drug and for maintaining the stability of formulation sometimes alkalinising agents are incorporated. E.g., triethanolamine (Elsheikh et al., 2012).

In SMEDDS the free energy that required forming the emulsion is either very low and positive or negative. Less interfacial tension gives a lesser free energy stable emulsion. The two phases of emulsion tend to separate with time to reduce the interfacial area and, simultaneously the emulsion is stabilized by emulsifying agents or surfactant, which then form a monolayer of emulsion droplets, and hence decreases the interfacial energy, similarly providing a barrier in order to avoid coalescence. In case of SMEDDS, the free energy of formation is very low and positive or negative even which results in thermodynamic spontaneous emulsification. It has been investigated that self-emulsification occurs due to incorporation of water into the Liquid Crystalline (LC) phase that is formed at the oil/surfactant-water interface into which water can penetrate assisted by gentle agitation during self-emulsification process. After water penetrates at certain extent, there is disruption of the interface and a droplet formation. This Liquid Crystalline (LC) phase is considered to be responsible for the high stability of the resulting nanoemulsion against coalescence. While in case of nutraceutical transcellular mechanism occur but exact mechanism depends upon composition of formulation.

**Potential advantages of SMEDDS**

1. Enhanced oral bioavailability enabling reduction in dose.
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. Protective of sensitive drug substances.
8. High drug payloads.
9. Liquid or solid dosage forms.

**Dosage form Development of SMEDDS-Nutraceutical Systems**

1. **Vitamin E:** It is a highly lipophilic molecule that cannot be directly dispersed into aqueous solutions. Instead, it must be incorporated into an appropriate colloidal delivery system prior to dispersion. One major problem with vitamin E is that it is only partially absorbed at the intestinal site, which reduces its bioavailability. Encapsulation of vitamin E has also been reported to improve its physicochemical stability during storage, in addition to its biological activity after consumption (Yang and Clement, 2013). Manufacturing procedure. Oil-in-water emulsions were prepared by homogenizing 10 %wt targeting lipid phase (MCT) with 90 %wt aqueous phase. The aqueous phase consists of surfactant (1 wt%
Tween 80 or Q-Naturale) and buffer solution (10 mM sodium phosphate buffer, pH 7.0). Previously coarse emulsion was prepared by blending the lipid and aqueous phases together using a high-speed mixer for 2 min at room temperature. Fine emulsions were formed by passing the coarse emulsions through an air driven microfluoridizer. The coarse emulsions were passed through the homogenization for 4 passes at 9000 psi.

2. Lycopene: It is a highly lipophilic carotenoid (C - Log P = 17.6), with poor aqueous solubility, and previous studies have predicted that lycopene will display solubility rate limited absorption characteristics. Hence formulation approaches which enhance solubility of lycopene within the gastrointestinal tract (GIT) are considered crucial to increasing oral absorption. A number of formulation approaches have been utilized to enhance solubility of poorly soluble drugs in the GIT, such as particle size reduction, or modifications of crystal habit to enhance dissolution. Solid dispersion formulations (SD), where the drug is dispersed within an inert carrier matrix, have also attracted considerable interest;

Manufacturing process: A solid dispersion (SD) of Lycopene in Gelucire 44/14 was prepared using a conventional solvent evaporation method, at the weight ratio of 1:20. Gelucire was dispensed into a glass vial and placed in a water bath held at approximately 55 °C. Lycopene and molten carrier were then dissolved in a minimum volume of dichloromethane (10 mg Lycopene/mL) and heated briefly to 40 °C. The solution was transferred to rotary evaporator and the solvent was evaporated under vacuum at 40 °C. The preparation was cooled and finally stored at ~80°C.

3. Carotenoids: These are organic pigments naturally synthesized by microorganisms and plants. The most widespread of all carotenoids is β-carotene, which is insoluble in water and only marginally soluble in oil at room temperature. This makes its incorporation difficult to many food matrices. Moreover, crystalline forms have poor bioavailability; these problems could be improved by encapsulating β-carotene in self-emulsified system (Guti et al., 2013). Two method are employed namely Hot high pressure homogenization and Cold high pressure homogenization.

4. Beverage emulsion: Soft drink such as Cola is the top soft drink flavor currently consumed in the United States, with lemon-lime and orange being the second and third. All three of these soft drink flavors contain hydrophobic citrus compounds extracted from fruit peels. These ingredients cannot simply be dispersed directly into an aqueous phase they would rapidly coalesce and separate through gravitational forces leading to a layer of oil on top of the product. Instead they first have to be converted into a colloidal dispersion consisting of flavour molecules encapsulated within small particles suspended within an aqueous medium to form oil in water microemulsion. Soft drinks may also contain a variety of other hydrophobic components, such as clouding agents, weighting agents, nutraceuticals, oil-soluble vitamins, and oil-soluble antimicrobials. Beverage emulsions are usually prepared using a two-step process: a beverage emulsion concentrate (3 – 30 wt% oil) is prepared, which is then diluted extensively to create the finished product (< 0.1 wt% oil), Beverage emulsion concentrates: In this step all aqueous phase components such as emulsifiers, thickening agents, buffers, minerals and other functional ingredients mix with all oil phase components. In this case, water-soluble surfactants and some other water-soluble components may initially be incorporated into the oil phase, which is then mixed with the aqueous phase (Piorkowski and Clement, 2013). This process can lead to the spontaneous formation of a microemulsion, nanoemulsion, or emulsion depending on system composition and preparation procedure. The finished product is created by diluting the beverage emulsion concentrate with another aqueous phase, which may contain various other ingredients, such as preservatives, pH regulators, colours and flavors.

Drug Delivery System-Dry Emulsions

Dry emulsions are powders from which emulsion spontaneously occurs in vivo or when exposed to an aqueous solution. Dry emulsions are useful for further preparation of tablets and capsules. Dry emulsion formulations are prepared from oil/water (O/W) emulsions containing a solid carrier (lactose, maltodextrin, and so on) in the aqueous phase by rotary evaporation, freeze-drying or spray drying. The technique of spray drying is more frequently used in preparation of dry emulsions formulation. The O/W emulsion was formulated after spray-dried to remove the aqueous phase.

Self-microemulsifying capsules

Oral administration of SE capsules has been found to enhance patient compliance compared with the previously used parenteral route. After administration of capsules containing conventional liquid formulations, it form micro emulsion droplets and subsequently disperses in the GI tract to reach sites of absorption. However, if non-reproducible phase separation of the micro emulsion occurs, an improvement of drug absorption, this result cannot be expected. For avoiding this problem, sodium dodecyl sulphate was added into the SE formulation. This system contains a reduced amount of a surfactant, results in minimizing GI side effects.

Self-micro-emulsifying sustained or controlled-release tablets

Combinations of lipids and surfactants have presented great potential of preparing SE tablets that have been widely searched. Some processing parameters
(colloidal silicates-A1, magnesium stearate mixing time-A2, and compression force-A3) on hardness and coenzyme.

**Dissolution from tablets of eutectic-based SMEDDS**

The optimized conditions \((X_1 = 1.06\%, \ X_2 = 2\,\text{min}, \ X_3 = 1670\,\text{kg})\) were achieved by a face-centered cubic design. SE tablets are of great utility in obviating adverse effect. The new advancement in the research field of SE tablet is the osmotic pump tablet, in which the elementary osmotic pump system was chosen as the carrier of SES. This system has excellent features such as stable plasma concentrations and controllable drug releasing rate, while allowing a bioavailability.

**Self-micro-emulsifying sustained or controlled-release pellets**

Pellets, as a multiple unit dosage form, possess potential over conventional solid dosage forms, such as manufacturing flexibility, diminishing intrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability. Thus, it is very desirable to combine the advantages of pellets with those of SMEDDS by SE pellets.

**Self-micro-emulsifying beads**

In an attempt to transform SES into a solid form with minimum amounts of solidifying excipient, it investigated that loading SES into the micro channels of porous polystyrene beads (PPB) using the solvent evaporation method. It is produced by copolymerizing styrene and divinyl benzene with complex PPB they are inert, and stable over a wide pH range and to extreme conditions of temperature and humidity.

**Self-micro-emulsifying sustained-release microspheres**

Solid SE sustained-release microspheres are used for tumour supressive, antibacterial, antithrombic-activity. The plasma concentration–time profiles were achieved after oral administration of such microspheres.

**Self-micro-emulsifying nanoparticles**

Nanoparticles techniques have been useful in the production of SE nanoparticles. Solvent injection is one of these selected techniques. In this method, drugs, lipid, and surfactant melted together, and injected drop by drop into a stirred non-solvent. The resulting SME nanoparticles were thereafter filtered out and dried. This approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74%. A second technique is that of sonic emulsion–diffusion–evaporation.

**Self-micro-emulsifying suppositories**

Some investigators proved that S-SEDDS may increase not only GI adsorption but also rectal/vaginal adsorption. Glycyrrhizin hardly achieves therapeutic plasma concentrations by the oral route and can be utilized by either vaginal or rectal SE suppositories.

**Self-micro-emulsifying implants**

Research into SE implants has greatly enhanced the utility and application of S-SMEDDS. However, its effectiveness was hindered by its short half-life. In order to enhance its stability as compared with that released from poly (dl-lactide-co-glycolide) (PLGA) wafer implants.

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**Microemulsion-based Gel for Sustained Transdermal Delivery**

The use of external drug reservoir (topical patch) is the common technique used to sustain the transdermal delivery of water soluble drugs, microemulsion based gel has reliable delivery system. Because of the major disadvantages of transdermal patches are their sophisticated method of manufacture and the possibility that a local irritation will develop at the site of application. Erythema and itching can be caused by the drug and the adhesive in the patch formulation.

**Method of Preparation**

(a) **Solidification techniques for transforming liquid/semisolid:** Various solidification techniques are as listed below;

1. **Capsule filling with liquid and semisolid self-emulsifying formulations:** For the encapsulation of liquid or semisolid SE formulations for the oral route. For semisolid formulations, it’s a four-step process:
   (a) Heating of the semisolid excipient to at least 20°C above its melting point.
   (b) Incorporation of the active substances (with stirring).
   (c) Capsule filling with the melt cooling at room temperature. For the liquid formulations, it involved the two-step process.
   (d) Filling of the formulation into the capsules followed by sealing of the body and cap of the capsule, either by banding or by micro spray sealing.

(b) **Spray drying:** This technique involves the preparation of a formulation by mixing surfactants lipids, drug, solid carriers, and solubilisation of the mixture before spray drying. The solubilised liquid formulation is then atomized into a spray of droplets. These droplets are introduced into a drying chamber, where the volatile phase evaporated and prepared into tablet pattern and the drying chamber design are selected according to the drying characteristic the product and powder specification.

(c) **Adsorption to solid carriers:** Free flowing powders can be obtained from liquid SE formulations by adsorption to the solid carriers. The adsorption process involves addition of the liquid on to carriers by mixing in a blender.

(d) **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.

(e) **Melt extrusion/extrusion spherization:** Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity. Extrusion is a procedure of product
of uniform dimension, by forcing it through a die under controlled temperature conditions, product flow, and pressure conditions.

**Evaluation Parameters**

**Thermodynamic stability studies**

The physical stability of a lipid-based formulation is also crucial to its performance. In addition, poor formulation physical stability can lead to phase separation of the excipient, affecting formulation performance, also visual appearance as well.

1. *Heating cooling cycle:* Six cycles between refrigerator temperature (40°C) and 45°C with storage at each temperature of not less than 48 hr is studied well. Those formulations, which are most stable at these temperatures, are introduced to centrifugation test.

2. *Centrifugation:* Passed formulations are centrifuged thaw cycles between 21°C and +25°C with storage at each temperature for not less than 48 hr is done at 3500 rpm for 30 min. Most of those formulations that does not show any phase separation are taken for the freeze thaw stress test.

3. *Freeze thaw cycle:* Three freeze for the formulations. For those formulations passed this test showed good stability with creaming, or cracking no phase separation.

**Dispersibility test**

The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus II. 1 ml 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 in vitro performance of the formulations is assessed using the following grading system:

- **Grade A:** Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.
- **Grade B:** Rapid forming, slightly less clear emulsion, having a bluish white appearance.
- **Grade C:** Very fine milky emulsion that formed within 2 min.
- **Grade D:** Off greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).
- **Grade E:** Formulation, that 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 this dispersed in GIT. While formulation categorized in Grade C could be recommend for SEDDS formulation.

**Turbidimetric evaluation**

Nepheloturbidimetric evaluation is done to monitor the growth of emulsification phase. Fixed amount of self emulsifying system is added to fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on magnetic plate at the ambient temperature, and the increase in turbidity is measure using a turbidimeter.

**Viscosity determination**

The SEDDS system is generally administered in soft gelatine or hard gelatine capsules, so it can be easily pourable into capsules. The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination for conformation whether the system is w/o or o/w. If system has less viscous then it is o/w type of the system and if highly viscous then it is w/o type of the system.

**Droplet size analysis and particle size measurements**

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 particles) using a Zetasizer able to measure sizes between 10 and 5000 nm.

**Refractive index and percent transmittance**

Refractive index and percent transmittance are evaluated for proving 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 UV-spectrophotometer keeping distilled water as blank.

**Electro conductivity study**

The SMEDD system contains ionic or non-ionic surfactant, water and oil. So, this test is used to measure the electroconductive nature of this system. The electro conductivity of resultant system is measured by electroconductometer.

**In vitro diffusion study**

In vitro diffusion studies are conducted to study the release behaviour of formulation from liquid crystalline phase around the droplet using dialysis technique.

**Drug content**

Drug from pre-weighed SEDDS is extracted by dissolving it in suitable solvent. Drug content in that solvent extract was analyzed by suitable analytical method against the standard solvent solution of drug.

**Emulsification time**

The efficiency of self-emulsification could be estimated primarily by determining the rate of emulsification which is an important index for the assessment of the efficiency of emulsification; the SMEDDS should disperse completely and quickly when subjected to aqueous dilution under mild agitation. The ability of emulsification time of these formulations was in the range of 15 to 35sec.
Optical clarity

Optical clarity directly measured by taking the absorbance of the diluted SMEDDS which is a measure of droplet stability. The result indicates that formulation were well stable till 24hr if their absorbance values did not change at the end of 24hr.

Stability studies

Chemical stability of SMEDDS was assessed under various storage conditions, as per ICH guidelines. viz., 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH, SMEDDS equivalent to 5 mg of formulation was filled in size “0” hard gelatine capsules. Ten such capsules were packed in Alu–Alu strip packs and stored at various aforementioned storage conditions up to the period of 1 month. Samples were removed at 0, 15, 30 days of interval and the content in the samples was analyzed by an in-house HPLC or UV Spectroscopy method.

Stability of drug in individual SMEDDS components

To understand the unusual and unexpected degradation of the drug, stability of drug in the components of SMEDDS was evaluated. Briefly, drug (5.0 mg) was dissolved in various components of SMEDDS (1.0 ml), viz., Transcutol P, Capryol90, and Tween-20, whereas in case of hydroxypropyl cellulose, drug powder was thoroughly mixed with equal amount of hydroxypropyl cellulose to physical mixture. All these samples and a pure drug powder were stored at 60°C/ambient RH for 15 days. The Drug content of the samples was analyzed by an in-house HPLC at the end of 15 days.

Particle size distribution (PSD) and potential analysis

The droplet size of the emulsion is a crucial factor self-micro-emulsification performance because it determines the rate and extent of drug release as well as drug absorption. Smaller particle size of the emulsion droplets may lead to more rapid absorption and improve the bioavailability. SMEDDS diluted with water and 0.1 mol/l HCl. All emulsions exhibited a singlet peak in their ultrasonic profile in terms of attenuation and sound speed in the megahertz frequency range, which allowed the characterization of the different zones of the ternary diagram such as micro emulsion, emulsion and gel zones, as well as the evaluation of water state and particle size (Palmieri et al., 2013).

Novel evaluation parameters

Acoustic spectroscopy: In SMEDDS particle size evaluation is rather essential parameter. Micro rheological extensional moduli and Particle size (i.e., G” and G’) of different systems were determined by employing acoustic parameters such as sound attenuation and speed. In which electric conductivity was also measured using the same instrument. The ultrasonic profile in terms of attenuation and sound speed in the megahertz frequency range, which allowed the characterization of the different zones of the ternary diagram such as micro emulsion, emulsion and gel zones, as well as the evaluation of water state and particle size.

Diffusing wave spectroscopy (DWS): The rheology of SMEDDS is not thoroughly characterized. To overcome these hurdle specific micro rheological technique called diffusing wave spectroscopy (DWS)is being employed to study different SMEDDS. The resulting data were then correlated with the dosing precision of automated capsule filling. And, the dynamic viscosities obtained from microrheology were in accordance with data from capillary viscometry (Niedrequella et al., 2012).

Raman spectroscopy and chemometrics: In SMEDDS the novel method can be successfully used to evaluate homogeneity in the drug content throughout the development of a lipid-based formulation (Das and Agrawal, 2011).

In vitro dissolution study: In vitro dissolution carried out using a USP30 Dissolution apparatus II with paddle. The test formulation was filled in size No. 0 hard gelatine capsules. Phosphate buffer solution (PBS) (0.2 M, pH 6.8) and 0.1N HCl solutions containing 0.5% of Tween 20 were used as media and were controlled at 37 ± 0.5 °C. Six replicate assessments were performed for each formulation in each of the media. During the release studies, the paddles were rotated at 100 rpm and a 5 ml aliquot was withdrawn at 0, 10…60 min. The removed volume was immediately replaced with 5 ml of fresh medium, samples were analyzed by HPLC.

Conclusions

Self microemulsifying drug delivery system is promising as well as reliable drug delivery system for increasing the solubility and bioavailability of not only poorly water soluble drugs categorized in BCS class II,IV but also in health care product such as nutraceuticals with the recent advances, this review also focus on recent formulation design and innovative evaluation parameters which are extensively used for successful delivery resulting in the expected pharmacological effects and surely enhances the patient compliances.

References


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