ejpmr, 2018,5(6), 717-725

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM: A NOVEL APPROACH TO ENHANCE THE ORAL BIOAVAILABILITY OF LIPOPHILIC DRUGS

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Article Received on 19/04/2018 **Article Revised on 09/05/2018** **Article Accepted on 30/05/2018**

ABSTRACT

Now days the present scenario is focusing more towards the targeted drug delivery systems because of the increasing interest in taking of safe drugs with less amount of drug, which is capable of reaching at the desired target site with minimal side effects. Novel drug delivery system has been introduced to overcome the drawback of fluctuating drug levels associated with conventional dosage forms.[1] Approximately 40% of new drug candidates have poor water solubility and the oral delivery of such drugs is frequently associated with low bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality.[1] To overcome these problems, various formulation strategies are exploited including the use of surfactants, lipids, permeation enhancers, micronisation, salt formation, cyclodextrins, nanoparticles and solid dispersions.[1] Recently, much attention has been paid to lipid-based formulations with particular emphasis on self-microemulsifying drug delivery systems (SMEDDS) to improve the oral bioavailability of lipophilic drugs.[2, 3]

KEYWORDS: SMEDDS, Drug targeting, Evaluation, Applications.

INTRODUCTION

LIPID FORMULATION CLASSIFICATION SYSTEM (LFCS)

LFCS was established by Pouton in 2000 and recently updated (2006) to help stratify formulations into those with similar component parts. The LFCS briefly classifies lipid-based formulations into four types according to their composition and the possible effect of dilution and digestion on their ability to prevent drug precipitation. A schematic illustration on lipid formulation classification system is given in Table No.1.

Table No.1: Compositions of lipid-based formulation[7]

Composition	Type I	Type II	Type III	Type IV	
	Oil	SEDDS	IIIA SEDDS	IIIB SMEDDS	Oil-Free
Glycerides (TG, DG, MG)	100%	40-80%	40-80%	< 20%	-
Surfactants (HLB < 12)	-	20-60%	-	-	0-20%
(HLB > 12)	-	-	20-40%	20-50%	20-80%
Hydrophilic co-solvents	-	-	0-40%	20-50%	0-80%
Particle size of dispersion(nm)	Coarse	100-250	100-250	50-100	< 50
Significance of aqueous Dilution	Ltd. important	Solvent capacity unaffected	Some loss of solvent capacity	Significant phase changes and potential loss of solvent capacity	Significant phase changes and potential loss of solvent capacity

***HLB: Hydrophilic Lipophilic Balance**

Type I lipid formulations

It consist of formulations which comprise drug in solution in triglycerides and/or mixed glycerides or in an oil in water emulsion stabilized by low concentrations of emulsifiers such as 1% (w/v) polysorbate 60 and 1.2% (w/v) lecithin.[26] Generally, these systems exhibit poor initial aqueous dispersion and require digestion by pancreatic lipase/ co-lipase in the GIT to generate more amphiphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase. Type I lipid formulations therefore represent a relatively simple formulation option for potent drugs or highly lipophilic compounds where drug solubility in oil is sufficient to allow incorporation of the required payload (dose).[5]

Type II lipid formulations

Self-emulsification is generally obtained at surfactant contents above 25% (w/w). However, at higher surfactant contents (greater than 50–60% (w/w) depending on the materials) the progress of emulsification may be compromised by the formation of viscous liquid crystalline gels at the oil/water interface.[28,29] Type II lipid-based formulations provide the advantage of overcoming the slow dissolution step typically observed with solid dosage forms and as described above generate large interfacial areas which in turn allows efficient partitioning of drug between the oil droplets and the aqueous phase from where absorption occurs.[5]

Type III lipid formulations

Commonly referred to as self-microemulsifying drug delivery systems (SMEDDS), are defined by the inclusion of hydrophilic surfactants (HLB>12) and co-solvents such as ethanol, propylene glycol and polyethylene glycol. Type III formulations can be further segregated (somewhat arbitrarily) into Type IIIA and Type IIIB formulations in order to identify more hydrophilic systems (Type IIIB) where the content of hydrophilic surfactants and co-solvents increases and the lipid content reduces. Type IIIB formulations typically achieve greater dispersion rates when compared with Type IIIA although the risk of drug precipitation on dispersion of the formulation is higher given the lower lipid content.[5]

Type IV lipid formulations

Type IV formulations do not contain natural lipids and represent the most hydrophilic formulations. These formulations commonly offer increased drug payloads when compared to formulations containing simple glyceride lipids and also produce very fine dispersions when introduced in aqueous media. Little is known however, as to the solubilization capacity of these systems in vivo and in particular whether they are equally capable of maintaining poorly water soluble drug in solution during passage along the GIT when compared with formulations comprising natural oils (Type II and Type III). An example of a Type IV formulation is the current capsule formulation of the HIV protease inhibitor Amprenavir (Agenerase) which contains TPGS as a surfactant and PEG 400 and propylene glycol as co-solvents.[5]

Biopharmaceutical Classification System (BCS):

Biopharmaceutics Classification System (BCS) was introduced in 1995 as a basis for predicting the likelihood of *In vitro-In vivo* correlations for immediate release dosage forms, based on the recognition that drug solubility/dissolution properties and gastrointestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption. According to BCS, drug substances are classified as, shown in Table No.2;

Table No.2: BCS classification.[10]

Class I	**High solubility High permeability**
Class II	**Low solubility High permeability**
Class III	**High solubility Low permeability**
Class IV	**Low solubility Low permeability**

SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEMS

SMEDDS are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) microemulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids.[11] 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 between 100 and 300 nm while SMEDDS form transparent micro emulsions with a droplet size of less than 100 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 which 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. 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.[11]

Advantages of SMEDDS

- **Improvement in oral bioavailability**

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 membrane leading to improved bioavailability.[12]

- **Ease of manufacture and scale-up**

SMEDDS require very simple and economical manufacturing facilities like simple mixer with agitator and volumetric liquid filling equipment for large-scale manufacturing.[12]

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

Food is a major factor affecting the therapeutic performance of the drug in the body. SMEDDS are a boon for such drugs.[13]

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

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.[15]

- **No influence of lipid digestion process**

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.[15]

- **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<logP>4) are typically low in natural lipids and much greater in amphiphilic surfactants, co surfactants and co-solvents.[15]

Advantages of SMEDDS over Emulsion

- SMEDDS is thermodynamically stable system.[15]
- SMEDDS exhibit optical transparency.[15]
- The size of the droplets of common emulsion ranges between 0.2 and 10 μm, and that of the droplets of microemulsion formed by the SMEDDS generally ranges between 2 and 100 nm (such droplets are called droplets of nano particles).Since the particle size is small, the total surface area for absorption and dispersion is significantly larger than that of solid dosage form and it can easily penetrate the gastrointestinal tract and be absorbed. The bioavailability of the drug is therefore improved.[15]
- 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.[15]

Excipients Used In SMEDDS:

The self-microemulsification process is specific to the nature of the oil/surfactant pair, the surfactant concentration and oil/surfactant ratio, the concentration and nature of co-surfactant and surfactant/co-surfactant ratio and the temperature at which self-microemulsification occurs. These important discoveries were further supported by the fact that only very specific combinations of pharmaceutical excipients led to efficient self- microemulsifying systems.[16]

1. OILS

The oil represents one of the most important excipients in the SMEDDS formulation not only because it can solubilize the required dose of the lipophilic drug or facilitate self emulsification 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. In general, when using LCT, a higher concentration of cremophor RH40 was required to form microemulsions compared with MCT.[16]

2. SURFACTANTS

The choice of surfactant 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). Non-ionic surfactants are less toxic than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen. Usually the surfactant concentration ranges between 30 and 60% w/w in order to form stable SMEDDS. It is very important to determine the surfactant concentration properly as large amounts of surfactants may cause GI irritation. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SMEDDS. Various non-ionic surfactants such as the polysorbates like Tween 40, 60, 80 and polyoxyls which cover the HLB range >12, may be used in combination with lipid excipients to facilitate self-emulsification or micro-emulsification.[16]

3. 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 which forms the microemulsion. 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.[16]

4. POLYMER

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 for the formulation of sustained release SMEDDS. Examples are hydroxypropylmethyl cellulose and ethyl cellulose.[16]

Benefits of SMEDDS

1. They led to enhanced oral bioavailability of drugs e.g. Ketoprofen
2. They decrease inter-subject and intra subject variability and food effects. e.g Cyclosporine.
3. SMEDDS are used to deliver peptides which are prone to enzymatic hydrolysis in GIT.
4. SMEDDS are used for both liquid and solid dosage forms. e.g. progesterone.
5. They can be produced at large scale.

Limitations of SMEDDS[3]

1. They are not used for drugs which are chemically unstable and have high stability concentrations.
2. The large amount of surfactant in formulations (30-60%) causes irritation in GIT.
3. Self emulsifying formulations which contain volatile co-solvents are incorporated in soft or hard gelatin capsules resulting in the precipitation of the lipophilic drug.

Drug properties suitable for SMEDDS[6]

1. Dose should not be so high.
2. Drug should be oil soluble.
3. High melting point of drug is poorly suitable to SMEDDS.
4. Log P value should be high.

Appropriate drug candidates for SMEDDS[7]

SMEDDS improve rate and extent of absorption of lipophilic/ hydrophobic drugs that exhibit dissolution rate-limited absorption. This may ultimately result in reproducible time profiles. However, we can apply SMEDDS approach to all drugs under biopharmaceutical classification system (BCS). The table 1 shows the various problems that can be solved through SMEDDS.

Table 3: Problems of BCS class entities that can be solved through SMEDDS.

BCS class	Problems
Class I	Enzymatic degradation and gut wall efflux
Class II	Solubilization and bioavailability
Class III	Enzymatic degradation, gut wall efflux and bioavailability
Class IV	Solubilization, bioavailability, Enzymatic degradation and gut wall efflux

Properties of the drug such as aqueous solubility and/or log P alone may not be sufficient for identifying suitability of lipid-based formulation, because they may not be able to effectively predict potential in vivo effects.

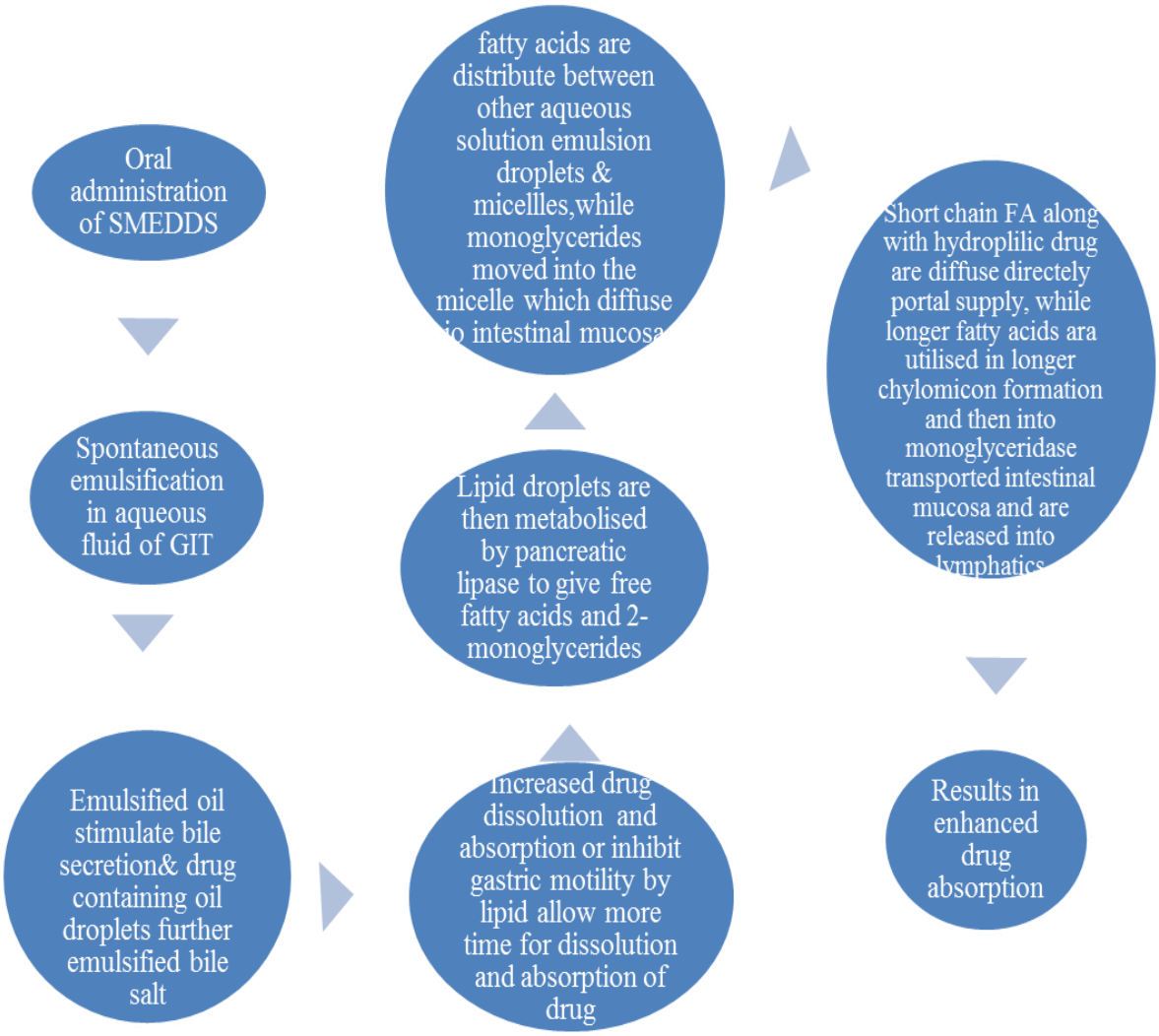
Mechanism of Self Emulsification: According to remiss, self emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion, The free energy of the convention all emulsion is a direct function of the energy required to create a new surface between the oil and water phases and can be described by the following equation.

DG = SNipri2s

Where- DG -the free energy associated with the process
N - The number of droplets of radius
r – The radius of droplet
S- The interfacial energy.

Two phases of emulsion tend to separate with time to reduce the interfacial area and subsequently, the emulsion is stabilized by emulsifying agents, which form a monolayer of emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence.[5]

MECHANISM OF BIOAVAILABILITY ENHANCEMENT FROM SMEDDS



Factors Affecting SMEDDS

- **Drug dose:** Usually drugs having high dose are not preferred for developing SMEDDS. However, such drug if extremely soluble in any components of SMEDDS particularly in lipid phase. The drug which are not well soluble both in water and oil, and also posses low Log P value (around 2) are not suitable candidates for SMEDDS.[20]
- **Drug solubility in oil phase:** Solubility of the drug in oil phase greatly influenced the ability of SMEDDS in maintaining the drug in solution state. When the drug is solubilized by the use of surfactant and co surfactant the dilution of SMEDDS can lead to lowering the solvent capacity of surfactant or co surfactant, their by resulting precipitation.[20]
- **Polarity of lipid phase:** The polarity indicates the affinity of the drug towards solvent, oil or water and the type of forces involved. The high polarity will promote rapid rate of release of the drug into the aqueous phase. The highest release was obtained with the formulation that had oily phase with highest polarity[20]

Biopharmaceutical Aspects

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

a) Alterations (reduction) in gastric transit, thereby slowing delivery to the absorption site and increasing the time available for dissolution.[20]

b) Increases in effective luminal drug solubility. The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipids (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilization capacity of the GI tract. However, intercalation of 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.[20]

c) Stimulation of intestinal lymphatic transport. For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly

or indirectly via a reduction in first-pass metabolism. A hydrophilic drug is less likely to be absorbed through the lymphatic (chylomicron) and instead may diffuse directly in to the portal supply. Hence in this case, increased dissolution from the large surface area afforded by emulsion may be a contributing factor to enhanced absorption of drugs.[20]

d) 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.[20]

Table No.4: Problems Associated with BCS class Drugs.

BCS Class I	**Enzymatic degradation, Gut wall efflux**
BCS Class II	**Solubilization & Bioavailability**
BCS Class III	**Enzymatic degradation, Gut wall efflux & Bioavailability**
BCS Class IV	**Enzymatic degradation, Gut wall efflux Solubilization & Bioavailability**

Pseudo ternary phase diagram

It is used to map the optimal composition range for three key excipients according to the resulting droplet size following self emulsification, stability upon dilution and viscosity. Phase diagrams are useful tools to determine the number and types of phases, the wt % of each phase and the composition of each phase at a given temperature and composition of the system. These diagrams are three-dimensional but are illustrated in two-dimensions for ease of drawing and interpretation. On the basis of the solubility study of drug, oil, surfactants, co-surfactants and aqueous phase were used for construction of phase diagram. Oil, surfactant, and co-surfactant are grouped in four different combinations for phase studies. Surfactant and co-surfactant (Smix) in each group were mixed in different weight ratio. These Smix ratios are chosen in increasing concentration of surfactant with respect to co-surfactant and in increasing concentration of co surfactant with respect to surfactant for detail study of the phase diagram for formulation of micro emulsion. For each phase diagram, oil, and specific Smix ratio are mixed thoroughly in different weight ratio in different glass vials. Different combination of oils and Smix were made so those maximum ratios were covered for the study to delineate the boundaries of phase precisely formed in the phase diagrams. Pseudo-ternary phase diagram was developed using aqueous titration method. Slow titration with aqueous phase is done to each weight ratio of oil and Smix and visual observation is carried out for transparent and easily flowable o/w micro emulsion. The physical state of the micro emulsion was marked on a pseudo-three-component phase diagram with one axis representing aqueous phase, the other representing oil and the third representing a mixture of surfactant and co-surfactant at fixed weight ratios (Smix ratio)15.

Preparation formulation

Briefly accurately weighted drug is placed in glass vial and oil, surfactant and co-surfactant added. Then the components are mixed gentle stirring and vortex mixing and are at heated 40 oc on magnetic stirrer, until drug is perfectly dissolved.[16]

Recent Advancements and Future Prospects[18]

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 suppositories
9. Self-emulsifying implants
10. Self-emulsifying fast dissolving tablets

Evaluation of SMEDDS[10,20,22,24]

The efficiency of self micro emulsification could be estimated by determining the evaluation parameters.

1. 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 droplet size values below 200 nm lead to the formation of SMEDDS, which are stable, isotropic and clear o/w dispersions.

2. Zeta potential measurement

This is used to identify the charge of the droplets. In conventional SEDDS, the charge on an oil droplet is negative due to presence of free fatty acids.

3. Refractive index and percent transmission

Refractive index and percent transmittance proves the clearness of formulation. The refractive index of the SMEDDS is measured by refractometer and compared with that of water. The percent transmittance of the system is measured at particular wavelength using UV-vis spectrophotometer keeping distilled water as blank. If refractive index of system should be similar to that of water. Formulation showing transmittance >99 percent is transparent in nature.

3. Thermodynamic stability studies

I) Heating cooling cycle

Six cycles between refrigerator temperature (40C) and 450C 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.

II) Centrifugation

Passed formulations are centrifuged thaw cycles between 21 C and +25 0C with storage at each temperature for not less than 48 h is done at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.

III) Freeze thaw cycle

Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

4. Dispersibility test

The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus 2. One millilitre of each formulation was added to 500 ml of water at 37 ± 0.5 0C. A standard stainless steel dissolution paddle rotating at 50 rpm 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 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 nano-emulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation.

5. Determination of emulsification time

Quantified the efficiency of emulsification of various compositions of the Tween85 and medium-chain triglyceride systems using a rotating paddle to promote emulsification in a crude nephelometer. This enabled an estimation of the time taken for emulsification. Once emulsification was complete, samples were taken for particle sizing by photon correlation spectroscopy, and self-emulsified systems were compared with homogenized systems. The process of self-emulsification was observed using light microscopy. It was clear that the mechanism of emulsification involved erosion of a fine cloud of small particles from the surface of large droplets, rather than a progressive reduction in droplet size.

6. Viscosity Determination

The SMEDDS system is generally administered in soft gelatin or hard gelatin capsules. Therefore, it should be easily pourable into capsules and such system should not be too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield Viscometer. This viscosity determination confirms 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.

7. Robustness to dilution

Formulations were subjected to 50,100,250 fold dilution with enzyme free simulated gastric fluid pH 1.2; enzyme free simulated intestinal fluid pH 6.8 and distilled water. The resultant diluted emulsions were observed for any physical changes like coalescence of droplets, precipitation or phase separation after 24 hrs.

8. Cloud point measurement

The optimized SNEDDS formulations were diluted with distilled water in the ratio of 1:250. The diluted samples were placed in a water bath and its temperature was increased gradually cloud point was spectrophotmetrically determined as the temperature at which there was a sudden appearance of cloudiness.

9. Drug content determination

Drug from pre-weighed SNEDDS 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.

10. Electron Microscopic Studies

Freeze-fracture electron microscopy has been used to study the surface characteristics of the SEDDS. Transmission Electron Microscopy (TEM), Cryo-Transmission Electron Microscopy (Cryo-TEM Studies) techniques are used to perform electron microscopic studies.

11. Conductivity Measurement

Conductivity Measurement based on the phase inversion phenomenon determines the point of aqueous phase addition where oil phase continuously changed in water continuous phase.

12. Polydispersibility Index

Polydispersity index (PDI) is measure of droplet size homogeneity and it varies from 0.0 to 1.0. Polydispersity is the ratio of standard deviation to mean droplet size in the formulation. The higher the Polydispersity, the lower the uniformity of the droplet size in the formulation. The closer to zero the Polydispersity value the more homogenous are the droplets.

13. % transmittance

The clarity of the formulations was observed by measuring % Transmittance of all formulations in UV spectrophotometer using double distilled water as blank.

APPLICATIONS

1. Oral bioavailability enhancement poorly water soluble drugs

In case of poorly water \soluble drugs dissolution rate dependent absorption is a major factor that limits the bioavailability. The ability of self-emulsification to release in the drug to GIT and disperses to micro emulsified form. As the globular size is so small 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.[9]

Table 5: A Table.

Drug	Bioavailability Enhancement of all the drugs whose bioavailability was increased by using SMEDDs
Simvastatin	1.5 folds
Ketoprofen	1.13 folds
Vitamin A	2 folds
Vinpocetin	17.3 folds

2. 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 degradation 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. Such drugs when presented in the form of SEDDS can be well protected against these degradation processes as liquid crystalline phase in SEDDS might be an act as barrier between degradation environment and the drug.[25]

CONCLUSION

Self micro-emulsifying drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility, having high molecular weight, pre systematic first pass effect, enzymatic degradation, gastric irritation, having limited dissolution rate and low bioavailability. This is the method suited for all BCS class drugs where resulting emulsification is gives faster dissolution and absorption rates. In future development SMEDDS will continue to novel applications in drug delivery and solve the problems associated with the delivery of poor water soluble drug, pre-systematic first pass effect, enzymatic degradation and having limited dissolution and low bioavailability.

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