Review Article

A Review on Self Microemulsifying Drug Delivery System: A Method for Enhancement of Oral Bioavailability

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ABSTRACT

Oral route has constantly been desired course for formulators and has dominated over other routes of administrations. But principal problem encountered in oral formulations, is low bioavailability, giving rise to similarly issues like, excessive inter and intra issue variability, loss of dose uniformity and ultimately main to healing failure. Approximately 40 % of new chemical entities show off negative aqueous solubility and present a primary task to trendy drug shipping device, due to their low bioavailability. Particularly for BCS class II drugs, the bioavailability may be more advantageous by using growing the solubility and dissolution charge of the drug inside the gastro-intestinal fluids. The more modern and novel technology developed for solubility enhancement. This assessment article gives a whole assessment of SMEDDS as a successful method to overcome the problem of poorly soluble molecules.

Keywords: Solubility, BCS class II drugs, solubility enhancement, bioavailability.

INTRODUCTION

The most popular route of administration is oral route in many diseases. Major problem in oral direction of drug administration is decreased bioavailability which in particular consequences from aqueous solubility. Nearly 40% of recent drug applicants show off low solubility in water, that is a undertaking in improvement of greatest oral solid dosage form. For better therapeutic reaction, solubility is one of the most important parameters to acquire preferred attention of drug in systemic stream. Poor solubility of drug in systemic flow leads to problems in dose uniformity. It is located that maximum of the active materials are poorly water-soluble. Many strategies were used to overcome those troubles both by modifying the solubility or maintaining the drug in dissolved shape in the course of gastric transit time. Much attention has targeted on lipid answers, emulsions and emulsion pre-concentrates, which may be prepared as completely solid formulations suitable for encapsulation of such poorly soluble capsules. Recently, self-micro emulsifying drug shipping structures (SMEDDS) especially have attracted increasing hobby in the main due to the fact those are completely solid, smooth to fabricate, can be stuffed in tender gelatin capsules after which will generate a drug containing micro-emulsion with a massive surface region upon dispersion within the gastrointestinal tract. In Self micro emulsifying drug shipping systems drug is encapsulated in a lipid base with or without pharmaceutical perfect surfactant. Self-micro emulsifying drug delivery systems are isotropic mixture of oil, surfactant, and co-surfactant and are critical tool in fixing low bioavailability issue of poorly soluble drug. SMEDDS form transparent micro-emulsions (a droplet size of much less than 50 nm). The attention of oil in SMEDDS is less than 20 %. SMEDDS will maintain to allow novel packages in drug transport and resolve problem related to the transport of poorly soluble tablets. The emulsions will similarly facilitate the absorption of the drug due through intestinal lymphatic pathway and by way of separating of drug into the aqueous section of intestinal fluids. [1, 2]

Biopharmaceutical classification system (BCS):

Biopharmaceutics Classification System (BCS) become delivered in 1995 as a foundation for predicting the chance of in vitro-in vivo correlations for immediate launch dosage paperwork, based totally on the popularity that drug solubility/dissolution homes and gastrointestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption. According to BCS, drug substances are labeled as:

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

Solubility : A drug substance is taken into consideration particularly soluble during the highest dose strength is soluble in 250 ml or much less of aqueous media over a pH range of 1 to 7.5 (equilibrium solubility at 37°C).

Permeability: In the absence of evidence suggesting instability inside the gastrointestinal tract, a drug substance is considered relatively permeable at the same time the quantity of absorption in people is determined to be 90 % or greater of an administered dose based totally on mass stability resolve or in contrast to an intravenous reference dose (absolute bioavailability study).[3]

Mechanism of self emulsification

The free energy of the emulsion can be described by means of the subsequent equation : $\Delta G = \sum N\Pi r2\sigma$. ΔG is the free energy, is the number of droplets, r is the radius of droplets, and σ is the interfacial electricity. From this equation, it is obvious that the decrease the interfacial electricity the lower the loose strength. Self-emulsification happens at the same time the power involvement within the dispersion is extra than the strength required for the formation of droplets.[4] The levels of emulsion generally tend to separate with time to reduce the interfacial region and in the end the emulsion is stabilized by using emulsifying agents, which form a monolayer of emulsion droplets, and as a result reduces the interfacial energy, as well as offering a barrier to prevent coalescence.[5] For example The temperature of the oil in water system, stabilized by using the use of non-ionic surfactant(s) is extended; the cloud point of the surfactant would be attained observed by phase inversion. The surfactant is highly vigorous on the phase inversion temperature; hence, the o/w interfacial energy is minimized, results to reduce in strength needed for emulsification.[1]

Advantages:

1. Minimizing inflammation with contact of GIT and intestine wall.

2. Ease of manufacture and scale up.

3. Deliver peptides which can be exposed to enzymatic hydrolysis in GIT.

4. It gives prolonged launch of medicaments meanwhile polymer is incorporated.

5. Safe and easy composition of SMEDDS.

6. More consistent temporal profiles of drug absorption.

7. Selective drug concentrated on in the direction of a selected absorption window within the GI tract.

8. Drug protection from the antagonistic environment inside the gut.

9. Novel technique to enhance water solubility and final bioavailability of lipophilic drugs.

10.It suggests large inter and intra difficulty versions in absorption leading to fluctuation in plasma profile of liquid or strong dosage forms.[6]

Disadvantages:

1. In vitro model desires in addition development and validation before its power may be evaluated.

2. Chemical instabilities of medication and high % of surfactant may also inflame GIT.

3. Co- solvents can migrate into the shells of tender or difficult gelatin drugs, resulting inside the precipitation tablets.

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

5. Formulations containing several excipients are greater hard to validate.[7]

6. Traditional dissolution strategies do no longer work, because these formulations probably depending on digestion previous to release of the drug.

7. This in vitro model desires similarly development and validation before its strength may be evaluated. Further improvement will be based on in vitro - in vivo correlations and consequently distinctive prototype lipid based formulations needs to be developed and tested in vivo in a appropriate animal model.

8. The drawbacks of this device include chemical instabilities of drugs and high surfactant concentrations in formulations (about 30-60%) which irritate GIT.

9. Moreover, risky co-solvents in the traditional self-micro emulsifying formulations are acknowledged to migrate into the shells of soft or hard gelatin pills, ensuing within the precipitation of the lipophilic tablets.

10. The precipitation tendency of the drug on dilution can be better because of the dilution impact of the hydrophilic solvent.

11. Formulations containing numerous additives become greater hard to validate.[8]

COMPOSITION OF SMEDDS

Many studies have revealed that the self micro emulsification process is specific to the nature of oil/surfactant ratio; oil/surfactant pair; surfactant concentration; concentration and nature of cosurfactant; surfactant and co-surfactant ratio and temperature at which he self micro emulsification occurs. Use of other excipients in the SMEDDS is governed by the type of dosage form. The formulated SMEDDS is specific to the particular drug only.

Components used in SMEDDs:

Oils

Surfactant

Co-surfactant

Co solvent.[9]

1. Oils

The oil is an important component as it facilate the self micro emulsion formation. The lipophilic drug can be solubilise in oils and increase the drug transport across intestinal lymphatic system and increased the drug absorption rate. Hydrogenated vegetable oils have many advantages as the foundation of lipid-based delivery systems. They are frequently ingested with food as they are fully digested and absorbed without any safety issues. Vegetable oils are glyceride product of glycerolysis esters

of mixed containing unsaturated long chain fatty acids which is commonly known as long-chain triglycerides (LCT). The Oils from different vegetable sources have different proportions of each fatty acid. The Coconut oil is carry over distillation to produce the 'medium-chain triglycerides' (MCT) (also known as glyceryl tricaprylate /caprate) which is available from several suppliers and commonly comprises glyceryl esters containing saturated C8 (50–80%) and C10 (20–45%) fatty acid. Castor oil is common source of Glyceryl ricinoleate, which uniquely has a hydroxyl group coupled to the alkyl chain.[6]

2. Surfactants

The necessity of surfactants is confined as just some surfactants are orally desirable. Non-ionic surfactants with high HLB price are utilized in method of SMEDDS along with : Ethoxylated polyglycolysed glycerides, Tween 80, LABRFAC CM1O-a mixture of saturated compounds containing 8 carbon polyglycolysed glycosides (HLB =10,Gattefosse Corporation, Westwood, N.J.) and different lengthy chain alkyl sulfonate sulfats surfactants, inclusive of sodium dodecyl benzene sulfonate, sodium lauryl sulfates and dialkyl sulfo succinate and quaternary ammonium salts, fatty alcohols inclusive of lauryl, cetyl and stearyl, glyceryl esters, acid esters and polyoxyethylene derivatives. Emulsifiers derived from natural assets are predicted to be safer than synthetic ones and are recommended for SMEDDS use regardless of their restrained capacity to self-emulsify.[10] Surfactant molecules may be classified on the basis of nature of the hydrophilic group within the molecule. The four main groups of surfactants are defined as follows:

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

Cationic surfactant, where the hydrophilic group contains a highly positive charge molecules. Example: quaternary ammonium halide.

Ampholytic surfactants (also known as zwitterionic surfactants) contain both charges such as positive and negative. Example: sulfobetaines.

Nonionic surfactants, where the hydrophilic groups consists of no charge but derives its water solubility from noticeably polar group inclusive of hydroxyl or polyoxyethylene (OCH2CH2O). Examples: Sorbitan esters (Spans), polysorbates (Tweens). The surfactants utilized in these formulations are known to enhance the bioavailability via numerous mechanisms along with improved drug dissolution, extended intestinal epithelial permeability.[11]

3. Co-surfactants

Co-surfactants with HLB value 10-14 are used in conjunction with surfactant for lowering the interfacial tension, interface could make bigger to shape satisfactory dispersed droplets. Fluid interfacial film is completed through the addition of a cosurfactant. Co-surfactant will enhance the fluidity of the interface and thereby increasing the entropy of the system.[12]

4. Co-solvents

Ethanol, polyethylene glycol, propylene glycol, transcutol are particularly used organic solvents for oral dosage shape. They help in dissolving big amount of surfactant or drug in lipid base, to help the dispersion technique, to lower amount of surfactant in components and can carry out motion of co-surfactant in microemulsion gadget. Alcohol and other volatile solvents migrate into soft gelatin capsule shell and causes precipitation of lipophilic drug. But, lipophilic drug of alcohol loose merchandise have constrained dissolution capability. Low molecular weight solvents are incompatible with capsule shell. So, proper solvent must be decided on. Propylene glycol, dimethyl isosorbide, mannitol, isopropanol, sorbitol, glycerol are typically used co-solvents in SMEDDS.[13]

Table 1: Examples of oils, surfactants and co-surfactant / co-solvent.[14]

Oils	Surfactants	Co-surfactant / co-solvent
Cotton seed oil Soyabean oil Corn oil Sunflower oil Castor oil Sesame oil Labrafac	Polysorbate 20 (Tween 20) Polysorbate 80 (Tween 80) D-alpha Tocopheryl polyethylene glycol 1000 succinate (TPGS) Polyoxy-35-castor oil (cremophore RH 40)	Span 20 Span 80 Capryol 90 Transcutol Isopropyl alcohol Ethanol Polyetylene glycol

Formulation design

1. Screening of excipients: The following parameters have to be considered at some point of the components of SMEEDS. Solubility of the drug in extraordinary oil, surfactants, and co-surfactants. The choice of suitable oil, surfactant, co-surfactant and preparation of phase diagram.

2. Solubility studies: These research are normally carried out with the goal of selecting an oil, surfactant and co surfactant that indicates most capability to solubilize the drug. The solubility of the medicine in numerous oils, surfactants and co-surfactants is decided by way of shake flask technique. In this method, the drug is typically delivered to the excipients in extra amount after which shaken for 48 hours in water tub or in air oscillator at room temperature. Then samples are subjected to centrifugation followed by means of filtration through 0.45µm filter out and drug content material is determined.[9]

Ternary phase diagram

Pseudo-ternary phase diagram of oil, surfactant / cosurfactant (Smix) and water were created using the

water titration system. The blends of oil and Smix at certain weight proportions had been diluted with water in a dropwise way. For every segment diagram at a specific share of Smix (i.e., 1:1, 2:1, 3:1, 1:2 and 1:3 w/w), uncomplicated and homogeneous blends of oil and Smix in percentage 1:9 to nine:1 w/w were prepared and shake for five minutes. At that point each mixture become titrated with water and outwardly watched for stage readability and flowability. The awareness of water at which turbidity-to-transparency and transparency to turbidity transitions occurred become derived from the burden measurements. These traits have been then used to decide the bounds of the microemulsion area relating to the chosen estimation of oils and similarly Smix blending share. The pseudo ternary degree outlines had been plotted with the assistance of CHEMIX Software.

Formulation of SMEDDS

Upon dilution, the SMEDDS formulation immediately forms a clean dispersion and stays stable. The hydrophobic drug dispersed within the SMEDDS components remains solubilized it is absorbed. Efficient release of the drug from the formula in particular depends on two elements, globule length and polarity of the droplets. In case of oil-in water micro-emulsions, the polarities of oil droplets aren't significant, because the drug included within the oil globules attain the capillaries. The following parameters need to be taken into consideration for the duration of the formula of SMEDDS:

1. Solubility of the drug in various oil, surfactants and co-solvents.

2. Selection of oil, surfactant and co-solvent based at the solubility of the drug, and preparation of the phase diagram.

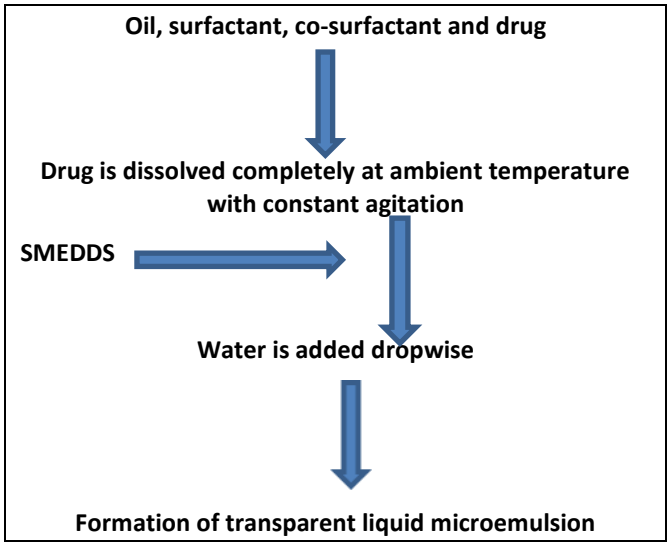

Figure 1: Flow chart for preparation of SMEDDS [15]

Selection of suitable drug candidate

Lipid primarily based formulations offer a potential platform for improving oral bioavailability of drugs specially those belonging to Biopharmaceutical Classification System (BCS) class II and class IV. A number one indication of the capability software of lipid based totally components can be acquired by using assessing the drug lipophilicity (log P) and its solubility in pharmaceutically-appropriate lipid excipients, which enough to allow the complete dose of the drug to be administered in a single dosage unit. Another indicator of the potential for fulfillment of lipid based totally method is the observance of a fatty meals impact when the drug is administered with a fatty meal in place of dosing inside the fasted. For lipophilic drug compounds that exhibit dissolution, dissolution-rate-limited absorption, SMEDDS can provide an development in rate and extent of absorption resulting in reproducible blood time profile. The structures SMEDDS generally provide advantage of elevated drug loading potential when comparison with lipid solutions as the solubility of poorly water soluble drugs with intermediate partition coefficient (2<log P<4) are normally low in natural lipids and more extra in amphiphilic surfactants, co-surfactants and co-solvents. The partition coefficient (log P) is the prime criterion of designing lipid based systems. High log P (greater than 4) is appropriate for lipidic structures. Next physicochemical criteria that play an essential position are melting point and dose. Low melting factor and occasional dose are applicable for development of lipidic structure.[15]

Recent advancement and future prospects of SMEDDS

Dry emulsions: Dry emulsions are powders from which emulsion spontaneously happens in vivo or whilst uncovered to an aqueous solution. Dry emulsions can be beneficial for in addition instruction of tablet and capsule. Dry emulsion formulations are usually prepared from oil/ water (O/W) emulsions containing a strong provider (lactose, malto dextrin, and so on) inside the aqueous segment via rotary evaporation, freeze-drying or spray drying. This formulation consisted of surfactant; a vegetable oil, and a pH-responsive polymer, with lyophilisation used.

Self-emulsifying Capsules: Oral administrations of capsules has been found to increase patient compliance compared with the previously used parenteral route. For example, low molecular weight heparin (LMWH) used for the treatment of venous thrombo-embolism turned into clinically to be had most effective via the parenteral course. So, oral LMWH therapy become investigated by using formulating it in difficult pills.

Self-emulsifying sustained/controlled release tablets: Combinations of lipids and surfactants have provided great ability of making ready SE drugs that have been broadly researched. SE tablets may enhance its penetration efficacy through the GI mucosal membranes, doubtlessly reducing GI bleeding. The resultant SME drugs continuously maintained a better active factor attention in blood plasma over the identical time body in comparison with a non-emulsifying tablet.

Self-emulsifying sustained/controlled release pellets: Pellets as a multiple purpose unit dosage form, possess many advantages such as flexibility of manufacture, reducing intrasubject and inter subject variability of plasma profiles and minimizing GI inflammation without reducing drug bioavailability. Pellets were prepared by using extrusion/ spheronization and contained water-insoluble model drugs (methyl and propyl parabens); SES contained monodiglycerides and Polysorbate 80.[16]

Characterization & evaluation of SMEDDS:

The number one method of self-microemulsification evaluation is visual assessment. The performance of self microemulsification could be determined with the rate of droplet size distribution and turbidity measurement.

Droplet size and particle size measurement

The molecule size of the micro emulsion is determined by photon correlation spectroscopy or SEM (Scanning Electron Microscopy) that could measure sizes somewhere round 10 to 5000 nm.[17]

Zeta potential measurement

Zeta potential indicates the stability of emulsion after appropriate dilution. The formula remains strong if it has higher zeta ability. However, a zwitterion rate is shown to have better biocompatibility and a better blood residence time compared to the particles displaying both surface charge.[18]

Refractive index and percentage transmission

Refractive index and percentage transmittance proves transparency and balance of system on dilution. Colour takes place on dilution due to presence of artificial oil and polyosorbate derivatives. Transparency decreases with increase in oil droplet size. The refractive index is measured by using refractometer and percent transmittance is measured at precise wavelength making use of UV-Vis spectrophotometer keeping distilled water as clean. Detailing suggests transmittance >85 percentage is transparent in nature.[13]

Thermodynamic stability studies

Freeze thawing is employed to assess the stability of formulations. The formulations are subjected to 3 to 4 freeze -thaw cycles, which include freezing at –4°C for 24 hours accompanied by means of thawing at 40°C for 24 hours. Centrifugation is achieved at 3000 rpm for 5 mins. The formulations are then determined for phase separation. Only formulations which are stable to phase separation are include in similarly research.[7, 19]

Dissolution study

The SMEDDS and the marketed system of the drug are introduced to dissolution vessels of United States Pharmacopeia (USP)-24 type 2 dissolution test apparatus. The dissolution medium used is 0.1 M hydrochloric acid (900 ml) maintained at 37.0˚C ± 0.5˚C and stirred at a100 r/min. A blank is tested for dissolution, concurrently, under same situations to check for interference, if any. Aliquots had been collected periodically and replace with clean dissolution medium. Aliquots, after filtration via whatman clear out paper are analyzed with the help of spectrophotometer for drug content.[20]

Viscosity Measurements

Viscosity measurements can suggest the presence of rod-like or worm like reverse micelles. Viscosity measurements as a characteristic of volume fraction were used to determine the hydrodynamic radius of droplets, as well as interaction between droplets and deviations from spherical shape with the aid of fitting the effects to suitable models (e.g For micro-emulsions showing Newtonian behaviour, Einstein's equation for the relative viscosity may be used to calculate the hydrodynamic volume of the particles.[21]

Temperature Stability

Shelf life as a function of time and storage temperature became evaluated by using visual inspection of the SMEDDS system at exceptional term. SMEDDS are diluted with purified distilled water and to check the temperature stability of samples, they had been kept at 3 extraordinary temperature range (2-8 °C (fridge), Room temperature) and found for any evidences of phase separation, flocculation or precipitation.[14]

Drug content material

The formulated SMEDDS equal to 10 mg of drug is taken and dissolved in methanol and the consequent sample with right dilutions are checked for their absorbance in UV and percent drug content is calculate.[22]

Dispersibility Test

The performance of self emulsification of oral nano or microemulsion is assessed using a widespread USP dissolution apparatus II. One milliliter of every system is brought to 500 ml of water at 37 ± 0.5 °C. A dissolution paddle rotating at 50 rpm presents mild agitation. The in vitro overall performance of the formulations is visually assessed the use of the subsequent grading system:

Grade A: Rapidly forming (in1 min) nanoemulsion, having a clean or bluish look.

Grade B: Rapidly forming, barely much less clear emulsion, having a bluish white look.

Grade C: Fine milky emulsion that shaped inside 2 min.

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

Grade E: Formulation, shows minimal emulsification with huge oil globules present on the bottom. Grade A and Grade B formulation will remain as nanoemulsion where they dispersed in GIT. While formula falling in Grade C could be suggest for SEDDS components.[23]

Cloud point measurement

The cloud point measurement is important issue in SMEDDS because it offers information about the stableness of micro-emulsion formed at body temperature. The components is diluted in water and kept on water bath and temperature is increase progressively. The factor at which cloudiness observed is determined as cloud factor.[6]

CONCLUSION

This review article gives a complete overview of SMEDDS as a capable approach to effectively capture the problem of poorly soluble molecules. It gives the novel approaches for evaluation of the SMEDDS. Dissolution of drug is the rate-determining step for oral absorption of the poorly water-soluble drugs, which can subsequently affect the in vivo absorption of drug. Hence, solubility enhancement becomes necessary. It is now possible to increase the solubility of poorly soluble drugs with the help of various techniques like SMEDDs and other new techniques.

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