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A Review on "Self Micro Emulsifying Drug Delivery System (SMEDDS)

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ABSTRACT

The most popular route of administration is oral route in many diseases. Major problem in oral route of drug administration is decreased bioavailability which mainly results from poor aqueous solubility. For better therapeutic response, solubility is one of the most important parameter to achieve desired concentration of drug in systemic circulation. Poor solubility of drug in systemic circulation leads to problems in dose uniformity. It is found that most of the active substances are poorly water-soluble. In Self micro emulsifying drug delivery systems drug is encapsulated in a lipid base with or without pharmaceutical acceptable surfactant. Self micro emulsifying drug delivery systems are isotropic mixture of oil, surfactant, and co-surfactant and are vital tool in solving low bioavailability issue of poorly soluble drug. Lipophilic drugs can be dissolved in that system, enabling them to be administered as a unit dosage form for per oral administration. SMEDDS will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

INTRODUCTION

Oral route is one of the most patient widely used routes for the most of the pharmacologically chronic treatment disease. [1,2] Up to 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which lead to poor oral bioavailability, high intra and inter subject variability and lack of dose proportionality.[3]To deal with the problem of poor solubility number of technologies are available. Self micro emulsifying drug delivery system (SMEDDS) is defined as isotropic mixture of oil and surfactants or alternatively one or more hydrophilic solvents and co-solvents. SMEDDS form transparent microemulsions (a droplet size of less than 50 nm). The concentration of oil in SMEDDS is less than 20 %.

SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS)

Upon mild agitation provided by peristalsis movement followed by dilution in aqueous media such as the gastrointestinal (GI) fluid, these systems can form fine oil in water (o/w) emulsions or microemulsions (self micro emulsifying drug delivery system). Self micro emulsifying formulations good spreadability in the GI tract and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. SEDDS typically produce emulsion with a droplet size between 100 and 300 nm while SMEDDS form transparent microemulsion with a droplet size of less than 50 nm. [4] Drug present in SMEDDS in small droplet size and well proportioned distribution, will increase the dissolution and permeability. An additional advantage of SMEDDS over simple oily solutions is that they provide a large interfacial area for partitioning of the drug between oil and water. [5]

DIFFERENCE BETWEEN SEDDS AND SMEDDS:

Sr. No	Property	Emulsion	Microemulsion
1	Appearance	Cloudy	Transparent
2	Droplet size	>500nm	20-200nm
3	Phases	Biphasic	Monophasic
4	Stability	Thermodynamically unstable	Thermodynamically stable
5	Viscosity	High	Low
6	Interfacial Tension	High	Ultra low
7	Energy required	Large input of energy required	Less energy required

POTENTIAL ADVANTAGES OF SMEDDS [6, 7]

1. Minimizing irritation with contact of GIT and gut wall.
2. Ease of manufacture and scale up.
3. Deliver peptides that are prone to enzymatic hydrolysis in GIT.
4. It gives prolonged release of medicaments when polymer is incorporated.
5. Safe and easy composition of SMEDDS.
6. More consistent temporal profiles of drug absorption.
7. Selective drug targeting toward a specific absorption window in the GI tract.
8. Drug protection from the hostile environment in the gut.
9. Novel approach to improve water solubility and ultimate bioavailability of lipophilic drugs.
10. It shows large inter and intra subject variations in absorption leading to fluctuation In plasma profile of liquid or solid dosage forms

COMPOSITION of SMEDDS

1. OILS

The oil represents the most important excipient in the SMEDDS formulation. Indeed it can solubilize relevant amount of the poorly water soluble drug. Both long-chain triglyceride (LCT) and medium chain triglyceride (MCT) oils with different degrees of saturation have been used in the design of SMEDDS E.g. Corn oil, olive oil, soybean oil, hydrolyzed corn oil.

2. SURFACTANT

Surfactant molecules may be classified based on the nature of the hydrophilic group within the molecule. The four main groups of surfactants are defined as follows,

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

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

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

d. Nonionic surfactants, where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene (OCH2CH2O) e.g. Sorbitan esters (Spans), polysorbates (Tweens). Nonionic surfactants with high hydrophilic lipophilic balance (HLB) values are used in formulation of SMEDDS. The usual surfactant strength ranges between 30-60% w/w of the formulation in order to form a stable SMEDDS. Surfactants having a high HLB and hydrophilicity assist the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amount of hydrophobic drug compounds.

3. CO-SOLVENTS

Organic solvents such as ethanol, propylene glycol (PG) and polyethylene glycol (PEG) are suitable for oral delivery and they enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in the lipid base[7]. These solvents can even act as co-surfactants in microemulsion systems. Alternately alcohols and other volatile co-solvents have the disadvantage that of evaporating into the shells of the soft gelatin or hard sealed gelatin capsules in conventional SMEDDS leading to drug precipitation.

4. OTHER COMPONENTS

Other components might be pH adjusters, flavors, and antioxidant agents. Indeed a characteristic of lipid products, particularly those with unsaturated lipids show peroxide formation with oxidation. Free radicals such as ROO, RO., and .OH can damage the drug and induce toxicity. Lipid peroxides may also be formed due to auto-oxidation, which increases with unsaturation level of the lipid molecule. Hydrolysis of the lipid may be accelerated due to the pH of the solution or from processing energy such as ultrasonic radiation. Lipophilic antioxidants (e.g. α-tocopherol, propyl gallate, ascorbylpalmitate or BHT) may therefore be required to stabilize the oily content of the SMEDDS.

FORMULATION OF SMEDDS [9]

1. The solubility of drug in different oil, surfactant, and co-solvent.

2. The selection of oil, surfactant, and co-solvent based on the solubility of the drug and the preparation of phase diagram.

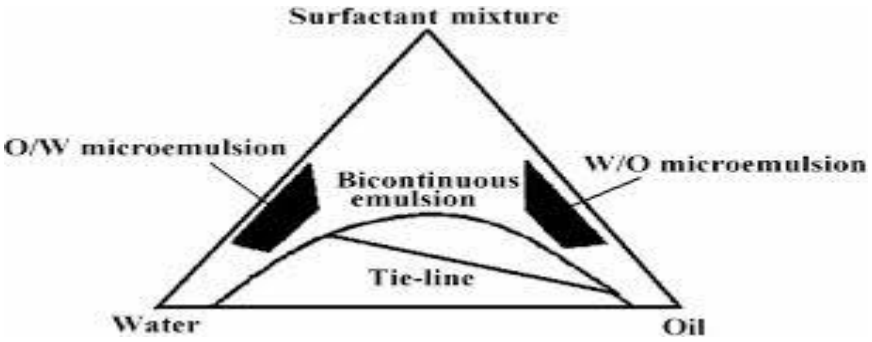
3. The preparation of SMEDDS formulation by dissolving the drug in a mixture of oil, surfactant, and co-solvent.

4. The drug interferes with the self emulsification process to certain extent during addition to a SMEDDS, which leads to a change in the optimal oil – surfactant ratio. So, the design of an optimal SMEDDS requires pre-formulation solubility and phase diagram studies.

METHOD OF PREPARATION:-[10]

1. Phase Titration Method :

Microemulsions are prepared by the spontaneous emulsification method (phase titration method) and can be depicted with the help of phase diagrams. Construction of phase diagram is a useful approach to study the complex series of interaction that can occur when different components are mixed. Microemulsions are formed along with various association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and various gel and oily dispersion) depending on the chemical composition and concentration of each component. The understanding of their phase equilibrium and demarcation of the phase boundaries are essential aspects of the study.



Because, quaternary phase diagram (four component system) is time consuming and difficult to interpret, pseudo ternary phase diagram is constructed to find the different zones including microemulsion zone, in which each corner of the diagram represents 100% of the particular component Fig. 5. The region can be separated into w/o or o/w microemulsion by simply considering the composition that is whether it is oil rich or water rich. Observation should be made carefully so that the metastable systems are not included.

2. Phase inversion Method:

Phase inversion of microemulsions occurs upon addition of excess of the dispersed phase or in response to temperature. During phase inversion, drastic physical changes occur including changes in particle size that can affect drug release both *in vivo* and *in vitro*. These methods make use of changing the spontaneous curvature of the surfactant. For non-ionic surfactants, this can be achieved by changing the temperature of the system, forcing a transition from an o/w microemulsion at low temperatures to a w/o microemulsion at higher temperatures (transitional phase inversion). During cooling, the system crosses a point of zero spontaneous curvature and minimal surface tension, promoting the formation of finely dispersed oil droplets. This method is referred to as phase inversion temperature (PIT) method. Instead of the temperature, other parameters such as salt concentration or pH value may be considered as well instead of the temperature alone.

Additionally, a transition in the spontaneous radius of curvature can be obtained by changing the water volume fraction. By successively adding water into oil, initially water droplets are formed in a continuous oil phase. Increasing the water volume fraction changes the spontaneous curvature of the surfactant from initially stabilizing a w/o microemulsion to an o/w microemulsion at the inversion locus. Short-chain surfactants form flexible monolayers at the o/w interface resulting in a discontinuous microemulsion at the inversion point.

MECHANISM OF BIOAVAILABILITY ENHANCEMENT FROM SMEDDS:-

The absorption of fats from the GIT [11]: Triglyceride molecules are fatty acid esters of glycerol. The ester groups of the triglycerides are prone to hydrolysis and this represents the major initial route of metabolism within the GI tract. On ingestion of the triglycerides, the lipids enter the stomach. On entering the upper section of the small intestine the triglyceride droplets are metabolized by pancreatic lipase, to free fatty acids and 2-monoglycerides, the last two contributing to the digestion process as they themselves are emulsifying agents.

Bioavailability of drugs from oily vehicles [12]: According to studies the absorption of Griseofulvin from commercial tablets, a corn oil emulsion (equivalent to 12 g oil) and an aqueous suspension in humans. The emulsion gave a much more rapid excretion of Griseofulvin

metabolite, Desmethyl - Griseofulvin. The inhibition of gastric motility caused by the presence of the lipid might have allowed more time for dissolution, absorption and of drug.

Drug absorption from SMEDDS [11]: The authors suggested that as the oil phase was a medium chain triglyceride, lymphatic uptake was unlikely to be enhanced; hence, the drug absorption may be a function of the increased surface area for dissolution provided by the emulsion.

FACTOR AFFECTING SMEDDS [11][13]

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 possess low Log P value (around 2) are not suitable candidates for SMEDDS.

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, there by resulting precipitation.

Polarity of lipid Phase: It is one of the factors that govern the release of the microemulsion. HLB, chain length and degree or unsaturation of the fatty acid, molecular weight of the hydrophilic portion and concentration of the emulsifier govern polarity of the droplet. In fact, the polarity reflects the affinity of the drug for oil and or water and the type of forces involved. The high polarity will enhance the rapid rate of release of the drug into aqueous phase. The highest release was obtained with the formulation that had oily phase with highest polarity. Equilibrium solubility measurement can be carried out to anticipate potential cases of precipitation in the gut. However, crystallization could be slow in solubilizing and colloidal stabilizing environment of the gut. Studies state that such formulation can take up to 5 days to reach equilibrium and that drug can remain in a supersaturated state up to 24 hr after the initial emulsification event.

EVALUATION OF SMEDDS [14][15][16][17]

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

1. Droplet size and particle size measurement: The particle size of the microemulsion is determined by photon correlation spectroscopy or SEM (Scanning Electron Microscopy) which can measure sizes between 10 and 5000 nm. The nanometric size range of the particle is retained even after 100 or 1000 times diluted with distilled water, which proves the system's compatible with excess water.

2. 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-visible 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. Zeta potential measurement: Zeta potential for microemulsion can be determined using a suitable Zetasizer, in triplicate samples.

4. Stability: SMEDDS was diluted with distilled water and to check the temperature stability of samples, they were kept at two different temperature range (2-8°C (refrigerator), room temperature) and observed for any evidences of phase separation, flocculation or drug precipitation. In order to estimate metastable systems, the optimized SMEDDS formulation was diluted with distilled water. Then microemulsion was centrifuged at 1000 r min-1 for 15 min at 37°C and observed for any alteration in homogeneity of microemulsions.

5. Centrifugation: Passed formulations are centrifuged thaw cycles between 21 0C 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.

6. *In vitro* release study: *In vitro* drug release study of SMEDDs formulation was performed by dialysis method, dissolution apparatus 2 and diffusion cell. Study of drug release was done by modified diffusion cell in 200 ml buffer solution 6.8 pH. 1 gm SMEDDs formulation was placed in boiling tube, both side of boiling tube was opened and one side of tube was tied with cellophane membrane and dipped in buffer solution kept in a beaker below. Upper side of the cylinder was clamped to hold. The beaker was continuously stirred by magnetic stirrer and sample was withdrawn after different time intervals it in straight position and analyzed by UV-

Spectrophotometer % drug dissolved at different time intervals was calculated using the beer Lambert's equation.

7. Bioavailability study: Based on the self-emulsification properties, particle size data and stability of microemulsion the formulation is selected for bioavailability studies. The *in vivo* study is performed to quantify the drug after administration of the formulation. Pharmacokinetic parameters of the maximum plasma concentration (Cmax) and the corresponding time (Tmax) for the drug following oral administration are calculated. The relative Bioavailability (BA) of SMEDDS form to the conventional table is calculated using the following Equation Relative BA (%) = (AUC test/AUC reference) X (Dose reference/Dose test).

8. Dispersibility test: The efficiency of self-emulsification of oral nano or microemulsion is assessed using a standard USP XXII dissolution apparatus 2. One milliliter of each formulation is added to 500 ml of water at 37 ± 0.5°C. A standard stainless steel dissolution paddle rotating at 50rpm provides gentle agitation. The *in vitro* performance of the formulations is visually assessed using the following grading system[16]. Grade A: Rapidly forming (within 1 min) nanoemulsion having a clear or bluish appearance. Grade B: Rapidly forming slightly less clear having a bluish-white appearance. Grade C: Fine milky emulsion that forms within 2 min. Grade D: Dull grayish white emulsion having slightly oily appearance that is slow to emulsify. Grade E: Formulation exhibiting either poor or minimal emulsification with large oil globules present on the surface. Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommended for SMEDDS formulation.

DISADVANTAGES [18][19][20]

1. One of the drawbacks of SMEDDS is the lack of good predictive *in vitro* models for assessment of the formulation.

2. Traditional dissolution method does not work because these formulations are dependent on digestion prior to release of the drug.

3. This *in vitro* model requires further development and validation before its strength can be evaluated.

4. Chemical instabilities of drugs and high surfactant concentration in formulation (30-60%) which irritate GIT.

5. Co-solvent in the conventional self micro-emulsifying formulation is known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.

APPLICATION OF SMEDDS, [21] [22]

1. Super Saturable SMEDDS: The high surfactant level present in SMEDDS formulation can lead to GI side effects. So, new class of super saturable SMEDDS formulation has been designed to reduce the GI side effect caused by surfactant. The SMEDDS approach is used to generate a protected supersaturated solution of the drug when the formulation is released from dosage form into an aqueous medium. Supersaturation is intended to increase the thermodynamic activity of the drug beyond its solubility limit. So, result in an increase in transition across the biological membrane.

2. Solid SEDDS: SMEDDS are normally prepared as liquid dosage forms that can be administered in soft gelatin capsules, but it has some disadvantages especially in manufacturing process. An alternative method is used which incorporate liquid self-emulsifying ingredient into a powder to create a solid dosage form (tablets, capsules).

3. Improvement in solubility and bioavailability: SMEDDS increase the solubility of the drug. In SEDDS, the lipid matrix interacts with water, which forms a fine particulate o/w emulsion. The emulsion droplets will deliver the drug to the GI mucosa in the dissolved state readily accessible for absorption. So, increase in AUC i.e. bioavailability and Cmax of the drug.

4. Protection against Biodegradation: Many drugs are degraded in physiological system because of acidic pH in stomach, hydrolytic degradation or enzymatic degradation etc. Such drug when formulated in form of SMEDDS can be protected against degradation processes as liquid crystalline phase in SMEDDS might be an act as a barrier between degradating environment and the drug.

DOSAGE FORM DEVELOPMENT [19] [20]:-

Various dosage forms of SMEDDS are as listed below [33, 34]

1. Dry emulsions
2. Self-emulsifying Capsules
3. Self-emulsifying Sustained/Controlled-Release Tablets
4. Self-emulsifying Sustained/Controlled-Release Pellets
5. Self-emulsifying Solid Dispersions
6. Self-emulsifying Beads
7. Self-emulsifying Sustained-Release Microspheres
8. Self-emulsifying Nanoparticles
9. Self-emulsifying Suppositories
10. Self-emulsifying Implant

CONCLUSION

Self micro-emulsifying drug delivery system is a novel approach for the formulation of drug compounds with poor aqueous solubility. Self micro-emulsifying drug delivery systems (SMEDDS) are mixtures of oils, co-solvents and surfactants, which is isotropic in nature. When introduced into aqueous phase, it emulsifies spontaneously to produce fine o/w emulsion under gentle agitation. SMEDDS represent a good alternative for the formulation of poorly water soluble drugs. SMEDDS improve the dissolution of the drug due to increased surface area on dispersion and solubility effect of surfactant. The oral delivery of hydrophobic drugs can be made possible by SMEDDSs, which have been shown to substantially improve oral bioavailability. By this approach, it is possible to prolong the release of drug via incorporation of polymer in composition. SMEDDS appears to be unique & industrially feasible approach for increasing bioavailability of poorly soluble drugs. In future, SMEDDS will continue to advance and will represent a viable alternative to increase oral use of various poorly soluble drugs. Increase in bioavailability is major challenges in oral route of administration of poorly soluble drugs.

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