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Review Article

Self Micro Emulsifying Drug Delivery System (SMEDDS): A Review

Sagar Savale, Shailesh Chalikwar

Department of Pharmaceutics, R. C .Patel Institute of Pharmaceutical Education and Research, Shirpur, MS, India

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Abstract

Objective: Much attention has been given to lipid-based formulation with particular emphasis on self-micro emulsifying drug delivery system (SMEDDS) to improve the solubility and oral bioavailability of lipophilic as well as hydrophilic drugs.

Method: Various reports were taken from review or research articles published in journals, data from various books and other online available literature.

Conclusion: This method is suitable for all BCS class drugs where resulting emulsification gives faster dissolution and absorption rate.

Keywords: SMEDDS, solubility, bioavailability, lipid-based formulation, emulsification.

Introduction

In modern drug discovery techniques, there has been a consistent increase in the number of poor water soluble drug candidate compounds, and currently more than 50% of new pharmacologically active chemical entities are lipophilic and exhibit poor water solubility. SMEDDS are class of emulsion that has received particular attention as a means of enhancing oral bioavailability of poorly absorbed drugs. These systems are essentially mixes of oil and surfactant: co-surfactant that form emulsion on mixing with water with less energy input.

***Address for Correspondence**
Mr. Sagar Kishor Savale,
Department of Pharmaceutics, R. C .Patel Institute of Pharmaceutical Education and Research, Shirpur, MS, India.
Mobile No: +919960885333.
Email ID: avengersagar16@gmail.com

Selfmicroemulsifying drug delivery system (SMEDDS) are defined as isotropic mixtures of natural or synthetic oils, surfactants, and co-surfactants that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. Droplet size between 300 and 500 nm while SMEDDS form transparent micro emulsions with a droplet size of less than 500 nm. Lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles (Spernath et al., 2006).

Advantages of SMEDDS

Novel approach to improve water solubility and ultimate bioavailability of lipophilic drugs. It shows large inter and intra subject variations in absorption leading to fluctuation in plasma profile of liquid or solid dosage forms.

In SMEDDS, the lipid matrix interacts readily with water, forming a fine particulate oil-in-water (o/w) emulsion. The emulsion droplets will

deliver the drug to the gastrointestinal mucosa in the dissolved state readily accessible for absorption. Therefore increase in AUC i.e. bioavailability and C_{max} is observed with many drugs when presented in SMEDDS.

Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT. It gives prolonged release of medicaments when polymer is incorporated (Sinde et al., 2011).

Dis-advantages of SMEDDS

Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug. This in vitro model needs further development and validation before its strength can be evaluated (Patel et al., 2011).

Factors Affecting SMEDDS

The drugs required to administer at high dose should possess good solubility in the components used at least in oil phase. The drug should be highly soluble which influences its bioavailability. The incorporation of surfactants and co-surfactants at high concentration can cause risk of precipitation. Release of drug is highly influenced by polarity of lipid phase. High polarity value increases the rate of release. Smaller the droplet size and larger the surface area increases absorption and if the droplet is positively charged the drugs can penetrate into the physiological barrier in deep leads to improved bioavailability (Kohli et al., 2010).

Mechanism of self emulsification

According to "Reiss" self emulsification occurs when the entropy changes that favour dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phase and can be described by the equation- DG = SNPr2; where, DG: free energy associated with the process (ignoring free energy in mixing), N: Number of droplets of radius r and s represent the interfacial energy (Maghani et al., 2013).

Composition of SMEDDS

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, hydrolysed corn oil. 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, 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. Cationic surfactants, where the hydrophilic group carries a positive charge. Example: quaternary ammonium halide. Ampholytic surfactants (also called zwitterionic surfactants) contain both a negative and positive charge. Example: sulfobetaines. 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. 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. 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. 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 (Kyatanwar et al., 2010; Yang et al., 2014).

Formulation of SMEDDS

The solubility of drug in different oil, surfactant, and co-surfactant was checked than selection of oil, surfactant, and co-surfactant based on the solubility of the drug and the preparation of phase diagram. SMEDDS formulation by dissolving the drug in a mixture of oil, surfactant, and co surfactant. Drug interferes with the self-emulsification process to certain extent during addition to a SMEDDS, which leads to a change in the optimal oil and surfactant: co-surfactant ratio. So, the design of an optimal SMEDDS requires pre-formulation solubility and phase diagram studies (Kawakami et al., 2002).

Method of Preparation

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. 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 (Khan et al., 2012).

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 (Craig et al., 1995).

Evaluation of SMEDDS

Droplet size analysis

Droplet size analysis of microemulsion was measured by a diffusion method utilizing the light-scattering particle size analyser (Nano ZS90, Malvern Pvt. Ltd. USA). It is also measured by correlation spectroscopy that analyses the fluctuation in scattering of light due to Brownian motion. Droplet size analysis of microemulsion was also performed by Transmission electron microscopy (TEM) and Photon correlation spectroscopy (PCS) (Tuleu et al., 2004).

Drug content

Drug content of microemulsion was determined by using UV spectrophotometric and HPLC method. In case UV, the 10 mg equivalent of drug loaded microemulsion was dissolved in 100 ml of Solvent (Drug having optimum solubility of that solvent). From this stock solution, take 1 ml and dilute it in 10 ml of solvent (This solvent was not contain drug loaded microemulsion). And Drug content was estimated at reported Lamda max of that drug molecule (Reddy et al., 2011).

Zeta Potential

Zeta potential was measured the charge on the surface of droplet of microemulsion. The formulation (0.1 ml) was diluted 100 times using double distilled water and analysed using Zetasizer. (Nano ZS90, Malvern Pvt. Ltd. USA) (Vanitasagar et al., 2013).

Phase behaviour study

Microemulsion System was determined by using Pseudo ternary phase diagram. It is also determine microemulsion existence area. Pseudo-ternary phase diagrams of oil, water, and surfactant: Cosurfactant (S_{mix}) mixtures was constructed. Then prepared Smix by mixing a specific ratio of surfactants: Cosurfactant (1:1, 2:1, 3:1, 4:1, 1:2 and 1:3) after that transparent and homogenous mixture of oil and S_{mix} was formed by using vertex. Each mixture was titrated with water and visually observed for phase clarity and flow ability. Equal quantity of drug in all formulation batches and Depending on each phase diagram, the microemulsion region was identified and different formulations were selected at desired component ratios, In order to form the stable microemulsion (Constantinides et al., 1995).

Thermodynamic Stability Studies

The formulated or optimized microemulsion was centrifuged at the 1000 RCF for 30 min. and observed for phase separation, creaming or cracking. Microemulsion was subjected heating and cooling cycle. Six cycle between the refrigerator temperatures 4°C and 45°C temperature were performed with storage at each temperature for not <48 hrs. The optimized formulation was exposed for three three freeze thaw cycles between -21°C and +25°C with storage at each temperature for not <48 hrs to check the thermodynamic stability of microemulsion (Shah et al., 1994).

***In Vitro* Skin permeation Studies**

In vitro drug release of optimized microemulsion was determined by dialysis bag method.1.0 ml of microemulsion was placed in dialysis bag (HIMEDIA dialysis membrane-150, Delhi, India) was subjected to release in 900 ml of diffusion media (pH 6.4 phosphate buffer or pH 6.8 phosphate buffer) stirred at a speed of 100 rpm and temperature 37 ± 0.5°C. Aliquots of 5 mL samples were withdrawn at regular time intervals from the dialyzing medium and volume withdrawn was replaced with the fresh medium each time to maintain sink condition. The sample were analysed in particular Lamda max of drug molecule by using UV analysis and the samples were percentage Cumulative drug release was calculated (Amidon et al., 1995)

***In Vivo* Pharmacodynamics Studies**

In vivo studies was conducted in four groups such as control, test, standard and normal group, each group was containing six male albino rats having 150-200 gm weight. The rat were fasted overnight and injection containing optimum dose of drug molecule. The control group of rats were

given in vehicle and standard groups were given plain sample or optimized microemulsion formulation and normal group of rat were given with normal diet. The oral dosing was performed by intubation using an 18-gauge feeding needle (the volume to be fed was 1.0 mL in all cases). Blood samples were drawn at 0 hrs, 24 hrs and 48 hrs. Serum was separated by centrifugation at 10000 rpm and used for biochemical analysis. Serum cholesterol, triglycerides and high density lipoprotein cholesterol (HDL-CH) were estimated in each group. Statistical analysis of the collected data was performed using one way analysis of variance (Kumar et al., 2010; Thomas et al., 2012).

Conclusion

Self micro emulsifying drug delivery system (SMEDDS) is one of the promising technologies to deliver the drugs in spite of low solubility. The bioavailability of the drugs can be achieved with low dose due to its high loading capacity. This system of drug delivery is easy to prepare and low in cost.

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