International Journal of Pharmacy and Pharmaceutical Science
www.pharmacyjournal.org
Online ISSN: 2664-7230, Print ISSN: 2664-7222, Impact Factor: RJIF 5.44
Received: 16-02-2021, Accepted: 06-03-2021, Published: 08-04-2021
Volume 3, Issue 1, 2021, Page No. 05-08

Self-emulsifying drug delivery systems: An overview

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DOI: https://doi.org/10.33545/26647222.2021.v3.i1a.16

Abstract
The oral route is most preferred for the administration of medications due to a painless approach. However, oral administration of lipophilic drugs presents a great challenge due to the low solubility of these compounds in water. Self-emulsification drug delivery systems (SMEDDS) alone have been touted for their ability to increase the solubility and bioavailability of poorly soluble drugs. It can be administered orally in soft or hard gelatin capsules. These systems form fine emulsions (or micro-emulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility. Surfactant concentration, oil to surfactant ratio, polarity of emulsion, droplet size and charge on droplet these parameter plays a critical role in oral absorption of drug from SEDDS. This formulation increases bioavailability due to the higher solubility of the drug and minimizes gastric irritation. The fact that almost 40% of the new drugs are hydrophobic in nature means that studies with SEDDS will continue and that more active compounds in the form of SEDDS will enter the pharmaceutical market in the future.

Keywords: SEDDS, surfactant, oil, co-surfactant, bioavailability, stability

Introduction

Several techniques have been used to increase the oral bioavailability of drugs that are not easily soluble in water. The oral route has been the main route of drug administration in the chronic treatment of many diseased because it offers a high degree of compliance on the part of the patient. However, the oral administration of 50% of the drug's components is limited due to the high lipophilicity of the drug itself. Near about 40% of the new candidate drugs presenting low water solubility, which poses a challenge for the development of an optimal oral solid dosage form in terms of the formulation design and bioavailability of new pharmaceutical products. Many strategies have been used to overcome these problems by adjusting the solubility or keeping the drug in dissolved form during gastric transit. These strategies may include the use of surfactants, cyclodextrins, micronization, liquisolid salt formation techniques, pH changes, nanoparticle delivery, solid dispersions, and permeation enhancers, and much attention has been paid to solutions, emulsions, and pre-concentrates of lipids prepared as physically stable formulations suitable for encapsulating such poorly soluble drugs [1-2]. Extension of GI residence time with the drug allows the presence of the drug extended GIT period, which facilitates drug absorption [3-6]. These formulations can also enhance drug absorption by a number of ancillary mechanisms, e.g. (a) including inhibition of P-glycoprotein-mediated drug efflux and pre absorptive metabolism by gut membrane-bound cytochrome enzymes (b) promotion of lymphatic transport, which delivers drug directly to the systemic circulation while avoiding hepatic first-pass metabolism and (c) by increasing GI membrane permeability.11-15 Modification of the physicochemical properties, such as salt formation and particle size reduction of the compound may be one approach to improve the dissolution rate of the drugs[7-8]. In recent years much attention has focused on lipid−based formulations to improve the oral bioavailability of poorly soluble drugs .In fact, the most popular approach is the incorporation of the drug compound into inert lipid vehicles such as oils, surfactant dispersions, self-emulsifying formulations, emulsions and liposomes with particular emphasis on self-emulsifying drug delivery systems (SEDDS) [9].

Need of SEDDS

The self-emulsifying formulation spreads easily in the gastrointestinal tract (GIT) and the gastrointestinal motility of the stomach and intestines provides the necessary mixing for the emulsion itself. SEDDS are a promising approach to oral delivery of sparingly water-soluble compounds [10-11].

Advantages of SEDDS [12-14]

Enhanced solubilization of bioactive substances Improvement in oral bioavailability Reduce intra and inter-subject variability and food effects. Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT Drugs which have propensity to be degraded by the chemical and enzymatic means in GIT can be protected by the formulation of SMEDDS as the drug will be presented to the body in oil droplets. Ease of manufacture and scale-up as compare to other lipid dosage forms Control of delivery profiles

Limitations of SEDDS [15]

Chemical instabilities of drug and high surfactant concentrations The large amount of surfactant in self-emulsifying formulations (30-60%) irritates GIT Moreover, volatile co-solvent in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsule, resulting in the precipitation of the lipophilic drug.

Lack of good predicative in vitro models for assessment of the formulations.

Composition of SEDDS

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 but also and 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 [16]. Both long and medium chain triglyceride oils with different degrees of saturation have been used for the design of self-emulsifying formulations. Unmodified medium-chain triglycerides (MCT) provide the most ''natural'' basis for lipid vehicles. MCTs are preferred in the earlier self-emulsifying formulations because of higher fluidity, better solubility properties and self-emulsification ability. e.g., Corn oil, olive oil, soybean oil, hydrolysed corn oil [17]. Non-ionic surfactants were used to develop the SMEDDS formulation as they are less toxic compared to ionic surfactants, more compatible with biological systems and less affected by pH and ionic strength. The selection of surfactants for using in a SEDDS formulation is based on theire mulsification efficiency rather than their ability to solubilise the drug. The efficiency of self-emulsification is related to the hydrophilic–lipophilic balance (HLB) value of the surfactant [18]. The addition of co-surfactant aids in the formation of fine droplets, increasing the solubility of hydrophobic drugs and improves the stability of the micro/naoemulsion through the reduction of the interfacial tension. Organic solvents, suitable for oral administration (1, 2-propylene glycol, polyethylene glycol (PEG) and Transcutol HP) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base [19-22]. 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. Role of the co-surfactant together with the surfactant is to lower the interfacial tension to a very small even transient negative value [23].

Mechanism of self-emulsification

Self-emulsification occurs when the entropy changes that favours 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 water and oil phases and can be described by the equation:

$$\Delta G = \Sigma N \pi r 2 \sigma$$

Where,
ΔG is the free energy associated with the process.
N is number of droplets with radius r.
σ is interfacial energy with time.

The above equation shows that spontaneous formation of interface between oil and aqueous phase is thermodynamically i.e., self-emulsification, in terms of the free energy required to form the emulsion which is either very low and positive, or negative [24-27].

Formulation components of SEDDS

For the formulation of SMEDDS the requirement is oil, surfactant, co-surfactant solubility studies, co-solvent and other components includes pH adjusters, flavors, and antioxidants, consistency builder, enzyme inhibiter, polymers etc [28-32].

Construction of phase diagram

Pseudo ternary diagrams are constructed by keeping the ratio of any two of the four components as constant and this ratio along with the remaining two components generally forms three corners of the phase diagram. This fixed (mixture) ratio is generally formed by the combination of surfactant and cosurfactant and sometimes it may be the mixture of oil and surfactant. This is mixed with the required volume of the third phase like oil or cosurfactant; then the other component which is usually water is added in incremental amounts and for every addition of fourth component, the solution should be tested for the clarity, flowability, time for self-emulsification, and dispersibility. The total percent concentration of all components in each mixture should be 100%. Then pseudo ternary diagram should be plotted with the help of suitable software. The samples which formed clear solution should be denoted by suitable symbols in the phase diagram. The area that is formed when these points are joined indicates the monophasic microemulsion existing area and wide area indicates the good emulsification efficiency [33-34].

Characterization of SEDDS

Droplet size analysis

Droplet size analysis of microemulsion are performed by Transmission electron microscopy (TEM) and Photon correlation spectroscopy (PCS) also by a diffusion method utilizing the light-scattering particle size analyzer [35].

Drug content

Drug content of microemulsion is determined by using UV spectrophotometric and HPLC method [36].

Zeta Potential

Zeta potential is measured, charge on the surface of droplet of microemulsion. The formulation (0.1 ml) was diluted 100 times using double distilled water and analyzed using Zetasizer.

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 (Smix) mixtures was constructed. 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 [33].

Thermodynamic Stability Studies

The optimized formulation was exposed for 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 [22].

***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 [38].

Applications

Enhancement in solubility and bioavailability: SEDDS formulation enhances the bioavailability by increasing the solubility of drug and also decreases the gastric irritation.

Super saturable SEDDS: Super saturable-SEDDS have been developed to overcome the toxic effect of surfactant or GI side effects produced by surfactant when used in very high concentration as typically used in SEDDS.

Protection from biodegradation: SEDDS is useful for such drugs those having solubility and degradation is low in the GIT due to the ability to reduce degradation as well as improve absorption [20].

Conclusion

Self-emulsifying drug delivery system in solid dosage form has improved solubility/dissolution, absorption and bioavailability for poorly water-soluble drug. This is the method suited for lipophilic drugs where resulting emulsification gives faster dissolution rates and absorption. Faster and enhanced drug release can be attained with smaller droplets which in turn promotes bioavailability.

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