WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 5, 840-852. Review Article ISSN 2277– 7105

SOLUBILITY ENHANCEMENT OF POORLY SOLUBLE DRUG BY SELF EMULSIFYING DRUG DELIVERY SYSTEM: COMPREHENSIVE REVIEW

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Article Received on
14 March 2021,

Revised on 04 April 2021,
Accepted on 25 April 2021

DOI: 10.20959/wjpr20215-20350

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ABSTRACT

The oral route is still the favoured route of medication administration in many disorders, and it is still the first approach explored in the production of new dosage types. Low and intermittent bioavailability is the biggest issue in oral drug formulations, primarily due to low aqueous solubility. This may contribute to high inter-subject heterogeneity, loss of proportionality of the dosage, and therapeutic insufficiency. 40 per cent of active compounds are known to be poorly water soluble. Self-emulsifying drug delivery systems (SEDDS) are an essential method for overcoming the low bioavailability of poorly soluble products. Hydrophobic medications may often be dissolved in SEDDS, enabling them to be encapsulated as unit dosage types for peroral administration. This article explores the formulation techniques for SEDDS, the methods for evaluating the emulsification effectiveness, and the functional effects of using SEDDS to improve the bioavailability of drugs in the gastro-intestinal tract.

KEYWORDS: Self Emulsifying drug delivery, SEDDS, Bioavailability, Composition, and Future Prospective.

INTRODUCTION

Oil, surfactant, co-solvent, and solubilized medication mixes behave as isotropic dispersions in self-emulsifying formulations (Gursoy and Benita, 2004). When spread in aqueous medium under moderate agitation, these special formulations will quickly turn into oil-in-water (o/w) emulsions with fine droplets (Khan et al., 2012) and self-emulsifying drug delivery systems (SEDDS) are the preparations mentioned (Akkuş Arslan and Tirnaksiz,

2013). Active molecules that are oil-soluble may be dissolved or scattered in the oily process and transported through biological systems in fine oil droplets carried in an aqueous medium (Gupta et al., 2014)(New and Kirby, 1997). SEDDS are classified as self-micro-emulsifying drug delivery systems if they form a micro-emulsion of droplet sizes in the nano scale (Gursoy and Benita, 2004), The gastrointestinal tract's rapid emulsification of these formulations may help to increase oral bioavailability and maintain a consistent plasma concentration (Tang et al., 2008). The formulation's self-emulsifying potential complements the GIT bio-normal structure's emulsifying abilities(Mahmood and Bernkop-Schnürch, 2019). Real or synthetic oils, surfactants, and co-solvents/co-surfactants make up self-emulsifying drug delivery mechanisms. Under the gentle disturbance or combining that happens in the gastro-intestinal tract attributable to peristaltic motions, these processes are able to self-emulsify quickly in gastro-intestinal fluids to create fine oil/water emulsions (Akkuş Arslan and Tirnaksiz, 2013).

The amount of potential drug candidates that are strongly hydrophobic and badly water-soluble has steadily increased (nearly 40%). Low solubility and slow degradation in the aqueous atmosphere of the GIT reduce the oral bioavailability of poorly water soluble products (Aldawsari and Singh, 2020; Singh et al., 2015; Singh and Lal, 2016). As a result, overcome the inherent sluggish degradation and impaired oral absorption of hydrophobic products is a major obstacle for pharmaceutical sciences. SEDDSs have emerged as a promising method for the bioavailability of hydrophobic drugs and thereby improving their biopharmaceutical safety.(Park et al., 2020) (Asija et al., 2014).

Poor bioavailability is one of the most difficult aspects of developing an oral dosage type. Since a substance cannot be ingested via the gastrointestinal tract until it is in solution form, low aqueous solubility is one of the main underlying causes of bioavailability. Aqueous solubility is a problem for several chemical organizations with important and promising pharmacological effects. As previously mentioned, over 30% of the most widely sold drugs and nearly half of new drug entities meeting formulation scientists are hydrophobic or lack the requisite aqueous solubility. Class II drugs have poor solubility yet good permeability, whereas class IV drugs have poor solubility and weak permeability across the gastrointestinal membrane according to the BCS (biopharmaceutical classification system) (Singh et al., 2020).

Oral Dosages form of SEDDS

In order to sufficiently dissolve hydrophilic macromolecular drugs in the oily phase of SEDDS hydrophobic ion pairing (HIP) turned out to be the likely most efficient technique. Utilizing the most appropriate hydrophobic counter ion as well as drug to counter ion ratio payloads even above 10% can be achieved (Its et al., 2019).

Advantages of SEDDS (Shahba et al., 2012)

- Formulation with faster respond.
- Drug misuse is reduced.
- Oral bioavailability is improved.
- The lipid digestion mechanism has no impact.
- Medications are tailored to a particular absorption window in the GI tract.
- Drug safety from the gut environment.
- Diet results were reduced in heterogeneity.
- As opposed to oil solutions, it offered a wide interfacial region for medication portioning.
- The gastric irritation caused by the medications is reduced by these dosages (Alghananim et al., 2020).

Disadvantages of SEDDS

- Traditional dissolution approaches are ineffective since these formulations can need digestion prior to drug release.
- Before the strength of this in vitro model can be measured, it must be further developed and validated.
- Future research would be focused on in vitro-in vivo associations, which means that various prototype lipid-based formulations must be produced and evaluated in vivo in an appropriate animal model.
- Chemical instabilities of medications and large surfactant concentrations in formulas (approximately 30-60%) are disadvantages of this scheme, according to GIT (Akkuş Arslan and Tirnaksiz, 2013; Zhang et al., 2015).
- There aren't any successful in vivo models for evaluating SEDDS formulations.
- Conventional dissolution procedures do not function since these formulations might be reliant on metabolism prior to medication release.

Mechanism of self-emulsification

The improved drug absorption and bioavailability of several drugs from these self-emulsifying systems has been due to a variety of mechanisms. Increased membrane fluidity, which aids transcellular absorption; opening of a biological system's close junction to enable paracellular transport; P-glycoprotein inhibition for increased intracellular substance concentration and GIT residence period (Wyman et al., 2011). The accelerated release of drug substances is aided by the large interfacial surface area provided by the formulation's finely distributed droplet scale. Lipids and these ingredients stimulate lipoprotein and chylomicron biosynthesis, which improves medication absorption and delivery (Garg et al., 2021). The P- glycoprotein efflux pump indicates that certain lipids and surfactants may increase the function of intestinal efflux transporters while decreasing enterocyte-based metabolism (Constantinides and Wasan, 2007). Lipoprotein production facilitates lymphatic transmission of strongly lipophilic drugs and enhances bioavailability by reducing first-pass metabolism (Trevaskis et al., 2008). Lipids affect drug oral bioavailability by improving dissolution rate and solubility in the intestinal fluid, protecting the active compound from chemical and enzymatic degradation, and promoting lymphatic transport of highly lipophilic drugs via the formation of lipoproteins (Gursoy and Benita, 2004). Administration of lipophilic drugs using lipids as carriers may improve drug absorption. Under the acidic pH of the intestine, several medications dissolve in the physiological system by enzymatic or hydrolytic cleavages. When given in the form of SEDDS, certain medications may defend against these degradative processes. SEDDS provide a buffer against degradation factors as used as carriers for bioactive drugs (Kohli et al., 2010).

Composition of Self emulsifying DDS (SEDDS)

These are main component of the SEDDS which are described as below-

1. API (Drug)
2. Oils
3. Surfactants
4. Co-solvents / Co-surfactants

Drug (APIs)

The Biopharmaceutical classification scheme classifies products with low solubility and high permeability as BCS 2 drugs.

Examples

Griseofulvin, Gliclazide, Glimepiride

It has the ability to promote self-emulsification by increasing the lipophilicity of the medication through the intestinal lymphatic system, thus increasing absorption from the GIT. Because of their low bioavailability and self-emulsification effectiveness, edible oils are used as the natural base without any alteration vehicles (Ogino et al., 2018; Patil et al., 1970).

Examples

Soya bean oils, Oleic acid, Castor oil etc.

The values of surfactants (HLB) are used in the formation of SEDDS (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). In order to shape a solid SEDDS, the surfactant strength usually varies from 30 to 60% w/w of the formulation. Surfactants have a strong HLB and hydrophilicity, which helps the formulation shape o/w droplets quickly and disperse quickly in aqueous media. Surfactants are amphiphilic in nature, meaning they can dissolve or solubilize large quantities of hydrophobic drugs. This will help keep the medication from precipitating in the GI lumen (Lopez-Toledano et al., 2019).

Cosurfactants/cosolvents

Co-solvents such as diethylene glycol monoethylene ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol, polyethylene glycol ether (glycofurol), and others can assist in the dissolution of large amounts of hydrophilic surfactants or hydrophobic drugs in the lipid base. In micro-emulsion systems, these solvents may also serve as a co-surfactant (Tiwari et al., 2010).

Formulation of SEDDS

There are several various combinations that may be developed for encapsulation in hard or soft gelatin, or mixtures that diffuse to give fine colloidal emulsions, with a wide range of liquid or waxy excipients usable, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants, and water-soluble co-solvents (Gao et al., 2003).

The solubility of the substance in numerous oils, surfactants, and co solvents should all be addressed when formulating a SEDDS. The step diagram is formulated and the oil, surfactant, and co solvent are selected depending on the drug's solubility(Knaub et al., 2019). SEDDS formulation is made by dissolving the medication in a liquid, surfactant, and co-solvent combination.

The addition of a drug to a SEDDS is necessary since the drug interferes with the self-emulsification mechanism to some degree, changing the ideal oil-surfactant ratio. As a result, pre-formulation solubility and phase-diagram studies are needed for the design of an optimal SEDDS. In the case of extended SEDDS, the polymer or gelling agent is applied to the formulation (Kumar et al., 2010), (Singh et al., 2011), (Aldawsari and Singh, 2020; Hussain et al., 2019, 2017).

Although the exact mechanisms are unknown, it is widely assumed that lipids can increase bioavailability via a variety of mechanisms.

Evaluation of the SEDDS

The evaluation parameters of SEDDS are given below-

1. Thermodynamic stability studies
2. Dispersibilty test
3. Turbedimetric test
4. Viscosity determination
5. Droplet size determination
6. Electro conductivity test
7. In-vitro conductivity studies
8. drug content determination

Test of thermodynamic stability

The physical stability of a formulation is critical for its success, as precipitation of the substance in the excipient matrix may have a negative impact. Excipient step separation may occur as a consequence of poor formulation physical stability, impacting bioavailability and therapeutic efficacy.

Incompatibilities between the formulation and the gelatin shell of the capsule (if the formulation is filled in the capsule) may result in brittleness, softness, and delayed or incomplete drug release. These experiments are carried out in the following cycles) (Bindhani et al., 2020; Czajkowska-Košnik et al., 2015).

Turbidimetric Test

Turbidity is a parameter that can be used to determine droplet size and self-emulsification duration (C.B. Penjuri et al., 2016; Zhu et al., 2020). The turbidity is determined using a

turbidity meter after a fixed amount of SEDDS is applied to a fixed amount of appropriate medium (0.1 N HCL or Phosphate Buffer) under constant stirring at 50 rpm on a magnetic stirrer at optimum temperature. The rate of shift of turbidity, or rate of emulsification, cannot be tracked because the period needed for full emulsification is too low. To monitor the development of droplets after emulsification, turbedimetric analysis is used (Mistry and Sheth, 2011).

Study of electro conductivity

Ionic or non-ionic surfactant, tar, and water make up the SEDD method. This test is used to determine the system's electro conductive existence. An electrical conduct meter is used to evaluate the resulting system's electro conductivity. Since free fatty acids are present in traditional SEDDSs, the charge on an oil droplet is negative.

Particle size measurements and droplet size analysis

Photon similarity spectroscopy (which analyzes variations in light scattering due to Brownian motion of the particles) and a Zeta sizer capable of measuring sizes between 10 and 5000 nm are used to calculate the droplet scale of the emulsions. Since external standardization of spherical polystyrene beads, light scattering is measured at 25°C at a 90° angle. And after 100 times dilution of water, the particle's nonmetric size spectrum is maintained, demonstrating the system's compatibility with excess water.

Determination of viscosity

Soft gelatin or hard gelatin capsules are often used to prescribe the SEDDS method. As a result, it should be easy to pour into capsules and should not be too dense. The Brookfield viscometer is used to assess the micro emulsion's rheological properties. This calculation of viscosities is based on whether the device is w/o or o/w. Whether the solution has a medium viscosity, it is an o/w system, and if it has a high viscosity, it is a w/o system.

Measurement of zeta potential

This is used to assess the droplet's fee. Since free fatty acids are present in traditional SEDDSs, the charge on an oil droplet is negative (Sachan et al., 2010).

Determination of self-emulsification time

In a rudimentary Nephelometer, we measured the efficiency of emulsification of different formulations of Tween 85/medium-chain triglyceride systems using a revolving paddle to

facilitate emulsification. This provided for the measurement of emulsification period. After emulsification, samples were taken for particle sizing using photon similarity spectroscopy, and self-emulsified and homogenized systems were matched. Light microscopy was used to investigate the self-emulsification process. The erosion of a fine cloud of tiny particles from the surface of large droplets, rather than a gradual decrease in droplet scale, was clearly the process of emulsification (Rahman et al., 2013).

Drug content determination

The drug is removed from pre-weighed SEDDS by dissolving it in an appropriate solvent. The substance content in the solvent extract was compared to a normal drug solvent solution using an appropriate analytical process (Rahman et al., 2013).

In-vitro Dissolution Studies

Using a dialysis technique, in vitro diffusion studies were performed on all of the formulations produced. Phosphate buffer pH 6.8 was used as the dialyzing medium. One end of pretreated cellulose dialysis tubing (7 cm in length) was threaded, and 1 ml of self-emulsifying formulation and 0.5 ml of dialyzing medium were inserted in it. The other end of the tubing was threaded and permitted to freely spin in 200 mL of dialyzing medium while being stirred at 100 rpm with a magnetic bead on a magnetic plate at 37°C. At varying time periods, 1 ml aliquots were extracted and diluted further. Every period, the amount of aliquots was substituted with new dialyzing medium. Using a UV-visible spectrophotometer, these samples were analyzed quantitatively for medication dialyzed around the membrane at the corresponding moment (Leichner et al., 2017; Patel et al., 2018).

Conclusion and future prospective

For the formulation of lipophilic products, SEDDS would be a promising solution. Since the production of SEDDS is speculative, the in vitro models used to assess oral bioavailability enhancement must be created. Maintaining the quality and consistency of drugs inside lipid structures necessitates vigilance. Some incompatibility between capsule shell components and lipid systems will need to be assessed. Given these barriers, the usage of lipid formulation has a promising future. Human bioavailability studies should be prioritized in future study, and further attention should be paid to studies on the modes of action of these types of SEDDS formulations. In vitro techniques for evaluating the complex modifications that arise with the medication in the intestine must be controlled, as well as the drug's solubilisation status in vivo.

Solid-SEDDSs (S-SEDDSs) have been studied as an alternative way to solve these issues. To manufacture different solid dosage formulations, such devices necessitate the solidification of liquid self-emulsifying systems into powders (SE capsules, SE tablets, SE pellets, SE beads, and so on). The medication release properties of liquid SEDDS can be preserved when transformed to solid dosage size. The published contents in GIT trigger self-emulsification.

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