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Review Article

Review article on self emulsifying system

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ABSTRACT

The solubility challenges faced by the pharmaceutical industry, particularly with orally administered drugs, are indeed significant. Low aqueous solubility often leads to poor dissolution and subsequently, low bioavailability, which can result in inconsistent drug effects among patients. Various methods have been explored to address this issue, including salt formation, solid dispersion, and complex formation.

Among these approaches, Self-Emulsifying Drug Delivery Systems (SEDDS) have emerged as a promising solution for enhancing the solubility of lipophilic drugs. SEDDS consist of isotropic mixtures of hydrophilic solvents, co-solvents, and surfactants. They possess the unique ability to form fine oil-in-water micro emulsions upon mild agitation and dilution in aqueous media, such as gastrointestinal fluids.

The advancement in SEDDS technology encompasses improvements in composition, evaluation methods, development of different dosage forms, and techniques for converting liquid SEDDS into solid forms. These advancements not only enhance solubility but also offer versatility in administration routes and dosage forms, thereby expanding the potential applications of SEDDS in pharmaceutical formulations.

This comprehensive review provides valuable insights into the latest developments in SEDDS, offering a detailed account of its composition, evaluation parameters, diverse dosage forms, and innovative techniques for solidification. Moreover, it highlights the diverse applications of SEDDS across various therapeutic areas, underscoring its growing significance in modern pharmaceutical research and development.

1. Introduction

SEDDS or Self-Emulsifying Drug Delivery Systems, offer an innovative solution to the challenge of low bioavailability encountered with poorly soluble and highly permeable compounds. These systems are particularly effective for hydrophobic drugs, as they can be dissolved within SEDDS formulations, enabling their administration as a single unit dosage form for oral delivery.

Upon release into the gastrointestinal tract, SEDDS formulations interact with the gastrointestinal fluid, triggering a process known as in situ emulsification or self-emulsification. This results in the formation of fine emulsions, either micro or nano-sized, which facilitates the solubilization of the drug. This transformation into a more soluble form allows for enhanced absorption, primarily via the lymphatic pathways.[1]

By utilizing the lymphatic route, SEDDS help circumvent the hepatic first-pass effect, a process where orally administered drugs are metabolized in the liver before reaching systemic circulation. By bypassing this initial metabolic pathway, SEDDS can improve the bioavailability of drugs that would otherwise be extensively metabolized and therefore poorly absorbed.

In summary, SEDDS offer a versatile and effective approach for enhancing the oral delivery of poorly

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soluble and highly permeable drugs. Through in situ emulsification and subsequent absorption via the lymphatic system, SEDDS address the challenges associated with low bioavailability, ultimately improving the therapeutic efficacy of these compounds. This bioavailability enhancing property has been associated with a number of in vivo properties of the lipid formulations including:

1. Formation of fine dispersions and micellar suspensions to prevent precipitation and re-crystallization of the drug compound.
2. Ability of certain lipid compounds and their metabolites to initiate changes in the gastrointestinal fluid to favor improved drug absorption.

2. Inhibition of cellular efflux mechanisms, which keep drugs out of circulation

Certain lipid excipients are associated with selective drug uptake into the lymphatic transport system, thereby reducing the effect of first-pass drug metabolism. Figure 1shows how self-emulsification of drugs occurs after oral administration.

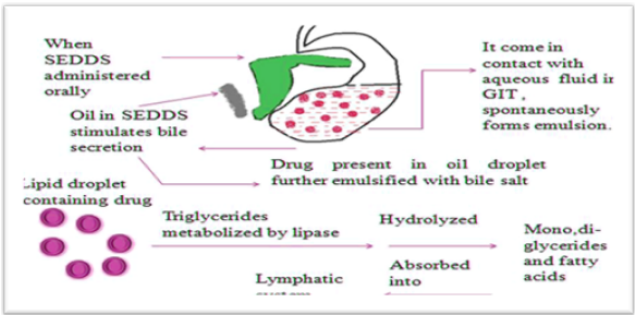

Figure 1: Process of self emulsification

2.1. Properties of SEDDS

1. They are able to self-emulsify rapidly in gastro-intestinal fluids & under the influence of gentle agitation provided by peristaltic and other movements of gastrointestinal tract, they form a fine o/w emulsion.
2. They can effectively incorporate drugs (hydrophobic or hydrophilic) within the oil surfactant mixture.
3. They can be used for liquid as well as solid dosage forms.
4. They require a lower dose of drug with respect to conventional dosage forms.

2.2. Advantages of SEDDS

Improvement in oral bioavailability: the ability of lipid based formulations to present the drug to GIT in solubilized and micro emulsified form (globule size between 1-100 nm) and subsequent increase in specific surface area, enables more efficient drug transport through the intestinal aqueous boundary layer and through the absorptive brush border membrane, leading to improved bioavailability (BA). Their contribution in improvement of the oral bioavailability of several poorly water soluble drugs.[2]

1. **Ease of manufacture and scale-up:** Ease of manufacture and scale-up is one of the most important advantages that makes lipidbased formulation unique when compared to other bioavailability enhancement techniques like solid dispersions, requiring very simple and economical manufacturing facilities for large-scale manufacturing.
2. **Reduction in inter-subject and intra-subject variability and food effects:** There are several drugs which show large inter-subject and intra-subject variation in absorption leading to decreased performance of drugs in the body.
3. **Prevention of enzymatic hydrolysis in GIT:** One unique property that makes lipid based formulation superior as compared to the other drug delivery systems is their ability to deliver macromolecules like peptides ,hormones, enzyme substrates and inhibitors and their ability to offer protection from enzymatic hydrolysis.
4. **Increased drug loading capacity:** lipid based formulations especially SMEDDS also provide the advantages of increased drugs. Loading capacity when compared with conventional lipid solution as the solubility of poorly water soluble drugs with intermediate partition coefficient (2<log p<4) are typically low in natural lipid and much greater in amphiphilic surfactant, co-surfactants and co-solvents.

2.3. Disadvantages of SEDDS

1. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
2. This in vitro model needs further development and validation before its strength can be evaluated.
3. Further development will be based on in vitro - in vivo correlations and therefore different prototype lipid based
4. Formulations need to be developed and tested in vivo in a suitable animal model.
5. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which GIT.[2,3]

3. Types of SEDDS in Drug Delivery Systems

3.1. Oral delivery

3.2. Self-emulsifying controlled/sustained release pallets

Indeed, extrusion/spheronization (ES), solution/suspension layering, and powder layering are widely utilized techniques for pellet production in the pharmaceutical industry, each offering distinct advantages.[4–6]

1. **Flexibility in Dosage Form Design:** These techniques provide a high degree of flexibility in designing and developing dosage forms. Pellets can be tailored to achieve specific release profiles, allowing for controlled and sustained drug release, which is particularly beneficial for medications requiring prolonged action or multiple dosing intervals.
2. **Improved Safety and Efficacy:** Pellets offer enhanced safety and efficacy of bioactive agents. By dispersing freely in the gastrointestinal tract, pellets maximize drug absorption. This leads to a reduction in peak plasma fluctuations, thereby minimizing potential side effects associated with sharp changes in drug concentration in the bloodstream. Importantly, this is achieved without compromising drug bioavailability, ensuring that the therapeutic effect is maintained.
3. **Reduction in Variability:** Pellets play a role in reducing variability in gastric emptying rates and overall transit time through the gastrointestinal tract. This reduction in variability leads to more consistent plasma profiles among individuals, resulting in decreased intra- and inter subject variability of plasma profiles. This predictability enhances the reliability of drug delivery, leading to more consistent therapeutic outcomes.

Overall, the production of pellets using these techniques is instrumental in optimizing drug delivery, enhancing patient safety, and improving treatment efficacy in the pharmaceutical industry. Their ability to offer precise control over dosage form characteristics makes them valuable tools in drug development and formulation.

3.3. Solid self-emulsifying drug delivery systems

Solid Self-Emulsifying Drug Delivery Systems (S-SMEDDS) have gained significant attention in recent years as alternatives to traditional liquid SMEDDS due to the advantages associated with solid dosage forms. While liquid SMEDDS are limited by the fact that many excipients used are not solid at room temperature, S-SMEDDS overcome this limitation by incorporating self-emulsification ingredients into solid matrices through various solidification techniques.

These solidification techniques include adsorption onto solid carriers, spray drying, melt extrusion, nanoparticle technology, among others. The resulting powders or nanoparticles, referred to as self-emulsifying nanoparticles, dry emulsions, or solid dispersions, can be further processed into various solid SE dosage forms or filled into capsules, known as SE capsules. SE capsules may contain either solidified SEDDS or directly filled liquid or semisolid SEDDS without solidifying excipients.

S-SMEDDS combine the properties of both SMEDDS and solid dosage forms, and as such, their characteristics and properties encompass those of both types. For example, the characterization of SE pellets includes assessments not only of self-emulsification but also of parameters such as friability and surface roughness.

Initially, in the 1990s, S-SEDDS were primarily in the form of SE capsules, solid dispersions, and dry emulsions. However, recent advancements have led to the development of various other solid SE dosage forms, including pellets, tablets, microspheres, nanoparticles, suppositories, and implants. These advancements have expanded the applicability and versatility of S-SMEDDS in pharmaceutical formulations, offering new opportunities for enhancing drug delivery and therapeutic outcomes.

3.4. Self-emulsifying capsule

After the administration of capsules containing conventional liquid self-emulsifying formulations (SEFs), micro emulsion droplets are formed and dispersed in the gastrointestinal tract (GIT) to reach the site of absorption. However, if irreversible phase separation of the microemulsion occurs, an improvement in drug absorption cannot be expected. To address this issue, sodium dodecyl sulfate (SDS) may be added to the SE formulation.

Additionally, super-saturatable self-emulsifying drug delivery systems (SS-SEDDS) can be designed using small quantities of hydroxypropyl methylcellulose (HPMC) to prevent the precipitation of the drug by generating and maintaining a supersaturated state in vivo.

Moreover, liquid SE ingredients can be filled into capsules in a solid or semi-solid state by adding solid carriers such as absorbents or polymers. For example, a solid polyethylene glycol (PEG) matrix can be chosen as a suitable carrier for this purpose. This approach ensures the stability and efficacy of the SE formulation while enhancing its ease of administration and potential for improved drug absorption.

3.5. Solid carriers

The process of incorporating liquid or semisolid self-emulsifying systems (SES) into solid carriers involves utilizing materials with adsorption properties. This procedure is relatively straightforward and involves

mixing the SES with a free-flowing powder material that has adsorption qualities. The mixture is then uniformly adsorbed by blending in a blender. The resulting solid mixture can be filled into capsules or further processed by adding additional excipients before compression into tablets.

To solidify the SES into powder forms, three types of adsorbents are commonly used: microporous calcium silicate, magnesium aluminum silicate, and silicon dioxide. These adsorbents have the ability to absorb and stabilize the liquid or semisolid SES, converting it into a solid powder form suitable for encapsulation or tableting.

Overall, the incorporation of SES into solid carriers using adsorbents provides a convenient and effective method for formulating solid dosage forms with improved stability and bioavailability. This approach allows for the transformation of liquid or semisolid formulations into solid forms while maintaining their self-emulsifying properties, facilitating ease of administration and enhancing drug absorption.

4. Self-Emulsifying Beads

The transformation of self-emulsifying systems (SES) into solid dosage forms often involves the use of minimal solidifying excipients. Patil and Paradkar explored a method for loading SES into the micro channels of porous polystyrene beads (PPB) using the solvent evaporation technique. PPB, characterized by complex internal void structures resulting from co-polymerizing styrene and divinyl benzene, was chosen due to its inertness and stability across a wide range of pH, temperature, and humidity conditions. PPB was identified as a promising carrier for solidifying SES, with the optimal SES to PPB ratio critical for achieving a solid form. The size and pore architecture of PPB were found to impact loading efficiency and in vitro drug release from SES-loaded PPB.

In another study, floating alginate beads containing self-emulsifying drug delivery systems (SEDDS) of tetrahydrocurcumin were developed to enhance drug solubility and prolong gastric residence time. Various proportions of sodium alginate, calcium chloride, and a water-soluble pore former (polyvinyl alcohol polyethylene glycol copolymer) were utilized in bead formulations to modulate floating abilities and in vitro drug release rates.

These investigations highlight the versatility of utilizing porous carriers such as PPB and alginate beads for solidifying SES and SEDDS, respectively, to create novel solid dosage forms with enhanced drug solubility, controlled release profiles, and improved bioavailability. Such approaches offer promising strategies for formulating solid oral dosage forms capable of overcoming challenges associated with poorly soluble drugs and achieving targeted drug delivery in the gastrointestinal tract.

1. **Topical Delivery:** Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first pass metabolism of the drugs and related toxicity effects.
2. **Oculars and Pulmonary delivery:** For the treatment of eye disease, drugs are essentially delivered topically o/w microemulsion have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile.
3. **Parenteral delivery**: Parenteral administration of drugs with limited solubility is a major problem in industry because of the extremely low amount of drug actually delivered as the target site.

5. Solidification Techniques for Transforming Liquid/Semisolid

5.1. Spray drying

In this process firstly the prepared formulation of oil,surfactant, drug, and solid carrier are transferred into the drying chamber. There the volatile vehicles are evaporated and only the solid particles left behind.The collected solid particles can be filled into capsules or compressed into tablets, depending on the desired dosage form and application requirements. [7–9]

5.2. Spray congealing

This technique is also known as spray cooling. In this process Lipids, surfactants, and drugs are mixed together to prepare a molten formulation. This mixture is heated to melt the components and ensure homogeneity. The molten formulation is then sprayed into a cooling chamber. The molten droplets congeal and recrystallize into spherical solid particles. These solid particles gradually collect at the bottom of the cooling chamber as fine powder; and harvested for further processing. To atomize the liquid mixture and generate droplets, various atomizers can be used. The fine powders obtained are then used for tablets and capsules.

5.3. Solid carriers

The SES formulation, typically consisting of lipids, surfactants, and possibly co-solvents, is prepared separately. This formulation is designed to form a stable emulsion or self-emulsify upon contact with aqueous fluids, aiding in the solubilization and absorption of poorly water-soluble drugs. The carriers are typically free-flowing powders with a high surface area, allowing them to efficiently absorb and retain the liquid or semi-solid SES formulation. This incorporation is achieved by mixing the SES formulation with the solid carrier material in a blender, ensuring uniform distribution.

solid carrier material is then filled into capsules or added to other excipients before compression into tablets.the solid mixture may undergo further solidification to convert it into powder forms using various adsorbents. These adsorbents include microporous calcium silicate (Florite^{TM} RE), magnesium aluminum silicate (Neusilin^{TM} US2), and silicon dioxide (Sylysia^{TM} 320). These materials can help improve powder flow properties, reduce moisture sensitivity, and enhance stability.

5.4. Melt extrusion

This formulation technique depends on the property of the plastic mass material which can be easily extruded and spheronized with pressure. There is no need for addition of liquid form of excipient but a constant temperature and pressure need to be maintained.

5.5. Dry emulsion

It is mainly o/w emulsion, which is then converted into solid form by spray drying/solid carrier/ freeze drying.

6. Evaluation of SEDDS

6.1. Drug content

Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract is analyzed by a suitable analytical method. [10–12]

6.2. Dispersibility test

The dispersibility test of SEDDS is carried out to assess its capability to disperse into emulsion and categorize the size of resulting globules. It is carried by using a standard USP dissolution apparatus 2 (Paddle Type). One ml of each formulation is added to 500 ml of water at 37 + 0.5ºC and the paddle is rotated at 50 rpm. On titration with water the SEDDS formulation forms a mixture or gel which is of different type depending upon which the in vitro performance of formulation can be assessed using the following grading system.

1. **Grade A:** Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.
2. **Grade B:** Rapidly forming, slightly less clear emulsion, having a bluish white appearance.
3. **Grade C:** Fine milky emulsion that formed within 2 min.
4. **Grade D**: Dull, grayish white emulsion having a slightly oily appearance that is slow to emulsify (longer than 2 min).
5. **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 SEDDS formulation.

Viscosity determination The rheological properties of microemulsion are evaluated by Brook Field viscometer if it is o/w types and if it is w/o types then high viscous.

Droplet size analysis The droplets size of the emulsion is determined by photon correlation spectroscopy using Zeta sizer, enables to measure the sizes between 10 and 5000 nm.

6.3. Applications

1. Improvement of solubility and bioavailability
2. Protection against biodegradation
3. Oral delivery of hydrophobic drugs can be made possible by SEDDS
4. SEDDS solved problems associated with the delivery of poorly soluble drugs [13]

7. Conclusion

Overall, SEDDS offer a versatile and promising approach to improving the delivery of poorly soluble drugs, with solid SEDDS formulations showing particular promise for enhancing patient compliance and therapeutic efficacy. Continued research and development in this area hold significant potential for advancing pharmaceutical science and benefiting patients worldwide.

1. Composition of SEDDS: SEDDS formulations typically consist of a mixture of drug, lipid phase (such as oils or lipids), emulsifiers, and possibly co-solvents. These components work together to form a stable emulsion when exposed to aqueous environments.
2. Benefits for Poorly Soluble Drugs: SEDDS offer a promising solution for drugs with poor aqueous solubility, particularly those classified under Biopharmaceutics Classification System (BCS) Class II and IV. Upon administration, the SEDDS system spontaneously forms an oil-in-water emulsion in the gastrointestinal tract (GIT), enhancing drug dissolution and permeation due to the increased surface area provided by fine droplets.
3. Solid SEDDS Formulations: While SEDDS are traditionally prepared in liquid dosage forms, solid SEDDS formulations (such as tablets, capsules, beads, or microspheres) are preferred due to their ease of handling, transportation, and improved stability. Solid SEDDS also offer advantages such as reduced gastrointestinal irritation and the potential for controlled and sustained drug release.
4. Challenges and Hurdles: Challenges in SEDDS development include the absence of suitable in vitro models for accurately predicting the behavior of

SEDDS formulations in the gastrointestinal tract. Additionally, compatibility and interaction studies between excipients, such as adsorbents, capsule shells, and formulation components, need to be thoroughly conducted to ensure efficacy and safety.

5. Platform Technologies for Bioavailability Improvement: SEDDS present an opportunity to develop platform technologies aimed at improving the bioavailability of BCS Class II and IV drugs. By effectively harnessing the potential of SEDDS formulations, it's possible to enhance drug absorption, optimize therapeutic outcomes, and address formulation challenges associated with poorly soluble drugs.

8. Source of Funding

None.

9. Conflict of Interest

None.

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