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Self-Emulsifying Drug Delivery Systems (SEDDS) As A Strategy for Improving Oral Bioavailability: A Systematic Review of Recent Advances

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Abstract

The concept of self-emulsifying drug delivery system (SEDDS) has emerged as one of the most extensively studied lipid-based systems aimed at addressing problems related to low aqueous solubility and unpredictable oral bioavailability of Biopharmaceutics Classification System (BCS) Class II and IV drugs. This systematic review aims to collate recent advances in terms of classification, formulation, mode of action, and evaluation of self-emulsifying drug delivery systems with a special focus on findings achieved over the past decade. This review discusses the impact of spontaneous emulsification, formation of nano-sized droplets, and manipulation of intestinal lymphatic transport on drug solubility and permeability. New trends, including solid-state SEDDS, supersaturated systems, as well as applications of artificial intelligence and machine learning to formulation optimisation, together with current issues like gastrointestinal precipitation, problems with capsule compatibility, and regulatory issues are critically discussed. The review concludes that despite the fact that SEDDS technology has been advanced to an appropriate stage of development and commercialisation, its further clinical implementation requires in vitro-in vivo correlation, lipolysis testing, and data-based formulation optimisation.

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1. INTRODUCTION

Oral administration of drug is still the most popular and most common route of drug administration due to its simplicity, economic nature, and high rate of compliance. However, a growing number of new chemical entities produced through contemporary drug discovery process, accounting for about forty percent of marketed drugs and close to ninety percent of drugs in the drug discovery pipeline, have been found to be poorly water soluble, hence difficult to dissolve, which impacts their oral absorption[1]. Formulations of drugs belonging to Classes II and IV of the BCS, which have been categorised as having low solubility/high permeability and low solubility/low permeability, respectively, have remained difficult to develop owing to the fact that solid oral dosage forms do not manage to dissolve sufficiently in the physiological time period in the gastrointestinal tract[2].

Thus, delivery systems for drugs based on lipids have become the object of continuous attention from scientists and industry professionals, as they represent a formulation approach which is able to overcome the rate-limiting dissolution of lipophilic molecules. In particular, self-emulsifying drug delivery systems (SEDDS) represent a unique class of these approaches, since they provide the drug molecule as it is already dissolved within the lipid vehicle without the need for a separate dissolution step[3]. This review performs an organised literature survey of SEDDS, documenting the development of the technique from basic oil-surfactant systems to advanced solid state and computational design techniques, with the goal of producing a compendium suitable as a reference guide for PhD students working in bioavailability enhancement using SEDDS.

2. The Biopharmaceutical Rationale for Lipid-Based Formulations

Oral drug absorption kinetics is determined by the balance of solubility, dissolution rate, and permeability. In the case of BCS Class II drugs, the permeability does not restrict the absorption process, while bioavailability is limited only by the dissolution of the drug into the volume of fluid in the intestine. Traditional strategies for improving the dissolution of BCS Class II drugs include reduction of particle size, salt formation, and solid dispersion. These approaches proved to be effective; however, each is limited by physical instability or drug specificity[4].

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3. Definition and Classification of SEDDS

Self-emulsifying drug delivery systems are described as homogeneous systems of oils, surfactants, and, in most cases, co-surfactants or co-solvents that automatically form fine oil/water emulsion on mixing in an aqueous medium with mild agitation like that present in the gastro-intestinal tract[6]. What makes these systems unique is the spontaneous nature of the emulsification process, resulting from the low interfacial free energy present at the oil/water interface and without any need for additional external mechanical energy input other than what is produced internally.

3.1 The Lipid Formulation Classification System

Pouton's lipid formulation classification is the most commonly used approach for classifying SEDDS based on their ingredients and the physico-chemical effects of their aqueous dispersion. Type I systems contain only oils and no surfactant, and depend upon the digestion by pancreatic lipases for successful dispersion. Type II systems are classical self-emulsifying systems and contain oils along with water insoluble surfactants to form coarse emulsions. Type IIIA and IIIB systems are called self-microemulsifying drug delivery systems (SMEDDS) that use larger amounts of hydrophilic surfactants and co-solvents to create more refined and transparent systems with droplets less than fifty nanometers in diameter. Type IV systems are rich in surfactants and co-solvents but contain little or no oil at all[7].

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Such a classification is very important from a practical point of view since it establishes a direct relationship between the formulation composition and its in vivo activity, including its susceptibility to digestion and the possible precipitation after dilution in the gastrointestinal cavity[8].

4. Composition and Formulation Components

Performance of SEDDS depends on proper choice and use of appropriate amount of three major groups of excipients: oils, surfactants, and co-surfactants. Oils act as the main vehicle for lipid soluble drugs and can be divided into long chain triglycerides, medium chain triglycerides, or, more commonly nowadays, semi synthetic mono- and diglycerides with higher drug loading and self-emulsifying properties compared to vegetable oils[9].

The surfactants, usually used at hydrophilic lipophilic balance values above ten, help in reducing the interfacial tension between the oil and water and also serve as a solid film required for the spontaneous formation of droplets. Non-ionic surfactants, like polysorbates, polyoxyl castor oils, and polyoxyethylene sorbitan esters, are preferred over the ionic surfactants because of their low gastrointestinal irritation and wide acceptance by regulators. The addition of co-surfactants and co-solvents, like short- and medium-chain alcohols, propylene glycol, and polyethylene glycols, helps in lowering the interfacial tension, increasing the fluidity of the interfacial film, and enhancing the solubilization power of the vehicle for the drug included.

The selection of the above components is never random but is based on the solubility studies of the drug candidate in individual components, followed by the preparation of pseudo-ternary phase diagrams for establishing the self-emulsifying region and the optimum composition thereof[10].

5. Mechanisms of Bioavailability Enhancement

SEDDS increase the oral bioavailability of drugs through multiple interconnected processes as opposed to one unifying mechanism. Firstly, the use of SEDDS eliminates the limitation of absorption imposed on crystalline BCS Class II compounds by ensuring the drug is delivered in a dissolved state inside very fine emulsion droplets that are able to maintain drug availability for absorption in the small intestine[11].

Secondly, the conversion of the particle size to the nano or micro emulsion form significantly raises the interface surface area for drug diffusion into the aqueous phase in the intestine and its absorption, as well as access of the lipid core to the digestive enzymes like pancreatic lipase and co-lipase.

Thirdly, and importantly in the context of highly lipophilic compounds having log P more than five, digestion of the lipid vehicle leads to long chain fatty acids and monoglycerides which get re-esterified in enterocytes to triglycerides and packed into chylomicrons, providing an alternate route for absorption through intestinal lymphatics[12]. The lymphatic pathway becomes relevant in case of highly metabolized or actively transported compounds by the CYP 450 3A4 enzyme or P-glycoprotein, respectively, due to the fact that some non-ionic surfactants in SEDDS such as polysorbate 80 and polyoxyl 40 hydrogenated castor oil, which are used as drug solubilizers, have been demonstrated to be inhibitors of both efflux transporters and pre-systemic metabolism enzymes[13].

Fourth, from the in vitro modelling of dynamic lipolysis, it has been shown that the degree and rate of precipitation of drugs during the simulation of the process of digestion are highly dependent on the formulation used, indicating that merely forming an emulsion does not necessarily mean that supersaturation will be maintained throughout the process.

6. Characterization and Evaluation Techniques

General characterization of SEDDS is normally done through a number of tests that complement each other. The visual examination of emulsification capacity, time of self-emulsification and dispersion capacity in normal dilution conditions offers preliminary information, whereas the determination of droplet size, polydispersity index and zeta potential of dispersion is done using photon correlation spectroscopy and dynamic light scattering methods[14].

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The thermodynamic stability of SEDDS is tested via cycles of centrifugation, freeze-thaw stresses, and heating-cooling because, despite being isotropic and monophase at room temperature, SEDDS are liable to phase separation when exposed to thermal and mechanical stress conditions which are not easily detectable from visual inspection over short periods of time. TEM and cryo-SEM are more commonly used for direct visualization of the morphologies of the droplets, while the indirect size determination of the droplets is done via light scattering methods. The drug release from SEDDS in vitro should be studied using dynamic and biologically relevant lipolysis methods which simulate lipolysis of lipids during pancreatic digestion in the presence of bile salts and phospholipids since routine dissolution in aqueous medium does not reflect the physicochemical changes a lipid carrier undergoes in vivo.

7. Recent Advances: Solid Self-Emulsifying Systems

One major limitation of the traditional liquid SEDDS is that they are incompatible with the production facilities normally required for solid oral preparations, in addition to the issues related to physical stability, drug leakage, and interaction with soft/hard shell capsules of gelatine over the long term. The solid SEDDS have been developed in response to these limitations by processing the liquid self-emulsifying dispersion into powder, granules, or pellets through spray drying, absorption on solid porous supports, melt granulation, or extrusion-spheronization[15]. Adsorption of active pharmaceutical ingredient to a high surface area carrier, such as colloidal silica, magnesium aluminometasilicate, and microcrystalline cellulose, is especially effective in this respect, because these carriers can accommodate significant amounts of liquid and still retain sufficient powder flowability and compressibility for the following tableting or encapsulation process. Granules of solid SEDDS have also been reported to provide superior dose homogeneity, as well as dissolution and bioavailability rates comparable or even better than those of the liquid drug product, in addition to facilitating the use of quality by design-based production controls which are not applicable to liquid filled capsules[16].

8. Recent Advances: Nanostructured and Supersaturable SEDDS

Taking a cue from the conventional self-microemulsifying delivery system, the supersaturating SEDDS uses a minimal amount of precipitation inhibitor, such as hydroxypropyl methylcellulose, polyvinylpyrrolidone, or hydroxypropyl cellulose, to inhibit or delay crystallization of the drug from its supersaturated state formed during dilution[17]. This technique allows a decrease in the overall surfactant concentration of the system, which is of practical significance owing to the potential irritation and surfactant toxicity caused by the higher surfactant concentrations commonly used in traditional Type IIIB systems. Nanostructured systems such as self-nanoemulsifying drug delivery systems, which produce droplets smaller than one hundred nanometers in size, have been shown to provide additional improvements in dissolution and absorption of several poorly water-soluble antibacterial, antihypertensive, and antiretroviral drugs[18]. Other studies have included self-emulsification of the system loaded with permeation enhancers, mucoadhesive polymers, and lipids-based nanocarriers like solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). This shows the evolution of SEDDS technology in conjunction with nanomedicine.

9. Artificial Intelligence and Machine Learning in SEDDS Optimisation

Conventional SEDDS formulations were developed based largely on empirical solubility testing and DoE techniques, where response surface methodology is employed to correlate the effects of various formulation parameters like the oil-to-surfactant ratio and cosurfactant concentration on the quality attributes of interest like droplet size, emulsification time, and drug content[19]. While DoE is certainly an essential method for local optimization in the given design space, it is limited in terms of its ability to model complex non-linear interactions among multiple process/formulation variables.

During the last few years, there have been more and more applications of various machine learning methods, such as artificial neural networks, random forests, support vector regression, and Gaussian process regression to predict the formulation properties based on existing historical data or the data collected systematically[20]. In the particular case of SEDDS

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systems, the models have been built for predicting the parameters of self-emulsification, the size of droplets, and the in vitro release based only on the formulation composition, thus significantly decreasing the amount of experimental work that was previously necessary using trial-and-error approach.
One of the regular features that can be observed in this relatively new field is the fact that the performance of the models, especially their ability to accurately predict properties of novel drug substances, heavily depends on the variety and number of the compounds in the training set, with the prediction accuracy being poor when the compounds are not in the applicability domain of the model.

10. Clinical Translation and Marketed Products

The clinical and commercial utility of the SEDDS system is evidenced by the successful use of this system in a number of commercial pharmaceutical products. Cyclosporin A, when designed as a self-microemulsification system, is among the first examples demonstrating how this platform can address the issues of unpredictability and food dependency of the initial oil-based system regarding absorption[21]. Further commercialized products based on SEDDS technology have covered disease areas such as antiretroviral, antifungal, and immunosuppressive treatments, which highlights the versatility of this drug delivery system among different physicochemical properties of the drugs.
However, despite their success, relatively few products using SEDDS technology have become approved as compared to the amount of academic research about them due to the fact that there is an extra challenge to manufacture these formulations at large scale.

11. Challenges and Limitations

Despite the proven benefits that SEDDS offers, a number of obstacles remain that prevent their extensive use. One of the primary concerns is the danger of precipitation of the drug when it is diluted within the gastrointestinal lumen, especially in the case of almost saturated drug loading in which small changes in luminal content could result in precipitation[22].
The compatibility of the lipidic phase with the capsule shell is another practical issue, as some surfactants and co-solvents may move from the lipidic phase into the gelatin shell, causing it to become brittle or leak out during the shelf life of the drug product. In addition, high levels of surfactants that are required for fine emulsification have been found to cause dose-related gastrointestinal irritation, posing a challenge in formulating emulsions where efficient emulsification and low irritation potential need to be optimized simultaneously. Lastly, the lack of a well-accepted and validated in vitro test that could predict the in vivo performance of such emulsions remains an issue in developing the formulations and compiling their regulatory dossiers, although dynamic lipolysis studies have strong scientific rationale behind them.

12. Future Directions

There are several areas that might play an important role in future evolution of SEDDS technology. Harmonization of standardized and biorelevant lipolysis protocols will greatly enhance the predictive power of in vitro screenings and help avoid expensive in vivo studies in early stages of the drug formulation development. Optimization of manufacturing process of solid state SEDDS using scalable approaches that can be integrated into a continuous manufacturing platform may lead to narrowing the gap between lab scale formulations and commercial products.
Development of physiologically based pharmacokinetics models in conjunction with in vitro lipolysis and permeability data can provide additional ways of building more accurate in vitro-in vivo correlations. Use of machine learning-guided formulation platforms, trained on large and chemically diverse datasets that cover all BCS classes, can significantly reduce the empirical part of SEDDS development.

13. CONCLUSION

The self-emulsifying drug delivery system, which has progressed from being a theoretically beautiful but practically derived formulaic technique to one that is now well understood in terms of mechanisms and has reached maturity, is one such strategy. The combination of traditional formulaic science, such as Pouton's classification system for lipid formulations, with recent developments in solid-state formulating techniques, supersaturation technologies, and computational formula design has greatly broadened the number of drugs that can be formulated using SEDDS. Nevertheless, problems like those related to precipitation in the gastrointestinal tract, capsule-compatibility issues, and the lack of a harmonized predictive test suggest that the field of SEDDS technology is still very much alive and evolving.

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