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A PARADIGM SHIFT IN BIOAVAILABILITY ENHANCEMENT USING SOLID SELF EMULISIFYING DRUG DELIVERY SYSTEM

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ABSTRACT
Background: Solids are physically and chemically more stable compared to liquid formulations. The Solid SEDDS form is preferred over the liquid SEDDS form to enhance the oral bioavailability of lipophilic medications. Solid SEDDS are isotropic mixtures of oil, surfactant, and co-solvent. **Methodology:** A liquid-solid compact approach is followed to convert liquid SEDDS into solid SEDDS. Melt granulation, melt extrusion, spray drying, adsorption to solid carriers, and freeze drying are some approaches to converting liquid SEDDS into solid SEDDS. Various solid self-emulsifying materials in several solid dosage forms, like solid dispersions, tablets, capsules, and powders. **Result and discussion:** Solid SEDDS results in solubility studies, particle size and polydispersity index (PDI), zeta potential, in vitro drug release, solid-state characterization (e.g., XRD, DSC), and stability studies. In summary, S-SEDDS seems to be a viable strategy for improving the distribution of poorly water-soluble drugs through enhanced bioavailability, stability, and administration simplicity. **Conclusion:** In this review, the research will be extended to the different approaches toward improving the bioavailability, stability, and solubility of poorly soluble drugs into solid SEDDS. All these components are intended to act as primary instructions for future development in SSEDDS.

INTRODUCTION

The primary goal of this review work is to create a solid SEDDS to improve the bioavailability of poorly water-soluble drugs [1]. The oral route is the most convenient route for non-invasive drug administration. One of the main factors influencing oral bioavailability is solubility behaviour [2]. It is most convenient for administration due to their rather poor water solubility. In the oral administration of class II and IV absorption, some drugs have good clinical therapeutic effects and frequently have low systemic availability. The bioavailability of these drugs depends upon their dissolution. The concept of drug delivery systems has surfaced to reduce the harmful effects of drugs [3]. The components of solid SEDDS isotropic mixtures are oils, surfactants, and co-solvents. This system's core idea is that a fine oil-in-water (o/w) emulsion forms instantly when the system is diluted with an aqueous phase while gently agitated. The active lipophilic component of SEDDS, inert lipid carriers like oils, and surfactant dispersions stimulate lipoprotein, resulting in micellar solubilization in the duodenum, and the drug becomes entrapped

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in colloidal micelles. As a result, the drug becomes more soluble, improving its absorption. Each formulation approach has unique benefits and drawbacks. The concept of a drug delivery system was developed to reduce the negative impact of drugs and increase their absorption [4-6]. Solid self-micro emulsifying drug delivery systems (SSMEDDS) and solid self-nano emulsifying drug delivery systems (SSNEDDS) are two subcategories of solid self-emulsifying drug delivery systems (SSEDDS) based on particle size [7]. A microemulsion that is a transparent or translucent oil dispersion in water that is thermodynamically stable and has droplet sizes that typically range between 10 and 100 nm is known as a solid self-microemulsifying drug delivery system. It has been possible to build solid self-nano emulsifying drug delivery devices that spontaneously form nano-sized emulsions when in contact with gastrointestinal fluids. Droplets typically range in size from 20 to 1000 nanometers. Drug release can also be regulated or prolonged with a solid SEDDS design. Drugs that are susceptible to light, heat, or moisture can be made more stable with SSEDDS. Techniques including melt granulation, melt extrusion, spray drying, adsorption to solid carriers, and freeze drying are used to turn the liquid SEDDS into solid form [8].

It can be prepared in liquid form or encapsulated in a hard or soft gelatin capsule. Since soft gel formulations are more expensive, it is better to approach solid SEDDS [9]. Solid SEDDS forms have more stability and a longer shelf life than liquid formulations. Compared to liquid SEDDS, solid forms are made of powders or particles. These powdered forms are intended to dissolve or disperse within the gastrointestinal tract when they create an emulsion in vivo [10].

Objective of SSEDDS

- To help render poorly soluble drugs more soluble, thus improving bioavailability for better therapeutic results.
- Increase patient compliance by offering a more convenient and user-friendly dosage form [11].
- To improve the dosage form's design for efficient use of drugs and to maximise the amount of drug loading in the solid dose form.
- For delivery of drugs to some areas of the GI tract or other parts of the body.
- Involves a regulated or prolonged release of drugs in a way that will prolong its therapeutic effects and reduce the need for conventional dosage [12].

COMPOSITION

Oil

Oils are used for solubilising lipophilic (hydrophobic) drugs of low water solubility. The drug dissolves and is more readily absorbed by the digestive system once it has been emulsified. Oil increases the formation of microemulsions or nanoemulsions by reducing the interfacial tension between the oil and aqueous phases when the formulation interacts with water. Oil helps improve a drug's solubility and promote its dispersion into fine droplets after emulsification, increasing the surface area that may be absorbed in the GI tract. Examples of oil medium-chain triglycerides (MCTs) are aprylic/capric triglycerides. Long-chain triglycerides (LCTs) are soybean, sesame, and corn. Fatty acid esters are isopropyl myristate, isopropyl palmitate, and ethyl oleate, as represented in Table 1. Exotic oil, fish oil, and borage oil are commonly used [13].

Table 1: Selection of Oil Solid SEDDS

Medium chain triglycerides (MCT)	Long chain triglycerides (LCT)	Fatty Acid Esters
Miglyol® 812	Olive Oil	Isopropyl Myristate
Labrafac™ Lipophile WL 1349	Corn Oil	Isopropyl Palmitate
Neobee® M-5	Sesame Oil	Oleic acid
Akoline MCM	Soybean Oil	Ethyl Oleate

Surfactant

Surfactants are very important for the formulation of microemulsions. In the case of surfactants, when a liquid self-emulsifying system is converted into a solid, for example, by adsorption onto solid carriers or simply by spray drying, the emulsification properties are maintained, ensuring effectiveness after the solidification phase. It reduces interfacial tension and enhances drug solubilisation by increasing the solubility of lipophilic drugs in the aqueous phase. Combined with these compounds, a stable emulsion is formed by reducing the surface tension between the aqueous and lipid phases. It helps to disperse the emulsion in gastrointestinal fluids. The non-ionic surfactants are polysorbates (tween) and polyoxethylene glycol derivatives; anion surfactants are sodium lauryl sulfate and sodium dodecyl sulfate; and amphoteric surfactants are lecithin and phospholipids, as represented in Table 2 [14].

Co-surfactant

Higher concentrations of surfactants in formulations cause gastrointestinal disturbances and irritation, which should be

avoided. This can only be accomplished by using co-surfactants to reduce the surfactant concentration. Due to the reduced interfacial tension among oil and water, co-surfactants improve emulsion formation, increase solubilisation, and reduce them. Also, co-surfactants may increase the permeability and solubility of poorly water-soluble drugs, increasing their bioavailability. Co-surfactants enhance the drug's rapid absorption by improving its dispersion in the gastrointestinal fluid.

Improved drug dispersion and solubilisation result from the formation of smaller, more homogeneous droplets during emulsification, which is made possible by this reduction. This preserves the self-emulsifying characteristics in the solid form. Some commonly used co-surfactants in SSEDDS include polyethylene glycol, transcutol HP, ethanol, sorbital, and mannitol, which are represented in Table 3. Co-surfactants are essential for SSEDDS, and obtaining the intended drug delivery result depends on these molecules' careful selection and optimisation [15].

Table 2: Selection of surfactants for Solid SEDDS

Chemical name	**Trade name**
Glycerol monooleates	Peceol™
Lauroyl macrogol-32 glycerides	Gelucire® 44/14
Polysorbate 20	Tween® 20
PEG-60 hydrogenated castor oil	Cremophor® RH 60
Glyceryl caprylate	Capmul® MCM
Propylene glycol monocaprylate	Capryol® 90
Sorbitan monopalmitate	Span 40
Polysorbate 80	Tween® 80
Sorbitan monooleate	Span® 80
Polyethylene glycol (15)-hydroxystearate	Solutol® HS 15
Polyoxylglycerides	Labrafil® M 2125

Table 3: Selection of co-surfactants for solid SEDDS

Alcohols & polyols	**Esters**	**Amides**
Transcutol	Triacetin	Pyrrolidone
Benzyl alcohol	Ethylene oleate	N-alkylpyrrolidone
Sorbitol, mannitol	Acetyl triethyle citrate	Polyvinyl pyrrolidone
Glycerol	Propylene glycol diacetate	N,N-Dimethylacetamide

Other Excipients used in SSEDDS

Polymers

Subsequently, after the liquid self-emulsifying system is transformed into a solid form, polymers help to stabilise the mixture of oils and surfactants. They may include co-surfactants to ensure the performance and stability of S-SEDDS while being handled and stored**.** SSEDDS include various polymers like hydroxypropyl methylcellulose, ethylcellulose, eudragit (methacrylic acid copolymers), polyvinylpyrrolidone, carbomers, chitosan, polycarbonate, etc [16].

Lubricants and Glidants

Stearic acid, talc, magnesium stearate, and colloidal silicon dioxide are widely utilised lubricants and glidants that enhance the flow ability of the solid dosage form during its manufacture, prevent the product's adhesion to machinery, and ensure proper powder flow during manufacturing [17].

PSEUDOTERNARY PHASE DIAGRAMS

Solid SEDDS are developed and optimised using a graphical representation called a pseudo-ternary phase diagram. The method of water titration was employed to produce a pseudo-ternary phase diagram. Phase diagram construction involves the use of oil, surfactants, and co-surfactants. Appropriate oils that could solubilise the drugs were chosen based on the solubility studies of the drug. Based on their ability to stabilise the emulsion and HLB value, surfactant and cosurfactant are chosen. Each group's surfactant and cosurfactant (Smix) were combined in various weight ratios. Oil and Smix are combined in various vials or tubes at varying ratios for every phase, progressively declining the oil concentration and elevating the water content. Water was added to the mixtures dropwise until an easily flowable o/w microemulsion with a clear or slightly bluish colour formed. An emulsion was a little less transparent system that appeared bright white or bluish-white. These values were utilised to determine the limits of the microemulsion region. The oil, surfactant, co-surfactant mixture (Smix), and water are the three components that each triangle axis represents. The phase diagram was constructed using Central Composite Design Software, CHEMIX school software, and Matlab software [18].

Advantages

- It provides a clear graphical representation of the phase behaviour of mixtures with three key components: oil, surfactant, and co-surfactant or solid matrix. This will help

formulators understand how different ratios between these three components can affect system performance.

- It will thus systematically screen many formulations with different oil, surfactant, and co-surfactant/solidifying agent ratios. Therefore, it reduces the number of trial-and-error experiments and quickly identifies the optimum formulation.
- This diagram helps identify regions where the drug is maximally solubilised in the lipid phase and, hence, better absorbed upon oral administration.
- The phase diagram guides the selection of solidifying agents, allowing the S-SEDDS to remain solid at room temperature while being effective at self-emulsification with the necessary integrity of the solid form [19].

Disadvantage

- Ternary diagrams are constructed for three-component systems comprising oil, surfactant, and co-surfactant or solid matrix. Many formulations, however, may contain other excipients (e.g., stabilisers, co-solvents) that cannot easily be represented in a ternary system.
- This may be time-consuming and labor-intensive, especially when unavailable high-throughput techniques.
- In most cases, the pseudo-ternary phase diagram is plotted without a drug. However, the drug can have some substantial effects on phase behaviour, especially when the drugs have poor solubility. Its exclusion may mean that it doesn't fully represent the behaviour of the final drug-containing formulation [20].

Significance of SSEDDS

Spontaneous self-emulsification within the GIT [21] results in the formation of oil in water emulsion; the small size of globules formed upon dilution in GIT offers a large surface area, which improves the drug absorption of class II & IV drugs [22]. To address the stability and high manufacturing cost of liquid SEDDS, that was converted into solid SEDDS [23]. This model improves the gastric residence time [24], controlled release of drug [25], improved solubility and bioavailability [26], and ease of handling and targeting drugs to specific regions of GIT [21].

METHOD OF SOLID SEEDS

A graphical representation of different methods of formulation of solid SEDDS is shown in Figure 1.

1. Spray Drying:

The liquid SEDDS is atomised into small droplets using a pressure nozzle, two-fluid nozzle, or rotary atomiser. The atomised droplets are exposed to hot air before they reach the drying chamber. Solid particles are left behind as the solvent evaporates, and dried powder is collected from collecting chambers and cyclone separators. Such particles are prepared into tablets and capsules, as shown in Figure 2 [27].

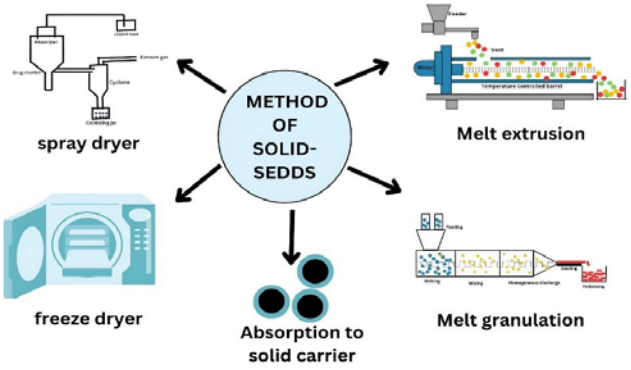

Figure 1: Various methods to formulate solid SEDDS

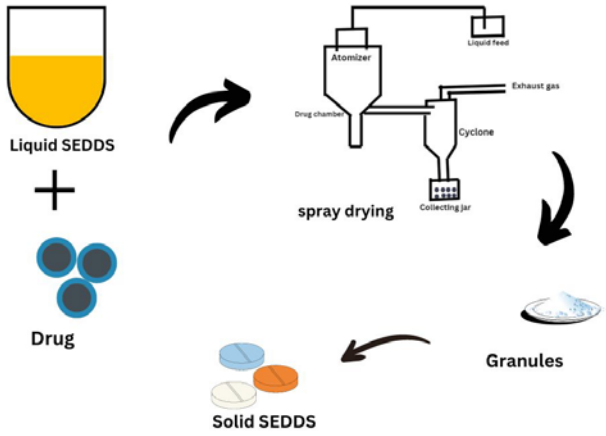

Figure 2: Conversion of liquid SEDDS into solid SEDDS by spray drying method

2. Melt extrusion

Melt extrusion is also known as hot-melt extrusion (HME). The extruder feeds lipids, drugs, and surfactants into its barrel. There are two types of feeding: batch and continuous feeding. The mixture is heated to its processing temperature inside the extruder. The components melt due to the combination of heat and mechanical shear caused by revolving screws. A homogenous melt is produced when the drug is dissolved or distributed throughout the molten mixture. To create extrudates, the molten liquid is forced through a die. On a cooling roller or

conveyor belt, the extrudates are rapidly cooled to solidify them. The solidified extrudates are ground or milled into smaller particles, granules, or pellets, as shown in Figure 3 [28].

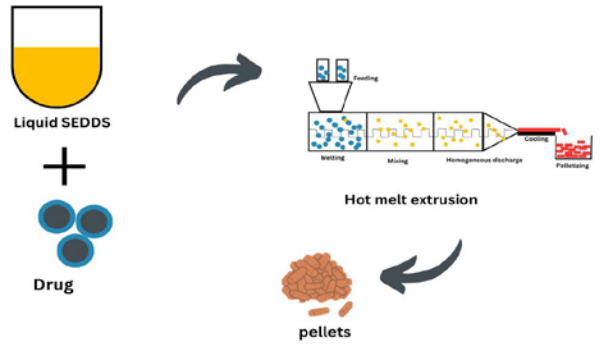

Figure 3: Conversion of liquid SEDDS into solid SEDDS by hot melt extrusion method

3. Adsorption to solid carrier:

The preparation of S-SMEDDS involved combining liquid SMEDDS with solid carriers. In short, liquid SEDDS was added to the solid carrier under continuous stirring. To avoid clumping or agglomeration, ensure the liquid SEDDS is spread equally across the solid carrier's surface. High-shear is used for mixing if necessary to improve homogeneity. The finished product needs to be a powder that flows freely and shows no evidence of being liquid. Powder being directly filled into capsules or compressed into tablets is shown in Figure 4. The frequently used carriers in solid SEDDS include lactose, microcrystalline cellulose, neusilin US2, malto dextrin, fujicalin, calcium silicate**,** syloid 550, and aerosil 200 [29].

Figure 4: Conversion of liquid SEDDS into solid SEDDS by solid carrier method

3. Melt granulation

Melt granulation is a method that produces powder agglomeration by adding a binder that softens or melts at comparatively low temperatures. Fill the hot granulator with the solid carriers, and slowly add the liquid SEDDS formulation while continuously mixing it with the solid carrier. Because of the equipment's heat, allow the binder to melt, then keep mixing until the drugs, carriers, and melted binder are all evenly mixed. Optimizing the temperature is necessary to prevent the degradation of drugs or excipients. Once there has been sufficient development of granules, turn off the heat source and allow the system to cool down gradually. After removing excess moisture from the granules using a fluid bed dryer, once the granules are formed, they can be mounted into hard gelatin capsules or consolidated into tablets, depending on the required dosage form, as shown in Figure 5 [30].

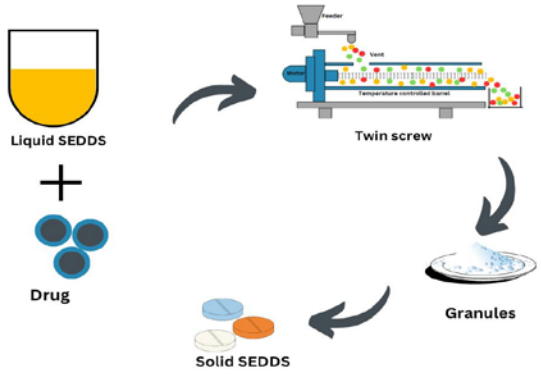

Figure 5: Conversion liquid SEDDS into solid SEDDS by melt granulation method

3. Freeze drying / lyophilisation:

During the process, liquid SEDDS are converted to solid SEDDS. The liquid SEDDS is added to liquid nitrogen or a freezer, where a temperature normally between -40°C and -80°C is maintained. At this point, heat is applied at regulated low temperatures while the pressure is decreased. This results in a direct sublimation of the formulation's frozen solvent (usually water), leaving behind a porous, dry solid matrix. There may still be bound water in the formulation after the sublimation or primary drying. The prepared SEDDS were placed at low pressure and high temperature to remove any residual moisture, called secondary drying. This stage improves the finished product's shelf life and stability, as shown in Figure 6 [31].

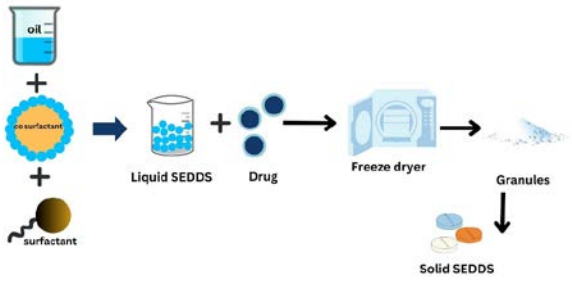

Figure 6: Conversion of liquid SEDDS into solid SEDDS by freeze-drying method

APPLICATION OF SSEDDS

Enhancing stability

S-SEDDS enhances drug stability. S-SEDDS enhanced the stability of tocotrienols using a solid carrier and a simple adsorption method [13].

Improved controlled or sustained Release

Research on furosemide S-SEDDS showed enhanced and predictable therapeutic responses with controlled release [32].

Enhanced bioavailability and solubility

S-SEDDS are particularly suitable for controlled substances in classes II, as per the BCS, which are typically weakly soluble in water but have good membrane permeability. Solid supersaturate self-emulsifying cilostazol tablets significantly improve drug solubility and absorption [33].

In the delivery of peptides and proteins

S-SEDDS provide good delivery systems for lipophilic peptides and proteins while protecting the entrapped agents from breakdown by enzymes in the GI tract. This was proven by developing a solid self-emulsifying drug delivery system for lysozyme to enhance its stability and oral bioavailability [34].

Drug targeting and delivery of hydrophobic compounds

S-SEDDS solubilise hydrophobic drugs in the gastrointestinal system and hence help in their more effective delivery for improved absorption. It significantly enhanced Ibuprofen and Cyclosporin A, solubility, permeability, and bioavailability [35].

Transport of lymphatic drugs

By promoting the lymphatic transport of drugs, S-SEDDS can ideally bypass the first-pass processing by the liver, which, in most cases, increases the bioavailability of some drugs. For example, paclitaxel-loaded S-SEDDS significantly enhanced bioavailability and lymphatic targeting and offered a promising approach for improving oral paclitaxel delivery [36].

Cancer therapy

S-SEDDS has high potential in cancer treatment. Paclitaxel S-SEDDS enhances drug oral bioavailability, cellular uptake, and anti-tumour efficacy by inhibiting P-gp and utilising lymphatic transport, showing improved apoptosis and tumour reduction in vivo studies [37].

Protection against degradation

SEDDS can deliver macromolecules like enzyme substrates, inhibitors, peptides, and hormones and protect them from enzymatic degradation [38-39].

Pediatric and geriatric drug delivery

The S-SEDDS benefit pediatric and geriatric patients who may find conventional capsules or pills challenging to swallow. The systems can also be included in readily dissolved pills or powders administered as carrier-based compositions. Dolutegravir sodium was designed to focus on ease of administration [29].

DIFFERENT BETWEEN LIQUID AND SOLID SEDDS

Liquid SEDDS have many drawbacks, such as being chemically and physically unstable compared to solid SEDDS. Soft gel capsules or liquid solutions fill liquids. Solid forms, such as tablets or capsules, are simpler to handle, store, and administer than liquid systems. Figure 7 shows the differences between liquid and solid SEDDS [40-42].

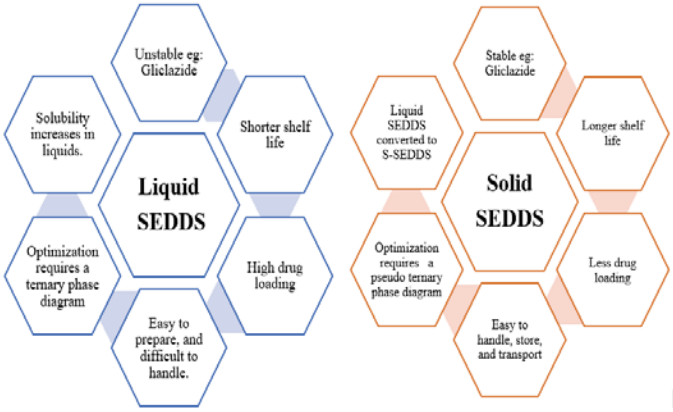

Figure 8: Distinctive features of liquid and solid SEDDS

EVALUATION OF SSEDDS

1. **Solubility studies**

Determining the drug's solubility in various lipid excipients is a foundational step in S-SEDDS formulation. Equilibrium solubility studies involve mixing an excess amount of the drug with different oils, surfactants, and co-surfactants, followed by agitation and equilibrium at a controlled temperature. After centrifugation, the supernatant is analysed, typically using high-performance liquid chromatography (HPLC), to quantify the dissolved drug concentration. These studies guide the selection of appropriate excipients that maximise drug solubility.

2. **Self-emulsification efficiency**

The ability of S-SEDDS to spontaneously form emulsions upon dilution is critical. This efficiency is assessed by diluting the formulation in aqueous media under mild agitation and observing the resultant emulsion. Parameters such as emulsification time, appearance (clarity or turbidity), and the tendency to form a stable emulsion are recorded. Efficient self-

emulsifying formulations rapidly produce fine, uniform emulsions, indicating potential for enhanced drug absorption.

3. Droplet size and polydispersity index

The size of the emulsion droplets significantly impacts drug absorption and stability. Dynamic light scattering (DLS) or laser diffraction techniques are commonly used to measure droplet size and polydispersity index (PDI). A smaller droplet size (<200 nm) with a low PDI (<0.3) indicates uniform dispersion and enhanced drug absorption.

4. Zeta potential analysis

Zeta potential measures the surface charge of the emulsion droplets, which influences the formulation's physical stability. A high zeta potential value (>±30 mV) suggests strong repulsion between droplets, preventing aggregation and improving stability. Zeta potential measurements are conducted using electrophoretic light scattering techniques.

5. Solid-state characterisation

Transforming liquid SEDDS into solid forms necessitates thorough characterisation to ensure the drug's stability and performance. Key techniques include:

- Differential scanning calorimetry (DSC) Assesses thermal transitions to determine the drug's crystalline or amorphous nature within the formulation.
- X-ray powder diffraction (XRPD) identifies the drug's physical state, detecting any changes in crystallinity post-formulation.
- Fourier transform infrared spectroscopy (FTIR): Detects potential chemical interactions between the drug and excipients by analysing characteristic functional group vibrations.
- Scanning electron microscopy (SEM): Visualizes the surface morphology of solid particles, providing insights into particle size, shape, and surface characteristics [23].
- Micromeritic properties: The micromeritic parameters of S-SEDDS, including bulk and tapped density, Hausner ratio (HR), compressibility index, and angle of repose, can be determined by the following methods.

a) Bulk density: The powder is placed into the measuring cylinder, and the apparent volume is determined. The following formula is used to determine bulk density.

$$Bulk\ density = \frac{Mass\ of\ powder}{Volume\ of\ powder}$$

b) Tapped density: The ratio between tapped volume and weight is used to calculate tapped density.

$$Tapped\ density = \frac{Mass\ of\ powder}{Tapped\ volume\ of\ powdeer}$$

c) Hausner ratio

The flowability of a powder is determined using the Hausner ratio. The ratio of tapped density to bulk density is called the Hausner ratio. The formula for determining the Hausner ratio is as follows:

$$Haunser\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

d) Compressibility Index:

Carr's compressibility index is used to evaluate the granules compressibility.

$$Carr´s\ compressibility\ index(\%) = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

e) Angle of repose:

The angle of repose can be determined using the fixed funnel method. The funnel is filled with the samples until a smooth mound forms. The powder can freely flow down the funnel and onto the surface. A graded scale is used to measure the height and diameter of the heap. The angle of repose can be calculated using the formula below.

$$tan\theta = h/r$$

where ɵ=angle of repose, h=heigh, r=average radius of the power cone [43].

6. In vitro dissolution studies

Dissolution testing is performed to compare the drug release profile of S-SEDDS with that of the pure drug or conventional dosage forms. This test uses a USP dissolution apparatus in various simulated gastrointestinal fluids. The drug release rate is determined using UV-visible spectroscopy or HPLC analysis. An enhanced dissolution rate indicates the efficiency of S-SEDDS in improving drug solubility.

7. In vitro lipolysis studies

Since S-SEDDS formulations contain lipids, they undergo digestion in the gastrointestinal tract. In vitro, lipolysis studies simulate the enzymatic digestion process to assess the potential precipitation of the drug upon lipid digestion. The formulation is incubated with digestive enzymes (pancreatic lipase) in a simulated intestinal environment, and the extent of drug precipitation is analysed [44].

8. Stability studies

Stability assessment is crucial to determine the shelf-life of S-SEDDS. These studies evaluate the impact of temperature, humidity, and light on the formulation over time. Stability studies include:

- **Accelerated stability testing:** Formulations are stored at elevated temperatures and humidity (e.g., 40°C/75% RH), and physical and chemical stability is analysed.
- **Long-term stability studies:** Monitoring formulation changes under standard storage conditions over extended periods.
- **Physical stability:** Observing phase separation, precipitation, or changes in droplet size over time.

9. In vivo bioavailability studies

In vivo, studies are conducted in animal models or human subjects to confirm the enhancement in drug absorption and bioavailability. These studies involve administering S-SEDDS and measuring pharmacokinetic parameters such as:

- Maximum plasma concentration (Cmax)
- Time to reach maximum concentration (Tmax)
- Area under the concentration-time curve (AUC)

An increase in Cmax & AUC values compared to conventional formulations indicates improved bioavailability [43].

10. Permeability studies

Assessing the drug's permeability from S-SEDDS formulations provides insights into its potential absorption in the gastrointestinal tract. Techniques such as Caco-2 cell monolayer assays or ex vivo intestinal perfusion studies evaluate the drug's transport across intestinal barriers. Enhanced permeability indicates the formulation's effectiveness in facilitating drug uptake [45].

11. Excipient compatibility studies

To ensure the long-term stability and efficacy of S-SEDDS**,** drug-excipient compatibility studies are conducted using techniques like DSC, FTIR, and HPLC**.** These studies help identify potential interactions that might affect the drug's stability [46].

CONCLUSION

Solid SEDDS are a significant development in drug delivery technology, especially for improving the bioavailability of drugs that aren't water-soluble. Solidifying liquid SEDDS will bring several advantages, including enhanced stability, better patient compliance, ease of handling, and a wider range of dosing forms, such as capsules and tablets. Solid SEDDS resolves most of the drawbacks associated with liquid formulations, including leakages and degradation, while maintaining the all-important self-emulsification features for improved solubilisation and absorption of drugs in the GI tract. Solid self-emulsifying drug delivery systems, in contrast to liquid SEDDS, are a promising and attractive approach for delivering lipophilic drugs in terms of consistency and efficiency, long-term stability, ease of processing, and versatile formulation. Their manufacture may, however, be more complex. 3D printing technology is one of the leading technologies explored in the pharmaceutical manufacturing sector to develop self-nano-emulsifying tablets [47]. Solid SEDDS will greatly expand the application of self-emulsifying systems in pharmaceutical product development.

Studies have shown that developing or formulating BCS class II and IV drugs as SEDDS increases oral bioavailability. Liquid or semi-liquid SEDDS are formulated or converted into tablets, capsules, pellets, powders, and other forms of SEDDS. The mentioned SEDDS can be converted into SSEDDS using techniques such as melt granulation, melt extrusion, spray drying and cooling, adsorption to solid carriers, and lyophilisation. Consequently, more research in this area is needed to develop a wide range of preparations using self-emulsification that could be commercially available. Selecting excipients is a principal task, or objective, in developing SSEDDS with the help of main directions. All these constituents shall work as principal directions in the future development of SSEDDS. Researching current trends, designing studies, and analysing data to demonstrate SSEDDS potential in improving bioavailability. Their collaborative efforts ensured comprehensive insights and innovative solutions to drug delivery challenges.

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NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

S. Umadevi supervised and guided the whole study. S. Rajathi prepared and edited the first draft of the manuscript. E. Ezhilarasan drafted the manuscript. All the authors approved the final draft.

REFERENCES

[1] Salawi, Ahmad. Self-emulsifying drug delivery systems: A novel approach to deliver drugs. *Drug Delivery.*, **29(1)**, 1811-1823 (2022) https://doi.org/10.1080/10717544.2022.2083724.

[2] Kim DS, Cho JH, Park JH, Kim JS, Song ES, Kwon J, Giri BR, Jin SG, Kim KS, Choi HG, Kim DW. Self-microemulsifying drug delivery system (SMEDDS) for improved oral delivery and photostability of methotrexate. *Int. J. Nanomedicine*., **14,** 4949-4960 (2019) https://doi.org/10.2147/IJN.S211014.

[3] Jain S. DoE-based solid self-microemulsifying drug delivery system (S-SMEDDS) approach for improving the dissolution properties of raltegravir potassium. *J. Pharm. Innov*., 1–14 (2022) http://dx.doi.org/10.1007/s12247-022-09621-5

[4] Zhang W, Zheng Q, Song M, Xiao J, Cao Y, Huang Q, Ho CT, Lu M. A review on the bioavailability, bio-efficacies and novel delivery systems for piperine. *Sci. Food Funct*., **12(19)**, 8867-8881(2021) https://doi.org/10.1039/d1fo01971f.

[5] Krishna VM, Kumar VB, Dudhipala N. In-situ intestinal absorption and pharmacokinetic investigations of carvedilol loaded supersaturated self-emulsifying drug system. *Pharm. Nanotechnol.*, **8(3)**, 207-224 (2020) https://doi.org/10.2174/2211738508666200517121637.

[6] Jo K, Kim H, Khadka P, Jang T, Kim SJ, Hwang SH. Enhanced intestinal lymphatic absorption of saquinavir through supersaturated self-microemulsifying drug delivery systems. *Asian J Pharm Sci*., **15(3)**, 336–346 (2020) https://doi.org/10.1016/j.ajps.2018.11.009.

[7] Mishra V, Nayak P, Yadav N, Singh M, Tambuwala MM, Aljabali AAA. Orally administered self-emulsifying drug delivery system in disease management. *Expert Opin. Drug Deliv.*, **18(3),** 315-332 (2021) https://doi.org/10.1080/17425247.2021.1856073.

[8] Cid AG, Simonazzi A, Palma SD, Bermudez JM. Solid dispersion technology as a strategy to improve the bioavailability of poorly soluble drugs. *Ther. Deliv.*, **10(6)**, 363-382 (2019) https://doi.org/10.4155/tde-2019-0007.

[9] Baghel P, Roy A, Verma S, Satapathy T, Bahadur S. Amelioration of lipophilic compounds in regards to bioavailability as self-emulsifying drug delivery system (SEDDS). *Futur. J. Pharm. Sci.*, **6**, (2020) https://doi.org/10.1186/s43094-020-00042-0.

[10] Saggar A, Upadhayay M, Goswami G. Formulation and evaluation of solid self-emulsifying drug delivery systems of bambuterol hydrochloride. *Indian J. Pharm. Sci.*, **81 (4),** 661-672 (2019) https://doi.org/10.36468/pharmaceutical-sciences.557.

[11] Rene Holm, Martin Kuentz, Alexandra-Roxana Ilie-Spiridon, Brendan TG. Lipid based formulations as supersaturating oral delivery systems: From current to future industrial applications. *European Journal of Pharmaceutical Sciences.*, **189**, 23-31 (2023) https://doi.org/10.1016/j.ejps.2023.106556.

[12] Lam HT, Le-Vinh B, Phan TNQ, Bernkop-Schnurch A. Self-emulsifying drug delivery systems and cationic surfactants. *J. Pharm. Pharmacol.*, **71(2)**, 156-166 (2019) https://doi.org/10.1111/jphp.13021.

[13] Lee YZ, Seow EK, Lim SC, Yuen KH, Abdul Karim Khan N. Formulation and in vivo evaluation of a solid self-emulsifying drug delivery system using oily liquid tocotrienols as model active substance. *Pharmaceutics.*, **13(11)**, 17-21 (2021) https://doi.org/10.3390/pharmaceutics13111777.

[14] Khairnar H, Jain S, Chatterjee B. lactoferrin reduces surfactant content in the self-emulsifying drug delivery system. *ACS. Omega.*, **9(12)**, 13612-13620 (2024) https://doi.org/10.1021/acsomega.3c06645.

[15] Zi P, Zhang C, Ju C, Su Z, Bao Y, Gao J, Sun J, Lu J, Zhang C. Solubility and bioavailability enhancement study of lopinavir solid dispersion matrixed with a polymeric surfactant - Soluplus. *Eur. J. Pharm. Sci.*, **134**, 233-245 (2019) https://doi.org/10.1016/j.ejps.2019.04.022.

[16] Kovvasu SP, Kunamaneni P, Joshi R, Betageri GV. Self-emulsifying drug delivery systems and their marketed products-A Review. *Asian Journal of Pharmaceutics.*, **13(2)** ,73-84 (2019) http://dx.doi.org/10.22377/ajp.v13i02.3102

[17] Yeom DW, Chae BR, Son HY, Kim JH, Chae JS, Song SH, Oh D, Choi YW. Enhanced oral bioavailability of valsartan using a polymer-based supersaturable self-microemulsifying drug delivery system. *Int. J. Nanomedicine.*, **8(12),** 3533-3545 (2020) https://doi.org/10.2147%2FIJN.S136599

[18] Alghananim A, Ozalp Y, Mesut B, Serakinci N, Ozsoy Y, Gungor S. A solid ultra-fine self-nanoemulsifying drug delivery system (S-SNEDDS) of deferasirox for improved solubility: optimization, characterization, and in vitro cytotoxicity studies. *Pharmaceuticals (Basel).*, **13(8)**, 162-69 (2020) https://doi.org/10.3390%2Fph13080162

[19] Cid AG, Simonazzi A, Palma SD, Bermudez JM. Solid dispersion technology as a strategy to improve the bioavailability of poorly soluble drugs. *Ther. Deliv.*, **10(6)**, 363-382 (2019) https://doi.org/10.4155/tde-2019-0007.

[20] Zaichik S, Steinbring C, Caliskan C, Bernkop-Schnurch A. Development and in vitro evaluation of a self-emulsifying drug delivery system (SEDDS) for oral vancomycin administration. *Int. J. Pharm.*, **554**, 125-133 (2019) https://doi.org/10.1016/j.ijpharm.2018.11.010.

[21] Seo EB, Du Plessis LH, Viljoen JM. Solidification of self-emulsifying drug delivery systems as a novel approach to the management of uncomplicated malaria. *Pharmaceuticals*., **15(2),** 120 (2022) https://doi.org/10.3390/ph15020120

[22] Nasr A, Gardouh A, Ghorab M. Novel solid self-nanoemulsifying drug delivery system (S-SNEDDS) for oral delivery of olmesartanmedoxomil: design, formulation, pharmacokinetic and

bioavailability evaluation. *Pharmaceutics*., **8(3)**, 20 (2016) https://doi.org/10.3390/pharmaceutics8030020

[23] Almeida SRD, Tippavajhala VK. A rundown through various methods used in the formulation of solid self-emulsifying drug delivery systems (S-SEDDS). *AAPS Pharm. Sci. Tech.*, **20(8)**, 323-327 (2019) https://doi.org/10.1208/s12249-019-1550-5.

[24] Hussain A, Shakeel F, Singh SK, Alsarra IA, Faruk A, Alanazi FK. Solidified SNEDDS for the oral delivery of rifampicin: evaluation, proof of concept, *in vivo* kinetics, and *in silico* gastroplusTM simulation. *Int J Pharm*., **566,** 203–17 (2019) https://doi.org/10.1016/j.ijpharm.2019.05.061

[25] Nazzal S, Khan MA. Controlled release of a self-emulsifying formulation from a tablet dosage form: stability assessment and optimization of some processing parameters. *Int J Pharm.*, **15(1–2),** 110–121 (2006) https://doi.org/10.1016/j.ijpharm.2006.02.019

[26] Potharaju S, Mutyam SK, Liu M, Green C, Frueh L, Nilsen A. Improving solubility and oral bioavailability of a novel antimalarial prodrug: comparing spray-dried dispersions with self-emulsifying drug delivery systems. *Pharm Dev Technol.*, **25(5),** 625–639 (2020) https://doi.org/10.1080/10837450.2020.1725893.

[27] Madagul JK, Parakh DR, Kumar RS, Abhang R. Formulation and evaluation of solid self-microemulsifying drug delivery system of chlorthalidone by spray drying technology. *Drying Technology*., ***35*(12),** 1433–1449 (2019) https://doi.org/10.1080/07373937.2016.1201833.

[28] Kallakunta VR, Sarabu S, Bandari S, Tiwari R, Patil H, Repka MA. An update on the contribution of hot-melt extrusion technology to novel drug delivery in the twenty-first century. *Expert Opin. Drug. Deliv.*, **16(5)**, 539-550 (2019) https://doi.org/10.1080/17425247.2019.1614912.

[29] Hemant A. Deokule, Smita S. Pimple, Kiran C. Mahajan, Praveen D. Chaudhari. Fabrication and evaluation of solid self-emulsifying drug delivery system of dolutegravir sodium by using adsorption to solid carrier techniques. *Research Journal of Pharmacy and Technology.*, **15(9)**, 4158-4165 (2022) https://doi.org/10.52711/0974-360X.2022.00698.

[30] Xia Y, Shi CY, Fang JG, Wang WQ. Approaches to developing fast release pellets via wet extrusion-spheronization. *Pharm. Dev. Technol.*, **23(5)**, 432-441 (2020) https://doi.org/10.1080/10837450.2016.1265556.

[31] Colucci D, Maniaci R, Fissore D. Monitoring of the freezing stage in a freeze-drying process using IR thermography. *International Journal of Pharmaceutics.*, **566**, 488-499 (2019) https://doi.org/10.1016/j.ijpharm.2019.06.005.

[32] Gul S, Sridhar SB, Jalil A, Akhlaq M, Arshad MS, Sarwar HS, Usman F, Shareef J, Thomas S. Solid self-nanoemulsifying drug delivery systems of furosemide in vivo proof of concept for enhanced predictable therapeutic response. *Pharmaceuticals (Basel).*, **7(4),** 500 (2024) https://doi.org/10.3390/ph17040500.

[33] Wannas, Ali N, Nidhal K, Maraie. Characterization and optimization of oral solid supersaturable self-emulsifying drug delivery system of cilostazol. *Res. J. Pharm. Technol.*, **14,** 3371-337(2021) https://doi.org/10.52711/0974-360X.2021.00586

[34] **S**ahinovic M, Hassan A, Kristo K, Regdon GJ, Vranic E, Sovany T. Quality by design-based development of solid self-emulsifying drug delivery system (SEDDS) as a potential carrier for oral delivery of lysozyme**.** *Pharmaceutics.*, **15(3),** 995 (2023) https://doi.org/10.3390/pharmaceutics15030995.

[35] Rani ER, Radha GV. Insights into novel excipients of self-emulsifying drug delivery systems and their significance: an updated review. *Crit. Rev. Ther. Drug Carrier Syst*., 38(2), 27-74 (2021) https://doi.org/10.1615/CritRevTherDrugCarrierSyst.2020034975 .

[36] Hea young co, jun –hyuk, Lien N. Preparation and evaluation of solid-self-emulsifying drug delivery system containing paclitaxel for lymphatic delivery. J. *Nanomater.*, **94,** 24-29 (2016) https://doi.org/10.1155/2016/3642418.

[37] Meher JG, Dixit S, Singh Y. paclitaxel-loaded colloidal silica and TPGS-based solid self-emulsifying system interferes Akt/mTOR pathway in MDA-MB-231 and demonstrates anti-tumor effect in syngeneic mammary tumors. *AAPS Pharm. Sci. Tech.*, **21,** 313 -321 (2020) https://doi.org/10.1208/s12249-020-01855-1.

[38] Ravindranath SM, Vishawas RP, Vijay RM. Review on: New approaches in self micro-emulsifying drug delivery system. *Res. J. Pharm. Technol.*, **10(4),** 1215-1224 (2017) https://doi.org/10.5958/0974-360X.2017.00218.9

[39] Govindan I, Rama A, Kailas AA, Hebbar S, Naha A. Transformative solidification techniques for self-emulsifying drug delivery and its foresight in modern-day drug delivery. *J Appl Pharm Sci.*, **14(07),** 001–013 (2024) https://doi.org/10.7324/JAPS.2024.184385.

[40] Suwarna RD, Suparna B, Kanchan U, Gouri D. Formulation and evaluation of solid self-emulsifying drug delivery system of Gliclazide. *Int. J. Pharm. Pharm. Sci.*, **8(11),** 144-151 (2016) https://doi.org/10.22159/ijpps.2016v8i11.14104.

[41] Yi T, Wan J, Xu H, Yang X. A new solid self-microemulsifying formulation prepared by spray-drying to improve the oral bioavailability of poorly water-soluble drugs. *Eur J Pharm Biopharm.*, **70(2)**., 439-44 (2008) https://doi.org/10.1016/j.ejpb.2008.05.001.

[42] Vasconcelos T, Marques S, Sarmento B. Measuring the emulsification dynamics and stability of self-emulsifying drug delivery systems. *Eur. J. Pharm. Biopharm.*, **123**, 1-8 (2019) https://doi.org/10.1016/j.ejpb.2017.11.003.

[43] Rehman FU, Farid A, Shah SU, Dar MJ, Rehman AU, Ahmed N, Rashid SA, Shaukat I, Shah M, Albadrani GM, Kamel M, Altyar AE, Abdel-Daim MM, Shah KU. Self-emulsifying drug delivery

systems (SEDDS): measuring energy dynamics to determine thermodynamic and kinetic stability. *Pharmaceuticals (Basel).*, **15(9),** 78-85 **(**2022) https://doi.org/10.3390/ph15091064.

[44] Maji I, Mahajan S, Sriram A, Medtiya P, Vasave R, Khatri DK, Kumar R, Singh SB, Madan J, Singh PK. Solid self-emulsifying drug delivery system: Superior mode for oral delivery of hydrophobic cargos. *J. Control Release.*, **337**, 646-660 (2021) https://doi.org/10.1016/j.jconrel.2021.08.013.

[45] Anam Z, Muhammad Z, Mahtab AK, Talha J, Muhammad HB. Preparation and evaluation of a self-emulsifying drug delivery system for improving the solubility and permeability of ticagrelor. *ACS Omega*.**, 9**, 10522-10538 (2024) https://doi.org/10.1021/acsomega.3c08700.

[46] Raman KV, Dudhipala N, Nyavanandi D, Sarabu S, Yadav Janga K, Ajjarapu S, Bandari S, Repka MA. Formulation and processing of solid self-emulsifying drug delivery systems (HME S-SEDDS) A single-step manufacturing process via hot-melt extrusion technology through response surface methodology. *Int J Pharm.*, **25**, 641 (2023) https://doi.org/10.1016/j.ijpharm.2023.123055.

[47] Algahtani MS, Mohammed AA, Ahmad J, Abdullah MM. Saleh E. 3D printing of dapagliflozin containing self-nanoemulsifying tablets: Formulation design and in vitro characterization. *Pharmaceutics.*, **13**, 993 (2021) https://doi.org/10.3390/Pharmaceutics13070993.