



Transformative solidification techniques for self-emulsifying drug delivery and its foresight in modern-day drug delivery

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ARTICLE HISTORY

Received on: 08/01/2024
Accepted on: 16/02/2024
Available Online: XX

Key words:

Self-emulsifying drug delivery system, solidification, 3D printing, supercritical fluid method, liquisolid, twin screw melt granulation.

ABSTRACT

Self-emulsifying drug delivery systems (SEDDSs) represent a significant breakthrough in addressing bioavailability challenges by enhancing the solubilization of poorly water-soluble drugs, ensuring consistent formulation properties, and facilitating easy industrial scale-up. Despite their liquid form posing some limitations, these challenges can be effectively addressed by solidifying SEDDSs, offering numerous advantages. The solidification of SEDDS has opened avenues for overcoming limitations associated with liquid formulations. Different approaches to solidification of SEDDS have been investigated to overcome the practical limitations of liquid formulations. Each method offers a plethora of benefits such as improved physicochemical stability, extended gastric residence time, controlled release of the drug, enhanced bioavailability, ease of handling, dose accuracy, and so on. While limitations persist, ongoing research is paving the path for the commercialization of solid SEDDS formulations with enhanced therapeutic effects. In light of previous publications, the current review paper makes an effort to give a comprehensive account of the most recent advancement in solid SEDDSs technology, with a focus on the formulation aspects of various types of novel solid self-emulsifying dosage forms for oral and nonoral drug delivery.

INTRODUCTION

The importance of advancing drug delivery systems lies in their potential to address existing challenges related to current drug formulations. The challenges arise from the inherent physical and chemical properties of drug molecules and the natural barriers present within the human body. These limitations manifest as poor drug solubility and permeability. A considerable number of pharmaceutical compounds (up to 70%) encounter difficulties due to limited water solubility, potentially influencing their absorption within the gastrointestinal system, emphasizing the importance of overcoming them for successful drug development [1]. Several approaches have been developed thus far, among which, lipid-based drug delivery systems

have emerged as a fundamental formulation method aimed at overcoming challenges related to poor bioavailability.

Self-emulsifying drug delivery systems (SEDDSs) are lipid-based drug delivery systems made up of oil, surfactant, and co-surfactant. SEDDS possess the ability to self-emulsify spontaneously within the gastrointestinal tract (GIT), resulting in the formation of an oil-in-water emulsion that improves the absorption of drugs [2]. Although SEDDS is not considered novel, there has been an increasing interest in developing it for therapeutic applications in recent years. The potential of SEDDS to enhance the dissolution rate of Biopharmaceutics classification system (BCS) II and IV drugs has prompted the growing interest in their development. The lipid component of SEDDS stimulates chylomicron/lipoprotein, resulting in micellar solubilization in the duodenum, and the drug becomes entrapped in colloidal micelles, as a result, the drug becomes more soluble, and its absorption is also improved [3]. The small globule size of the emulsion formed upon dilution of SEDDS offers a large surface area for interaction with the GIT, Improving absorption and reducing drug absorption variability [4].

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SEDDS are generally classified into two types based on the emulsion formed upon dilution: self-nanoemulsifying drug delivery systems (SNEDDSs) and self-microemulsifying drug delivery systems (SMEDDSs). The characteristic of SMEDDS is the formation of an optically clear to slightly translucent microemulsion when exposed to the aqueous medium. Microemulsion offers small droplet sizes that range from 100 to 400 nm. SMEDDS requires low interfacial tension for the formation of emulsion which offers a wide surface area for absorption. SNEDDS forms an oil-in-water nanoemulsion with droplet sizes less than 100 nm. SNEDDS are kinetically stabilized, whereas SMEDDS is thermodynamically stable [5,6].

Commercially available formulations of SEDDS are liquids, encapsulated in hard or soft gelatin capsules. Table 1 shows various marketed formulations of SEDDS.

The limited number of marketed products is primarily a result of their high cost of manufacturing, stability, and portability challenges, the risk of drug precipitation upon dilution, the absence of accurate *in-vitro* prediction tools, and the complexity of manufacturing equipment. The prevalent approach for overcoming these challenges is the solidification of liquid SEDDS. The primary objective is to improve both its physicochemical stability and reduce the overall manufacturing costs [15]. In addition, solidification has several advantages such as extended gastric residence time [16], controlled release of drug [17], improved solubility and bioavailability [18], ease of handling, dose accuracy, targeting drugs to a specific absorption region in the GIT, protecting the drugs from the harsh gut environment, spontaneous emulsification, [19] and so on. Solidification of liquid SEDDS can reduce the surfactant amount and enhance the oxidative stability of lipids by protecting them from degradation [20]. Achieving effective oral delivery of liquid SEDDS of macromolecules such as proteins and peptides is challenging due to the precipitation and conformational changes. Solid SEDDS (S-SEDDS) demonstrate the ability to stabilize peptides and proteins [21].

This review aims to build on earlier review articles in the field by highlighting current developments and challenges associated with the solidification of SEDDS. The focus of the article is to review various applications of S-SEDDS found in existing works of literature.

BUILDING BLOCKS OF S-SEDDS

The building blocks of S-SEDDS are lipid, surfactant, cosurfactant, and solid carrier. These components synergistically contribute to the formulation and performance of S-SEDDS. Types of oil and surfactant, along with their concentrations, are important for designing a highly effective self-emulsifying system. Adequate solubility drugs in lipids, surfactants, and cosurfactants and the self-emulsification efficiency of surfactants and cosurfactants are to be considered before formulation [22]. The performance, stability, and release profile of S-SEDDS are impacted by the types of solid carriers. It is crucial to choose a solid carrier that guarantees the best drug solubility, dispersion, and bioavailability after administration in addition to offering a stable matrix for the formulation. The compatibility of solid carriers with other components is a critical factor in achieving the intended therapeutic effect [23].

Lipids

Lipids play a vital role in the functionality of SEDDS. The solubility of the drug in the oil phase is the key consideration in the selection of oils. The drug solubility in the oil phase has a significant impact on the efficiency of nanoemulsion in maintaining the drug in a solubilized state; this is particularly significant when it comes to oral formulations [15]. The oil phase improves drug bioavailability by enhancing solubility and facilitating lymphatic transport. However, having high solubility does not ensure optimal *in vivo* efficiency [24]. A variety of long- and medium-chain triglyceride oils that are distinguished by their saturation levels, are used for the development of SEDDS. Natural oils and fats are composed of triglyceride combinations that comprise fatty acids with

Table 1. Commercially available SEDDS formulations.

SL No	Drug	Class	Type of dosage form	Brand name/Company	References
1	Amprenavir	Antiretroviral drug	Soft gelatin capsule	Agenerase/Glaxo smithkline	[7]
2	Bexarotene	Antineoplastic agent	Soft gelatin capsule	Targretin/Ligand	[8]
3	Cyclosporin A	Immunosuppressant	Soft gelatin capsule	Sandimmun/Novartis	[9]
			Hard gelatin capsule	Gengraf/Abbvie	
4	Cyclosporin	Immunosuppressant	Soft gelatin capsule	Neoral/Novartis	[10]
5	Calcitriol	Vitamin	Soft gelatin capsule	Rocaltrol/Roche	[11]
6	Dutasteride	5-alpha reductase inhibitors	Soft gelatin capsule	Avodart/GlaxoSmithKline	[12]
7	Dornabinol	cannabinoids	Soft gelatin capsule	Marinol/Roxane and Unimed	[7]
8	Fenofibrate	Antilipidemic agents	Hard gelatin capsule	Lipirex/Genus	[13]
9	Isotretinoin	Retinoids	Soft gelatin capsule	Absorica/Sun pharam	[7]
10	Ritonavir	Antiretroviral drug	Soft gelatin capsule	Norvir/Abbott	[14]
11	Saquinavir	Antiretroviral drug	Soft gelatin capsule	Fortovase/Hoffmann-La Roche inc.	[14]
12	Tretinoin	Retinoids	Soft gelatin capsule	Vesanoid/Roche	[14]
13	Valproic acid	Antiepileptic	Soft gelatin capsule	Convulex/Pharmacia	[14]

varying chain lengths and levels of unsaturation. The melting point of a particular oil increases as the chain lengths of its fatty acids lengthen and drop as the degree of unsaturation increases. Furthermore, increased unsaturation makes the oil more susceptible to oxidation [25]. Unmodified vegetable oils, especially those with medium-chain triglycerides (Examples: Palm kernel oil and coconut oil), are considered favorable due to their natural origin. However, limited drug loading and inefficient self-emulsification, reduce their usage in SEDDS formulation [15]. Long-chain lipids (Examples: Oleic acid and castor oil) were found to be able to maintain drug concentrations at significant levels, avoiding precipitation, in contrast to medium-chain triglycerides [20]. The use of modified vegetable oils (Campul MCM, Acconon CC-6) has become prevalent recently due to their high emulsification capabilities when combined with suitable surfactants [26]. Table 2 represents commonly used natural, semi synthetic, and synthetic oils for the formulation of SEDDS.

Surfactants

SEDDS requires a high concentration of surfactant to create fine oil-in-water emulsions in the GIT, reducing the chance of drug precipitation after dilution. The concentration of surfactants, which normally varies from 30% to 60% in SEDDS formulations. For optimal SEDDS formulation, the surfactant must lower interfacial tension, ensure smooth droplet dispersion, and have flexible, lipophilic properties [28]. A surfactant with strong drug solubility may not have good oil affinity. The self-emulsification efficiency rather than the drug solubilizing ability will determine the criterion for selecting the surfactant and co-surfactant [4]. Nonionic surfactants, particularly those with Hydrophilic lipophilic balance value (HLB) >12, are highly favorable for SEDDS formulations, given their lower toxicity compared to ionic surfactants. The high HLB surfactants facilitate fast and easy dispersion within the aqueous gastrointestinal fluid, forming an extremely fine oil-in-water emulsion. Consequently, this leads to good self-emulsification performance [1]. Polyoxyethylene (10) oleyl ether, polyoxyethylene (20) oleyl ether, Cremophor® EL, Cremophor® RH40, and polysorbates are examples of nonionic surfactants commonly used for SEDDS formulations [29]. Higher concentrations of surfactants in SEDDS may cause gastric irritation, underscoring the importance of addressing safety concerns related to cytotoxicity. Solidifying SEDDS by substituting a portion of surfactants with solid carriers, such as hydroxypropyl methylcellulose (HPMC), can reduce toxicity [30].

Cosurfactants

Cosurfactants aid in the dissolution of drugs and higher concentrations of hydrophilic surfactants. Cosurfactants also improve the fluidity of the interface between the two phases of the emulsion, which inhibits the generation of liquid crystals and speeds up the emulsification process [20]. The choice of the co-surfactant depends on its ability to optimize the nanoemulsion area along with the surfactant. Both the surfactant and co-surfactant create a mechanical barrier against coalescence and reduce interfacial energy, resulting in good

Table 2. Various oils used for the formulation of SEDDS.

Types	Examples	References
Natural oils	Coconut oil, palm oil, castor oil, sesame oil, clove oil, soyabean oil	[27]
Semi synthetic oils	Campul MCM, Imwitor®, Peceol™	[25]
Synthetic oils	Labrafil® M1944CS, Labrafil® M2125CS, Gelucire® 44/14	

thermodynamic stability. Co-surfactants are often alcohols with medium-to-short chain lengths (C3–C8) such as propylene glycol, transcutool HP, ethanol, and isopropyl alcohol [15]. However, alcohols and other volatile cosolvents in conventional SEDDS have a disadvantage, as they can evaporate into the shells of soft gelatin or hard gelatin capsules, resulting in drug precipitation [1].

Solid carriers

Solid carriers have a critical role in the conversion of liquid SEDDS into solid form. Solidification enhances the physical and chemical stability of SEDDS, preventing them from deterioration. Furthermore, controlling the rate of drug diffusion from the matrix provides sustained drug release. Various solid carriers used for the transformation of liquid SEDDS into solid are mainly divided into two types: silica-based carriers and nonsilica-based solid carriers (Fig. 1).

Silica-based solid carriers

Solid carriers made of silicon dioxide (SiO₂), also known as silica, are porous substances with a large surface area and a highly porous structure. Silica-based solid carriers provide various advantages in the formulation of S-SEDDS, including enhanced drug solubility, stability, and drug release. The porous nature of silica-based solid carriers can help in drug dissolution and release from the SEDDS, resulting in increased drug bioavailability. Fumed silica nanoparticles (Aerosil), porous amorphous silica gels (Syloid and Sylysia), mesoporous silica materials, and magnesium aluminum silicate (Neusilin) are the commonly used silica-based solid carriers [31]. The utilization of Aerosil 200 as the solid carrier in the solid SNEDDS of olmesartan exhibited good flow properties and a significant drug content [4]. Snela *et al.* [32] and colleagues developed two novel SEDDSs for atorvastatin calcium. The SEDDSs were adsorbed onto solid inorganic carriers such as Aerosil® 200, Neusilin® UFL2, and Neusilin® US2 to improve stability and effectiveness. Scanning electron microscopic images of SEDDS formulations adsorbed on three different solid carriers revealed the absence of crystals, which was also confirmed by differential scanning calorimetry. Inverse gas chromatography on solid SEDDSs (S-SEDDSs) demonstrated that the strongest interactions were observed for Neusilin® UFL2 samples, while the weakest were observed for Aerosil®-based materials [32]. A study focused on the development of solid supersaturable SEDDS of celecoxib via the adsorption method, utilizing various grades of silica-based solid carriers (Sylysia 350 fcp, Aerosil 200, Aerosil 300, Aerosil R 972), were chosen based on their features such as

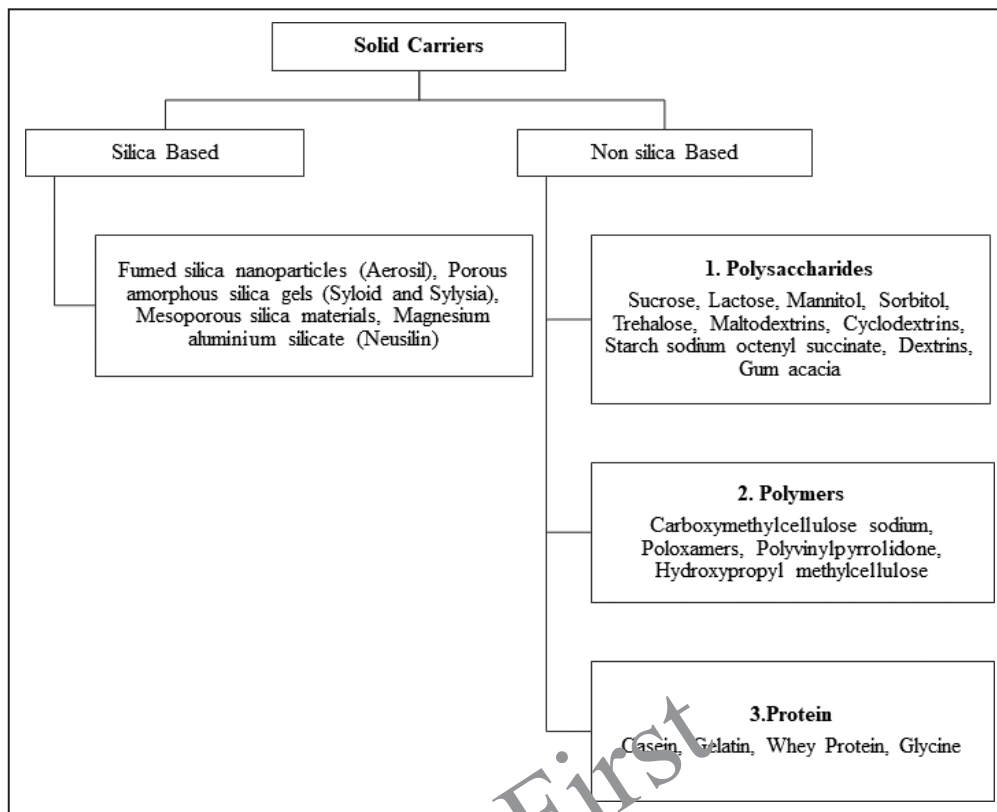


Figure 1. Solid carriers used for the conversion of liquid SEDDS into solid SEDDS.

porosity, hydrophobicity-hydrophilicity and surface area. The drug release characteristics of solid supersaturable SEDDS made from these solid carriers showed significant variances, despite the fact that they were various grades of the same solid carrier. The variations in drug release were due to their unique physicochemical properties. The solid supersaturable SEDDS with solid carrier Sylysia 350 fcp demonstrated a higher and more consistent drug release, resulting in improved oral bioavailability among all solid supersaturable SEDDS. This study proves that the characteristics of solid carriers are crucial in influencing the drug release profile of S-SEDDS and can help to make formulation development more rational [33].

Nonsilica-based solid carriers

Nonsilica-based solid carriers such as polysaccharides, polymers, and proteins are also used in the formulation of S-SEDDS. Polysaccharides are commonly considered safe for pharmaceutical applications due to their high biocompatibility and low toxicity. Polysaccharide-based solid carriers include low molecular weight sucrose, lactose, mannitol, sorbitol, and trehalose, as well as higher molecular weight maltodextrins, cyclodextrins, starch sodium octenyl succinate, dextrins, and gum acacia. The crystal structure and moisture sensitivity of polysaccharide solid carriers should be considered while designing formulations. When subjected to spray-drying, lyophilization, and rotary evaporation, these carriers are susceptible to undergoing partial or total transformation into an unstable, amorphous state with high energy levels [34].

Polymer solid carriers can be used to generate a matrix in which the liquid SEDDS may be incorporated to develop solid dosage forms such as tablets, capsules, or granules. Polymer solid carriers are effective as emulsifiers, solid carriers, and inhibitors of drug precipitation. Carboxymethylcellulose sodium, poloxamers, polyvinylpyrrolidone, and HPMC are a few examples of polymer-based solid carriers. At high temperatures and humidity levels, polymer-based solid carriers tend to absorb moisture, due to their hygroscopic nature. Amphiphilic properties of protein-based solid carriers allow them to serve as both emulsifiers and solid carriers for lipid formulations. Casein, whey protein, gelatin, glycine, and soy protein are examples of protein-based solid carriers that provide improved biocompatibility and biodegradability. Although they might not be stable enough to function effectively with some drug molecules [35]. Gelatin and glycine are less frequently reported for the solidification of lipid colloids due to their poor compressibility [34].

SOLIDIFICATION STRATEGIES FOR LIQUID SEDDS

Physical adsorption

Physical adsorption is an uncomplicated solidification method wherein liquid SEDDS is mixed with solid carriers, including high surface-area colloidal inorganic adsorbent substances, microporous inorganic substances cross-linked polymers, or nanoparticle adsorbents (Fig. 2) [20]. Cross-linked polymers such as polymethyl methacrylate and carboxymethyl

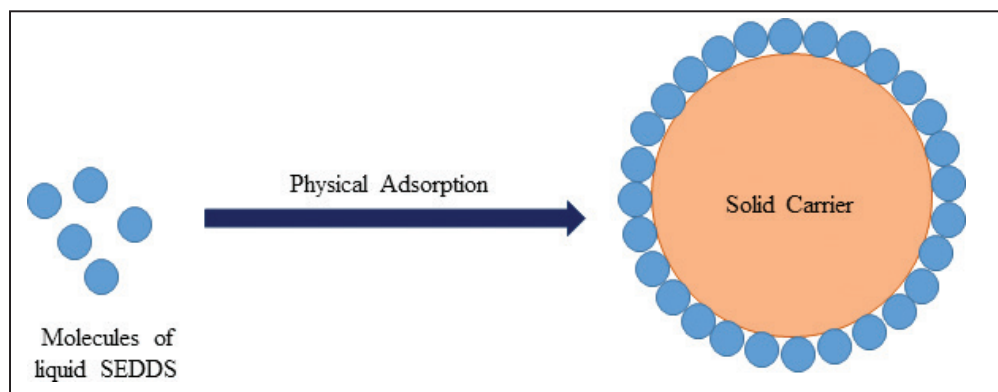


Figure 2. Schematic representation of solidification of liquid SEDDS by physical adsorption.

cellulose facilitate sustained drug release and prevent drug re-precipitation. Porous SiO₂, fullerenes, charcoal, and carbon monomers are nanoparticle adsorbents [36].

The selection of solid carriers is important as the nature (hydrophilic/hydrophobic) of solid carriers can influence the properties of the drug. X-ray diffraction studies on a self-nanoemulsifying granule of ezetimibe using hydrophobic colloidal SiO₂ as a solid carrier revealed that the presence of the drug is in its amorphous form. Intriguingly, when the same SNEDDS adsorbed onto a different solid carrier, led to the formation of a eutectic mixture [37]. Furthermore, it is essential to thoroughly analyze the porosity of the chosen adsorbent, considering the significant influence of pore length, shape, and specific surface area on the dissolution of S-SEDDS [38]. A novel S-SNEDDS of valsartan utilizing different porous solid carriers Aerosil 200, Sylysia 350, Sylysia 550, Sylysia 750, and Neusilin US2 exhibited a 3–3.5 fold increase in bioavailability of valsartan [39]. The drug dissolution rate of S-SEDDS can be affected by interactions between solid carriers and the components of SEDDS. Therefore, it is important to consider the characteristics of solid carriers such as their particle size, nature, quantity, and specific surface area. In addition, an important factor to be considered is drug crystallinity. Amorphous drugs are more prone to re-crystallization and chemical instability. The stability and dissolution rate of S-SEDDS formulations must, therefore, be optimised with careful consideration of these aspects [40].

The physical adsorption method uses a minimal number of excipients and avoids the use of organic solvents to produce the final formulation. Moreover, good content uniformity and significantly high drug loading are obtained using only basic equipment.

The leakage of liquid components during the compression of S-SEDDS is a major limitation of this approach. It may result in the development of soft tablets and can give rise to problems such as sticking, chipping, and variable hardness. In certain cases, a substantial quantity of solid carriers may be required, which undesirably increases the volume of the final product [20].

Spray drying

Spray drying is thought to be an efficient and cost-effective way to produce micro-particle systems that can

be easily scaled up. This method is suitable for solidifying SEDDS, and the end product can be developed into tablets [41]. The spray drying apparatus is made up of a feeding system, hot air source, atomizer, drying chamber, solid-gas separator, and final product collection chamber. The characteristics of the material being dried and the desired features of the resulting powder are taken into consideration while choosing the specific layout of the drying chamber, as well as the temperature, airflow pattern, and atomizer orifice size [1].

The spray drying process of SEDDS involves the mixing and the solubilization of lipids, surfactants, active constituents, and solid carriers. The solubilized formulation is atomized to produce a spray of droplets that travel into a drying chamber and facilitate water evaporation from SEDDS to form the dried particles with the aid of controlled temperature and airflow (Fig. 3) [42].

The selection of solid carriers has a significant impact on drug release in addition to drug bioavailability since it affects the entrapment efficiency of SEDDS and the droplet size of the reconstituted emulsion. Microcrystalline cellulose, HPMC, hydroxypropyl cellulose, lactose, and maltodextrin are a few examples of hydrophilic solid carriers used in spray drying. These carriers promote rapid emulsion formation and water penetration [43].

Spray drying offers highly accurate control over particle size, crystallinity level impurities, bulk density, and residual solvent. In addition, it maintains a good quality powder throughout the drying process [44].

Spray-dried SEDDS offers enhanced stability, solid particles with a narrow size distribution, good flow properties, and an enhanced dissolution rate. However, a reduced yield may be obtained because of the elimination of the nonencapsulated drug with the exhausted gas. Reduction in the volume of volatile surfactant in liquid SEDDS at high temperatures may also affect the drug loading capacity [19]. High temperatures and rapid drying rates hinder the solidification of temperature-sensitive substances. Clogging of the nozzle with oil components poses a challenge in this approach [45].

Successful SEDDS solidifications using the spray drying approach are shown in Table 3.

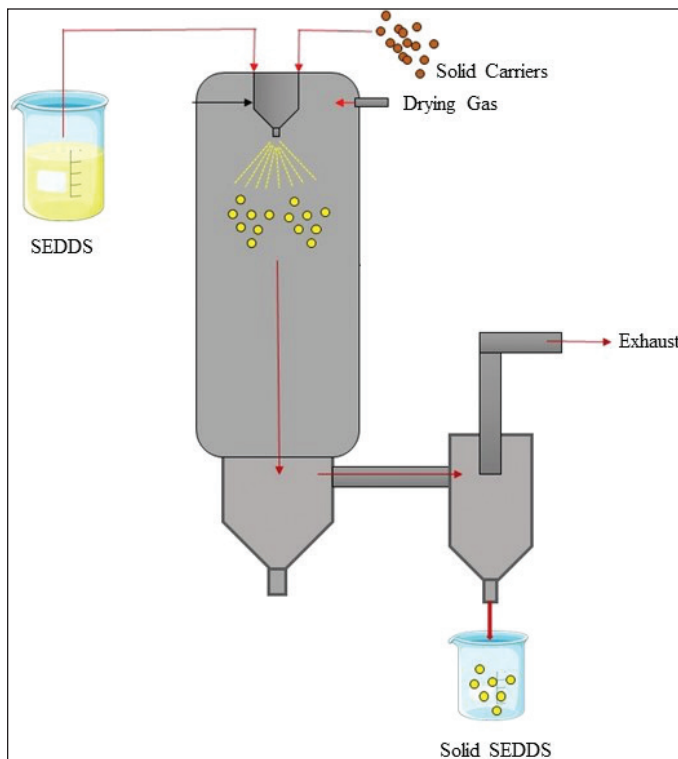


Figure 3. Process of conversion of liquid SEDDS into solid by Spray Drying method.

Spray congealing

The spray congealing method is mainly used for the preparation of self-emulsifying microparticles. The process involves the spraying of molten SEDDS into a cooling chamber, where the liquefied droplets undergo solidification and are followed by re-crystallization to form fine powders. The absence of solvent evaporation makes congealed particles robust and impermeable. Spray congealing holds promise for improving the bioavailability of weakly soluble drugs through different mechanisms. These include improving wettability, forming dispersed systems, reducing the size of drug crystals, and converting the drug into metastable polymorphs or the amorphous form [53].

The spray congealing approach has a continuous flow, is simple to use, and can be adjusted for automatic procedures with rapid response. Despite the longer cooling times required, the quality of the powder does not deteriorate during cooling. The fine powder can then be subjected to further processes that produce a variety of solid oral dosage forms, such as tablets. Spray congealing technology was employed in the development of S-SEDDS of glibenclamide to enhance the solubilization rate. It is suggested that spray congealing could serve as a promising approach for designing S-SEDDS, offering a remedy to challenges associated with liquid SEDDS [54]. Spray congealing is a solvent-free, low-cost, and quick manufacturing method for increasing the bioavailability of poorly water-soluble drugs like praziquantel [55].

Although molten SEDDS usually melt at temperatures higher than their melting point, this is not always a viable option as certain drugs have higher melting points than lipids. However, the use of spray-congealing as a unit process to increase the solubility of active ingredients is possible [56].

Gelucire®, vitamin E tocopheryl polyethyleneglycol succinate, solutol, and poloxamer are commonly used excipients for the production of spray-congealed SEDDS [43]. Among them, Gelucire 50/13, with an average HLB of 11 and a melting temperature of around 50°C, is frequently employed [57].

Lyophilization

The lyophilization method, commonly known as freeze drying, is a novel approach for solidifying SEDDS. SEDDS can be easily solidified through lyophilization, which also increases their solubility, stability, and patient compliance [13]. In this method, the liquid SEDDS is frozen and followed by conversion into a dry powder via sublimation at low temperatures and pressures. On reconstitution, dry powder can be easily turned back into a fine emulsion. The lyophilization process consists of three stages: fast freezing of the product is the first stage, and then it goes through a primary drying phase where most of the water content is sublimated out. The third stage, known as secondary drying, eliminates any leftover water molecules to produce a stable and dehydrated powder [58].

Lyophilization has several benefits, one of which is the use of an aseptic procedure that reduces the chances of contamination. This technique helps stabilize chemicals that are prone to oxidation, and a slow cooling rate of the lyophilization method stabilizes the SEDDS formulation throughout the process. In addition, the preservation duration is prolonged because 95%–99.5% of the water content is removed, and chemicals that are heat-sensitive are particularly well-suited for lyophilization [15]. Cryoprotectants are used to avoid the mild stresses that the lipid bilayers experience during freezing and drying states. Sugars such as maltose, sucrose, mannitol, trehalose, and glucose are commonly used as cryoprotectants [1].

S-SMEDDS of Lornoxicam was formulated utilizing the lyophilization method for solidification and assessed its bioavailability in Wistar rats. *In vitro* drug release assessment of S-SMEDDS of Lornoxicam showed significant improvement in solubility and dissolution rate. *In vivo* pharmacokinetic studies also exhibited higher bioavailability of S-SMEDDS compared with marketed tablets [59]. Furthermore, a study on S-SNEDDS of meloxicam investigated the use of water-soluble and water-insoluble solid carriers in lyophilization. The study found that the S-SNEDDS formulations prevented Meloxicam crystallization and increased the drug release by three to four times. In comparison to the insoluble solid carrier, the soluble carrier did not affect the formation of the nano-emulsion [60].

Though it has benefits, lyophilization has some disadvantages as well. This method involves extended handling and processing time and also lyophilization apparatus can be highly complex and costly [61].

Table 3. A literature review on successful SEDDS solidification using the spray drying method and its outcome.

SL No	Type	Drug	Composition	Solid carrier	Outcome	Reference
1	S-SEDDS	Curcumin	Sulforaphan, Cremophor EL, Acconon CC6	soluplus® or neusilin® US2	Soluplus® S-SEDDS released 100% of the curcumin within 2.5 hours, but neusilin® US2 S-SEDDS only released 55% of the drug. Tablets of S-SEDDS showed a controlled drug release for 24 hours.	[46]
2	Solid SMEDDS	Nimodipine	Ethyl oleate, Labrasol, Cremophor RH	Dextran	Similar AUC and Cmax values were obtained with liquid and solid SMEDDS; however, the maximum absorption was delayed by the solid SMEDDS. AUC and Cmax on oral delivery of the solid SMEDDS were 2.6- and 6.6-fold greater than the marketed tablet, respectively.	[47]
3	S-SEDDS	Dexibuprofen	Labrasol, Capryol 90, Labrafil M 1944 CS	Aerosil 200	Solid SEDDS of dexibuprofen had a higher rate of release compared to the powdered form. <i>In vivo</i> absorption studies in rats showed S-SEDDS a considerable enhancement in the bioavailability of dexibuprofen compared to the powdered formulation.	[48]
4	Solid lipid-Based SEDDS	Curcumin	Lauroglycol Fcc, Labrasol, Transcutol HP	Aerosil 200	S-SEDDS showed a faster <i>in vitro</i> dissolution rate than crude powder while maintaining the self-emulsification property of liquid SEDDS. A significant increase in the bioavailability of curcumin in rats following oral administration as compared to a powder suspension formulation.	[49]
5	SMEDDS	Mebendazole	Labrafil 2125 CS, Tween 20, and Maisine 35-1	Aerosil 200	Solid SMEDDS demonstrated an improvement in bioavailability of 24.87 folds when compared to pure medication and an increase of 8.39 folds when compared to commercially available mebendazole tablets. The shelf life of the optimized batch of solid SMEDDS was determined to be 3.1726 years.	[50]
6	SEDDS	Agaricoglyceride	Miglyol® 812, Cremophor® RH40, Tween80, Transcutol® P	Aerosil 200	S-SEDDS exhibited a faster <i>in vitro</i> dissolution rate compared to crude powder. Oral bioavailability of Agaricoglyceride is enhanced.	[51]
7	SNEDDS	Sertraline	Labrafil M 2125 CS, Maisine, Tween 80, Lauroglycol 90	Dextran 40	Comparing the absorption of sertraline from solid SNEDDS to that from the commercially available capsule and an aqueous suspension of sertraline, a considerable increase is seen.	[52]

Melt extrusion-spheronization method

Melt extrusion-spheronization is a method of choice for producing pellets and one of the most investigated approaches for producing self-emulsifying pellets. This method involves mixing SEDDS with a carrier, agglomerating the mixture, and then spheronizing it. During spheronization, the extrudate is broken down to generate pellets or spheroids. Spheroids have a narrow particle size distribution, favorable flow characteristics, and low friability. In addition, the process allows for achieving high drug loading [19]. In addition, extrusion/spheronization is a potential strategy for developing self-emulsifying pellets of phytotherapeutic agents [62].

The interplay between the proportion of SEDDS and water holds an important role in determining the extrusion force, size distribution, disintegration time, and surface roughness of

pellets. It is important to highlight that, the maximum amount of SEDDS that can be solidified by extrusion spheronization method is 42% of the dry pellet weight [36]. Achieving favorable physical characteristics and high drug loading in pellets necessitates a reduction in the solid carrier quantity and a concurrent increase in the liquid SEDDS content. In contrast to other excipients, a formulation with a higher proportion of absorbent material permits the inclusion of a greater portion of the SEDDS.

According to Abdalla *et al.* [63] more than 40 % of the SEDDS load in pellets may result in the sticking of the extrudate to the apparatus. Pellets without suitable adsorbents may have poor hardness, poor flowability, and a tendency to agglomerate. Commonly used adsorbents are lactose, methylcellulose, microcrystalline cellulose, HPMC,

croscarmellose sodium, and crospovidone [64]. The tensile strength and irregularity of the spheroids can be affected by the ratio of SEDDS to water as well as the relative proportions of absorbent and other components. The extrusion force and the sphericity of the pellets are positively correlated with the proportion of SEDDS. Rapid drug release is an additional advantage of using a disintegrant [63].

Melt extrusion is a closed process that uses minimal equipment, provides high blending efficiency, and minimizes the risk of cross-contamination. The processing time of this method is less, and the variables are easy to control. [1]. However, melt extrusion has some limitations, such as high-energy input, a limited number of polymers, and the challenges of using thermal-sensitive material. Extensive research should be done on the various properties of components, such as stability, flow characteristics, wettability, and compatibility before the selection [65].

Melt granulation

Melt granulation is a single-step method, that can be used to produce S-SEDDS. This process does not include the liquid addition and drying phases, making it an effective substitute for methods that rely on solvents [66]. Nonswellable and water-insoluble properties of the dried product are considered safe for human use. The melt granulation process produces agglomerates through two mechanisms: immersion and dispersion. The primary particle is submerged onto the binder surface in immersion mode, while the molten binder spreads on the primary particle's surface in dispersion mode [65]. Neutral solid carriers such as silica and magnesium aluminometasilicate and lipid-based carriers such as gelucire and lecithin are common adsorbents used in melt granulation [67].

Regardless of whether high or low impeller speeds are used, the viscosity of SEDDS or binders is critical in nucleation and particle size. Binders having lower melting points melt and soften continuously during handling and storage, making them prone to agglomeration, whereas binders with higher melting points require greater temperatures, which might cause instability, especially in heat-sensitive materials [36]. The requirement for high temperatures during the melt granulation process is a main limitation, as it may deteriorate the constituents [66].

The melt granulation method was employed to develop immediate-release self-emulsifying tablets of carbamazepine and it was found that drug stability improved through this process and also melt granulation had no impact on the immediate-release properties of carbamazepine self-emulsifying tablet [68].

Twin screw granulation (TSG)

Common solidification techniques fall under the category of batch manufacturing, where the quantity of material processed is constrained by the capacity of the manufacturing equipment. Furthermore, the optimization of several process parameters is required for these manufacturing processes. This optimization is particularly important when there is a need to either scale up or scale down the batch size. However, these

limitations make these methods less acceptable for large-scale production.

TSG has received the greatest attention in recent years as a single-step continuous process. Furthermore, depending on the physical state of the binder, the TSG process is divided into three categories: twin-screw melt granulation (TSMG), twin-screw dry granulation (TSDG), and twin-screw wet granulation (TSWG) [69].

TSMG depends on a low-melting-point binder that acts as a binding liquid after melting, necessitating a low concentration. This process involves a blend of drugs, binders, and excipients processed at a temperature near or above the melting point of the binder, ensuring uniform distribution of binder between the particles and forming granules. TSDG is an economical method of granulating blends as it does not require the use of solvents. It is like the conventional roller compaction process, which was used to achieve dry granulation. In TSDG, a mixture containing the drug, binder, and other components is fed into the extruder using a gravimetric hopper and then conveyed to the mixing zone. The temperature is maintained below the glass transition temperature or melting point of the components to keep all materials in a dry state. The combination of temperature and shear in the mixing zone causes the materials to soften and distribute uniformly in the extruder barrel, resulting in the formation of granules. This method increases the drug loading capacity by using a low binder concentration. Granulating fluid helps produce granules in the TSWG process.

Wet granulation involves moving the materials through an extruder's barrel while a peristaltic pump forces the granulating fluid into the barrel zone. Granule formation results from the complete mixing of the wet mass formed in the extruder [70].

The TSMG approach was confirmed to be suitable for solidifying SEDDS, as demonstrated by the formulation of S-SEDDS of Ibuprofen. Optimized granules of SEDDS were compressed into tablets. The compressed tablets exhibited enhanced dissolution profiles in comparison to the pure drug. The characteristics of liquid SEDDS were maintained within the S-SEDDS [69]. The effectiveness of the TSMG method for increasing fenofibrate solubility was investigated, with Gelucire® 48/16 as the solubilizer and Neusilin® US2 as the adsorbent. The solubility of fenofibrate improved in all formulations when compared to pure drugs. However, the rate of dissolution was primarily influenced by the concentration of adsorbent and the ratio of molten portion to adsorbent in the formulation [71].

Liquisolid method

Liquisolid approach involves mixing liquids with chosen solid carriers and coating materials to develop freely flowing, easily compressible dry powder. A coating material with a high capacity for adsorption and a significant specific surface area gives good flow properties to the formulation. The primary limitation of the liquisolid method lies in the challenge of incorporating high doses of water-insoluble drugs since it demands large quantities of liquid, carrier, and coating material to produce liquisolid powder with desired properties. The proportion of carrier and coating material can be reduced by incorporating additives such as polyethylene glycol 35,000 and polyvinyl pyrrolidone (PVP) into the liquid formulation [72].

Javadzadeh [73] demonstrated that the addition of PVP into the liquid formulation enables the loading of a high quantity of drug into liquisolid tablets. The liquisolid tablets of carbamazepine prepared with the addition of PVP exhibited an increased dissolution rate [73].

Liquisolid approach is preferred for increasing drug solubility and dissolution rate of BCS classes II and IV drugs. The liquisolid method was employed to develop a self-emulsifying tablet of leflunomide, a BCS class II drug, which showed a higher dissolution rate compared to the marketed tablet [74].

Method based on supercritical fluids

Unique features of supercritical fluids (SCFs) in the solidification of liquid formulations have received a lot of interest nowadays. Various methods have been proposed to exploit the ability to manipulate the properties of SCFs, aiming to produce fine powders characterized by a narrow particle size distribution [75]. Lipids are used in this technique to develop solid dispersions or to give a coating for drugs. In this process, drug particles are dispersed in a SCF such as carbon dioxide which includes one or more coating materials. Carbon dioxide is inexpensive, less toxic, nonflammable, and can be

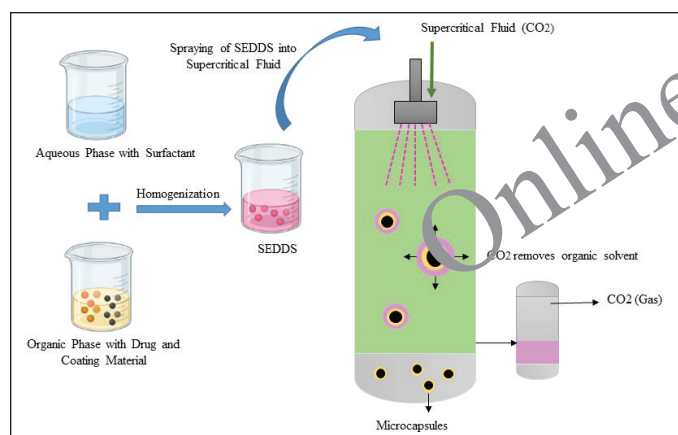


Figure 4. Schematic representation of solidification of liquid SEDDS based on the Supercritical fluid method.

easily recycled. In addition to carbon dioxide commonly used supercritical solvents are nitrous oxide, ethylene, propylene, propane, and n-pentane [76].

SCF acts as an antisolvent and extracts the organic phase of SEDDS. As the solubility of the coating material decreases over time, it is displaced onto the drug particles and precipitates. Precipitation of drug and coating material leads to the formation of microcapsules. Figure 4 shows the solidification of liquid SEDDS based on the SCF method. Solubility of the drug and other components in the SCF is a crucial factor to be considered during this method. Poor drug loading capacity limited this method to low-dose and potent drugs [19].

3D printing (3DP) of SEDDSs

A significant number of solid carriers must frequently be used with several solidification techniques to absorb the liquid formulation. However, the incorporation of these additional carriers may provide issues with dose dilution, tolerance, and potential toxicity. The act of diluting liquid formulations with solid carriers and other excipients might make it difficult to administer high-dose medications accurately, which also impacts the compressibility of the formulation. Optimal reproducibility and increased production time also limit the acceptance of these solidification methods. Therefore, it would be highly desirable to find a way to develop S-SEDDS formulations without the need for high-concentration solid-phase carriers [77]. (Fig. 5) represents the schematic representation of 3D printing of SEDDS.

3DP is an emerging technology that offers digitally controlled personalized doses and geometry. It is an additive method that proceeds through the layer-by-layer development of 3-dimensional structures [78]. The US FDA approved the first 3DP levetiracetam (SPRITAM®) tablet in 2015, which skyrocketed interest in the area of pharmaceutical 3DP [79]. In 3DP, computer-aided design instructions are used to successively deposit layers of materials onto the build plate, resulting in the construction of a three-dimensional model (Fig. 5).

3DP offers numerous advantages in the pharma sector, generation of complex geometries, deposition of a relatively tiny portion of materials, resource conservation, quick production of various compositions for effective assessment activities, and precise control over the drug distribution pattern within the

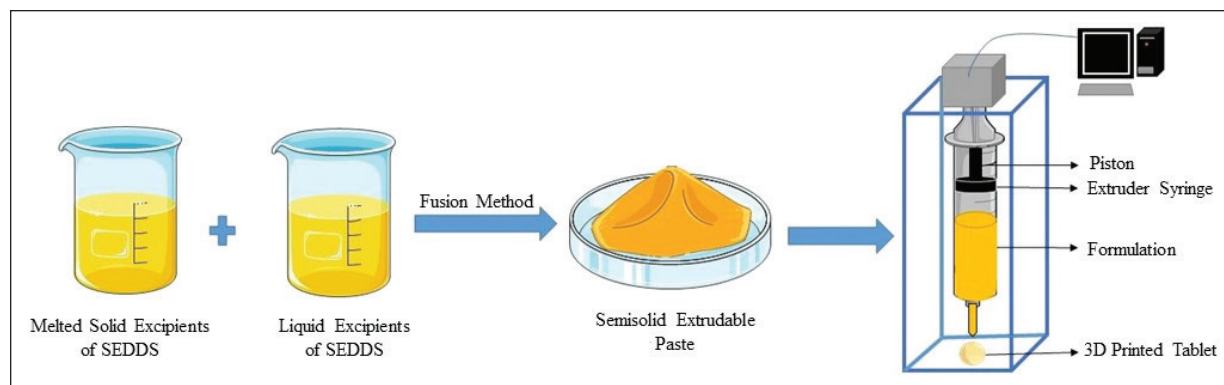


Figure 5. Novel 3D printing technology to convert the liquid SEDDS into solid.

dosage form, as well as the ability to create customized dosage forms. Different technologies, including stereolithography, selective laser sintering, inkjet, fused deposition modeling, binder jetting, and semi-solid extrusion printing, are employed in the 3DP approach. The method of layer generation used to create a 3D object is the key distinction between the technologies [80].

Recent research has investigated using pressure-assisted micro syringes (PAM) or extrusion-based 3DP to develop SNEDDS-based lidocaine suppositories for customized drug delivery [81]. A proof of concept by Vithani *et al.* [80] demonstrates the possibility of 3DP for the creation of customized solid SMEDDS without the use of solid carriers. They used the syringe-based extrusion method and prepared four different geometrical shapes of cinnarizine and fenofibrate-loaded SMEDDS. This proof-of-concept shows that 3DP can provide a new approach to developing optimized solid SMEDDS dosage forms that are complex and geometrically flexible enough to be used for the production of customized lipid-based dosage forms [80]. Algahtani *et al.* [77] explored 3DP for the development of self-nanoemulsifying tablets of dapagliflozin to overcome poor water solubility. They used a 3DP technique based on semisolid PAM extrusion. 3D-printed self-nanoemulsifying tablet of dapagliflozin showed rapid drug release, and more than 75% of drug release was within 20 minutes. The study confirmed that 3DP is an alternative method to design solid dosage forms of SEDDS [77].

3DP may be able to manufacture S-SEDDS in a single step by eliminating the solidification processes and their associated limitations. However, the application of 3DP for SEDDS is still in its early stages.

The solidification of SEDDS is an important turning point in pharmaceutical science, paving the way for the development of different solid dosage forms. This transition not only preserves the favorable properties of SEDDS, but also opens a range of possibilities for other solid dosage forms such as tablets [17], pellets [82], dry emulsion [83], self-emulsifying nanoparticles [84], beads [85], suppositories [86], and implants [87].

FUTURE PERSPECTIVE

In the realm of pharmaceutical advancement, the future of S-SEDDS is quite promising. Solidification provides versatility in the design of tablets, pellets, and even granules. This advancement in solidification broadens the application of SEDDS, leading to the development of patient-friendly formulations with controlled release profiles, increased stability, and enhanced therapeutic efficacy, ultimately redefining the drug delivery landscape. The goal of ongoing research is to improve S-SEDDS formulation to improve drug solubility, stability, and overall performance, with a focus on customizing solutions to drug properties. Careful selection of excipients and the exploring of novel excipients can further optimize S-SEDDS formulations. Unlocking the full potential of S-SEDDS in therapeutic applications requires overcoming the present obstacles. The effective solidification of SEDDS containing temperature-sensitive substances is a significant challenge,

which restricts their application in formulations that necessitate precise temperature controls. Overcoming this issue would make it possible to successfully develop S-SEDDS of biologics. Advances in solidification methods are expected to streamline production processes, making S-SEDDS more scalable and accessible in pharmaceutical industries. Furthermore, the possibility of personalized medicine is approaching, wherein formulations of S-SEDDS could be customized to the unique characteristics of each patient to enhance compliance and effectiveness. S-SEDDS has the potential to transform drug delivery techniques and enhance personalized and targeted therapy as regulatory guidance clarifies, opening the door for clearance, and commercialization.

CONCLUSION

In summary, we have explored the components of S-SEDDS and solidification methods, and discussed their advantages and limitations. In addition, we have highlighted several significant earlier studies in this sector. An exciting development in SEDDS formulation is solidification. The transition from liquid to solid formulations addresses key issues with stability, convenience, and dose accuracy. Different approaches to solidification of SEDDS have been investigated to overcome the practical limitations of liquid formulations. Each of these solidification processes has distinct advantages for SEDDS in pharmaceutical formulations. The potential of S-SEDDS lies not only in improving the stability of formulation but also in facilitating controlled release, enhancing solubility and bioavailability, and developing personalized medicine. The selection of the solidification method relies on the unique properties of the drug, the desired release profile, and the intended dosage form. Researchers are constantly developing new approaches to overcome the limits of existing technologies to obtain superior S-SEDDS formulations.

ACKNOWLEDGMENTS

The authors express gratitude to the Manipal Academy of Higher Education for their unwavering support throughout the duration of this study.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

FINANCIAL SUPPORT

We thank the Manipal Academy of Higher Education for the funding support via Intra-Mural Fund.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest related to the publication.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All information and data discussed in this review have been sourced from the existing literature. The references cited in this article provide a comprehensive overview of the studies and findings included in our analysis.

USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

PUBLISHER'S NOTE

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How to cite this article:

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.* 2024. <http://doi.org/10.7324/JAPS.2024.184385>