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A review of strategies for the development of solid self-microemulsifying drug delivery system

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Abstract
Solid Self-Microemulsifying Drug Delivery Systems (S-SMEDDS) have emerged as a promising approach to enhance the oral bioavailability and therapeutic efficacy of poorly water-soluble drugs. These formulations combine the advantages of SMEDDS, which improve drug solubility and dissolution, with the stability and convenience of solid dosage forms. S-SMEDDS are developed by converting liquid SMEDDS into solid forms through various techniques, including adsorption onto solid carriers, spray drying, and granulation. The adsorption method involves loading liquid SMEDDS onto porous carriers like silica, microcrystalline cellulose, or lactose. Upon contact with gastrointestinal fluids, the adsorbed SMEDDS rapidly disperses, forming a microemulsion that enhances drug solubility and absorption. Spray drying involves atomizing the liquid formulation into fine droplets and drying them using heated air to produce solid particles. Granulation involves agglomerating fine drug particles and excipients into granules, ensuring consistent component distribution and maintaining the amorphous or liquid state of the formulation. S-SMEDDS offer numerous advantages, including enhanced drug solubility, stability, patient adherence, formulation flexibility, and compatibility with existing manufacturing processes. These formulations find applications in enhancing oral bioavailability, controlled release formulations, tailored formulations for specific populations, improved stability, combination therapy, and repurposing of established drugs. Overall, S-SMEDDS have demonstrated potential in enhancing the solubility, dissolution, and bioavailability of poorly soluble drugs, offering a promising approach for improving therapeutic outcomes.

Keywords: Self-microemulsifying drug delivery system, adsorption, spray drying, melt granulation

Introduction
The oral route is the most practical means of delivering medication for treating various diseases and is typically the primary focus of research when developing new dosage forms. However, the formulation of oral medications poses challenges, mainly due to poor water solubility, which results in low and inconsistent bioavailability. This limited dissolution rate and absorption of poorly water-soluble drugs have led to the development of innovative drug delivery systems that can achieve the desired therapeutic effects with minimal dosing requirements. As a result, SMEDDS have gained importance in addressing these issues [1]. SMEDDS is an isotropic mixture of medicament, surfactants, cosurfactants, and oil that has the extraordinary capacity to create fine o/w microemulsion with brief shaking and dilution with liquid, such as gastrointestinal fluid [2]. Due to the incomparable potential of hydrophobic (water-repelling) drugs, SMEDDS have emerged as a novel approach for overcoming the challenges of low bioavailability, high intra- and inter-subject changeability, and lack of dose proportionality. This method allows for the formulation of medications that are insoluble in water by solubilizing them in the lipid vehicle so that they can be absorbed through the membrane. Lipids and surfactants are used to enhance the solvency and absorption of drugs. Increasing the drug's solubility raises its rate of dissolution [3].
A S-SMEDDS is a formulation technique used to enhance the oral bioavailability and therapeutic efficacy of poorly water-soluble drugs. It combines the advantages of SMEDDS with the stability and convenience of solid dosage forms [4]. This formulation overcomes the challenges associated with liquid SMEDDS by converting them into solid dosage forms, such as powders or pellets. This conversion is achieved by adsorbing this liquid formulation onto a solid carrier, such as porous silica, microcrystalline cellulose, or lactose. The solid carrier acts as a matrix for the adsorbed liquid formulation and stabilizes it. When the S-SMEDDS formulation comes into contact with water in the gastrointestinal tract, it rapidly disperses and forms a microemulsion due to mechanical agitation and the presence of bile salts and digestive enzymes.

The resulting microemulsion enhances the drug's solubility, thereby promoting its absorption across the intestinal membrane. This leads to improved bioavailability and therapeutic outcomes [5].

Requirements of S-SMEDDS

- **Enhanced Drug Solubility**

Poorly water-soluble drugs often have limited dissolution and low bioavailability, leading to suboptimal therapeutic outcomes. The S-SMEDDS improve drug solubility by forming microemulsions when dispersed in the gastrointestinal tract. This enhances drug dissolution and absorption, resulting in improved bioavailability and therapeutic efficacy [6].

- **Stability and convenience**

While liquid SMEDDS are effective, they can be inconvenient for manufacturing, storage, and transportation. Liquid formulations are prone to stability issues, such as drug degradation, phase separation, and leakage. By converting SMEDDS into solid dosage forms such as powders or pellets, this drug delivery system provides improved stability and convenience in handling, storage, and transportation [7].

- **Improved Patient Compliance**

Solid dosage forms, such as tablets or capsules, are commonly used in oral drug delivery due to their ease of administration and patient acceptance. The S-SMEDDS enables convenient and accurate dosing, promoting patient compliance with the prescribed medication regimen.

- **Formulation Design Flexibility**

S-SMEDDS offers flexibility in formulation design. Various solid carriers, such as porous silica, microcrystalline cellulose, or lactose, can be employed to adsorb liquid SMEDDS. This allows for customization based on the specific drug and desired release profile. These formulations can be tailored for modified release formulations, enabling controlled or sustained drug release.

- **Compatibility with the Existing Manufacturing Process**

Solid dosage forms are widely manufactured using established processes like tablet compression or capsule filling. S-SMEDDS can be easily integrated into these existing manufacturing processes without significant modifications, making it a practical and scalable approach for pharmaceutical production [6].

Applications of S-SMEDDS:

- **Enhanced Oral Bioavailability**

The use of S-SMEDDS is advantageous for enhancing the oral bioavailability of poorly water-soluble drugs. Moreover, this approach enhances drug absorption and systemic availability by improving solubility and dissolution rates. This application is particularly valuable for drugs with low aqueous solubility, as it facilitates their therapeutic efficacy [5].

- **Controlled Release Formulation**

The S-SMEDDS can be tailored to achieve controlled or sustained drug release. Through the incorporation of suitable excipients and modifications to the formulation composition, the release rate of the drug can be controlled. This capability is beneficial for drugs that necessitate a prolonged therapeutic effect or those with a narrow therapeutic window.

- **Pediatric and Geriatric Formulations**

The S-SMEDDS can be formulated as an age-appropriate drug delivery system for pediatric and geriatric populations. This solid dosage form offers ease of administration and accurate dosing, addressing challenges associated with liquid formulations. This makes it particularly suitable for children and elderly patients who may have difficulties swallowing liquids or who may require precise dosing.

- **Improved Stability**

The conversion of liquid SMEDDS into solid dosage forms improves stability. Solid formulations are less susceptible to degradation, phase separation, and other stability-related issues observed in liquid formulations. This application is particularly advantageous for drugs sensitive to environmental factors such as moisture, temperature, or light [7].

- **Combination Therapy**

S-SMEDDS can be used to develop combination therapy formulations by incorporating multiple drugs with different solubilities and releasing kinetics into a single dosage form. This approach enables improved therapeutic outcomes, simplified dosing regimens, and enhanced patient compliance.

- **Biopharmaceutical Classification System (BCS) Class II and IV Drugs**

S-SMEDDS formulations are beneficial for BCS Class II and IV drugs, which are characterized by poor water solubility and low oral bioavailability. This delivery system enhances the solubility, dissolution, and absorption of these drugs, thereby improving their therapeutic efficacy [9].

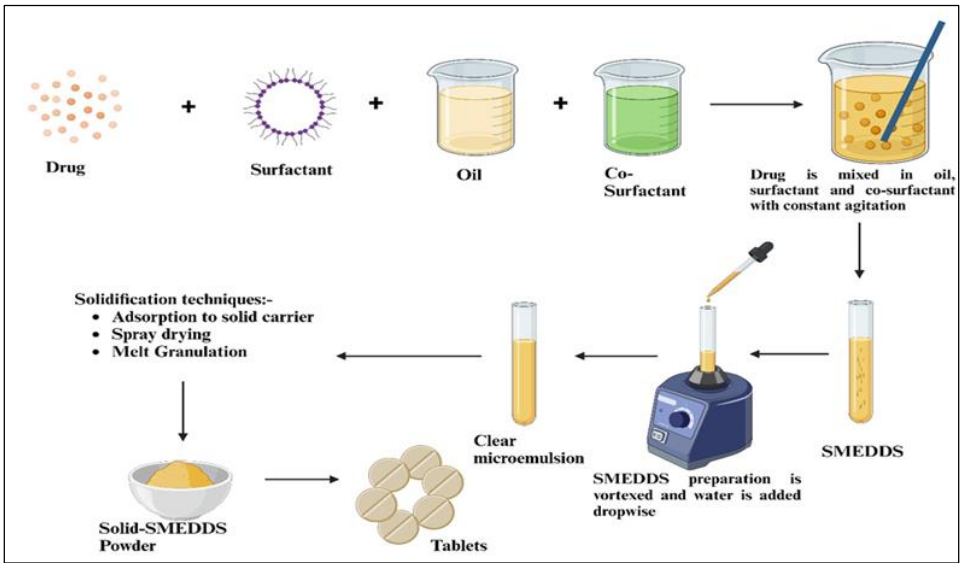
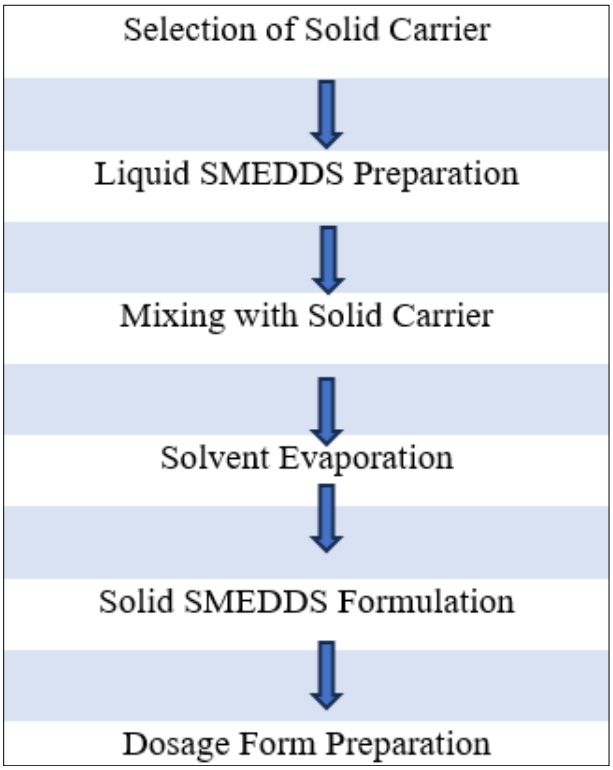


Fig 1: Methods of formulation of S-SMEDDS [8].

- **Repurposing of Existing Drugs**

S-SMEDDS can be utilized to reformulate and repurpose existing drugs with limited solubility or bioavailability. By formulating these drugs into S-SMEDDS, their therapeutic potential can be unlocked, expanding their application in different therapeutic areas [10].



Methods for developing S-SMEDDS:

- Adsorption onto solid carriers
- Spray drying
- Melt granulation

A brief description of the formulation of the SMEDDS and S-SMEDDS is provided in Fig. 1.

- **Adsorption onto solid carriers**

The process of adsorption onto a solid carrier involves the conversion of liquid SMEDDS into solid forms through absorption onto porous solid carriers. This method enhances the stability and ease of handling of SMEDDS while retaining their self-emulsifying characteristics upon reconstitution. The porous solid carrier effectively adsorbs the liquid SMEDDS, resulting in an S-SMEDDS, which offers improved dosing precision and enhanced bioavailability, especially for poorly water-soluble drugs. This technique holds promise for advancing drug delivery systems [11]. This method is illustrated in Fig. 2, and the steps of the adsorption method are shown in Table 1.

Mali *et al*., 2021, demonstrated the formulation and characterization of S-SMEDDS using the adsorption technique. The primary goal was to enhance the oral bioavailability of Artemether, a drug with low water solubility. The process involved initially preparing liquid SMEDDS formulations, which were subsequently transformed into solid forms through the use of adsorbents such as silicon dioxide, magnesium hydroxide, and aluminum hydroxide. The physical properties, drug content, reconstitution properties, emulsification efficiency, globule size, thermodynamic stability, and solid-state features of the resulting solid SMEDDS were thoroughly examined. *In-vitro* dissolution studies demonstrated a significant improvement in the dissolution rate of Artemether compared to that of the pure drug. Additionally, the solid-state characterization revealed alterations in the crystal structure and melting point of the SMEDDS formulations. This study underscores the successful application of the adsorption method for producing solid SMEDDS, offering a promising approach for enhancing the solubility and bioavailability of poorly soluble drugs [13].

Chudiwal *et al*., 2018, elaborated on the development and assessment of an S-SMEDDS for primaquine (PQ) utilizing the adsorption technique. The primary objective was to improve the antimalarial efficacy of PQ by enhancing its liver uptake. The study investigated the emulsifying capacity and stability of the SMEDDS, determining that Cremophor RH 40 was the most effective emulsifying agent. The optimal composition of the SMEDDS was determined using pseudo-ternary phase diagrams, with a 40% w/w oil loading found to be ideal. The essential components of the SMEDDS included PQ as the oil phase, Cremophor RH 40 and Gelucire 44/14 as the surfactant/cosurfactant, and Aerosil 200 as the adsorbent. The particle size of the SMEDDS was 75 nm, demonstrating the stability of the SMEDDS, and the ability to form a microemulsion across various pH levels. The SMEDDS exhibited efficient emulsification, appropriate flow characteristics, and favorable dissolution profiles. Its stability was maintained for 6 months, during which a minor decrease in the drug concentration was observed. *In vivo* tests illustrated notable antimalarial effectiveness, with the 15 mg dose displaying the highest activity. Biodistribution analysis revealed increased SMEDDS uptake in the liver compared to that in the suspension. In summary, the study concluded that the solid SMEDDS of PQ, created through the adsorption method, was a stable and effective formulation for improving liver uptake. Targeted delivery of PQ to the liver was particularly advantageous for treating the hepatic form of the malaria parasite [15].

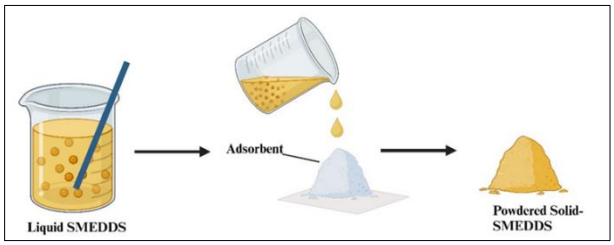
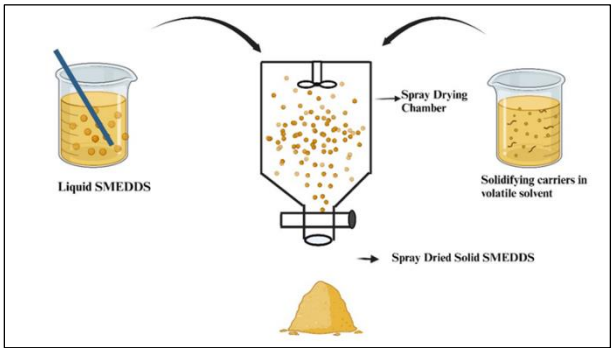


Fig 2: Adsorption onto solid carrier [14]

Prajapati *et al*., 2023, formulated S-SMEDDS using the adsorption method, focusing on improving the solubility and *invitro* release of azelnidipine, a poorly soluble drug. A full factorial design and a 32 factorial design were used to optimize the liquid SMEDDS formulation, considering variables such as surfactant concentration and emulsification time. The optimized liquid formulation was then converted into a solid SMEDDS using Neusilin US2 as the carrier material. The flow properties and dissolution studies of the solid formulation were evaluated. The results demonstrated that the adsorption method effectively enhanced the solubility and bioavailability of azelnidipine, as evidenced by improved drug release compared to that of a marketed tablet and increased stability over 30 days. This study highlighted the potential of S-SMEDDS as a promising approach for enhancing the solubility and bioavailability of poorly soluble drugs [16].

Nandgude *et al*., 2020 demonstrated that the SMEDDS formulation included simvastatin, capryol 90, tween 80, and polyethylene glycol 400. The SMEDDS was adsorbed onto an inactive solid carrier, aerosil 200, and avicel PH 102, resulting in an S-SMEDDS. Characterization of the S-SMEDDS was performed using scanning electron microscopy and differential scanning calorimetry. Tablets were subsequently produced using magnesium stearate, polyvinylpyrrolidone, and Avicel PH 102. *In vitro* release assessments were also conducted to compare the release profiles of the tablets with those of the SMEDDS and the pure drug. The outcomes indicated a considerably higher release rate for the SMEDDS and S-SMEDDS tablets than for the plain drug. This study underscores the potential of the adsorption method for formulating solid SMEDDS tablets, offering a means to enhance the solubility and bioavailability of simvastatin [17].

Bhagwat *et al*., 2012, aimed to develop S-SMEDDS from telmisartan (TEL) using an adsorption technique, where Aerosil 200 served as the solid carrier. The liquid SMEDDS was initially prepared using Acrysol EL 135, Tween 80, and PEG 400 as the oil, surfactant, and cosurfactant, respectively. This liquid formulation was then converted to an S-SMEDDS by adsorbing it onto Aerosil 200. The resulting S-SMEDDS was comprehensively evaluated and demonstrated good flow properties, high drug content (99.45 ± 0.02%), and effective spontaneous microemulsification upon dilution. Characterization revealed a small droplet size of 0.34 µm, inhibited crystallization of TEL, and a smooth surface morphology of S-SMEDDS. Importantly, the drug released from S-SMEDDS exhibited a significantly greater dissolution rate than those released from the plain TEL. Additionally, *ex vivo* intestinal permeability studies highlighted the substantial enhancement in drug diffusion from S-SMEDDS, indicating improved bioavailability. The study concluded that the adsorption technique was a promising method for formulating S-SMEDDS, resulting in an enhanced dissolution rate and, consequently, improved bioavailability [18].



- **Spray Drying**

The spray drying technique is a highly effective method used to convert liquid SMEDDS into solid-state materials. This process comprises the atomization of the liquid formulation into minute droplets through specialized nozzles, followed by swift drying of these droplets employing a heated air current. The outcome is solid particles containing the constituents of the formulation. This method is beneficial in augmenting stability, accelerating drug release kinetics, and facilitating the ease of handling and storing SMEDDS [20]. Spray drying has emerged as a highly effective method for developing solid SMEDDS formulations and has been widely employed by numerous researchers, scientists, and industrialists for their product formulations. This method is briefly described in Fig. 3 and Fig. 4.

Bhandari *et al*., 2017, formulated the liquid SMEDDS, which was optimized with artemether and lumefantrine and was subsequently transformed into S-SMEDDS using Neusilin US2® and the spray drying technique. S-SMEDDS displayed impressive drug release, with almost 90% of both medications released within 15 mins in the specified dissolution media. Even after storage at 40°C and 75% relative humidity for three months, the drug content and dissolution rate remained stable. Reconstitution of the S-SMEDDS in water resulted in a microemulsion containing globules sized at 67.74 nm. Comparatively, the solid SMEDDS demonstrated complete and rapid *in vitro* drug release, outperforming commercial tablets. This study emphasized the successful application of the spray drying technique in formulating S-SMEDDS, suggesting a potential strategy for improving the bioavailability of artemether and lumefantrine [5].

Kim *et al*., 2019, aimed to develop a novel, bioavailable, and photostable S-SMEDDS loaded with methotrexate (MTX). The liquid SMEDDS was optimized by blending castor oil, Tween® 80, and Plurol® diisostearique at specific ratios. The S-SMEDDS was created via spray drying with calcium silicate as a solid carrier. Characterization through various techniques confirmed the physicochemical properties of the materials, including the z-average diameter of the emulsion and the amorphous form. The S-SMEDDS demonstrated significantly greater dissolution rates and improved pharmacokinetics compared to MTX powder. Additionally, the formulation exhibited enhanced photostability. This S-SMEDDS presented a promising solution for enhancing the oral bioavailability and stability of MTX, highlighting the application of spray drying in S-SMEDDS formulation [22].

Deshmukh *et al*., 2015, explored the advancements of a lipid-based formulation known as SMEDDS to enhance the solubility and bioavailability of the inadequately water-soluble drug atorvastatin calcium. The research demonstrated that the chosen components, including oleic acid as the oil, Tween 20 as the surfactant, and a combination of PEG 400 and transcutol P as cosurfactants, exhibited excellent solubilization capabilities for atorvastatin. Pseudo-ternary phase diagrams were meticulously constructed to ascertain the optimal ratio of surfactant to cosurfactant for the formulation. Subsequently, the resulting SMEDDS was solidified using the spray drying technique, utilizing Aerosil 200 as a solid carrier. The drug release study showcased a significantly improved release of atorvastatin within the SMEDDS formulation in comparison to that of the plain drug. *In vitro* dissolution studies confirmed a noteworthy enhancement in the dissolution rate of atorvastatin with the SMEDDS formulation. Furthermore, stability assessments confirmed the robust stability of the SMEDDS formulation across various conditions. Overall, this research explored the promising potential of SMEDDS for enhancing the solubility and oral bioavailability of poorly water-soluble drugs such as atorvastatin, with spray drying playing a pivotal role in solidifying the SMEDDS formulation for enhanced efficacy and practical application [23].

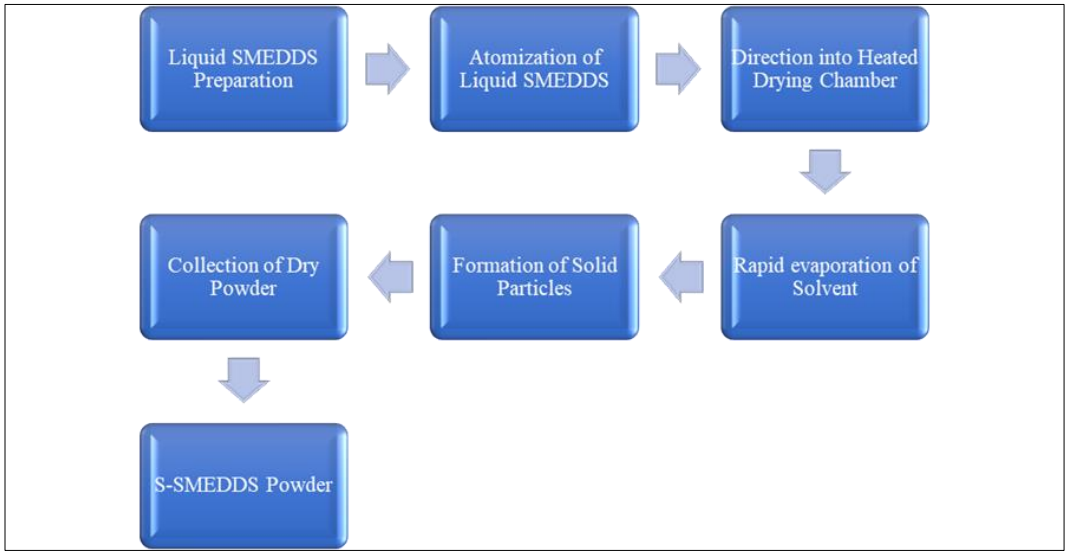


Fig 4: Process of spray drying [21].

Pimple *et al*., 2013, developed SMEDDS to enhance the solubility and dissolution of risperidone (RIS), a drug with low water solubility. The liquid formulation of RIS-SMEDDS was carefully optimized and transformed into a solid form through the process of spray drying. The resulting solid SMEDDS exhibited significantly enhanced dissolution properties compared to those of commercially available preparations. The formulation and fine-tuning of the liquid SMEDDS were carried out using a central composite design, pinpointing key factors affecting crucial responses such as globule size, transmittance, and self-emulsification time. Moreover, solid-state analysis of spray-dried SMEDDS revealed that the drug was in an amorphous state, implying improved solubility [24].

Mandic *et al*., 2021, demonstrated the development of solidified carvedilol-loaded SMEDDS using an efficient spray drying method with various porous silica-based carriers. The process was optimized to achieve a high SMEDDS loading of up to 67% w/w. Notably, higher atomization gas flow rates and extended mixing times significantly improved process yield. The choice of carrier and SMEDDS: carrier ratio influenced drug loading, self-microemulsifying properties, drug release rates, and released drug fractions in the resulting solid SMEDDS. The solidified SMEDDS showcased swift drug release due to retained self-microemulsifying characteristics and the lack of crystalline carvedilol, as validated by XRD and Raman mapping. Stability investigations indicated a decline in drug content, partly due to chemical degradation, notably the synthesis of amides through an in-situ reaction between carvedilol and fatty acids within the oily phase of SMEDDS. In summary, the spray drying technique proved exceptionally efficient in developing S-SMEDDS, hinting at its capability to improve drug delivery and stability [25].

- **Granulation**

Granulation is a crucial method employed in the formulation of S-SMEDDS. It involves the agglomeration of fine drug particles and other excipients into granules, which enhances the handling, flow properties, and overall efficacy of the formulation. In the context of S-SMEDDS, granulation serves to bind together the active drug, lipid-based carriers, surfactants, and cosurfactants in a homogenous and uniform manner. This process ensures the consistent distribution of components, which is crucial for achieving desirable drug loading and self-microemulsifying properties in the final solid dosage form. By carefully controlling the granulation process, it is possible to achieve an optimized particle size distribution and drug release profile, facilitating rapid and efficient drug absorption upon administration. Additionally, granulation aids in maintaining the amorphous or liquid state of the formulation, a vital characteristic for enhancing solubility and bioavailability of poorly water-soluble drugs such as those found in SMEDDS [27]. This method is briefly described in Fig. 5.

Vadlamudi *et al*., 2016, developed an S-SMEDDS for entacapone, a drug used to treat Parkinson's disease. Different formulations of liquid SMEDDS were prepared and characterized. The S-SMEDDS were then prepared using adsorption and melt granulation techniques. The S-SMEDDS showed good reconstitution ability, good drug content, and *in-vitro* drug release. The stability of entacapone SMEDDS was also maintained. The S-SMEDDS formulation demonstrated anti-Parkinson's activity in an animal model. The granulation process used in the preparation of S-SMEDDS offered several benefits, including enhanced stability, accurate dose, extended shelf life, and improved patient compliance. However, further research and clinical studies are needed to explore the full potential of the S-SMEDDS in the treatment of Parkinson's disease [28].

Cho *et al*., 2013, optimized a solid formulation of sirolimus using SMEDDS, focusing on improved solubility, stability, and bioavailability. To achieve this, appropriate excipients were carefully chosen and screened to enhance the drug's solubility and stability. Subsequently, a granulation method was applied to convert the liquid SMEDDS into a solid while retaining its essential properties. This granulation process involved combining the liquid SMEDDS with suitable solid carriers and utilizing techniques such as spray drying. The resulting solid SMEDDS retained the fundamental self-microemulsifying traits of the liquid version. This transformation into a solid form significantly enhanced drug release rate and stability, showcasing the potential of granulation for advancing the oral delivery of poorly water-soluble drugs like sirolimus. The S-SMEDDS formulation exhibited notably improved bioavailability compared to that of raw sirolimus powder or the commercial oral solution, underscoring the effectiveness of this approach in enhancing drug delivery [29].

Vadlamudi *et al*., 2018, demonstrated the formulation of S-SMEDDS of quetiapine fumarate. This drug, known for its low solubility and poor bioavailability, presents challenges for effective oral administration. To overcome this limitation, a microemulsification technique was employed. The solubility of quetiapine was assessed in various liquid vehicles, aiding in the selection of carriers for SMEDDS formulation. The microemulsion region was identified through pseudo-ternary phase diagrams, and quetiapine was loaded into predetermined microemulsion region preconcentrates. Characterization of quetiapine-loaded SMEDDS involved various analyses. The optimized liquid SMEDDS was converted into S-SMEDDS using adsorption and melt granulation methods. The S-SMEDDS demonstrated favorable micromeritics, containing a drug content ranging from 80 to 90%, and released up to 96% of the drug. Particularly, formulation AO13 of S-SMEDDS exhibited robust stability and enhanced antipsychotic efficacy owing to improved biomembrane permeability. The spontaneous formation of a microemulsion from adsorption-based S-SMEDDS led to rapid drug release. This study suggests that the self-microemulsification of quetiapine followed by solidification holds promise for optimizing pharmacotherapy in patients with psychosis [30].

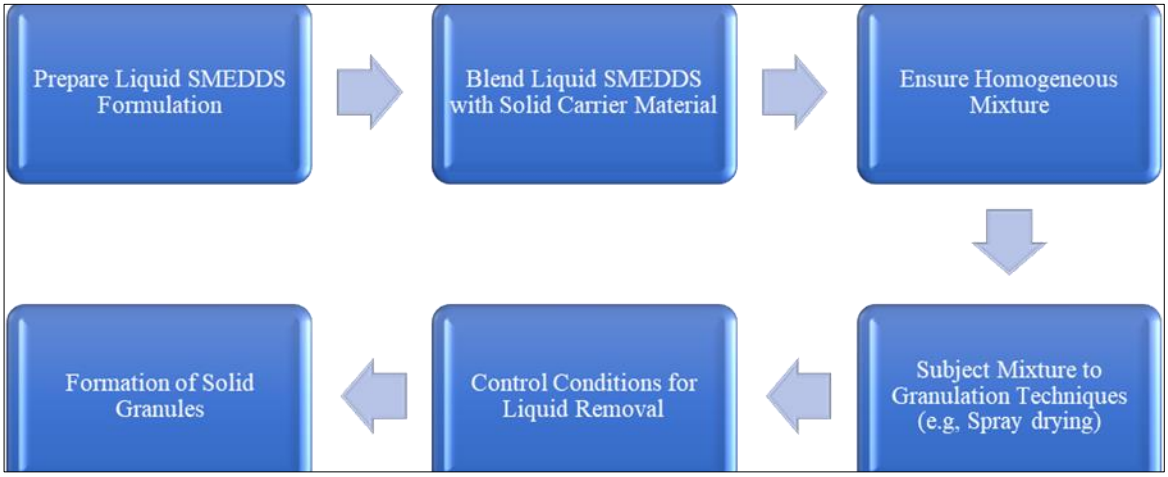


Fig 5: Process of granulation for formulation of S-SMEDDS [26]

Kishore *et al*., 2014, demonstrated the formulation of S-SMEDDS of atorvastatin via the melt granulation method. Clear and transparent SMEDDS were formulated using a combination of coconut oil, isopropyl myristate, and Tween 80 as surfactants and PEG 400 and glycerine as cosurfactants at various ratios. Ternary phase diagrams were utilized to pinpoint the microemulsion region, while the SMEDDS underwent comprehensive assessment for various attributes such as zeta potential, polydispersity index, globule size, pH, viscosity, and drug release. The transition to S-SMEDDS was accomplished through adsorption and melt granulation techniques, leading to further examinations of micromeritics, morphology, solid-state properties, reconstitution capability, drug release, and stability. Findings indicated that micro formulations with a particle size of 25 nm demonstrated a notable threefold increase in drug release. The S-SMEDDS swiftly reconstituted into a microemulsion within 1–3 minutes, releasing 94.62% of the drug within 30 minutes, akin to immediate-release capsules. These S-SMEDDS exhibited a shelf life of 1.3 years. SMEDDS with a 1:3 ratio exhibited greater drug release due to their smaller particle size. Additionally, the solid formulation displayed improved dissolution profiles compared to those of pure atorvastatin, indicating enhanced solubility. In conclusion, this study successfully formulated a solid version of atorvastatin liquid SMEDDS with an extended shelf life and improved solubility, highlighting the promising application and advantages of the granulation method in developing solid SMEDDS for challenging drug formulations [11].

Discussion

S-SMEDDS have emerged as a promising approach to enhance the oral bioavailability and therapeutic efficacy of poorly water-soluble drugs. This formulation strategy combines the advantages of SMEDDS, which improves drug solubility and dissolution, with the stability and convenience of solid dosage forms [31].

The development of S-SMEDDS involves transforming liquid SMEDDS into solid forms through various techniques, including adsorption onto solid carriers, spray drying, and granulation [32]. These methods aim to overcome the challenges linked with liquid formulations, such as stability issues, handling difficulties, and patient compliance. One of the key techniques for developing S-SMEDDS is adsorption onto porous solid carriers [33]. In this process, the liquid SMEDDS is adsorbed onto carriers like porous silica, microcrystalline cellulose, or lactose. Upon exposure to the gastrointestinal fluids, the adsorbed SMEDDS rapidly disperses, forming a microemulsion that enhances drug solubility and absorption [34]. This method has been successfully employed for various drugs, including artemether, primaquine, azelnidipine, simvastatin, and telmisartan, resulting in improved dissolution rates, bioavailability, and therapeutic efficacy. Spray drying is another effective technique for converting liquid SMEDDS into solid dosage forms. This process involves atomizing the liquid formulation into fine droplets, followed by rapid drying using heated air to produce solid particles [35]. Spray drying has been widely utilized for solidifying SMEDDS formulations of drugs like artemether, lumefantrine, methotrexate, atorvastatin, and risperidone, leading to raised dissolution rates, stability, and bioavailability [36]. Granulation is a crucial method employed in the formulation of S-SMEDDS, involving the agglomeration of fine drug particles and excipients into granules. This process ensures the consistent distribution of components and facilitates the maintenance of the amorphous or liquid state of the formulation, which is vital for enhancing solubility and

bioavailability. Granulation techniques, such as melt granulation, have been successfully applied to develop S-SMEDDS formulations for drugs like entacapone, sirolimus, quetiapine fumarate, and atorvastatin, leading to improved drug release, stability, and therapeutic efficacy [37]. The development of S-SMEDDS offers multiple advantages, including enhanced drug solubility, stability, patient adherence, formulation flexibility, and compatibility with existing manufacturing processes. These formulations find applications in various domains, such as enhancing oral bioavailability, controlled release formulations, tailored formulations for specific populations, improved stability, combination therapy, and repurposing of established drugs [38]. Furthermore, S-SMEDDS formulations have demonstrated potential for controlled-release formulations, enabling sustained or targeted drug delivery. They can also be tailored for specific populations, such as pediatric or geriatric patients, by addressing challenges associated with liquid formulations and ensuring accurate dosing.

The creation of S-SMEDDS via methods like adsorption onto solid carriers, spray drying, and granulation has demonstrated effectiveness in enhancing the solubility, dissolution, and bioavailability of drugs with low water solubility. These formulations offer potential for improving therapeutic results, broadening the uses of current drugs, and streamlining the development of new drug delivery systems.

Conclusion

SMEDDS and S-SMEDDS are pivotal formulations that address the need for enhancing the oral bioavailability and therapeutic effectiveness of poorly water-soluble drugs. These formulations are crucial for overcoming the challenges associated with the low solubility and restricted dissolution rates of such drugs, ultimately leading to less-than-optimal therapeutic outcomes. The necessity for SMEDDS and S-SMEDDS stems from the shortcomings observed in traditional oral dosage forms when delivering poorly water-soluble drugs. These innovative systems enhance drug solubility, dissolution rates, and absorption, thereby significantly amplifying therapeutic effectiveness. SMEDDS represent isotropic mixtures of drugs, surfactants, cosurfactants, and oils that can form microemulsions upon dilution with gastrointestinal fluid. Conversely, S-SMEDDS transform liquid SMEDDS into solid powders or pellets, offering improved stability and simplifying handling and storage.

Looking ahead, the future of SMEDDS and S-SMEDDS is promising. These systems can be customized to attain controlled release profiles, making them a viable option for drugs necessitating prolonged therapeutic effects or having a narrow therapeutic window. Moreover, the development of combination therapy formulations is possible by integrating multiple drugs with different solubilities and releasing kinetics into a single dosage form, ultimately improving therapeutic outcomes and ensuring better patient compliance. Additionally, S-SMEDDS can be utilized to reformulate and repurpose existing drugs with limited solubility or bioavailability, broadening their application across various therapeutic domains.

To conclude, both SMEDDS and S-SMEDDS are crucial in boosting the oral bioavailability and effectiveness of drugs with limited water solubility. They efficiently tackle the challenge of enhancing solubility and dissolution rates, providing benefits like increased drug absorption, stability, user-friendliness, and versatility in formulation design. Looking ahead, the evolution of these systems is focused on their capacity for controlled-release formulations, combination therapy, and repurposing existing medications.

List of Abbreviations

SMEDDS = Self-microemulsifying Drug Delivery System.
S-SMEDDS = Solid Self-microemulsifying Drug Delivery System.

Consent for publication

Not applicable

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Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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