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Innovative Advances in Self-Microemulsifying Drug Delivery Systems (SMEDDS): Toward Enhanced Oral Bioavailability and Patient-Centric Formulations

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ABSTRACT

Owing to their approach to improve oral drug bioavailability when drugs have poor water solubility, tremendous research interest has been received in the SMEDDS concept in years ahead. Having increased numbers of NCEs in the market with a high proportion of BCS Class II and IV drugs that are poorly soluble and permeable, the introduction of SMEDDS offers a new way for drug solubilization, dissolution, and absorption. Those drugs with low solubility but high permeability is classified as BCS Class II, while drugs that have poor solubility and permeability belong to the BCS Class IV. Such drugs, with oils, surfactants, and co-surfactants, naturally form oil-in-water emulsion of fine droplets when they come in contact with gastrointestinal fluids, therefore facilitating drug release and absorption. Therefore, most of the research studies in SMEDDS have actually focused on overcoming the constraints associated with traditional formulations involving limited drug release and absorption variation through the optimization of the composition as well as characterization of the system for maximum therapeutic performance. A general outline of the main elements forming the SMEDDS and high emphasis on the role oils, surfactants, and cosurfactants play during the solubilization and emulsion formation process. It also encompasses the recently developed SMEDDS formulation, incorporation of new excipients, and novel advancements of lipid-based delivery technology for drugs with the objectives of better stability and tailoring drug release profiles. The work based on research and development, which has had a focus on Class II and IV BCS drugs, will help in developing more complex formulations that eliminate hindrances due to poor solubility and permeability. This thus opens vast possibilities of making the therapeutic efficacy of drugs having unmanageable physicochemical properties, thereby establishing the field of SMEDDS as a rapidly expanding area in drug delivery systems.

***Keywords**: SMEDDS, oral bioavailability, BCS Class II/IV, poor solubility, permeability enhancement, lipid-based delivery, drug release, surfactants, co-surfactants, novel excipients, NCEs, emulsion formation.*

INTRODUCTION

Over the last few decades, there has been an increase of poor water solubility and low bioavailability drug candidates in new drug development. These lead to severe drawbacks to deliver drugs in an effective way into the targeted tissues. Several formulation strategies have been explored to overcome these limitations, such as lipid complexation, pH adjustment, nanoparticles, solid dispersions, and surfactants. Among these, the lipid-based drug delivery

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systems, especially the self-emulsifying drug delivery systems (SEDDS), have attracted much attention due to their ability to enhance the oral bioavailability of lipophilic drugs.(1) SEDDs, particularly Self-Microemulsifying Drug Delivery Systems, are one of the most interesting tools available to enhance the absorption of poorly soluble drugs. SMEDDS form isotropic mixtures of oils, surfactants, and co-surfactants; once these are exposed to gastrointestinal fluids, fine oil-in-water emulsions are formed, which increases drug solubilization and enhancement of absorption.(2)

Recent advances in SMEDDS formulation entailed research in a variety of ways in which solid-state conversion was not just the only alternative. Instead, there were Nano-SMEDDS, which reduced the droplet size of the emulsion to the nanometer scale to increase distribution and provide a larger surface area with a better contact with absorption surfaces. Self-double emulsifying drug delivery systems (SDEDDS) have also been developed, and both lipophilic and hydrophilic drugs could be encapsulated in the same formulation.(3) Another significant development has been the adsorption of SMEDDS on porous carriers; for example, sponges or matrices for changeover from liquid to a solid dosage form, thereby enhancing stability as well as ease of administration.(4) These other recent changes aimed to improve SMEDDS more drastically by introducing variation in the types and amounts of surfactants used, supersaturated SMEDDS to prevent the drug from precipitating, and also pH-sensitive SMEDDS for the controlled release of a drug. All of these innovations reflect the increasing prospects of SMEDDS for use in the prescription of pharmaceutical problems of such a broad area and further expand their application in modern pharmaceutics.

MECHANISM OF SMEDDS

The emulsion is stabilized by the surfactant molecules that form a film around the internal phase droplet. In case of SMEDDS, the free energy of formation is very low and positive or even negative which results in thermodynamic spontaneous emulsification. It has been suggested that self-emulsification occurs due to penetration of water into the liquid crystalline (LC) phase that is formed at the oil/surfactant-water interface into which water can penetrate assisted by gentle agitation during self-emulsification. After water penetrates to a certain extent, there is disruption of the interface and a droplet formation (Fig. 1). This LC phase is considered to be responsible for the high stability of the resulting microemulsion against coalesce [5].

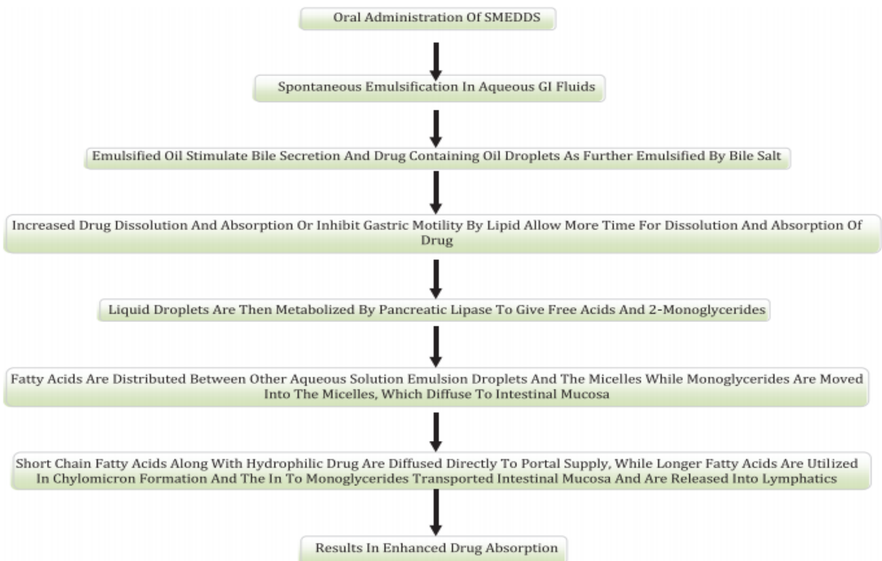

Fig. 1: Mechanism of Action of SMEDDS Formulation (6)

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COMPONENTS OF SMEDDS

Lipid

Lipids are responsible for the solubilization of hydrophobic drugs, fluidization of the intestinal cell membrane, enhancement of dissolution rate, and solubility in gastrointestinal (GI) fluids, and they further protect the drug from chemical and enzymatic degradation by altering pharmaceutical properties of drug. Most drugs used in SMEDDS are hydrophobic in nature and have greater solubility in triglycerides than surfactants. Hence, they are used in 40–80% concentration. Various lipids used in SMEDDS are summarized in Table 1.[7,8,9]

Surfactant

Surfactants play an important role in the enhancement of solubility of hydrophobic drug in oil, dispersion of liquid vehicle on dilution in GIT fluids, improvement of bioavailability by increasing permeability, prevention of precipitate formation within the GI lumen, and prolonging the presence of drug moiety in soluble form, which results in effective absorption, and 30–60% concentration is used. They concentrate at the oil-water interface and settle at inner stage (internal phase) in emulsion and make more stable microemulsion. Various surfactants used in SMEDDS are summarized in Table 1.[10,11]

Cosurfactant

In SMEDDS, to reduce interfacial tension, high concentrations of surfactants are required that may cause gastric irritation. Thus, cosurfactants are employed to lessen the concentration of the surfactant, to dissolve large amounts of either lipophilic drug or hydrophilic surfactant in lipid base, and to decrease the interface of oil/water, which results in the immediate formation of microemulsion. Cosurfactants ranging between hydrophile-lipophile balance (HLB) values of 10–14 are widely used with the surfactant to reduce interfacial tension to a great extent to achieve transient negative value and to provide sufficient flexibility to the interfacial film.[12,13,14] Various cosurfactants used in SMEDDS are enclosed in Table 1.

Cosolvents

Cosolvents used for oral dosage form are ethanol, polyethylene glycol (PEG), and propylene glycol as they help in the improvement of solubility of the drug or surfactants in a lipidic base, facilates in the dispersion process, and start the earlier phases of dispersion and can perform action of co-surfactant in a micro-emulsion system. Alcohol and other volatile solvents migrate into the soft gelatin capsule shell and cause precipitation of the lipophilic drug. However, the lipophilic drug of alcohol-free products has limited dissolution ability. Hence, the proper choice of solvent is made when selecting components. Commonly used cosolvents in SMEDDS are summarized in Table 1.[13-19]

Table 1: List of various excipients used in SMEDDS formulation[6-18]

Lipids	Surfactants	Cosurfactants	Cosolvents
Labrafac CC	Tween 85	Hexanol	Ethanol
Isopropyl myristate	Span 20	Pentanol	PEG
Capmul MCM	Capryol 90	Octanol	Carbitol
Maisine 35-1	Lauroglycol 90	Ethanol	Transcutol P
Akoline MCM	Labrafil M 1944 CS	PEG 400	PG
Capmul MCM C-8	Cremophor EL	Labrasol	Glycerin
Capmul GMS-50K	Cremophor RH40	Transcutol P	Tetrahydrofurfuryl alcohol
Labrafil M 1944 CS	Acconon MC8	Capryol 90	Methoxy PEG
Brij	Tween 20	Capyrol PGMC	Isopropanol
Stepan GDL	Labrasol	PEG 300	Butanol
Caprol ET	Tween 80	PEG 600	Benzyl alcohol
Labrafac 1349	Pluronic F 127	PG-dicaprylate/dicaprate	PEG ether (glycofurol)
Labrafac PG	Pluronic L 64	Carbitol	Ethylene glycol
Labrasol	Tagat TQ	Akoline MCM	PG
Lauroglycol 90	Span 80	Tween 85	Glycerol

SMEDDS: Self-microemulsifying drug delivery system, PEG: Polyethylene glycol, PG: Propylene glycol

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Factors Influencing SMEDDS Formulation

1) **Nature and dose of the drug:** Drugs with very high doses are generally not suitable for Self-Microemulsifying Drug Delivery Systems (SMEDDS) unless they exhibit excellent solubility in at least one component, particularly in the lipophilic phase. Drugs that are poorly soluble in both water and lipids, often with log P values around 2, present significant challenges for SMEDDS. The system's effectiveness hinges on the drug's solubility in the oil phase; if surfactants or co-surfactants are crucial for solubilization, dilution may lead to precipitation. To assess potential precipitation issues in the gut, equilibrium solubility measurements can be conducted, but crystallization may occur slowly due to the gut's complex environment. [14]

2) **Polarity of the lipophilic phase:** The polarity of the lipid phase significantly influences drug release from microemulsions. This polarity is determined by factors such as the hydrophilic-lipophilic balance (HLB), the fatty acid chain length, and the degree of unsaturation. Additionally, the molecular weight of micronized substances affects their ability to inhibit crystallization and sustain a supersaturated state over extended period. [20]

3) **Charge of emulsion droplets:** Multiple physiological studies have demonstrated that the electrical potential at the apical surface of absorptive cells, as well as in other cell types throughout the body, is negatively charged when compared to the mucosal solution present in the lumen. [20]

Evaluation of Self-Microemulsifying Drug Delivery Systems (SMEDDS)

The performance and stability of SMEDDS formulations are critically assessed using a range of physicochemical and in vitro parameters to establish their suitability for oral drug delivery.

1) **Visual Appearance and Self-Emulsification Time:** Formulations should generate clear or slightly opalescent emulsions upon gentle agitation in aqueous media. The time required for complete emulsification, ideally less than one minute, is indicative of spontaneous emulsification efficiency.(21)
2) **Droplet Size and Polydispersity Index (PDI):** Droplet size analysis via dynamic light scattering (DLS) provides insights into nanoemulsion quality. Uniformity is quantified through the PDI, with values less than 0.3 indicating narrow size distribution and formulation homogeneity.(22)
3) **Zeta Potential:** Measured to evaluate electrostatic stability, zeta potential values above ±30 mV typically ensure physical stability through repulsion between emulsion droplets, reducing the likelihood of coalescence.(23)
4) **Thermodynamic Stability Studies:** SMEDDS undergo centrifugation, heating–cooling cycles, and freeze–thaw tests to assess robustness under stress conditions. Formulations failing these tests are excluded from further study.(21)
5) **Refractive Index and Percent Transmittance:** A refractive index close to that of water and high transmittance values (>99%) confirm formation of transparent microemulsions and support isotropic character.(21)
6) **Drug Content and Content Uniformity:** Drug quantification is performed using UV–Vis spectrophotometry or HPLC to ensure accurate dosing and consistency across capsules or batches.(21)
7) **In Vitro Dissolution Studies:** Conducted using USP Type II apparatus in simulated gastric and intestinal fluids. SMEDDS often display rapid drug release (>90% within 30 minutes), surpassing conventional formulations.(22)(23)

8) **Solid-State Characterization (for Solid SMEDDS):** Techniques such as Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC), and X-ray Diffraction (XRD) are employed to study drug amorphization and carrier interactions.(21)

Application of SMEDDS

1) **Improvement in Solubility and bioavailability:** Increasing the solubility and rate of dissolution of BCS class II medications to multiple times their bioavailability.(24)
2) **Formulation for Controlled Release:** The incorporation of polymer into the SMEDDS composition allows for a controlled and sustained release of the drug.(24)
3) **Protection from Biodegradation:** Many drug formulations degrade in physiological fluids and systems as a result of the drug's proximity to a change in pH. The LC phase creates a barrier between the drug and the degrading environment because the acidic pH value in the stomach causes hydrolytic or enzymatic degradation.(24)

Recent Development in SMEDDS

1) Supersaturated smedds

Supersaturable self-microemulsifying drug delivery systems (S-SMEDDS) are innovative formulations designed to enhance the oral bioavailability of poorly soluble drugs. These systems utilize a reduced amount of surfactant and incorporate water-soluble polymers, known as precipitation inhibitors, to maintain a supersaturated state and prevent drug precipitation in the gastrointestinal tract. The S-SMEDDS approach allows for a more prolonged solubilization of the drug, significantly improving its absorption compared to traditional formulations. For instance, studies have shown that S-SMEDDS can achieve up to a five-fold increase in bioavailability for drugs like carbamazepine, while also minimizing gastrointestinal side effects associated with higher surfactant levels. This technology represents a promising advancement in drug delivery, particularly for compounds that are challenging to absorb due to their low solubility. [25] Polyvinylpyrrolidone and water-soluble cellulosic polymers such as hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), and hydroxyl propyl MC phthalate are useful in generating a supersaturatable state with a number of poorly water-soluble drug. [26]

2) Self-microemulsifying mouth dissolving film

A self-micro-emulsifying mouth dissolving film (SMMDF) is a dosage form which is based on mouth dissolving film integrated with self-micro emulsifying components. Self-emulsifying mouth dissolving film is promising approach for the formulation of drugs with poor aqueous solubility, high molecular weight, pre systemic first pass effect, enzymatic degradation, gastric irritation, limited dissolution rate and low bioavailability. SMMDF is economic as it requires less quantity of drug and less complicated machineries. SMMDF appear to be unique and industrially feasible approach to overcome the problem of low oral bioavailability associated with the lipophilic drugs. This drug delivery system enjoys both advantages of self-micro emulsifying drug delivery system (SMEDDS) along with mouth dissolving film (MDF). Self-micro-emulsifying mouth dissolving film formulations can be used to improve the oral bioavailability of hydrophobic drugs due to their efficiency of presenting the hydrophobic drug in solubilized form. The oral films are essentially complex polymeric matrices that can use efficiently as drug delivery system. These polymeric matrixes are composed by several components in order to achieve well designed drug-delivery.

A fast-dissolving film is a film containing drug that dissolves or disintegrates in the saliva remarkably fast, without the need for water or chewing. Some drugs are absorbed well from the mouth, pharynx and esophagus as the saliva passes down into the stomach. The bioavailability of drug is significantly improved. [27]

3) Sponge Carrying SMEDDS

The concept is to load the SMEDDS into a sponge to develop a solid dosage form for a better delivery of hydrophobic drugs against the problems of being liquid in nature. The encapsulation of lipophilic drugs inside the sponges is possible using the naturally occurring hydrophilic polymers like alginate, which allows for the controlled and slow release.(28) Several preparation techniques such as freeze-drying, solvent evaporation, etc have been used for gelifying the SMEDDS in the sponge matrix. These will also influence the microstructure and pore size, which is suspected to affect the rates of drug release. Microstructural analyses by SAXS and SEM confirmed that the oil droplets of SMEDDS were not broken up during drying in the sponge, with size ranges around 9 nm, indicating intact structures throughout the drying process.(29)

Rehydration restores the sponges into the microemulsion state and will permit the sustained release of the hydrophobic drug. The incorporation method simplifies the formulation process as it does not require extra steps such as filling of capsule or compression of tablets, in addition to enhancing stability and storage of hydrophobic drugs, making SMEDDS-sponges a potential strategy in drug delivery systems.(29)

4) Herbal SMEDDS

Herbal drugs often face challenges like poor solubility and low oral bioavailability, limiting their therapeutic efficacy. To address this, Zhang et al. developed self-microemulsifying drug delivery systems (SMEDDS) using herbal extracts combined with oils, surfactants, and co-surfactants to form nanoemulsions upon contact with gastrointestinal fluids. These formulations were optimized through solubility studies, phase diagram construction, and characterized for droplet size and stability. In situ absorption studies in rats confirmed enhanced bioavailability. Solid SMEDDS prepared via spray drying and extrusion further improved stability and patient compliance (30)

5) Self-double-emulsifying drug delivery systems (SDEDDS)

Self-double-emulsifying drug delivery systems (SDEDDS) are an innovative oral formulation designed to enhance the bioavailability of drugs with high solubility but poor permeability. Unlike conventional SMEDDS that form simple oil-in-water emulsions, SDEDDS spontaneously generate water-in-oil-in-water (w/o/w) double emulsions in the gastrointestinal tract without mechanical agitation, thanks to peristaltic movements and tailored surfactant blends. This dual-phase encapsulation not only improves absorption and protects active ingredients from degradation but also offers superior stability—allowing formulations like Pidotimod to achieve a 2.56-fold increase in plasma concentration. These systems are suitable for encapsulation in soft or hard gelatin capsules and remain stable at room temperature for up to six months. Critical evaluation parameters include visual self-emulsification assessment, viscosity profiling, and phase diagram mapping, often supplemented by confocal scanning laser microscopy (CSLM). Overall, SDEDDS represent a promising advancement in oral drug delivery, combining efficiency, shelf stability, and patient-friendly dosing in one platform. (3)

6) Positively Charged Self Microemulsifying Drug Delivery System

Advanced formulations aim to improve oral bioavailability and have poor water solubility. Positive charged self-emulsifying drug delivery systems contain oils, surfactants, and cationic lipids like oleylamine, often used for forming emulsions which carry positive charges. A lot of the interaction between the droplets and the biological components in GI tract is influenced greatly by a positive charge, which finally leads to enhanced drug absorption.The charge characteristics and emulsions behavior distinguish positively charged SMEDDS from conventional SMEDDS. Cationic lipids in the positively charged SMEDDS attract negative physiological components present in the GI tract, whereas in conventional SMEDDS it is more often neutral or negative. Moreover, positively charged SMEDDS produce stable emulsions with smaller sizes of droplets upon dilution, which present better bioavailability. Such interactions enhance a higher absorption profile of lipophilic drugs such as Ibuprofen than what is normally seen in SMEDDSs.(31)

The positive charges of SMEDDS ensure better absorption of the drugs because they interact strongly with the negatively charged mucosal surfaces of the GI tract. Formulations also show improved stability in droplet size and emulsion properties, which will ensure that drug efficacy is maintained. Optimized formulations based on the ratios of oleylamine, surfactants (Tween 80 and Span 80), and oil components have been proven to significantly enhance the bioavailability of drugs.(32)Regarding analysis, some variables developed in terms of stirring speed and time appear crucial in achieving the desired droplet size and stability of the positively charged SMEDDS. These were intended to be characterized in terms of emulsion type, drug content, zeta potential, and in-vitro absorption profiles so that they could adequately find their way to meaningful improvements over drug delivery systems, especially for lipophilic drugs. Generally, these technologies ensure a better bioavailability with the optimum formulation strategies along with electrostatic interactions.(33)

7) Floating solid self-microemulsifying drug delivery systems

Floating solid self-microemulsifying drug delivery systems (SMEDDS) represent a promising advancement in gastroretentive drug delivery, particularly for poorly water-soluble drugs requiring prolonged gastric residence. These systems combine lipid-based excipients—such as isopropyl myristate, Tween 80, and PEG 400—with solid carriers like magnesium hydroxide to produce buoyant capsules that remain afloat in the stomach for extended durations, typically up to 10 hours. Upon contact with gastrointestinal fluids, the formulation spontaneously forms fine oil-in-water microemulsions, enhancing solubilization and absorption while bypassing hepatic first-pass metabolism. The optimized floating SMEDDS demonstrated over 90% drug release and followed Korsmeyer–Peppas kinetics, indicating Fickian diffusion. Solidification techniques such as spray drying and extrusion not only improve formulation stability but also facilitate patient-friendly dosing. Overall, floating SMEDDS offer a dual advantage of improved bioavailability and site-specific delivery, making them a valuable tool in the development of effective oral therapies.(34)

8) Self-Emulsifying Phospholipid Suspension (SSEPS)

It is the novel formulation referred to as a solid self-emulsifying phospholipid suspension (SSEPS), that has been prepared in order to enhance the solubility and bioavailability of such poorly soluble drugs as carbamazepine (CBZ). Using SSEPS, diatoms were utilized as a carrier with a high surface area for greater dispersion and absorption in the gastrointestinal tract. The concept here employs the principle of self-emulsifying drug delivery systems (SEDDS) in which active agents such as caproyl macrogol-8 glycerides, lecithin, and triglycerides create stable emulsions on coming into contact with water.(35) SSEPS differs

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from SMEDDS in the aspect of structure and physical state. In SSEPS, liquid self-emulsifying components are embedded onto a solid carrier thus making it solid and more stable as against the liquid formulation nature of SMEDDS. The benefits with SSEPS result from its controlled release characteristics resulting from its solid matrix, which improves the dissolution rate and bioavailability as against SMEDDS which relies on rapid microemulsion formation and faster drug release without much control (36)

Advantages of SSEPS include increased solubility of the drugs improved by its enhanced dissolution rate over pure drug counterparts for CBZ. The fact that its solid nature enhances stability, so that the characteristic features of the drug are retained over time, and reduces the risk of controlled release; thus, the therapeutic efficacy may be improved potentially.SSEPS further minimizes the chance of polymorphic transition while assuring that the pharmaceutically acceptable P-monoclinic form of CBZ is obtained instead of the trigonal form sought by the non-solid counterpart.(35)Dissolution studies in SSEPS have been found to show a high rate of dissolution studies in SSEPS prepared by method B. This happens due to better localization within the pores of diatoms. XRD study confirms the P-monoclinic form gets retained. In the case of the SEM study, it is considered that with an increase in the compaction of liquid SEPS in the structure of diatoms, there will be a further enhancement of the dissolution rate. This is promising with its technique since SSEPS presents a good method of improving the delivery of drugs that are poorly soluble by giving them improved stability, solubility, and controlled release compared to the traditional formulations such as SMEDDS.(37)

9) Capsule SMEDDS

A study published in *Carbohydrate Polymers* (2013) explored hydroxypropyl methylcellulose (HPMC) capsules as a versatile matrix for incorporating self-microemulsifying drug delivery systems (SMEDDS). This formulation strategy allows for controlled drug release while preserving the self-emulsifying characteristics upon contact with gastrointestinal fluids. The HPMC shell contributed to improved stability, uniformity, and reduced drug precipitation. Notably, enhancements in dissolution and drug dispersion were observed, underscoring its potential for improving oral bioavailability of poorly soluble compounds in BCS Class II/IV. Such capsule-based systems align with the growing focus on scalable, patient-centric delivery platforms. (38)

10) Dry Emulsion SMEDDS

Dry emulsion-based SMEDDS are a promising advancement in oral drug delivery for poorly soluble compounds. These systems involve transforming conventional liquid SMEDDS—comprising oils, surfactants, and co-solvents—into solid powders via spray drying or adsorption onto carriers like Aerosil 200. Upon reconstitution in gastrointestinal fluids, they form microemulsions that enhance dissolution and bioavailability while offering improved physical stability and patient compliance. Supersaturable dry microemulsions can further benefit from precipitation inhibitors such as HPMC to maintain the drug in a solubilized state. Encapsulation into hard gelatin capsules facilitates ease of administration, as demonstrated in formulations for Nebivolol where rapid emulsification and enhanced drug release were achieved.(39)

11) SMEDDS SR MICROSPHERE

SMEDDS-based sustained-release (SR) microspheres are formulated via the quasi-emulsion solvent diffusion method, where oily drugs are encapsulated within a polymeric matrix using excipients like HPMC, Aerosil 200, and talc to boost solubility, self-emulsification, and microsphere stability (40). These systems offer controlled drug release and extended absorption, outperforming conventional SMEDDS by maintaining therapeutic levels over time. For instance, ZTO-loaded SR microspheres exhibited a 135.6% increase in bioavailability compared to standard formulations (41). Their solid-state nature improves physical stability and adaptability across various drugs, with consistent dosing reducing adverse effects. Characterization through SEM, in vitro dissolution, and animal pharmacokinetics confirm enhanced release behavior under gastrointestinal conditions (40).

12) Self-emulsifying sustained/controlled-release tablets

Numerous potent drugs, including carvedilol, suffer from low oral bioavailability due to poor aqueous solubility and presystemic metabolism. Carvedilol, specifically, has low solubility and is subject to significant presystemic metabolism. To address these challenges, a novel formulation known as the self-emulsifying osmotic pump tablet (SEOPT) has been developed. This formulation enhances the bioavailability of carvedilol, regulates the release rate, and stabilizes plasma concentrations. Dissolution experiments indicate that carvedilol's release from the SEOPT is controlled and nearly follows a zero-order release profile. In contrast, self-emulsifying capsules contain a liquid or semisolid form of a self-emulsifying system. Upon reaching the gastrointestinal tract (GIT), these capsules disperse into a self-emulsifying system that reduces particle size to the micron range, thereby improving bioavailability. Another variant of self-emulsifying capsules involves solid self-emulsifying systems filled into capsules, further enhancing drug delivery efficiency. [42]

13) Self-emulsifying sustained/controlled-release tablets

Self-emulsifying sustained/controlled-release tablets synergize the solubilization power of SEDDS with the benefits of prolonged drug release, offering improved bioavailability and consistent plasma levels—especially vital for drugs with narrow therapeutic indices. Though manufacturing presents challenges in balancing rapid emulsification with controlled release, recent advances such as polymeric matrices, solid carriers, and coating technologies enhance stability and modulate drug release effectively. Studies show solid dispersion techniques can maintain self-emulsifying properties while enabling sustained therapeutic action, making these tablets promising for poorly soluble drugs and patient compliance [43].

14) SE beads

Self-emulsifying beads offer an advanced solution for enhancing the bioavailability of poorly water-soluble drugs by converting liquid SEDDS into solid bead forms. Upon exposure to gastrointestinal fluids, these beads spontaneously form fine emulsions that maintain the drug in a solubilized state, improving absorption. Their solid structure ensures better stability, palatability, and handling, while enabling sustained or delayed drug release. This controlled delivery improves therapeutic outcomes by maintaining consistent plasma levels and reducing dosing frequency—making them a valuable strategy in oral drug formulation [44].

15) Sustained or controlled-release (SE-controlled) pellets

Sustained or controlled-release (SE-controlled) pellets are advanced dosage forms that ensure gradual drug delivery over time, enhancing therapeutic efficacy and patient compliance. Using polymers like ethyl cellulose, HPMC, and polyvinyl acetate, they achieve either diffusion- or erosion-controlled release. These pellets help maintain stable plasma concentrations, reduce side effects, and can be tailored to specific gastrointestinal sites. Recent innovations, including fluid bed coating and pH-sensitive polymers, enable precise release kinetics and improve formulation stability under physiological conditions—making them suitable for various poorly absorbed drugs [45].

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FUTURE PERSPECTIVE

The future of SMEDDS lies in its transition from traditional lipid-based systems to multifunctional, patient-centric platforms capable of overcoming solubility, permeability, and delivery barriers in BCS Class II/IV drugs. With the integration of advanced techniques such as S-SMEDDS, SDEDDS, floating SMEDDS, and solid-state conversions like beads, pellets, and sponges, the scope of SMEDDS is expanding into controlled and targeted release domains. Emerging approaches involving pH-sensitive polymers, positively charged emulsions, and phospholipid suspensions pave the way for enhanced stability, site-specific absorption, and tunable release kinetics. The application of SMEDDS to herbal compounds and high-throughput strategies also offers exciting opportunities for natural therapeutics and personalized medicine. Going forward, optimization using machine learning models, IVIVC refinement, and scalable manufacturing protocols will be essential to transform SMEDDS into clinically reliable and commercially viable drug delivery systems.

CONCLUSION

The evolution of Self-Microemulsifying Drug Delivery Systems (SMEDDS) reflects a significant leap in addressing challenges associated with the oral delivery of poorly soluble and permeable drugs. By leveraging lipid-based excipients, advanced surfactant systems, and solidification strategies—such as S-SMEDDS, floating formulations, beads, sponges, and positively charged emulsions—researchers have substantially improved dissolution, bioavailability, and therapeutic consistency. Innovations like mouth-dissolving films, phospholipid suspensions, and capsule-based SMEDDS demonstrate the platform's versatility across diverse delivery needs. With ongoing optimization in formulation design, evaluation parameters, and mechanistic understanding, SMEDDS continue to emerge as a robust and adaptable solution for enhancing oral drug performance, ensuring greater patient compliance and expanding pharmaceutical possibilities for BCS Class II/IV compounds.

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