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Advancements and Innovations in Herbal and non-herbal, Self-Micro emulsifying Drug Delivery Systems (SMEDDS): A Comprehensive Review

Review Article

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Abstract

Self-microemulsifying drug delivery systems (SMEDDS) formulations have emerged as crucial methods for improving the bioavailability of poorly water-soluble drugs. However, they exhibit several limitations, including oxidation of unsaturated fatty acids, restricted lymphatic absorption, handling challenges, in vivo drug precipitation, a lack of predictive in vitro research—and their high surfactant content can cause gastrointestinal irritation. These factors can impede their broader application. Incorporating precipitation inhibitors or polymers within lipid-based formulations helps maintain drug supersaturation after dispersion, thereby reducing exposure variability and enhancing bioavailability. Converting liquid SMEDDS into solid forms also addresses issues related to liquid handling and stability. This review highlights recent developments, such as the use of nanotechnology, innovative excipients, and solidification techniques in the formulation of herbal SMEDDS. It also evaluates their advantages and drawbacks in drug delivery, with a particular focus on key performance parameters like droplet size, zeta potential, and stability. Additionally, self-nanoemulsifying drug delivery systems (SNEDDS) show considerable promise for improving the bioavailability and solubility of poorly water-soluble herbal extracts by encapsulating them in nanoemulsions. In summary, SMEDDS offer a viable oral platform for administering poorly soluble medications and herbal extracts, with the potential to significantly enhance therapeutic outcomes. For wider clinical adoption, however, challenges related to formulation stability, scalable manufacturing, and regulatory compliance must be addressed. Future research should aim to overcome these barriers and expand SMEDDS applications across diverse therapeutic areas.

Keywords: Emulsion, Herbal SMEDDS Formulation, Stability, Factors, Composition, Medication.

Introduction

Several strategies have been explored to increase the oral bioavailability of poorly water-soluble medicines (1–3). Oral administration is the most common route for continuous therapy due to its excellent patient compliance. However, the high lipophilicity of many drugs hinders the oral administration of nearly half of all active pharmaceutical ingredients. In fact, approximately 40% of new drug candidates exhibit poor water solubility, which complicates the development of effective oral solid dosage forms in terms of formulation and bioavailability.

Various approaches have been employed to address these challenges, such as enhancing solubility or maintaining the drug in a liquid state throughout gastric transit (4, 5). These include the use of surfactants, cyclodextrins, micronization, liquid–solid conversion techniques, salt formation, pH modification, nanoscale delivery systems, solid dispersions, and penetration enhancers (6).

Among these methods, lipid-based solutions—including emulsions and pre-emulsion concentrates—have attracted significant attention, as they offer physically stable formulations capable of encapsulating poorly soluble drugs (7). Nevertheless, emulsion

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systems present inherent challenges, such as stability concerns and manufacturing complexities during commercialization (8). Self-emulsifying systems offer a promising formulation technology to address these issues.

Self-emulsifying drug delivery systems (SEDDS) are effective tools for enhancing the bioavailability of weakly water-soluble drugs (9). SEDDS are isotropic mixtures of drugs, lipids, and surfactants, often supplemented with hydrophilic co-solvents or co-emulsifiers (10). Upon mild agitation and dilution with aqueous media, they rapidly form fine oil-in-water emulsions, typically with droplet sizes ranging from 100 to 300 nm. In contrast, self-micro-emulsifying drug delivery systems (SMEDDS) form clear microemulsions with droplets smaller than 50 nm (11). In recent years, significant attention has focused on lipid-based formulations—especially SMEDDS.

Poor water solubility remains a major obstacle in oral drug formulation, since drugs must be in solution to be absorbed through the gastrointestinal tract (12). Many pharmacologically promising substances suffer from poor aqueous solubility. Furthermore, approximately 30% of marketed drugs and nearly 50% of novel compounds exhibit high lipophilicity and low aqueous solubility. According to the Biopharmaceutical Classification System (BCS), Class II drugs are highly permeable but poorly soluble, while Class IV drugs are low in both solubility and permeability (13). Both classes face variable absorption and poor oral bioavailability.

To improve solubility and absorption, various strategies have been proposed, including solid dispersions, crystal habit modification, particle size reduction, solid solution techniques, and salt formation (14). Recently, lipid-based carrier systems have regained interest for enhancing the bioavailability of poorly soluble drugs. The primary aim of these formulations is to maintain lipophilic molecules in a solubilized state throughout the gastrointestinal tract.

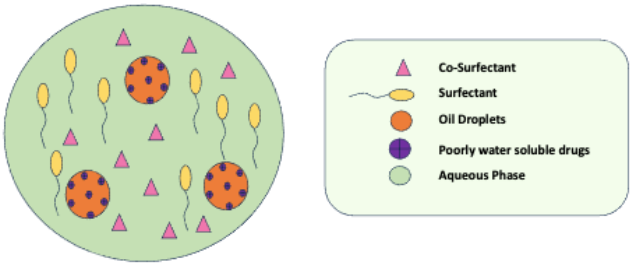
Lipid-based carriers take several forms: emulsions, microemulsions, solutions, suspensions, SEDDS, and dry emulsions (15). SEDDS, in particular, have demonstrated efficacy for the absorption of lipophilic drugs (e.g., cyclosporine A) in microemulsions. They have received more attention for oral drug development than conventional formulations of lipophilic compounds.

The Lipid Formulation Classification System (LFCS) categorizes lipid-based formulations. According to LFCS, SEDDS (Type II) are isotropic mixtures of oils and surfactants that form oil-in-water emulsions upon contact with gastric fluids. The terminology has evolved: SEDDS now often refers to Self-Nano Emulsifying Drug Delivery Systems (SNEDDS) or falls under Type IIIA or IIIB, which include co-surfactants and sometimes co-solvents. Their optimization commonly involves Response Surface Methodology (RSM) (16).

RSM reduces the experimental burden required to develop SEDDS with desirable characteristics. Multiple research groups have investigated lipid-based systems—including macroemulsions, SMEDDS, microemulsions, nanoemulsions, lipoplexes, solid lipid nanoparticles, and liposomes. This progress has led to SMEDDS featuring smaller droplets and improved thermodynamic stability. Emulsions are composed of microscopic droplets dispersed in another liquid phase containing surfactants; they are often thermodynamically unstable, transparent (or sometimes opaque), and exhibit viscous, liquid-like properties (17).

The various components of SMEDDS are shown in Figure 1.

Figure 1: Different components of the SMEDDS.



In self-emulsifying formulations, the resulting emulsion enhances membrane permeability through the action of surfactants and improves lymphatic transport when medium- and long-chain oils are used. These factors can significantly enhance the performance of the formulation (18). In recent years, there has been growing interest in SMEDDS in particular. This is primarily because SMEDDS are physically stable, easy to manufacture, suitable for encapsulation in soft gelatin capsules, and capable of producing drug-loaded microemulsions with a large surface area upon dispersion in the gastrointestinal system. These microemulsions not only facilitate the rapid breakdown of the formulation by gastrointestinal enzymes but also promote drug partitioning into mixed micelles and enable direct absorption from emulsion droplets into the aqueous phase of intestinal fluid.

Here, we present SMEDDS as a leading approach for formulating lipophilic drugs and improving their oral bioavailability (19).

Composition of SMEDDS (20,21,22)

The self-emulsification process is unique to the characteristics of the oil-surfactant pair. The method is dependent on:

1. Oils
2. Surfactant
3. Co-Surfactant
4. Co-Solvents
5. Consistency Builder
6. Polymer

1. Oil (Lipid)

Lipids are a crucial component of SMEDDS, as the quantity of oil in the formulation influences how effectively drugs are solubilized and reach the lymphatic system. Typically, lipids are soluble in non-polar organic solvents but insoluble in water; they are characterized by their fatty acid content, melting point, hydrophilic-lipophilic balance (HLB), and solubility in

these solvents. Lipids with a high melting point and a low HLB value are particularly suitable for sustained-release applications, while semi-solid excipients with high HLB values promote rapid drug release and increased bioavailability.

SMEDDS have been developed using both long-chain triglycerides (e.g., soy oil) and medium-chain triglycerides (e.g., Capmul MCM) with varying levels of saturation. Due to their biocompatibility, modified or hydrolyzed vegetable oils have significantly contributed to the success of SMEDDS (23). Recently, innovative semi-synthetic medium-chain triglyceride-based excipients, such as Gelucire, have been developed to replace traditional medium-chain triglycerides. Other suitable oils and fats include olive oil, maize oil, soy oil, and certain animal fats (25).

Examples of Oils: Corn oil, peanut oil, and beeswax oil.

2. Surfactant

In the creation of SMEDDS, non-ionic surfactants with high HLB values are used, such as Common surfactants used in SMEDDS include ethoxylated polyglycolysed glycerides, Tween-80, LABRAFAC CM10, a mixture of saturated compounds with eight carbon atoms, polyglycosylated glycosides (with an HLB of 10), and long-chain alkyl sulfonate surfactants such as sodium dodecyl benzene sulfonate, sodium lauryl sulfate, and dialkyl sulfonates. Surfactant concentrations in SMEDDS formulations typically range from 30% to 40% by weight (w/w) (24, 25).

A high HLB value and resulting hydrophilicity are essential for the rapid formation of oil-in-water (o/w) droplets and for ensuring effective dispersion and self-emulsifying behavior in aqueous environments. The amphiphilic nature of these surfactants allows them to solubilize and stabilize relatively large amounts of hydrophobic drugs, which is crucial for maintaining the drugs in a soluble form that facilitates efficient absorption and prevents precipitation within the gastrointestinal lumen (26, 27).

A surfactant molecule consists of two components with different solvent affinities—one that is more attracted to water (the polar head group) and another that is more attracted to oils (the non-polar tail). By forming an interfacial film between these two liquids, the surfactant reduces interfacial tension and facilitates the creation of stable emulsions.

Examples Of Surfactant: Polysorbate 80, Polysorbate 20, Sorbitan mono oleate

Types of surfactants

(a) Anionic Surfactant: where the hydrophilic group carries negative charge, such as carboxyl, sulphate, and sulphonate. Ex-Potassium laurate

(b) Cationic Surfactants: where the hydrophilic group carries positive charge, such as ammonium. Ex-Quaternary ammonium halides.

(c) Ampholytic Surfactants (Zwitter Ionic Surfactants): where the hydrophilic group carries both positive and negative charge. Ex-Sulfobetaines.

(d) Non-Ionic Surfactants: where the hydrophilic group does not carry any charge but its water solubility is forming highly polar group such as hydroxyl or polyoxyethylene. Non-ionic surfactant is most widely recommended as they possess relatively high HLB value.

3. Co-Surfactant

A co-surfactant with an HLB value between 10 and 14 is typically employed in SMEDDS. The preferred hydrophilic cosurfactant is an alcohol with an intermediate chain length, such as hexanol, pentanol, or octanol, which is known to lower the oil/water contact and enable the spontaneous production of microemulsion (24, 25).

Production of optimum SMEDDS requires a high concentration of surfactant in order to sufficiently reduce interfacial tension, which can be harmful. So cosurfactant is needed to reduce the concentration of surfactant. Surfactants and cosurfactants give the interfacial film enough flexibility to accept the various curvatures required to form micro-emulsion in a wide range of compositions. Cosurfactants that are suitable for use in medicine include ethanol, propylene glycol, and polyethylene glycol 400. Lipid-soluble solvents are employed in the creation of SMEDDS because they make it possible to dissolve significant amounts of hydrophilic surfactants.

4. Co-Solvents

Organic solvents suitable for oral administration —such as ethanol, propylene glycol, and polyethylene glycol—are frequently incorporated into SMEDDS. They enhance the dissolution of hydrophilic drugs or support greater quantities of hydrophilic surfactants within the lipid base. To further aid solubilization, co-solvents like triacetin (glyceryl triacetate) are added; triacetin is particularly effective due to its compatibility with lipid phases and ability to solubilize hydrophobic drugs.

For optimal performance, SMEDDS formulations typically include a high surfactant concentration—generally over 30% w/w—which promotes efficient self-emulsification and ensures the rapid formation of fine oil-in-water micro- or nano-emulsions upon dilution. (24,25).

5. Consistency Builder

The consistency of the emulsion can be changed by adding more material, such as acetyl alcohol, tragacanth, stearic acid, and beeswax (28).

6. Polymer

Inert polymer matrix that makes up between 5% and 40% of the composition by weight, is not ionizable at physiological pH, and can create matrices. Examples include ethyl cellulose, hydroxypropyl methyl cellulose, etc. (29).

Emulsion

Emulsions are mixtures of two or more liquids, with one liquid dispersed as small or ultra-small

droplets within the other. These emulsions typically form through mechanical agitation, provided the liquids are immiscible.

Types of Emulsions

1. **Water-in-Oil Microemulsion (W/O)**
2. **Oil-in-Water Microemulsion (O/W)**
3. **Multiple Emulsions**
   a. Oil-in-Water-in-Oil (O/W/O)
   b. Water-in-Oil-in-Water (W/O/W)

1. Water-in-Oil Emulsions (W/O)

The continuous phase in a W/O emulsion is hydrophobic (oil), with water serving as the dispersed phase (30). In crude oil contexts, over 95% of emulsions are the W/O type (31). Stability is critical in W/O emulsions, and they are typically stabilized using natural surfactants like resins and asphaltenes (32, 33). Fingas and Fieldhouse classified W/O emulsions into four categories: stable, mesostable, unstable, and entrained water. Stable emulsions, which are brown, contain 60–80% water (34).

2. Oil-in-Water Emulsions (O/W)

In O/W emulsions, water is the continuous phase and oil is the dispersed phase. If poorly managed in petroleum operations, either W/O or O/W emulsions can result in considerable financial losses (35). O/W emulsions, often termed reverse emulsions, are less common than W/O and typically classified as mesostable—brown or black emulsions with properties intermediate between stable and unstable types. Unstable emulsions rapidly separate into two phases, while entrained water emulsions (initially 30–40% water) settle to about 10% over a week. Only the mesostable and stable categories are generally recognized as emulsions.

3. Multiple Emulsions

Multiple emulsions include O/W/O and W/O/W forms. These complex systems are stabilized by both hydrophobic and hydrophilic surfactants. They feature small droplets nested within larger droplets, all suspended in a continuous phase. For example, W/O/W emulsions consist of water droplets within oil droplets, themselves dispersed in a continuous aqueous phase. Stabilization typically requires two surfactants: one with low HLB and another with high HLB (36–39).

Emulsion Formation

Emulsification refers to the process by which emulsions form—a dynamic, energy-driven process. Mechanical energy (e.g., shaking, rotor-stator mixing, membrane injection, high-pressure homogenization, or ultrasound) is used to disperse one liquid into finely sized droplets within another phase (40, 41). Deformation under shear or agitation breaks droplets into smaller units (40, 41).

In crude oil processing, stabilizing emulsions with waxes, resins, and asphaltenes is a primary challenge. The highly stable W/O emulsions in this industry owe their stability to these natural surfactants (42). The formation of a stable emulsion requires:

- Immiscibility of phases
- Agitation to disperse one liquid into another
- Sufficient surfactant

An emulsion's properties will evolve post-formation based on variables like time, mixing speed, temperature, and pressure. A stabilizing agent is essential for maintaining a stable emulsion.

Stability of Emulsion

Emulsion stability is governed by both the type and concentration of surfactants, which form interfacial films around water droplets, reducing interfacial tension and increasing interfacial viscosity (43). Temperature, water content, and mixing speed also influence stability (44, 45). Increasing energy input yields smaller droplets and greater stability. However, higher temperatures can alter interfacial film properties, surfactant solubilities, and reduce emulsion viscosity—especially in the oil phase (46). Although emulsions are thermodynamically unstable and prone to changes over time, understanding both kinetic and thermodynamic stability is key to controlling their behavior.

Kinetic vs. Thermodynamic Stability

Thermodynamic stability refers to the inherent tendency of emulsions to separate due to unfavorable oil-water interactions. Over time, emulsions may break down unless stabilized by surfactants (47). Kinetic stability, on the other hand, is achieved by adding stabilizing agents that inhibit droplet coalescence, delaying separation (48).

Types of SMEDDS

1. Herbal SMEDDS

Definition: SMEDDS that incorporate plant-derived (phytochemical) active ingredients.

Examples:

Herbal Drug	Application	Benefit via SMEDDS
Curcumin (from turmeric)	Anti-inflammatory, anticancer	Poor water solubility improved significantly
Thymoquinone (from Nigella sativa)	Antioxidant, anticancer	Enhanced oral bioavailability
Berberine	Antidiabetic, antimicrobial	Enhanced intestinal permeability
Resveratrol	Antioxidant	Better stability and systemic availability

Challenges:
Herbal compounds are often chemically unstable.
Standardization and reproducibility are difficult.

2. **Non-Herbal SMEDDS**

Definition: SMEDDS used for synthetic or semi-synthetic pharmaceutical compounds.

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Examples

Drug	Class	SMEDDS Benefit
Cyclosporine A	Immuno-suppressant	Marketed SMEDDS product (Neoral®) for enhanced bioavailability
Fenofibrate	Anti-hyperlipidemic	Poor water solubility; improved systemic absorption
Tacrolimus	Immuno-suppressant	Improved solubility and reduced variability
Ritonavir	Antiviral (HIV)	Enhanced oral bioavailability in lipid-based formulations

3. COMPARISON: HERBAL VS. NON-HERBAL SMEDDS

Feature	Herbal SMEDDS	Non-Herbal SMEDDS
Active Ingredients	Phytochemicals	Synthetic drugs
Regulatory complexity	Higher (due to natural variability)	More standardized
Clinical data availability	Limited	Well-established for many drugs
Appeal	"Natural" appeal for consumers	Widely accepted in pharmaceuticals
Solubility challenges	Often extreme	Variable but better characterized

Preparation of SMEDDS

A glass vial is charged with a precisely weighed drug, followed by oil and co-surfactant. The mixture is gently stirred and vortexed for 30 minutes, then heated at 40 °C on a magnetic stirrer until the drug dissolves. The solution is stored at room temperature until use.

Methods for Preparing Solid SMEDDS (S-SMEDDS)

1. **Capsule Encapsulation**
   - Liquid SMEDDS can be encapsulated directly or sealed via banding or micro-spraying.
   - For semisolid SMEDDS: heat excipients ~20 °C above melting point, dissolve drug in the molten blend, fill capsules, and cool to room temperature. Ideal for high-potency, low-dose drugs (49).
2. **Spray Drying**
   - Liquid SMEDDS mixed with a solid carrier and solvent, then atomized into fine droplets. These are dried to yield solid particles (50).
3. **Melt Granulation**
   - Similar to spray drying, involving atomized droplets in a controlled drying setup (50).
4. **Extrusion–Spheronization**
   - Liquid SMEDDS mixed with extrusion aids and water to form a wet mass, extruded, spheronized, dried, and sized pellets (51, 52).

Mechanism of SMEDDS

Self-emulsification occurs when the entropy gain from dispersion exceeds the energy required to increase surface area. The free energy of emulsion formation is given by:

$$\Delta G = \Sigma N \pi r 2 \sigma$$

where ΔG is the free energy change (ignoring mixing energy), N is the number of droplets, r is droplet radius, and σ is interfacial tension (53).

As emulsion phases separate to reduce free energy and interfacial area, traditional emulsifiers stabilize droplets by forming monolayers that lower interfacial tension and prevent coalescence. With sufficiently low or negative ΔG, self-emulsification becomes spontaneous with minimal energy input. During this process, non-ionic surfactants and aqueous interfaces interact, leading to phase inversion behaviors related to emulsifier properties (54).

On gentle agitation, water infiltrates the surfactant-oil mixture, disturbing the interface and generating droplets. Microemulsions remain thermodynamically stable, maintaining equilibrium through a dynamic balance of droplet coalescence and fragmentation (55).

Evaluation of SMEDDS

- **Visual Assessment:** Indicates self-emulsifying capacity and dispersion behavior (56, 57).
- **Emulsification Efficiency:** Measured via rate of emulsification and particle size distribution. Poulton used turbidity measurements to evaluate equilibrium achievement (58).
- **Droplet Polarity:** Influenced by oil HLB, fatty acid properties, emulsifier characteristics, and correlating to drug release (59).
- **Droplet Size:** Critical for drug release and absorption; measured using dynamic light scattering instruments for 10–200 nm particles (60, 61).
- **Dissolution Studies:** Assess sustained-release characteristics, particularly for drugs insoluble at acidic pH (62).
- **Zeta Potential:** Used to determine droplet charge and stability (62).

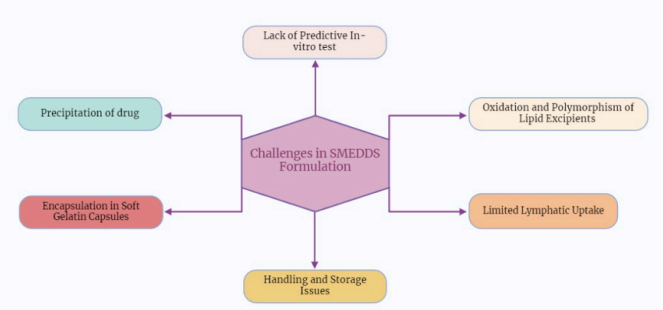
Factors Affecting SMEDDS

- **Drug Dose:** Drugs with poor water and lipid solubility, especially at high doses, are less suitable unless highly soluble in at least one component (63).
- **Drug Solubility in Oil:** Influences the ability to maintain the drug in solution; dilution may cause precipitation if surfactants solubilize the drug more than oil.
- **Equilibrium Solubility:** Predicts GI precipitation; some formulations remain supersaturated for up to 24 hours post-emulsification (64).
- **Oil Droplet Polarity:** Governs drug release rate; higher polarity facilitates faster drug transfer to the aqueous phase (64).

SMEDDS's Limitations

Despite the SMEDDS formulation's many benefits, there are certain drawbacks to this system, which are illustrated in the below image.

Figure 2: Limitations of SMEDDS formulation



Precipitation of Drug upon Dilution:

SMEDDS, once diluted in digestive fluids, often experience drug precipitation. Maintaining the drug in a solubilized form throughout the GI tract is a fundamental requirement for lipid-based formulations; otherwise, the benefits are nullified. The increased water content from dilution raises the risk of precipitation, so polymers are typically added to minimize this effect in vivo (65, 66).

Soft-Gelatin Capsule Encapsulation

Most SMEDDS formulations on the market are delivered in soft-gelatin capsules, but gelatin presents some drawbacks. Animal-derived gelatin may carry risks such as transmissible spongiform encephalopathy (TSE) and raises concerns related to consumer preference and religious beliefs (67). Moreover, volatile co-solvents in self-microemulsifying formulations can permeate gelatin capsules—both hard and soft—resulting in the precipitation of lipophilic drugs (68). Consequently, HPMC capsules have emerged as a preferred alternative (69).

Storage and Handling

Liquid SMEDDS face practical challenges in handling, stability, and storage, making the development of solid SMEDDS a logical solution (49).

Limited Lymphatic Targeting

Lymphatic delivery has two main advantages over traditional portal absorption: it bypasses pre-systemic hepatic metabolism, enhancing systemic drug levels, and facilitates targeted delivery to lymphatic tissues. However, effective lymphatic transport typically requires drugs with high log P values and triglyceride solubility, and uptake varies by drug. Thus, more accurate predictive models are needed, along with a better understanding of how lipophilicity and lipid solubility affect lymphatic transport (70, 71).

Insufficient In Vitro Models

The development of SMEDDS and other lipid-based formulations is hindered by the lack of reliable in vitro models for evaluation (72). Conventional dissolution tests fail to capture the lipid digestion process necessary for drug release. Although in vitro models that simulate duodenal digestion have been developed (73), they require further validation. Many prototype formulations still need in vivo testing to establish credible in vitro–in vivo correlations (74).

Oxidation and Lipid Polymorphism

Unsaturated fatty acid excipients in SEDDS or SMEDDS are prone to oxidation (75), necessitating the inclusion of lipid-soluble antioxidants in the formulation. Additionally, process controls are essential to prevent polymorphic changes in the lipid matrix caused by thermal softening during production (76).

Table 1: List of recently used oral drugs in SMEDDS formulation

S. No	Drug	Route of Administratio	Potential	Delivery System	Excipients Used	Outcomes Achieved	References
1	Agomelatine	Oral	Antidepressant	Solid-SMEDDS	Capmul MCM, KolliphorEL, PEG 400,	Enhanced drug	Priyankae 2023 (77)
2	Azilsartan medoxo	Oral	In hypertension	Solid-SMEDDS	Soya lecithin comp clove oil, tween20, glycol	Improved dissol	Madanet al (78)
3	Curcumin	Oral	Antidepressant	SMEDDS	Oleicacid, tween 80 glycol	Increased brain p and impro pharmacologica	Manojet al. (79)
4	Ferulic ac	Oral	In insomnia	FA-SMEDDS	Glyceryl triacetate, OP-10and Labrasol, PEG 400	Enhanced hypno	Liuetal., (80)
5	Hydrochlorothiazide (HCTZ)	Oral	In hypertension and edema	Self-micro emulsifying tablet (SMET)	Oleicacid, tween 20, propylene glycol, neusilinUS2,	Enhanced drug	Arpanaet al (81)
6	Licochalcor	Oral	Anti- hyper uricemic activity	SMEDDS	Ethyl oleate, Cremophor, EL 35, n-	Increase solub release rate of lic A	Zhongane 2021 (82)
7	Loratadine and Su	Oral	In pancreatic	SMEDDS	CapmulC8, Tw PEG 40(	Enhanced chemo preventive	Desai et al. (83)

8	Myricitrin	Oral	Anti-inflammatory, hypoglycemia,	SMEDDS	Ethyl oleate, Cremophor EL35, dimethyl carbinol	Enhanced drug r oral bioavail	Namanet al (84)
9	Nilotinib	Oral	In chronic myel leukemia (C	SMEDDS	Capryol90, Tra HP and Twe	Improved solub oral bioavail	Zakkulaet a (85)
10	Phillygenin	Oral	Antioxidant, hypc inhibition of tyrosi and antihypert effects	SMEDDS	Labrafil M1944CS, PEG-400, Cremophor EL	Improved oral a and enhanc bioavailab	Lingzhiet al (86)
11	Raloxifene hydrochloride	Oral	In breast canc osteoporis	Liquid-SMEDDS	Capryol 90 (oil),T Labrasol, PE	Enhanced therapeutic	Ansariet al. (87)
12	Resveratrol	Oral	Anticancer, antiox inflammatory and a	SMEDDS	Isopropyl myristate, Cremophor RH40, PEG 400	Enhanced solubility and oral	Hongwei 2019 (88)
13	Rosuvastatin	Oral	Antihyperlipidemi c	Solid-SMEDDS	Capryol90, KolliphorEL, TranscutolHP	Enhanceme physiochemical a biologic attribute	Suparnaet a (89)
14	Saquinavir	Oral	Antiretroviral	Supersaturated - SMEDDS	Capryol90, Labrasol, propylene glycol, HPMC	Enhanced lymphatic absorption	Kangheee 2020 (90)
15	Zingerone	Oral	Antioxidant, anticancer,	SMEDDS	Ethyl oleate, tween80,	Improved oral bioavailability	Xiaetal., (91)
16	**Commiphora Wightti extract**	Oral	Obesity	SMEDDS	CapryolPropylene GlycolCremophore	Improved oral bioavailability	Singh et al, 2022
17	***Beta vulgaris L.*** l	Oral	hepatoprotective activity	SMEDDS	linseed oil or olive oil, Tw80 and DMSO at two SA/	Improved oral bioavailability	Kassem et al., 2020

Conclusion

SMEDDS are being actively investigated for delivering poorly water-soluble drugs. However, the demand for lipid-based drug delivery systems exceeds the availability of commercially formulated SMEDDS. Most marketed SMEDDS are packaged in soft gelatin capsules, which complicates handling and increases costs. Developing solid SMEDDS can resolve these handling challenges, reduce production expenses, and improve the stability issues associated with liquid formulations. Additionally, these formulations should be designed to suit physiological conditions, ensuring SMEDDS reach their full potential—especially for poorly soluble drugs

Future prospectives

Self-Microemulsifying Drug Delivery Systems (SMEDDS) hold great promise in the pharmaceutical field, offering innovative solutions for poorly water-soluble drugs. Although many formulations exist, commercially available SMEDDS remain limited compared to the demand. The majority of marketed SMEDDS are soft-gelatin capsules, which present handling difficulties and higher costs. Solid SMEDDS, by contrast, can address these issues by improving stability, simplifying handling, and lowering production costs. To fully harness their potential, these systems must also be tailored to physiological conditions, ensuring their safe and effective application—especially for poorly soluble medications.

With continued research and development, SMEDDS could revolutionize drug delivery by enhancing solubility, bioavailability, and enabling targeted therapeutic strategies. Their adaptability supports a diverse range of compounds, from lipophilic drugs to biologics, paving the way for breakthroughs across multiple therapeutic areas. As regulatory frameworks evolve and industry standards mature, the integration of SMEDDS into pharmaceutical pipelines is expected to accelerate. Overall, SMEDDS offer a compelling future in drug development, with the capacity to address unmet medical needs and significantly improve patient outcomes.

Conflict of Interest

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

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