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Review Article

Recent Advances and Novel Strategies in Formulation Development: SMEDDS

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Abstract

Drug delivery systems that self-microemulsify (SMEDDS) have become a viable solution to the problems caused by poorly soluble medications. When these systems are diluted in aqueous media, a combination of oil, surfactant, cosurfactant, and drug spontaneously forms microemulsions. Owing to this special characteristic, SMEDDS can improve drug absorption, solubility, and overall bioavailability. The increasing frequency of poorly soluble compounds has demonstrated the urgency of developing creative formulation techniques. By designing a suitable environment for drug release and absorption, SMEDDS present an interesting approach. Microemulsions created by SMEDDS help to increase the effective surface area of the drug, thereby promoting its disintegration and absorption from the gastrointestinal system. SMEDDS have been employed in a range of therapeutic contexts, including topical, parenteral, and oral administration. For poorly soluble drugs, SMEDDS can significantly improve oral bioavailability, thus allowing smaller doses and fewer dosing intervals. By attaining continuous release during parenteral administration, SMEDDS can prolong the therapeutic effects of drugs. When applied topically, SMEDDS can enhance skin penetration and help medications reach target regions. In addition to their traditional use, SMEDDS are under investigation for other therapeutic fields based on nasal and ocular distribution. These methods of administration pose special challenges given the delicate nature of these tissues and the need for precise medicine delivery. SMEDDS enable a controlled and continuous release of drugs by reducing pain and improving therapeutic effectiveness, thus perhaps providing cures.

In conclusion, SMEDDSs are a potential approach to increasing the bioavailability and potency of poorly soluble drugs. This study aims to provide a comprehensive overview of the current state of research in this field by elucidating the underlying concepts of SMEDDSs and exploring recent breakthroughs in their formulation and implementation. SMEDDSs have a promising future due to their potential to alter modes of drug delivery and improve patient outcomes.

1. Introduction

Self-micro emulsifying drug delivery systems (SMEDDS) have proven to be a feasible solution to the challenges created by poorly soluble drugs. These systems comprise a mixture of drug, oil, surfactant, and cosurfactant that spontaneously generates microemulsions upon dilution in aqueous solutions. SMEDDS can increase drug solubility, absorption, and overall bioavailability owing to their unique properties. [1] [4] [5]. The growing number of medications that are poorly soluble has highlighted the pressing need for creative formulation techniques. Many medications have restricted solubility in aquatic settings, especially those with high lipophilicity. This results in partial absorption and decreased therapeutic effectiveness. SMEDDS provide an appealing remedy by fostering an environment that is conducive to drug release and absorption. SMEDDS can enhance the effective surface area of a drug by generating microemulsions, which aids in the drug's absorption and dissolution from the gastrointestinal tract. [2] [5]. SMEDDS were developed in response to the increased need for oral drugs, growing complexity of medicinal molecules, and desire for improved patient compliance. [1] SMEDDS provide several advantages over traditional formulations, such as improved patient acceptance, reduced dosing frequency, and enhanced bioavailability. [3] [4].Significant progress has been made in the development and use of SMEDDS in recent years. To increase the stability and functionality of SMEDDS, researchers have investigated innovative excipients, such as natural oils and biocompatible surfactants. In order have also been developed to maximize drug delivery and minimize adverse effects, such as pH-responsive and time-dependent formulations. [5].[5] SMEDDS have been used in numerous therapeutic settings, including topical, parenteral, and oral delivery. SMEDDS can greatly increase the oral bioavailability of poorly soluble medications, enabling lower dosages and fewer dosing intervals. SMEDDS can extend the therapeutic benefits of medications by achieving sustained release during parenteral delivery. When applied topically, SMEDDS can improve drug delivery to target tissues and increase skin penetration. [2].

In addition to their conventional uses, SMEDDS are being investigated for new therapeutic domains, such as nasal and ophthalmic administration. Because of the fragile nature of these tissues and the requirement for accurate medication delivery, these routes of administration pose particular difficulties. By delivering a regulated and prolonged release of medications, minimizing discomfort, and enhancing therapeutic efficacy, SMEDDS provide viable remedies. [3].

Notwithstanding SMEDDS' encouraging potential, several issues must be resolved. For SMEDDS to be successfully commercialized, regulatory factors such as safety and effectiveness evaluations are crucial. Overcoming manufacturing and scale-up obstacles is necessary to guarantee consistent product quality and pricing. Furthermore, customized SMEDDS formulations could be necessary to meet the demands of certain patients and enhance therapy results. [6].

In conclusion, SMEDDS offers a potential technique to boost the bioavailability and effectiveness of poorly soluble drugs. By understanding the underlying concepts of SMEDDS and analyzing recent breakthroughs in their formulation and applications, this review provides a complete overview of the current status of research in this field. The future of SMEDDS is optimistic, with the potential to transform drug administration and enhance patient outcomes.

2. Basic principles of SMEDDS:

Self-micro emulsifying drug delivery systems (SMEDDS) are advanced formulations designed to enhance the solubility and bioavailability of poorly water-soluble drugs (Figure 1).

1. Composition: Surfactants, co-surfactants, and an oil phase are the usual components of SMEDDS. The selection of components is essential to achieve the best possible emulsification and stability.
2. Self-Emulsification: SMEDDS come into contact with gastrointestinal fluids and naturally create microemulsions. Rapid dispersion is facilitated by surfactants, which lower the interfacial tension.
3. Microemulsion Formation: The resultant microemulsion is a thermodynamically stable system owing to improved solubility and absorption in the gastrointestinal tract.
4. Particle size: Improved bioavailability results from a small droplet size, which is usually between 20 and 200 nm. This improves the surface area available for drug absorption.
5. Enhanced drug delivery: SMEDDS can reduce adverse effects by increasing solubility and stability, resulting in superior therapeutic outcomes at lower dosages.
6. Stability: When a system is properly formulated, it resists phase separation and retains its microemulsifying qualities over time.
7. Customization: SMEDDS can be adapted for a range of therapeutic applications as formulations may be customized according to the unique pharmacological characteristics and intended release patterns.

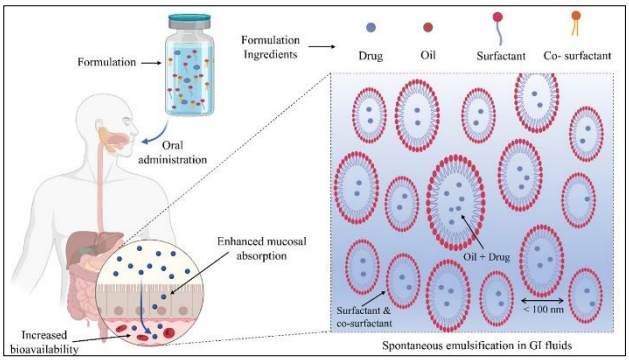

Figure 1 Basic Principles of SMEDDS

2.1 Components of SMEDDS

Active Pharmaceutical Ingredient (API): Drug qualities that make it appropriate for loading in SMEDDS: The active pharmaceutical ingredient should dissolve in the oil phase, as this impacts SMEDDS's power to retain the API in a solubilized condition. It is difficult to administer drugs via SMEDDS, which are poorly soluble in lipids or water. Unless a medication has extremely good solubility in at least one of the components of the SMEDDS, notably the oil phase, it is not appropriate for formulation when administered at very large dosages. A drug candidate's optimal log p value for SMEDDS should be larger than 2. (log p>2).[7] Oil: Since it solubilizes the lipophilic medication in the requisite amount or facilitates self-emulsification, oil is the most critical excipient in the formulation of SMEDDS. It also enhances the fraction of lipophilic drugs that are transported through the GIT, which improves absorption. The drug's high solubility in oil is the major factor for choosing it, as this will minimize the formulation's volume and guarantee that a proper dosage is supplied. The lipid component of the SMEDDS formulation, which is generally composed of nonpolar lipids, generates the core of the emulsion particle. SMEDDS have been made utilizing oils of medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs) with variable degrees of saturation. [8]. The most biocompatible lipid carriers are unaltered edible oils; however, their propensity to dissolve high dosages of lipophilic medicines and their inefficient self-emulsification prohibit them from being employed in SMEDDS formulations. In contrast, modified and hydrolysed vegetable oils function well in these formulations due to their formulation and physiological advantages[7].

Surfactant: When constructing self-emulsifying systems, several chemicals with surfactant capabilities can be employed; however, the selection is constrained because few surfactants are suitable for oral use. Non-ionic surfactants with a comparatively high hydrophilic-lipophilic balance (HLB) are most commonly suggested. Safety is an important consideration when selecting a surfactant. Natural emulsifiers are favored because they are thought to be safer than synthetic surfactants [9].Nevertheless, the ability of these surfactants to self-emulsify is limited. Although non-ionic surfactants are less harmful than ionic ones, they may cause the intestinal lumen's permeability to alter in a reversible way[10]. To develop stable SMEDDS, the surfactant concentration generally falls between 30 and 60% w/w. Since high surfactant concentrations may irritate the gastrointestinal tract, it is vital to correctly evaluate the surfactant concentration. Owing to their amphiphilic nature, surfactants have the potential to dissolve or solubilize comparatively large quantities of hydrophobic pharmaceutical compounds. SMEDDS are generated by lipid mixtures with increased surfactant and co-surfactant/oil ratios. [11]. The size of the droplets and the concentration of the surfactant being sprayed are related. The stability of the oil droplets owing to the surfactant molecules' localization at the oil-water interface may be the reason why increasing the surfactant concentration in some scenarios may result in droplets with a smaller mean droplet size. [12]. In some instances, however, the mean droplet size may increase with increased surfactant concentrations [13]. This behavior may be explained by the enhanced water penetration into the oil droplets generated by the higher surfactant concentration, which breaches the interfacial barrier and causes the oil droplets to be expelled into the aqueous phase [14].

Co-surfactants are used to lower the concentration of surfactants because a high concentration of surfactant is essential to effectively reduce interfacial tension for the production of an ideal SMEDDS, which can be harmful. When paired with surfactants, co-surfactants offer the interfacial layer the flexibility it requires to absorb various curvatures and create microemulsions within a broad composition range. The correct surfactant and co-surfactant must be chosen to build an SMEDDS efficiently and for the drug to dissolve in it. [7].

Oils: Oil is a significant excipient because it may solubilize a lipophilic medication in a given quantity, stimulate self-emulsification, and increase the proportion of lipophilic drug that is carried via the intestinal lymphatic system. Long- and medium-chain triglycerides are the most commonly used types of oil. Owing to their increased solubility and improved self-emulsifying characteristics, modified and hydrolyzed vegetable oils are often present in SMEDDS at concentrations of 40–80%. To improve the solvent

capacity of less hydrophobic medicines, triglycerides can be bent with mono- and di-glycerides. [15]. e. Consistency Builder: To adjust consistency in emulsion, beeswax, cetyl alcohol can be added to it.[16]

Enzyme Inhibitors: Enzyme inhibitors, such as amino acids and modified amino acid aminoborinine derivatives, can be added to SMEDDS if the active medicinal element is vulnerable to enzymatic degradation.[17] g. Other components, such as polymers, are necessary.

2.2 Mechanism of self-emulsification: Self-emulsification mechanism: When entropy changes and dispersion is bigger than the energy needed to increase the energy needed to extend the surface area of the dispersion [18], there occurs self-emulsification. The following equation describes the free energy of classic emulsion formation, which is defined by the energy required to establish a new surface between the two phases.

$$\delta G = \sum Niri\ 2\ \sigma$$

(i) Where, δG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius r, σ is interfacial energy with time. To lower the interfacial area and, subsequently, the system's free energy, the two emulsion phases tend to separate. Consequently, typical emulsifying agents stabilize emulsions formed by aqueous dilution by producing a monolayer covering the emulsion droplets, which decreases the interfacial energy and acts as a barrier to coalescence. [19]. [19] The emulsion process proceeds spontaneously in a self-emulsifying system when the free energy required to form the emulsion is either very low, positive, or negative. [20] Emulsification comprises destabilization via the shrinkage of tiny interfacial regions and requires relatively little input energy. The interfacial structure must not be resistant to surface shearing for emulsification to occur[21]. When an oil/non-ionic surfactant binary combination is introduced into water, an interface between the oil and aqueous continuous phases is generated. Water then becomes soluble in the oil phase as a consequence of aqueous penetration through the interface, continuing until the solubilization limit is reached near the contact. [22] Furthermore, a dispersed liquid crystalline phase emerges as a result of water penetration. With the aid of mild agitation of the self-emulsification process, water penetrates the aqueous cores rapidly, generating interfacial rupture and droplet production. Eventually, all materials near the interface will be liquid crystals, with the specific amount depending on the surfactant concentration in the binary mixture once produced. These self-emulsified systems' high solubility in coalescence is hypothesized to be induced by the liquid-crystal interface that envelops the oil droplets. The self-emulsifying features of a number of Imwitor 742 (a mixture of mono-and di-glycerides of caprylic acids/Tween 80) systems were examined utilizing a combination of particle size analysis and low-frequency dielectric spectroscopy. The results suggested that emulsion creation may be connected to liquid crystal formation; however, the relationship was evidently convoluted. [20] By interacting with the liquid crystal phase, the drug may affect the characteristics of the emulsion.

2.3 Preparations of SMEDDS formulations: The production of SMEDDS follows previously reported protocols [23][24]. Different volumes of oil, surfactant, and cosurfactant were added to a 10 mL screw-capped glass tube, and the liquid was agitated slowly. Following thorough dissolution, a translucent or transparent SMEDDS solution was generated. The proportions of oil, cosurfactant, and surfactant were selected at 30-65%, 30-65%, and 5-40%, respectively, to obtain the optimal SMEDDS formulation, based on the findings of the experiment and the specified concentration range of the three ingredients forming SMEDDS [25][26]. The figure illustrates the formulation (figure2).

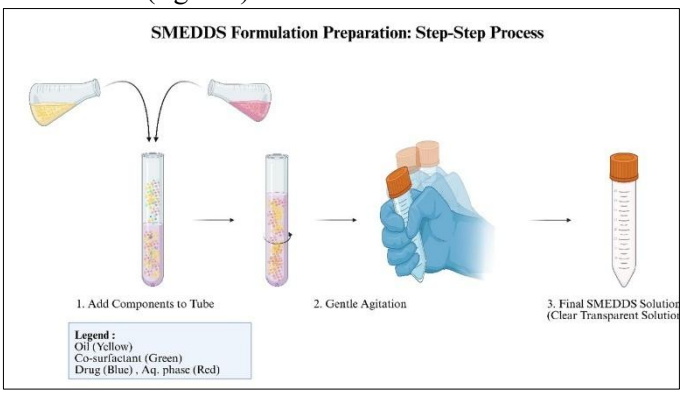

Figure 2 SMEDDS Formulation Preparation: Step-Step Process

3. Applications of SMEDDS in Drug Delivery:

Oral drug delivery has emerged as the preferred method of drug administration. However, typical medications for chronic illnesses often have low solubility, are poorly soluble in water, and undergo first-pass metabolism, resulting in low bioavailability and ineffectiveness. Lipid-based formulations work well with all types of dosage forms and have the significant advantage of employing flexible excipients. Self-microemulsifying drug delivery systems (SMEDDS) improve drug solubility and absorption by encouraging drug self-emulsification in a mixture of oil, surfactant,

and co-surfactant. The practical formulation of SMEDDS offers a viable way to address the shortcomings of oral lipophilic medications. Therefore, choosing a good combination of these elements is crucial for the effectiveness of SMEDDS. A methodical approach to drug development is provided by quality by design (QbD), which has the potential to greatly enhance SMEDDS' manufacturing quality performance. Additionally, pre-formulation studies combined with statistical design of experiments (DoE) may be an effective way to gain from it. In this review, we focus on the latest research on the creation of microemulsions and SMEDDS utilizing DoE techniques to optimize drug formulations with various excipients at regulated ratios. The technological advantages of DoE in enhancing SMEDDS formulations are briefly reviewed, along with its principles [27].

3.1 Oral administration of poorly soluble drugs

Many medications fail during drug development because of low bioavailability, even when they have pharmacodynamic or target actions. Conventional dosage forms of poorly soluble pharmaceuticals that are currently on the market use high dosages, which may be harmful. The Biopharmaceutic Classification System (BCS) has made it possible to classify medications according to the two main factors influencing absorption: permeability and solubility. Based on the BCS concept, several methods may be used to improve the absorption and bioavailability of poorly soluble and poorly permeable medications. The development of several formulation techniques used to improve the bioavailability of poorly soluble medications taken orally is summarized in this article [28].

Poor biopharmaceutical qualities cause up to 41% of drug candidates to fail throughout the drug development process [29]. Understanding the basic idea of BCS helps in coping with different situations and fighting against issues related to the bioavailability of different medications that are taken orally. Before a medicine reaches the site of action, it must pass through several biological membranes. The complete process for medications taken orally may be characterized as the LADME system, which demonstrates that evoking a response involves the liberation, absorption, distribution, metabolism, and elimination of the drug [30]. The study of how the physicochemical characteristics of medications and goods affect how well they enter the body in both healthy and diseased states is known as biopharmaceutics [31]. Biopharmaceutical factors are crucial in determining a drug's bioavailability. The US Code of Federal Regulations (CFR 21.320.1) defines bioavailability as " the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of action.

Because Class I medications have no bioavailability issues, they are easy to manufacture for oral administration. Class IV medications are the most challenging to administer owing to their subpar biological characteristics. Certain medications are not recommended for oral administration unless they are sufficiently potent to be effective at low plasma levels. Pharmaceutical scientists and medicinal chemists play a crucial role in the development of Class II and Class III medications, the characteristics of which can be easily altered to improve their oral bioavailability.

3.2 Parenteral administration for sustained release

Bypassing the digestive system, parenteral administration delivers drugs directly into the body. Drugs that require precise blood level control, rapid onset of action, or poor oral absorption are frequently administered using this method.

3.21 Methods of Parenteral Administration for Sustained Release

Several methods can be employed to achieve sustained drug release through parenteral administration:

Depot Injections:

- Intramuscular (IM) injections: The drug is injected into the muscle, where it forms a depot from which it is slowly released [32].
- Subcutaneous (SC) injections: The drug is injected beneath the skin, forming a depot that gradually releases the medication [32].

Controlled-release implants:

- Subcutaneous implants: Small, solid devices containing the drug are inserted under the skin [33]. These implants release drugs at a predetermined rate.

Microspheres:

- Intravenous (IV) infusion: microspheres containing the drug are infused into the blood stream. These microspheres are designed to circulate in the body and release drugs over a prolonged period [34].

Liposomes:

- Intravenous infusion: The drug is encapsulated in liposomes, which are tiny spherical vesicles that release it gradually as they travel through the circulation [35]. Increased interest in nanomedicine has boosted lipid–drug and lipid–protein research. These studies have laid the groundwork for creating lipid particles that increase therapeutic potency and reduce off-target effects.

Developments in lipid membrane research have enabled therapeutic progress.

4. Advanced Characterization Techniques

The effective formulation of self-micro emulsifying drug delivery systems (SMEDDS) depends on in-depth knowledge and a robust characterization of their physicochemical, interfacial, and performance properties. State-of-the-art analytical methods play a key role in providing knowledge on the droplet size distribution, stability, phase behavior, digestion kinetics, and overall bioavailability of SMEDDS formulations. Modelling and in vitro characterization using the characterization methods described herein, based on ASCI's application to the self-compacting tablet (SCT), are applicable for investigating both the emulsifying performance of a CT involving two immiscible components (water and oil) and its hydrating effect(s) with respect to dexamethasone delivery, within various forms the specific CT can theoretically take upon release.

4.1 Droplet Size and Distribution

Droplet size is important in determining the solubilization capacity, absorption kinetics, and bioavailability of drugs incorporated in SMEDDS. Smaller droplet sizes lead to increased surface area for drug diffusion and interaction with gastrointestinal (GI) fluids, thereby promoting absorption. Dynamic light scattering (DLS) measurements were used to calculate the average droplet size, PDI, and stability of the microemulsion after dilution. DLS is a rapid and non-destructive technique for measuring particle dynamics at the nanoscale, with generally identified droplet sizes of 20–200 nm for optimized SMEDDS formulations [28].Additional imaging methods, such as transmission electron microscopy (TEM) or scanning electron microscopy (SEM), presented images corroborating the fat droplet shape and structural uniformity. TEM images frequently exhibit spherical, isolated, and uniformly dispersed nanodroplets, which are supported by DLS results [35]. Furthermore, the internal microstructure and interfacial curvature of SMEDDS were investigated via small-angle X-ray scattering (SAXS), providing information on phase transformations and the organization of the surfactant layer [36]. The joint use of these techniques allows us to obtain a complete description of droplet formation and stability at both the macroscopic and molecular scales.

4.2 In Vitro Lipolysis and Digestion Systems In vitro lipolysis studies imitate digestion dynamics that are specific to various types of LBF introduced into the GI tract. These in silico models are indispensable for predicting in vivo behavior and evaluating drug release and solubilization under lipid digestion conditions. In a common in vitro lipolysis setup, an SMEDDS is exposed to pancreatic lipase in the presence of a bile salt and phospholipid-containing buffer resembling the conditions of intestinal fluid [37].Lipid digestion and drug solubilization are determined by free fatty acid release, pH changes, and drug distribution between the aqueous and precipitated fractions. This method assists in understanding the likelihood of drug precipitation upon digestion and informs the optimization of formulations intended to achieve supersaturation. Finally, Verma and Mittal (2018) applied lipolysis models to investigate the influence of lipid digestion on in vitro drug dissolution and absorption, relating CD data with the pharmacokinetic behavior of valsartan-loaded SMEDDS [38].

4.3 Stability and Precipitation Studies

The stability of SMEDDS in vitro is a critical factor affecting shelf life and therapeutic efficacy. Instabilities, such as phase separation, precipitation of the drug, and oxidation, can affect product performance. Stability studies are typically performed under different storage conditions in accordance with ICH guidelines (40°C ± 2°C/75% RH ± 5%), and parameters such as droplet size, refractive index, drug content, and visual clarity are observed over time [39]. The dissolution of S-SMEDDS is important because the drug tends to precipitate in supersaturable SMEDDS (S-SMEDDS) after dilution. The utilization of polymers, such as HPMC or polyvinylpyrrolidone (PVP), can retard drug crystallization due to the sustained metastable supersaturated state when combined with drugs [40]. Besides, technologies such as DSC and PXRD are applied to analyze polymorphic conversion and amorphous state for drug in the formulation [41].

Extensive stability testing was performed to confirm that SMEDDS retained its emulsification ability, drug dropletization, and solubilization efficiency during the storage period.

4.4 Bioavailability Assessment

Ultimately, the success of SMEDDS formulations is believed to rest on their ability to increase the oral bioavailability of poorly soluble drugs. In vitro and in vivo techniques are used to measure this parameter. Peptic and disintegration tests in simulated gastric and intestinal fluids measure the rate and magnitude of drug dissolution. These in vitro investigations are usually related to in vivo pharmacokinetic data from animal or human studies, including values of Cmax, Tmax, and AUC, to describe the extent of absorption enhancement.

In another instance, fenofibrate-loaded SMEDDS resulted in > 7-fold increase in oral bioavailability with respect to the conventional tablets, owing to improved dissolution and lymphatic transport. Similarly, a

curcumin-loaded SMEDDS formulation had higher systemic exposure and greater therapeutic effect, ascertaining the potential of lipid-based systems in enhancing oral absorption [42].

As Johnson et al. have described [43], the subsequent integration of bioavailability analysis with droplet size characterization and lipolysis modeling offers a comprehensive picture of the formulation behavior, spanning physicochemical and in vivo phenomena, which in turn guides future optimization attempts on SMEDDS.

5. Emerging Trends in SMEDDS Research:SMEDDS are now better understood owing to recent developments in characterization methods. The size, shape, and stability of SMEDDS are frequently examined using methods, including Fourier transform infrared spectroscopy (FTIR), transmission electron microscopy (TEM), and dynamic light scattering (DLS).The use of self-microemulsifying drug delivery systems (SMEDDS) may increase the bioavailability of medications that are not highly soluble in water. SMEDDS enhance the solubility, dissolution rate, and absorption of medications by producing microemulsions when diluted in aqueous environments. Recent developments in SMEDDS research are examined in this review, with particular attention paid to new developments in targeted drug delivery, oral disintegration, combination therapies, nanotechnology integration, biodegradable and biocompatible components, personalized medicine, and sophisticated characterization methods. These advancements have a great deal of promise to increase medication delivery's effectiveness and safety, especially for poorly soluble compounds.[17] The bioavailability and therapeutic effectiveness of many chemicals are limited by their poor water solubility, which continues to be a significant obstacle in drug development. SMEDDS, or self-microemulsifying drug delivery systems, have become a viable approach to address this problem. When diluted in an aqueous medium, the components of the SMEDDS oil, surfactant, and cosurfactant spontaneously produce microemulsions. With droplet sizes usually between 10 and 100 nm, microemulsions are thermodynamically stable systems that can improve medication solubility and dissolution rate.[19]

5.1Emerging Trends:

5.1.1 Nanotechnology Integration

The combination of nanotechnology and SMEDDS has led to an increase in options for enhancing medication delivery. Nanoparticles can be added to SMEDDS to improve medication stability, targeting, and controlled release. For example, medications can be encapsulated in SMEDDS using polymeric nanoparticles, which prevent degradation and enable continuous release [44][45].

Nanotechnology, or the manipulation of matter at the atomic and molecular levels, has revolutionized several sectors. Its impact on the pharmaceutical industry has been particularly noteworthy. By developing materials and structures on the nanoscale, scientists and engineers have developed innovative drug delivery systems that provide significant advantages over traditional methods.

5.1.1.1 Applications of Nanotechnology in Pharmaceutics

- **Cancer therapy:** Nanoparticles can reduce harm to healthy organs by delivering chemotherapy medications directly to tumor cells.
- **Vaccine Delivery:** Nanotechnology-based vaccines can decrease the unpleasant effects and enhance immune responses.
- **Gene therapy:** Genes can be delivered to cells using nanoparticles to treat genetic disorders.
- **Drug Delivery to the Central Nervous System:** Nanoparticles can enhance the entry of drugs that can treat neurological disorders into the brain by crossing the blood-brain barrier.
- **Tissue Engineering**: Nanotechnology may be utilized to fabricate scaffolds for tissue regeneration and repair.

5.1.2 Biodegradable and Biocompatible Components

To increase safety and lower the possibility of negative consequences, biodegradable and biocompatible components are increasingly being used in SMEDDS formulations. Natural oils, surfactants, and cosurfactants derived from renewable resources can be used to improve biocompatibility and reduce toxicity. Biodegradable polymers can also be added to SMEDDS to provide safe and regulated medication release [46].

Biodegradable and biocompatible components have a wide range of applications, such as

- Medical Devices: These materials are utilized to manufacture medication delivery systems, implants, and sutures that the body can absorb safely.
- Packaging: Waste and pollution may be reduced by using biodegradable packaging materials. They consist of food containers, biodegradable bags, and electrical device packaging.
- Textiles: Clothing and other textiles may be produced using biodegradable materials derived from natural fibers, such as hemp, bamboo, and maize.

- Agriculture: Biodegradable mulch and plant containers can be made from biodegradable materials.
- Industrial Products: Biodegradable ingredients are used in coatings, adhesives, and cleaning solutions. Benefits of Using Biodegradable and Biocompatible Components
- Environmental Sustainability: Biodegradable and biocompatible components can help protect the environment by reducing waste and pollution.
- Human Health: These materials are generally safer for human health than traditional synthetic materials.
- Resource Conservation: Biodegradable materials can be derived from renewable resources, thereby reducing dependence on fossil fuels.

5.1.3 Targeted Drug Delivery

Targeted drug delivery seeks to improve therapeutic efficacy and minimize systemic adverse effects by delivering medications precisely to the site of action. SMEDDS can be altered by adding ligands or antibodies that identify certain receptors on target cells to enable tailored delivery. This method can improve the drug's absorption by the targeted organ or tissue.[7][8] [9]

5.1.4 Oral Disintegration

Rapidly disintegrating SMEDDS can decrease swallowing problems and increase patient compliance, especially in older and pediatric populations. SMEDDS can be made to dissolve rapidly in saliva by adding disintegrants or employing porous carriers, which will aid in the absorption of drugs.[5][7] When a chemical, usually a drug, dissolves or breaks down quickly in the mouth, it is referred to as oral disintegration. Special formulations that include hydrophilic excipients, such as substances that attract water and porous structures, are frequently used to achieve this.

What Makes Orally Disintegrating Drugs Useful-

- Convenience: Patients with swallowing problems or those who are always on the go can take these drugs more easily because they do not require water.
- Rapid absorption: The medication may enter the bloodstream more quickly because of its rapid disintegration, which could result in a quicker onset of action.
- Increased compliance: Orally disintegrating formulations may be more convenient and easier for patients with difficulty remembering to take their medications regularly.

Common Examples of Orally Disintegrating Medications

1. Sublingual nitroglycerin: This is used to treat acute angina (chest pain) and often comes in the form of a small tablet that is placed under the tongue.
2. Certain Antidepressants: Some antidepressants are available as orally disintegrating tablets for patients who find swallowing traditional pills difficult.
3. Cold and Flu Medications: Over-the-counter cold and flu remedies often come in orally disintegrating forms for quick relief.

5.1.5 Combination Therapies

By delivering several medications simultaneously, SMEDDS can streamline treatment plans and enhance therapeutic results. It is feasible to treat complicated disorders or produce synergistic effects by combining many medications into a single SMEDDS formulation. Generally, therapies that aid spinal cord healing either encourage tissue preservation (neuroprotection) or axon development (regeneration/plasticity). The former, proregenerative, therapies attempt to overcome the restricted ability of damaged central nervous system (CNS) neurons to proliferate or the inhibitory chemicals present in the damaged tissue [47]. For example, nanotechnology offers a new method for delivering combination medications with spatiotemporal drug release control. The latest developments in combination cancer therapies mediated by nanotechnology are examined in this study. For mechanism-based combination treatments, multifunctional nanomedicines are likely to deliver the appropriate medications at the appropriate time and location to achieve the best possible therapeutic outcomes with the least amount of morbidity. Currently, there is no authorized clinical nanomedicine that combines two or more medications in a single platform. This is because there are still several obstacles to overcome in the development of nanomedicines, such as determining the optimal drug ratios for these nanomedicines, controlling these drug ratios across several batches, producing these nanomedicines on a large scale in a reproducible manner, and determining the cost of these nanomedicines, among other issues. To ensure that nanomedicines meet their goals, these issues must be resolved quickly through a multidisciplinary strategy, including partnerships between academics, the pharmaceutical sector, and the relevant regulatory agencies, to achieve improved treatment results and a significant decrease in morbidity, which will enhance the quality of life of cancer patients [48].

5.1.6 Personalized Medicine

Personalized medicine aims to customize care for each patient according to their genetic composition, the features of their illness, and other variables. SMEDDS formulations may be tailored to each patient's unique needs by changing the formulation ingredients or by adding unique targeting moieties.

5.1.7 Advanced Characterization Techniques

Advanced characterization methods are necessary to comprehend SMEDDS performance and behavior. Drug release kinetics, droplet size distribution, and microemulsion production may all be studied using methods, including transmission electron microscopy (TEM), dynamic light scattering (DLS), and small-angle X-ray scattering (SAXS) [49].

6. Challenges and Future Perspectives

Although SMEDDS formulations offer several advantages, there are various challenges and future perspectives, some of which are discussed below:

6.1 Drug precipitation upon dilution

Drug precipitation occurs in gastrointestinal fluids upon dilution of SMEDDS. The ability to retain the solubilized condition of the drug throughout the gastrointestinal tract (GIT) is a typical criterion for lipid formulations. The benefit conferred by the lipid-based formulation strategy is nullified when the drug precipitates from the system [50].

6.2 Precipitation of drug in vivo:

Because hydrophilic solvents dilute the medication, the latter has a greater propensity to precipitate upon dilution. Polymers must be included to reduce drug precipitation in vivo. One adverse consequence of administering the SMEDDS formulation is in vivo drug precipitation. This is a process in which a drug solute precipitates in vivo after the drug formulation's ability to solubilize it diminishes. Sharp pH changes, formulation dilution with bodily fluids, or solubilizing excipient digestion in formulations can all cause drugs to precipitate in vivo [51].

6.3 Encapsulation in soft gelatin capsules:

The majority of SMEDDS formulations on the market are soft gelatin capsules. However, gelatin capsules have a few drawbacks. The few difficulties with animal gelatin are the production price, transmissible spongiform encephalopathy (TSE), and customer preference/religion [52].
Volatile co-solvents in self-microemulsifying formulations can migrate into the soft or hard gelatin capsule shells, causing lipophilic medicines to precipitate. Therefore, soft gelatin capsule alternatives are required in the market [53]. Currently, HPMC-prepared capsules are the preferred replacement for animal gelatin. An alternative approach for encapsulating supersaturable SMEDDS formulations has been investigated: HPMC capsule shells [54].

6.4 Storage and handling:

Liquid SMEDDS formulations have stability, handling, and storage issues. Therefore, developing robust SMEDDS formulations appears to be a sensible approach to address these issues [55].

6.5 Limited targeting of lymphatics

Targeting the lymphatics offers two key benefits compared to typical absorption through the portal blood. First, the concentration of oral drugs that enter the systemic circulation is enhanced because transport via intestinal lymph circumvents presystemic hepatic metabolism. Second, it may be feasible to administer medications to lymphatic organs at exact areas. Lymphatic transport frequently requires a high log P and high triglyceride solubility [56]. However, each treatment has a distinct quantity of drug transported into the lymphatics. Therefore, a better prediction model is needed, and the interaction between the drug's lipophilicity and triglyceride solubility and lymphatic transport must be extensively examined [57].

6.6 Lack of good in vitro models

The lack of robust in vitro models for assessing formulations is another impediment to the development of SMEDDS and other lipid-based formulations. Conventional dissolution procedures are unsuccessful because these formulations may rely on fat breakdown in the stomach before drug release. However, an in vitro model that replicates the digestive processes of the duodenum has been developed to recreate this. Before the strengths of this in vitro model can be judged, it needs to be further enhanced and verified. Different prototype lipid-based formulations must be generated and analyzed in vivo in a suitable animal model, as subsequent development may be reliant on in vitro–in vivo correlations [58].

6.7 Oxidation and polymorphism of the lipids used in formulating SEDDS/SMEDDS

Lipid oxidation is a major concern for lipid excipients comprising unsaturated fatty acids and their derivatives [59]. Lipid-soluble antioxidants must be incorporated into capsule formulations. To avoid polymorphic modifications in the excipient matrix, the polymorphism associated with thermo-softening lipid excipients requires specific process control in their application [60].

6.8 Scale-up challenges and strategies for maintaining product quality during scale-up

Scale-up of SMEDDS formulations presents several challenges that must be addressed to maintain product quality. Some common challenges and strategies to overcome them during scale-up are as follows:

6.8.1 Variability in Raw Materials

Challenge: Batch-to-batch variability in raw materials employed in small-scale formulations may affect the quality of the final product when it is scaled up. Strategy: It is critical to conduct in-depth characterization and qualification of raw materials, such as lipids, co-surfactants, and surfactants. To guarantee consistency in raw material performance, requirements can be established, and quality control tests can be carried out. Reliable raw material procurement may also be achieved through regular supplier audits and by preserving positive relationships with suppliers [61][62].

6.8.2 Mixing and Homogeneity

Challenge: Achieving uniform mixing and homogeneity becomes more difficult as the batch size increases during scale-up. Inadequate mixing can impact drug distribution and solubility, resulting in poor formulation consistency. Strategy: It is critical to use the appropriate equipment and mixing methods. Factors, including impeller type, vessel design, and mixing speed, should be considered. Optimization studies, including validation and scale-up experiments, should be conducted to ensure consistent mixing throughout larger-scale batches. Process analytical technology (PAT) and other in-line monitoring technologies can help evaluate mixing efficiency in real-time [63, 64].

6.8.3 Process Transfer and Validation

Challenge: Process variances and possible quality problems may arise when a manufacturing process is moved from a small-scale laboratory setting to a larger-scale production facility. Strategy: A clear process transfer strategy that includes thorough documentation and communication between the manufacturing and development teams is crucial. The identification and resolution of any issues can be aided by conducting process validation studies and scale-up experiments. Close cooperation between production engineers and process development scientists ensures a seamless transition and effective scale-up [65].

6.8.4 Equipment Compatibility and Performance

Challenge: Processing durations, heat transfer, and mixing efficiency may vary depending on the equipment utilized for scale-up compared to the laboratory-scale configuration. Strategy: It is essential to select equipment that is suitable for the scaling parameters and formulation requirements. Accurate measurements and performance are ensured by performing equipment qualification and calibration. Maintaining consistency during scale-up is facilitated by confirming the equipment's capabilities and setting suitable operating ranges [66].

6.8.5 Quality Control and Testing

Challenge: Maintaining consistent quality control and testing procedures may be difficult when scaling up SMEDDS formulations. Increasing batch sizes may require modification of analytical techniques and sampling protocols. Strategy: Create a thorough quality control plan that considers the specific needs of larger-scale manufacturing. Ensure that the correct sample strategies are used to accurately reflect the batch. Verify the accuracy, precision, and specificity of analytical techniques in a larger-scale context. To identify any patterns or deviations, periodically examine and monitor quality control data [67].

6.8.6 Regulatory Compliance:

Good Manufacturing Practices (GMP) and regulatory requirements must be followed when scaling up SMEDDS formulations. During scale-up, compliance with quality, safety, and documentation regulations becomes increasingly important. Planning: Create a thorough quality management system that covers all aspects of production, such as record-keeping, training, equipment maintenance, and documentation. To ensure that regulations are being followed, conduct routine audits and inspections. Throughout the scale-up process, enlist regulatory specialists to provide guidance and assistance [68][69]. In conclusion, rigorous planning, optimization, and attention to quality control procedures are necessary to overcome the challenges associated with scaling up SMEDDS formulations. Manufacturers can effectively scale up while guaranteeing consistent product quality and satisfying regulatory criteria by implementing the right plans, conducting validation studies, and upholding strict quality management procedures [70].

6.9 Manufacturing Considerations

When considering the large-scale manufacturing of SMEDDS (self-microemulsifying drug delivery systems), several factors must be considered regarding equipment selection and qualification. The following is a brief overview:

Selection of appropriate equipment is crucial for the efficient and consistent manufacturing of SMEDDS.

Mixing Equipment: Selecting the appropriate mixing apparatus that can effectively and consistently combine the medication, oil, surfactant, and co-surfactant ingredients to create the microemulsion. High-speed mixers and homogenizers are examples of high-shear mixers that are often employed. Filtering Equipment: Utilizing filtering equipment throughout the production procedures to eliminate any aggregates or particle matter from the formulation [71][72].

Equipment for Filling and Packaging: Choosing devices, such as automated filling machines or encapsulating systems, that enable precise SMEDDS filling and packaging.

Equipment Qualification: To guarantee consistent product quality, it is crucial to ensure that the equipment utilized in the large-scale production of SMEDDS is suitably certified. The following procedures are usually included in equipment qualification:

- Installation Qualification (IQ): Confirming that the equipment is installed correctly and complies with the necessary standards and specifications is known as installation qualification or IQ.
- Operational Qualification (OQ): Verifying that the machinery performs consistently within predetermined operating limits and ranges.
- Performance Qualification (PQ): Demonstrating that the apparatus reliably generates SMEDDS formulations with the required quality, thereby satisfying the pre-established acceptance standards [66].

6.9.2 Process Validation

To guarantee the repeatability and reliability of SMEDDS formulations on a broad scale, manufacturing process validation is essential. The following steps are commonly included in process validation.

Process design is the process of creating a reliable, efficient production method that satisfies legal and quality standards. Process qualification: Conducting process validation studies to demonstrate that SMEDDS formulations that satisfy predefined parameters are consistently produced by the manufacturing process.

Establishing a monitoring and control system to guarantee the continuous performance and reliability of the manufacturing process is known as "continued process verification" [73–75].

6.9.3 Good Manufacturing Practices (GMP)

To guarantee product quality, safety, and regulatory compliance, GMP criteria must be followed at every stage of the production process. GMP regulations cover a wide range of topics, such as personnel training, paperwork, equipment maintenance, facility design, and quality control methods. To ensure that equipment selection and qualification meet particular needs and regulatory standards, it is advisable to consult with specialists in pharmaceutical production, process engineering, and regulatory compliance when planning to manufacture SMEDDS on a large scale [76].

6.10 Scale-up challenges

Scale-up of self-microemulsifying drug delivery systems (SMEDDS) from the laboratory to commercial manufacturing presents several challenges. The key challenges associated with scale-up are explored herein.

6.10.1 Impact on Physical Properties and Stability

Changes in equipment and process factors during scale-up may affect the stability and physical characteristics of SMEDDS. Among the difficulties are:

Phase Separation: When SMEDDS are scaled up, larger batch sizes or modifications in mixing dynamics may make them more susceptible to phase separation. To preserve the intended microemulsion structure and avoid phase separation, the mixing conditions and equipment must be optimized [76].

Droplet Size Distribution: As batch sizes increase, it becomes more difficult to maintain a constant droplet size distribution. Preserving medication solubility and bioavailability during the scale-up process requires retaining the intended particle size range. Drug Loading and Homogeneity: The efficiency and homogeneity of drug loading may be affected by larger batch sizes. To guarantee consistent medication distribution throughout the formulation, proper mixing and formulation parameter optimization are required. SMEDDS formulation.

Stability: Scale-up can introduce challenges related to the physical and chemical stability of SMEDDS. Changes in the manufacturing equipment, handling procedures, or storage conditions may affect the stability characteristics. Thorough stability testing is essential to assess and address stability issues during scale-up [77].

6.10.2 Uniformity in Larger Batch Sizes

Maintaining batch-to-batch uniformity becomes increasingly challenging with larger-scale production. Challenges include:

Mixing Efficiency: Ensuring efficient mixing at a larger scale can be demanding, especially for viscous formulations. Proper equipment selection, process optimization, and validation are necessary to achieve consistent mixing and uniformity.

Blending of Components: Achieving uniform blending of the oil, surfactant, co-surfactant, and drug components is critical with larger batch sizes. Proper equipment design, process parameters, and blending techniques should be employed to ensure uniformity.

Sampling and Analysis: Scaling up often requires adjusting sampling protocols to adequately represent the entire batch. Proper sampling techniques, representative sample collection, and robust analytical methods are vital for accurately assessing uniformity [78][79].

6.10.3 Cost Considerations and Optimization Strategies

Cost-effective production is a key factor when scaling up. Among the difficulties and optimisation techniques are:

Raw Materials: Purchasing more raw materials may be necessary to scale up the manufacturing of SMEDDS, which might affect availability and cost. One strategy is to optimize the formulation such that fewer costly or rare ingredients are used without sacrificing effectiveness.

Process efficiency: Cost optimization depends on streamlining production processes to increase productivity and reduce waste. Automation, process control systems, and continuous improvement initiatives can all help to increase productivity and lower production costs [80].

Equipment and facility: It is crucial to choose the right equipment and construct a facility that strikes a balance between cost, output, and regulatory compliance. Lowering capital and operating costs can be achieved by maximizing equipment utilization and identifying cost-effective alternatives [81].

Regulatory Compliance: It is critical to ensure that quality standards and regulatory guidelines are followed throughout scale-up. Costly delays and rework may be avoided by interacting with regulatory bodies early on and adhering to the rules.

A thorough understanding of formulation science, process engineering, and regulatory concerns is necessary to address scale-up issues for SMEDDS. To effectively manage the scale-up process while preserving product quality, stability, and cost-effectiveness, cooperation between formulation scientists, process engineers, quality specialists, and regulatory professionals is essential [82].

7. Conclusion:

Recent advancements in self-microemulsating drug delivery systems (SMEDDS) have significantly altered the landscape of formulation research, particularly for poorly soluble medications. As these systems create microemulsions that boost bioavailability using lipids, surfactants, and cosurfactants, they represent a significant field of pharmaceutical study. One of the most noticeable changes is the shift toward natural excipients. Biocompatible and biodegradable surfactants derived from natural sources, such as fatty acids and lecithin, are increasingly utilized. This enhances the safety profile of SMEDDS and satisfies the growing need for patient-friendly, ecologically friendly formulations. Furthermore, adding solid lipid nanoparticles (SLNs) to SMEDDS offers a unique approach to controlling drug release patterns and enhancing stability.The development process has changed as a result of the application of design of experiments (DoE) in formulation optimization. Scientists can establish optimal conditions with little trial-and-error and save time and money by carefully analyzing the impacts of several formulation components. Furthermore, the use of nanotechnology, such as nanoemulsions and nanosuspensions, helps increase the rates of solubilization and absorption, especially for hydrophobic compounds.

Our knowledge of SMEDDS performance has also grown as a result of improvements in assessment methods. More accurate bioavailability forecasts are made possible by methods such as dynamic light scattering (DLS) and in vitro digestion models, which offer crucial insights into how these systems function in the gastrointestinal tract. Customizing SMEDDS formulations according to specific patient characteristics presents intriguing opportunities as the concept of customized medicine gains traction. Optimizing treatment benefits and improving patient compliance can be achieved by customizing formulations to certain genetic, age-related, or illness-state characteristics.

Recent research has focused on increasing the shelf life of SMEDDS by adding chelating agents and antioxidants along with optimal storage settings because stability is still a significant problem. This focus on stability guarantees the ongoing efficacy of the compositions.

Regulatory agencies are also revising their standards to address the unique issues raised by SMEDDS,

highlighting the importance of comprehensive safety and efficacy investigations. In conclusion, SMEDDS have the potential to significantly enhance drug delivery systems, as seen by their ongoing development through novel excipients, formulation strategies, and improved assessment procedures. With prospective uses across a wide range of administration methods, SMEDDS are poised to play a crucial role in boosting the bioavailability of challenging pharmaceuticals as research progresses.

Author Contributions

Dr. Satya Praksh Singh defined the scope of the review, offered critical revisions, oversaw the project, and guaranteed the study's academic rigor. Manglam Shekhar Rai. Manglam Shekhar Rai carried out the thorough literature search, synthesized the data on innovative SMEDDS formulation strategies, and wrote the first draft of the manuscript. All authors have reviewed and approved the published version of the work.

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Data are contained within the article.

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Conflicts of Interest

The authors declare no conflicts of interest.

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