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LIPID-BASED INNOVATION IN ORAL DRUG DELIVERY: A COMPREHENSIVE REVIEW ON SMEDDS

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ABSTRACT

Self-Microemulsifying drug delivery systems (SMEDDS) represent an advanced strategy to enhance the oral bioavailability of drugs with poor water solubility. These systems consist of isotropic blends of oils, surfactants, and co-surfactants that form fine oil-in-water microemulsions upon dilution in gastrointestinal fluids, leading to improved solubilization and absorption of lipophilic drugs. This review outlines the key formulation components, mechanisms underlying self-emulsification, and various evaluation parameters used to characterize SMEDDS. It further examines recent innovations, common formulation challenges, and strategies to enhance stability and large-scale production. In addition, regulatory aspects and therapeutic applications of SMEDDS are discussed to underscore their growing relevance in pharmaceutical development. This article aims to offer a detailed understanding of SMEDDS as a practical solution for overcoming solubility-related barriers in oral drug delivery.

Keywords: - SMEDDS, Oral bioavailability, Drug solubilization, Lipid-based delivery, Microemulsion.

1. INTRODUCTION

Oral Drug Delivery and Challenges

Among the various routes for drug administration, the oral pathway is widely favored due to its simplicity, patient convenience, cost-effectiveness, and non-invasive nature. Despite these advantages, a significant hurdle in oral drug delivery is the limited water solubility of many active pharmaceutical ingredients (APIs), particularly those falling under Class II and Class IV of the Biopharmaceutical Classification System (BCS). Class II compounds are characterized by low solubility and high permeability, whereas Class IV drugs exhibit both poor solubility and limited permeability. This solubility challenge often results in poor drug dissolution, unpredictable absorption, and reduced bioavailability. It is estimated that approximately 40% of commercially available drugs and nearly 90% of new drug candidates face solubility-related issues. [1]

Strategies to Improve Solubility

Improving the bioavailability of drugs with poor aqueous solubility remains a critical area of pharmaceutical development. Several techniques have been explored, such as particle size reduction (e.g., micronization, nanonization), formation of solid dispersions, cyclodextrin inclusion complexes, lipid-based carriers, and use of supersaturation techniques. Among these, lipid-based delivery systems—especially Self-Microemulsifying Drug Delivery Systems (SMEDDS)—have demonstrated significant promise in enhancing the solubility and absorption of hydrophobic compounds. [1]

Understanding SMEDDS

SMEDDS are isotropic blends of oils, surfactants, and co-surfactants (or co-solvents). Upon contact with gastrointestinal fluids and under gentle agitation (such as that provided by peristalsis), these systems spontaneously form fine oil-in-water microemulsions. The resulting droplets typically range from 100 to 250 nanometers in diameter, though even smaller sizes (20–100 nm) are achievable. Unlike traditional emulsions that require mechanical energy for formation, SMEDDS self-emulsify and remain thermodynamically stable over time.

The main advantage of SMEDDS lies in their ability to deliver drugs in a solubilized state, thereby bypassing the dissolution step—a common barrier for poorly water-soluble drugs. In the gastrointestinal environment, where such drugs are prone to precipitation, SMEDDS help maintain solubility and enhance absorption. The nano-sized droplets also provide a large surface area, facilitating improved drug transport across the intestinal lining. [2]

Mechanisms Enhancing Bioavailability

SMEDDS enhance oral drug absorption through several mechanisms:

- Improved solubilization: The formulation keeps the drug in a dissolved state throughout its journey in the gastrointestinal tract, eliminating the dissolution bottleneck.
- Increased surface area: The fine droplets generated offer a larger surface for absorption, boosting uptake.
- Lymphatic transport: Lipophilic drugs delivered via SMEDDS can enter systemic circulation through the lymphatic system, avoiding first-pass hepatic metabolism.

- Enhanced membrane permeability and efflux inhibition: Surfactants present in SMEDDS may improve membrane transport and inhibit efflux proteins like P-glycoprotein, increasing drug absorption.
- Protection from enzymatic degradation: The encapsulation in microemulsions can shield drugs from degradation by gastrointestinal enzymes.

These multifaceted benefits make SMEDDS a compelling choice for enhancing the bioavailability of drugs that struggle with solubility and metabolic limitations.

Key Considerations in Formulation

Creating an effective SMEDDS involves precise selection and optimization of its components:

- Oil phase: Oils act as solubilizing agents and promote lymphatic transport. Common choices include medium-chain triglycerides (MCTs), long-chain triglycerides (LCTs), and natural oils like olive or castor oil.
- Surfactants: These agents' lower interfacial tension and assist in forming emulsions. Non-ionic surfactants such as Tween 80, Cremophor RH40, and sorbitan esters are often used for their compatibility and safety profile.
- Co-surfactants or co-solvents: These helps stabilize the emulsion by enhancing interfacial flexibility. Typical examples include polyethylene glycol (PEG), ethanol, and propylene glycol.

To ensure effective emulsification, phase diagrams are often employed to determine the optimal ratios of oil, surfactant, and co-surfactant. Critical parameters like droplet size, drug loading capacity, zeta potential, and overall formulation stability must also be carefully evaluated during development. [2]

Formulation Strategies for SMEDDS

The effectiveness of SMEDDS lies in its capability to spontaneously form fine oil-in-water microemulsions when diluted with gastrointestinal fluids. This self-emulsification behavior is highly dependent on selecting and optimizing the right combination of formulation ingredients and their respective proportions. The primary formulation objective is to choose excipients that enhance drug solubility, facilitate efficient emulsification, improve bioavailability, and maintain both formulation stability and patient safety. [3]

Component Selection

a. Oil Phase

The oil serves as a solvent for lipophilic drugs and can aid in their absorption through the lymphatic system. Oils used in SMEDDS are generally classified as:

- Long-chain triglycerides (LCTs) (e.g., soybean oil, castor oil): Ideal for sustained drug release due to slower digestion.
- Medium-chain triglycerides (MCTs) (e.g., Captex 355, Labrafac™): Preferred for quicker emulsification and faster drug release.
- Synthetic/Modified oils (e.g., Capmul MCM): Offer improved solubility and emulsification characteristics.
- Selection Criteria: High drug solubilization capacity, compatibility with other excipients, and strong emulsifying properties. [3]

b. Surfactants

Surfactants lower the interfacial tension between oil and water, aiding the formation of microemulsions.

- Commonly used non-ionic surfactants include Tween 80, Cremophor RH40, Labrasol, and Polysorbate 20 due to their high emulsifying ability and low toxicity.
- Surfactants with HLB values above 12 are generally ideal for forming oil-in-water systems.
- Selection Criteria: Low irritancy, regulatory approval, high emulsification efficiency, and strong solubilization of the drug. [3]

c. Co-surfactants / Co-solvents

These helps further reduce interfacial tension and enhance the interfacial film's fluidity, promoting the creation of finer emulsions.

- Examples include Transcutol P, PEG 400, propylene glycol, and ethanol.
- Co-solvents can also support solubilization of the active drug and surfactant.
- Selection Criteria: Should be non-volatile, safe, and compatible with other formulation components. [3]

Solubility and Screening Studies

Before developing the formulation, solubility testing is conducted to identify which oils, surfactants, and co-surfactants dissolve the drug most effectively.

- An excess amount of the drug is mixed with each component and agitated for 48–72 hours.
- The mixtures are then centrifuged, filtered, and analyzed using methods like UV spectrophotometry or HPLC.
- Components showing maximum solubility are shortlisted for formulation development.
- This ensures the drug remains in solution during gastrointestinal transit and minimizes the risk of precipitation. [3]

Pseudo-ternary Phase Diagram Construction

To identify optimal self-emulsifying regions, pseudo-ternary phase diagrams are created using the water titration method.

- Various ratios of oil, surfactant, and co-surfactant (S_mix) are prepared.
- Water is added gradually, and observations are made regarding clarity or turbidity.
- Transparent, single-phase mixtures denote the microemulsion region.

These diagrams are valuable tools for pinpointing the most effective component ratios for spontaneous emulsification. [4]

SMEDDS Preparation

Once suitable components and their ratios are finalized:

- The drug is dissolved in either the oil or surfactant phase.
- The surfactant and co-surfactant are then added and mixed thoroughly (e.g., using vortexing).
- The final formulation is stored in airtight containers to protect against moisture and volatility losses.

Evaluation parameters include emulsification time, droplet size, zeta potential, and drug content. [4]

Formulation Optimization through Experimental Design

Advanced statistical tools like the Taguchi method, Box-Behnken design, or Central Composite Design (CCD) are employed to optimize the formulation. These methods help:

- Assess how various factors influence critical quality attributes (CQAs) such as droplet size, emulsification time, and drug release.
- Reduce the number of experimental trials needed.
- Ensure the formulation is both robust and reproducible.

The Taguchi approach, in particular, is favoured in SMEDDS development for its simplicity and ability to handle multiple variables efficiently. [4]

Evaluation Parameters for SMEDDS

Visual Assessment and Emulsification Time

Objective: To evaluate how easily and quickly the formulation disperses in an aqueous environment. Procedure:

- A small volume (typically 0.1–1 mL) of the SMEDDS is introduced into 100–300 mL of either distilled water or simulated gastric fluid maintained at 37°C, under mild stirring.
- The time required for the system to form a clear or uniform emulsion is noted. Analysis:
- A transparent emulsion formed in less than 1 minute suggests efficient self-emulsification.
- Cloudiness or phase separation indicates inadequate emulsifying capacity. [5, 6]

Droplet Size and Polydispersity Index (PDI)

Objective: To assess the droplet dimensions and size distribution uniformity, both of which influence absorption.

Procedure:

- Droplet size is measured post-dilution using techniques like Dynamic Light Scattering (DLS) or Photon Correlation Spectroscopy (PCS).
- PDI evaluates how evenly sized the droplets are.

Optimal Values:

- Mean droplet size should be below 100 nm for microemulsion formation.
- PDI values under 0.3 reflect a consistent droplet size distribution. [5, 6]

Zeta Potential Measurement

Objective: To determine the surface charge on droplets, which affects their physical stability. Procedure:

- Measured using instruments like a Zetasizer.

  Interpretation:

- Zeta potential values greater than ±30 mV suggest good electrostatic stabilization and reduced aggregation risk. [5, 6]

Thermodynamic Stability Testing

Objective: To ensure formulation stability under various environmental stress conditions. Stability Tests Include:

- Centrifugation: 3000–5000 rpm for 30 minutes to check for separation.
- Temperature Cycling: Alternating between 4°C and 45°C for 48 hours across 3 cycles.
- Freeze–Thaw Cycling: Alternating between −20°C and 25°C for 48 hours over 3 cycles. Interpretation:
- Formulations showing no separation, precipitation, or turbidity are deemed stable. [5, 6]

Dilution Robustness

Objective: To test the ability of the formulation to remain stable upon dilution in GI fluids. Procedure:

- Dilute the SMEDDS to different extents (e.g., 1:50, 1:100, 1:1000) in water, simulated gastric fluid (SGF), and simulated intestinal fluid (SIF).
- Monitor physical appearance over 24–48 hours.
  Interpretation:
- A robust formulation remains clear and stable without precipitation or separation. [5, 6]

In Vitro Drug Release / Dissolution Testing

Objective: To examine drug release profiles in conditions that mimic the gastrointestinal tract. Procedure:

- Carried out using USP apparatus (paddle or dialysis bag method).
- Media used includes pH 1.2 SGF, pH 6.8 SIF, or phosphate buffer.
- Samples are collected at set intervals and analysed using UV or HPLC. Interpretation:
- SMEDDS are expected to show faster and more complete drug release compared to non-formulated drug. [5, 6]

Electron Microscopy (TEM/SEM)

Objective: To observe the droplet morphology and surface characteristics.

Procedure:

- A sample of diluted formulation is applied on a carbon-coated grid for imaging under TEM or SEM. Observations:
- Presence of spherical, smooth, and uniform droplets confirms microemulsion formation. [5, 6]

Cloud Point Determination

Objective: To test the thermal stability of SMEDDS containing non-ionic surfactants.

Procedure:

- Gradually heat the formulation and note the temperature where it becomes turbid or separates—this is the cloud point.
- Interpretation:
- A cloud point above body temperature (>37°C) indicates that the formulation is likely to remain stable in vivo. [5, 6]

Ex Vivo and In Vivo Absorption Studies

Objective: To verify the improvement in drug absorption and bioavailability. Procedure:

- Ex vivo: Techniques like everted gut sac or isolated intestinal sacs from animals.

- In vivo: Pharmacokinetic testing in animals to measure parameters such as Cmax (peak plasma concentration), Tmax (time to reach Cmax), and AUC (area under the curve). Interpretation:
- SMEDDS should exhibit improved absorption metrics due to better solubilization and potential lymphatic uptake. [5, 6]

Marketed Products Utilizing SMEDDS Technology

The development and success of Self-Microemulsifying Drug Delivery Systems (SMEDDS) in enhancing the solubility and bioavailability of poorly water-soluble drugs have led to the commercialization of several pharmaceutical products. These formulations effectively address the biopharmaceutical limitations of lipophilic drugs, particularly those in Biopharmaceutics Classification System (BCS) Classes II and IV. [7]

1. Sandimmune® (Cyclosporine A)

- Company: Novartis (formerly Sandoz)
- Formulation: Soft gelatin capsules and oral solution
- Indication: Immunosuppressive agent used post-organ transplantation
- Overview:
  Sandimmune® was the first approved product employing SMEDDS technology. Cyclosporine A, being highly lipophilic with erratic absorption, benefited significantly from the self-emulsifying formulation, leading to more reliable absorption through the gastrointestinal tract.
- Bioavailability: Approximately 30%, higher than conventional oral forms
- Approval Year: 1994 (FDA, USA) [7]

2. Neoral® (Cyclosporine A)

- Company: Novartis
- Formulation: Capsules and oral solution
- Indication: Used for organ transplant patients and autoimmune disorders
- Overview:
  Neoral® is a reformulated version of Sandimmune®, employing a microemulsion preconcentrate for superior absorption and reduced variability between patients.

Benefits:

- Enhanced bioavailability (around 60–70%)
- Reduced patient-to-patient variability
- Improved therapeutic control

Clinical Significance: Recognized as a standard in transplant immunosuppression. [7]

3. Fortovase® (Saquinavir)

- Company: Roche
- Formulation: Soft gelatin capsule
- Indication: HIV-1 antiretroviral therapy
- Overview:
  A SMEDDS-based version of saquinavir that improved upon the earlier Invirase® formulation. Despite its eventual withdrawal due to side effects, Fortovase® underscored the potential of SMEDDS in HIV treatment. [7]

4. Norvir® (Ritonavir)

- Company: AbbVie
- Formulation: Soft gelatin capsules and oral solution
- Indication: HIV protease inhibitor
- Overview:
  Ritonavir's poor water solubility was effectively managed using a SMEDDS formulation, enhancing its oral bioavailability and allowing flexible dosing.

Key Features:

- Enhances absorption
- Acts as a pharmacokinetic enhancer when combined with other HIV medications. [7]

5. Lipirex® (Fenofibrate)
   - Company: Gattefossé, France
   - Formulation: Capsule
   - Indication: Treatment of high lipid levels in blood
   - Overview:
     This SMEDDS-based fenofibrate formulation improves solubility, ensures more predictable plasma levels, and allows for dose reduction without loss of efficacy. [7]

6. Avodart® (Dutasteride)
   - Company: GlaxoSmithKline
   - Formulation: Soft gelatin capsule
   - Indication: Management of benign prostatic hyperplasia (BPH)
   - Overview:
     Dutasteride's limited water solubility is mitigated through SMEDDS, resulting in consistent and efficient drug absorption and improved therapeutic outcomes. [7]

7. Targretin® (Bexarotene)
   - Company: Eisai Inc.
   - Formulation: Capsule
   - Indication: Treatment for cutaneous T-cell lymphoma
   - Overview:
     A lipid-based SMEDDS formulation enhances the oral delivery of bexarotene, a drug with inherently poor aqueous solubility, ensuring effective systemic exposure. [7]

8. Kaletra® (Lopinavir/Ritonavir)
   - Company: AbbVie
   - Formulation: Oral solution and tablets
   - Indication: HIV antiretroviral therapy
   - Overview:
     This combination therapy incorporates a SMEDDS-based liquid formulation particularly suitable for paediatric patients and individuals with difficulty swallowing.

- Benefit:
  Enhanced stability and bioavailability of both active components [7]

Summary Table of Marketed SMEDDS Products

Product Name	Drug	Company	Therapeutic Use	Formulation Type
Sandimmune®	Cyclosporine A	Novartis	Immunosuppressant	Oral SMEDDS
Neoral®	Cyclosporine A	Novartis	Immunosuppressant	Microemulsion-based
Fortovase®	Saquinavir	Roche	HIV treatment	Soft gel capsule
Norvir®	Ritonavir	AbbVie	HIV treatment	Oral SMEDDS
Lipirex®	Fenofibrate	Gattefossé	Lipid control	Oral capsule
Avodart®	Dutasteride	GSK	BPH	Oral SMEDDS
Targretin®	Bexarotene	Eisai	Oncology	Soft capsule
Kaletra®	Lopinavir + Ritonavir	AbbVie	HIV treatment	Oral solution

Applications of SMEDDS

Self-Micro emulsifying Drug Delivery Systems (SMEDDS) are primarily employed to enhance the oral bioavailability of drugs with poor water solubility, particularly those categorized under BCS Class II and IV. However, their application extends beyond this primary role into several therapeutic and pharmaceutical areas: [8, 9]

Improved Oral Bioavailability

SMEDDS enhance the dissolution and intestinal absorption of lipophilic drugs by spontaneously forming oil-in-water microemulsions when exposed to gastrointestinal (GI) fluids.

- Example: Cyclosporine A formulations like Sandimmune® and Neoral® demonstrate improved bioavailability and reduced pharmacokinetic variability.
- Mechanisms: These include improved drug solubilization, inhibition of P-glycoprotein (P-gp)-mediated efflux, and potential lymphatic transport that helps bypass first-pass hepatic metabolism. [8, 9]

Lymphatic Absorption

Drugs with high lipophilicity may be absorbed via the lymphatic system, thereby avoiding the first-pass effect in the liver.

- Key Drugs: Testosterone, cyclosporine, and specific anticancer agents.
- Mechanism: Inclusion of long-chain triglycerides in SMEDDS promotes chylomicron production, facilitating lymphatic uptake. [8, 9]

Controlled and Targeted Delivery

SMEDDS can be adapted for modified drug release or site-specific delivery, particularly when used alongside polymers or in hybrid delivery platforms such as tablets, capsules, or nanoparticles.

- Example: SMEDDS formulations tailored for targeted delivery to lymphatic tissue or inflamed sections of the gastrointestinal tract. [8, 9]

Suitability for Special Populations

Liquid and semi-solid SMEDDS formats (e.g., emulsions or dispersions) are ideal for pediatric, geriatric, or dysphagic patients due to their ease of administration and flexible dosing. [8, 9]

Delivery of Nutraceuticals and Herbal Compounds

Many bioactive plant extracts and nutraceuticals suffer from limited absorption when taken orally. SMEDDS enhance their therapeutic potential by increasing bioavailability.

- Example: Improved delivery systems for curcumin, Pongamia pinnata extract, and guggul lipids. [8, 9]

Use in Antiviral and Anticancer Therapies

SMEDDS are particularly useful in delivering poorly water-soluble antiretroviral and anticancer agents like paclitaxel, docetaxel, ritonavir, and saquinavir. These systems improve systemic drug levels and reduce associated toxicities. [8, 9]

Challenges and Limitations of SMEDDS

Despite their advantages, SMEDDS face a variety of formulation, physiological, and regulatory challenges:

Risk of Drug Precipitation

Upon dilution in the gastrointestinal tract, changes in pH or surfactant concentration may lead to drug precipitation.

- Solution: Adding polymers like HPMC or PVP can help maintain supersaturation and prevent precipitation. [10, 11]

Limited Drug Solubilization

Only highly lipophilic drugs can be effectively loaded into SMEDDS due to their solubility requirements in the lipid and surfactant phases.

- Challenge: Moderately lipophilic or hydrophilic compounds may not be suitable for this system. [10, 11]

Surfactant-Related Toxicity

High concentrations of surfactants (e.g., Tween 80, Cremophor RH40) can lead to gastrointestinal irritation or allergic reactions.

- Solution: Use of milder, pharmaceutically acceptable excipients like PEG 400, Labrasol, or Vitamin E TPGS. [10, 11]

Stability Issues

SMEDDS formulations may suffer from chemical degradation (e.g., oxidation of oils) or physical instability (e.g., phase separation).

- Solution: Incorporation of antioxidants like BHT, careful excipient selection, and protective packaging can help. [10, 11]

Capsule Compatibility

Some lipid-based excipients may negatively interact with gelatin or HPMC capsule shells, affecting disintegration or drug release.

- Solution: Choosing compatible excipients or applying protective enteric coatings. [10, 11]

Lack of Predictive Testing Models

Standard in vitro models often fail to accurately predict the in vivo performance of SMEDDS.

- Need: Development of biorelevant dissolution methods and computational tools to establish a reliable in vitro/in vivo correlation (IVIVC). [10, 11]

Regulatory and Manufacturing Constraints

Guidelines specific to lipid-based formulations like SMEDDS are less established than for traditional dosage forms, complicating regulatory approval and manufacturing scale-up.

- Scale-Up Issues: Consistency in droplet size and emulsification during commercial production must be maintained. [10, 11]

Recent Strategies to Address SMEDDS Limitations

- Super saturable SMEDDS (S-SMEDDS): These include precipitation inhibitors to maintain drug solubility after dilution.
- Solid SMEDDS: By adsorbing liquid SMEDDS onto solid carriers (e.g., Aerosil, Neusilin), the system can be converted into powders or pellets.
- Nano-SMEDDS: Droplet sizes below 100 nm enhance absorption and reduce variability, especially useful for lymphatic targeting. [12, 13]

Recent Innovations in SMEDDS Technology

Substantial progress has been made in the field of Self-Microemulsifying Drug Delivery Systems (SMEDDS), extending their application well beyond conventional formulations. Modern SMEDDS are being strategically developed to resolve solubility issues, enable targeted delivery, boost patient adherence, and enhance formulation stability. These advancements are transforming the landscape of drug delivery systems. [12, 13]

Solid SMEDDS (S-SMEDDS)

A notable development is the transformation of liquid SMEDDS into solid forms, improving stability, handling, and patient compliance.

Techniques Used:

- Adsorption on porous carriers (e.g., Aerosil®, Neusilin®)
- Spray drying and freeze drying
- Melt granulation and hot-melt extrusion

Advantages:

- Prevents leakage from soft capsules
- Allows conversion into tablets, pellets, or capsules
- Offers improved shelf-life
- Example: A solid SMEDDS formulation of curcumin using Aerosil showed superior dissolution properties and physical stability. [12, 13]

Super saturable SMEDDS

These systems aim to produce and maintain a supersaturated state of the drug in gastrointestinal fluids, minimizing the risk of drug precipitation.

- Formulation Aids: Polymers like HPMC, PVP, and Soluplus are included to stabilize supersaturation.
- Benefit: Enhanced oral absorption with reduced surfactant concentration.
- Example: Itraconazole super saturable SMEDDS demonstrated improved bioavailability with a lower surfactant load. [12, 13]

Nano-SMEDDS

Nano-sized SMEDDS (typically <100 nm) are designed to increase drug absorption, intracellular uptake, and systemic bioavailability.

Applications:

- Promotes lymphatic drug transport
- Enhances anticancer delivery through the enhanced permeability and retention (EPR) effect

Example: Paclitaxel nano-SMEDDS exhibited significantly higher oral bioavailability than the standard Taxol® formulation. [12, 13]

Targeted Delivery with SMEDDS

Customized SMEDDS systems are being developed for site-specific drug delivery by incorporating targeting ligands, pH-responsive agents, or enzyme-sensitive polymers.

Innovations Include:

- Liver-targeting via folate or galactose ligands
- pH-triggered release for gastrointestinal targeting
- PEGylated formulations for improved mucus penetration

Example: Folate-linked SMEDDS enabled targeted delivery of doxorubicin in breast cancer therapy. [12, 13]

SMEDDS for Herbal Actives and Nutraceuticals

Poor bioavailability of herbal compounds such as curcumin, silymarin, and resveratrol due to limited solubility and rapid metabolism can be overcome using SMEDDS.

- Impact: Improved absorption and clinical efficacy, confirmed through preclinical and clinical data.
- Example: Curcumin SMEDDS demonstrated enhanced anti-inflammatory and antioxidant effects. [12, 13]

SMEDDS for Biologics and Macromolecules

Recent research has focused on formulating SMEDDS suitable for macromolecular drugs like peptides, proteins, and vaccines.

Strategies Employed:

- Incorporating absorption enhancers
- Utilizing enzyme inhibitors
- Applying protective mucosal strategies
- Ongoing Challenge: Ensuring biological stability within lipid-based carriers remains a key research area. [12, 13]

Incorporating QbD and AI in SMEDDS Development

- Quality by Design (QbD): Utilization of tools such as Design of Experiments (DoE), risk assessment, and control strategies is streamlining SMEDDS optimization.
- Popular designs include Taguchi, Box-Behnken, and Central Composite Design.
- Artificial Intelligence (AI): Machine learning algorithms are being tested to predict optimal formulations using large datasets, enhancing formulation efficiency and prediction accuracy. [12, 13]

Regulatory and Clinical Perspectives

As lipid-based delivery systems gain prominence, regulatory authorities are providing clearer guidance on formulation standards, excipient safety, and in vitro-in vivo correlation (IVIVC).

- Current Trends: SMEDDS are increasingly considered for generic product development and under 505(b)(2) NDA pathways for drugs with poor solubility. [12, 13]

2. CONCLUSION

Self-Micro emulsifying Drug Delivery Systems (SMEDDS) are a revolutionary approach in pharmaceutical sciences that address the widespread problem of many therapeutic medicines' low oral bioavailability and poor water solubility. SMEDDS greatly improve the dissolving, absorption, and eventually the systemic availability of lipophilic medications by spontaneously producing fine oil-in-water microemulsions under gastrointestinal circumstances. The creation, optimization, and characterisation of SMEDDS have advanced significantly over the last 20 years as a result of intensive study, and several formulation strategies, including solid-SMEDDS, super saturable SMEDDS, and targeted delivery platforms, have been developed. These developments have broadened the use of SMEDDS from straightforward solubility enhancers to complex drug delivery systems that can transport biologics, peptides, and herbal active ingredients.

SMEDDS have many benefits, but they also come with formulation and regulatory issues, such as choosing safe and suitable excipients, predicting in vivo performance, and scaling up. But these obstacles are being addressed

by the combination of artificial intelligence, Quality by Design (QbD), and predictive modelling tools, opening the door to more intelligent and effective SMEDDS development.

In summary, SMEDDS have enormous potential for future advancements in drug administration, particularly in meeting the growing need for oral formulations that are both patient-friendly and highly effective. SMEDDS are anticipated to be crucial to the development of pharmaceutical and nutraceutical products as formulation science and regulatory frameworks continue to advance.

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