REVIEW ARTICLE

A Comprehensive Review on Self-Microemulsifying Drug Delivery Systems: From Design and Evaluation to Regulatory Challenges

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Abstract

Weak aqueous solubility still remains one of the major problems encountered in the discovery and development of new drugs, particularly for BCS Class II and IV drugs where the low solution and permeability lead to low oral bioavailability. Formulation systems used for these drugs have often only partially incorporated this limitation. Thus, there is huge scope for integrating formulation strategies with a self-micro-emulsification tool to optimize absorption, solubilization and permeability of drugs of low aqueous solubility. Self Micro-emulsifying drug delivery systems (SMEDDS) have proved to be lipophilic formulations developed to improve solubility and systemic availability of drugs which are poorly water soluble. SMEDDS are makeup of a mixture of oil, surfactant and co-surfactants which form forming transparent micro-emulsions containing the drug, when in contact with the luminal environment of GI tract. Nanometer sized droplets have a very large interfacial area which facilitate the liquid digestion process and enhance the rate of intestinal absorption of drug. The biopharmaceutical performance can be greatly enhanced by improved permeability, lowered interfacial tension and thermodynamic stability. The selection of excipients should be done carefully while designing SMEDDS; excipients should be safe for human use, compatible with drug, enhance safety profile of parenteral design while ensuring ease of manufacturing, stability and parameters acceptable for regulatory approval. These systems are prepared as a liquid formulation or converted into solid form SMEDDS using techniques such as spray drying, melt granulation or adsorption onto solid carriers. Characterization of Liquid Smeeds involve studying of droplet size, cloud point, zeta potential etc. In the process of developing liquid SMEDDS for a drug, both in vitro and in vivo results should be studied. Studies involving evaluation of bioavailability of various drugs confirms the potential of this formulation. With successful commercial products and an expanding interest in clinical applications, SMEDDS are showing the way forward to future oral drug delivery

Keywords: SMEDDS, poor solubility, self-emulsification, oral bioavailability, lipid-based delivery

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Introduction

The emergence of novel chemical entities (NCEs) and active pharmaceutical ingredients (APIs) has increased dramatically over the last few decades; however, despite the enormous effort there remains to be one of the most significant problems in oral drug delivery associated with inappropriate aqueous solubility.[1] Around 40-60% of marketed drugs and for almost 90% of drugs in the pipeline have poor water solubility. This can hinder the API's dissolution rate, leading to low level of oral absorption and hence poor bioavailability and high inter- and intra-subject variability. It has been estimated that such compounds largely fall into the Class II of the Biopharmaceutics Classification System (BCS) (low solubility/high permeability drugs), with the remainder of low solubility drugs (Class IV -low solubility/low permeability drugs) have additional implications for intestinal membrane permeability, hence further complicating their formulation and clinical development.It has been estimated that such compounds largely fall into the Class II of the Biopharmaceutics Classification System (BCS) (low solubility/high permeability drugs),[2,3] with the remainder of low solubility drugs (Class IV -low solubility/low permeability drugs) have additional implications for intestinal membrane permeability, hence further complicating their formulation and clinical development.

Despite this problem, oral drug delivery is still the preferred route of administration because it is simple, economical, non-invasive and highly acceptable to patients. The effectiveness of oral therapy largely depends on the easy dissolution of the API in the GI fluids followed by the easy penetration across the intestinal membrane.[4] Formulation of conventional dosage forms such as tablets, capsules and suspensions have not routinely provided adequate. Several formulation strategies, including salt formation, particle size

reduction, solid dispersions, and cyclodextrin complexation, have been explored to enhance solubility. Although these methods can improve dissolution to some extent, they frequently suffer from drawbacks such as physical and chemical instability, precipitation upon dilution, limited scalability, and inconsistent enhancement of bioavailability.[5,6]

Several formulation approaches such as salt formation, particle size reduction, solid dispersions and complexation with cyclodextrins have been investigated for enhancing dissolution and solubility. However, these methods may have some disadvantages such as physical and chemical instabilities, drug precipitation upon dilution, limited scalability and varying degree of bioavailability enhancement. Due to these limitations, the lipid-based drug delivery systems have been receiving increasing research attention as an attractive alternative for improving oral delivery of lipophilic drugs. This potential finding is associated with the lipophilic solubilising properties of various types of oils, surfactants and co-surfactants to solubilise the drugs and keep in solubilised form inside the GIT. Various types of lipid-based drug delivery systems have been elaborately studied.[7] Out of that, self-microemulsifying drug delivery system (SMEDDS) is considered as an extremely versatile strategy

SMEDDS are thermodynamically stable isotropic mixtures of oils, surfactants and co-surfactants which spontaneously, under gentle agitation, GIT motility when administered into the aqueous environment of the stomach and small intestine, generate oil-in-water (o/w) microemulsions. The spontaneous formation of nanometer sized microemulsion droplets with possibly enormous surface area leads to an increase in absorption and solubilisation across the GIT mucosa. Unlike the existing conventional dosage forms lipids-based systems of delivery including SMEDDS are thermodynamically stable thereby avoiding drug precipitation during dispersion in gastrointestinal system. Such combined effects refer to improvement in and gliding predictable pharmacokinetic patterns, decreased food effect and increased oral bioavailability of lipophilic drugs. The ability to tailor formulation components is advantageous as it accounts for specific drug related parameters, improving chemical stability and compatibility. [8]

Novel techniques have been developed to convert liquid SMEDDS into solid properties termed as solid SMEDDS (S-SMEDDS) utilising methods including spray dryings, incorporation into solid carriers via adsorption, paste extrusion and a freeze drying process. Solid SMEDDS tend to alleviate problems of leakage, capsule incompatibility and processing while improving storage stability and acceptability. A convenient perspective of pharmaceutical usage is noted by the inclusion of SMEDDS in marketed products such as Neoral (cyclosporine) Norvir (ritonavir) and Sandimmune with evident performance benefits.[9]

Needs of Lipid-Based Formulations (LBFs)

- **1.** Poor Water Solubility of New Chemical Entities. Most NCEs 40-70% are water insoluble with low aqueous solubility.
- Lipid Formulations improve solubilization of poorly water-soluble compounds in the gastrointestinal (GI) fluids, by Elimination of the dissolution rate barrier.
- Lipids systems in maintaining drugs in a solubilized state in the GI lumen one step before the absorption step, they eliminate the issue of drug precipitation.[10]
- Lipid systems aiding faster absorption and dissolution they especially aid the absorption of BCS Class II and IV compounds.
- Variable Absorption of Lipophilic drugs depending on whether dosed in fed or fasted state is a concern. Lipid Formulations eliminate the variations by mimicking fed state solubilization**.**
- Overcoming First Pass Effect Lipid systems promote transport of drugs via the intestinal lymphatics, thereby avoiding the liver. This in particular aids drugs that are prone for hepatic metabolism (e.g. cyclosporin, testosterone derivatives).[11]
- Enhancing Permeability of Drugs Surfactants as well as lipids have been shown to alter intestinal membrane permeability and aid paracellular as well as transcellular transport.
- Lipid systems enable delivery of sensitive molecules Peptides, Proteins, Vitamins, Nutraceutics.
- Versatility in handling Lipid Formulations Lipid systems can be formulated as liquid filled capsules, or self-emulsifying formulations or subsequently converted into solid dosage forms (S-SMEDDS, S-SNEDDS) for practical use.
- Regulatory/ Clinical Precedent There is a clear clinical precedent for the successful use of Lipid based formulations as evidenced in the number of FDA/EMA approved formulations (e.g. Neoral, Norvir, Sporanox).[12,13]

Commercially used SMEDDS in the market

Biopharmaceutical Basis Of Smedds

Oral drug delivery is often limited by biopharmaceutic barriers such as poor solubility, low permeability and poor absorption which can lead to high interstitial drug concentrations, decreased dissolution and minimum systemic exposure.[28] These issues are most relevant for poorly-water-soluble drugs where the result can be low plasma levels and variable therapeutic response. Self-Microemulsifying drug delivery systems (SMEDDS) can circumvent these problems through enhanced solubilization and improved intestinal absorption to solidify oral biavailability.[29]

Solubility and Permeability Challenges:

As classified by the Biopharmaceutics Classification System (BCS), Class II and Class IV drugs are known to be the most difficult to formulate. Class II drugs (low solubility, high permeability) are dissolution rate-limited while Class IV drugs (low solubility, low permeability) are rate-limited for both dissolution and permeation of the intestinal epithelial cell

Table 1

Drug/Product (Brand Name)	*Mechanism of Action of SMEDDS*	*Therapeutic Application*	*References*
Cyclosporine A (Neoral®)	Enhances solubilization of the lipophilic drug and promotes lymphatic uptake via microemulsion droplets.	Immunosuppressant for organ transplantation.	14
Cyclosporine A (Sandimmune®)	Forms microemulsion in GI fluids, improving dissolution and reducing variability in absorption.	Immunosuppression in transplant and autoimmune conditions.	15
Ritonavir (Norvir®)	Maintains drug in solubilized state, bypassing precipitation in GI tract, enhancing systemic exposure.	Antiretroviral therapy (HIV protease inhibitor).	16
Saquinavir (Fortovase®)	Microemulsion formation increases dissolution rate and intestinal permeability.	HIV protease inhibitor in combination therapy.	17
Lopinavir/Ritonavir (Kaletra®)	SMEDDS maintains both drugs in solubilized form, reducing food effect and boosting oral bioavailability.	Antiretroviral therapy for HIV.	18
Fenofibrate (Lipirex®)	Improves dissolution and intestinal absorption by forming fine emulsions in GI fluids.	Dyslipidemia and hypertriglyceridemia.	19
Fenofibrate (Triglide®)	Enhances solubility and reduces dose variability by self-emulsification mechanism.	Management of high cholesterol and triglycerides.	20
Itraconazole (Sporanox®)	Microemulsion formation enhances dissolution and intestinal permeability of poorly soluble antifungal.	Systemic fungal infections.	21
Itraconazole (Lozanoc®)	SMEDDS improves gastric solubilization and consistent absorption regardless of fed/fasted state.	Antifungal therapy.	22
Tipranavir (Aptivus®)	Enhances solubility and absorption of lipophilic protease inhibitor through microemulsion system.	HIV-1 infection in resistant cases.	23
Amprenavir (Agenerase®)	Self-emulsification ensures solubilization and improves oral exposure of protease inhibitor.	HIV infection management.	24
Valproic Acid (Depakene® Liquid Capsules)	SMEDDS maintains solubilized state and improves mucosal permeation.	Epilepsy and bipolar disorder.	25
Cannabidiol (Epidiolex® solution – lipid-based)	Improves solubilization of lipophilic cannabinoid and enhances intestinal absorption.	Lennox–Gastaut syndrome and Dravet syndrome.	26
Nelfinavir (Viracept®)	Improves oral absorption by maintaining drug in micro emulsified form.	Antiretroviral (HIV protease inhibitor).	27

membrane. A large proportion of conventional dosage forms fail to provide a stable high intestinal drug concentration that results in drug precipitation and incomplete absorption which leads to low bioavailability. Physiological factors such as colloidal bile salt concentrations, GI motility and fed versus fasted conditions can also alter solubilization from a lifestyle dynamics perspective, and hence, induce food effects, variable inter patient absorption and erratic pharmacological results. In view of this, a delivery system that can sustain a high drug concentration in the solubilized form across all possible conditions in the GI tract becomes an imperative. [30]

Mechanisms of Solubilization and Absorption Enhancement

Self-microemulsifying drug delivery systems (SMEDDS) can overcome this hurdle since these self-emulsify spontaneously, without any application of external mechanical energy, to generate oil-in-water microemulsion of droplet size 10-250 nm. Consisting of oils and surfactants and often comprising a co-surfactant, SMEDDS provide reductions in interfacial tension and spontaneously produce thermodynamically stable oil-in water dispersions having relatively large surface areas. This, in turn, results in rapid drug dissolution. The surfactants in SMEDDS elicit other beneficial effects on absorption including increasing membrane fluidity, modulating permeabilising pathways, and inhibiting efflux transporters (e.g., P-glycoprotein) and metabolic enzymes (e.g., CYP3A4). Products of lipid digestion interact with bile salts and phospholipids in the gastrointestinal lumen to form mixed micelles, which maintains the drug in a solubilized form and permitting transepithelial transport.[31]

Bioavailability

Blends of drug that result from solubilisation in SMEDDS and increase in membrane permeability collectively ensure improved oral bioavailability and, unlike the majority of other enhancers, seem able to optimize absorption from the intestine. The solubilizing nature of the delivery system means that dissolution and not permeabilising effects are limiting for BCS Class II drugs although surfactant effects on permeability will also benefit Class IV drugs. Both in vitro and in vivo pharmacokinetic data reveal increased plasma concentrations, improved pharmacokinetic parameters, lower inter-patient variability and a notable diminution

of the effects of food on bioavailability relative to more conventional preparations. [32]

Composition Of Smedds

The composition of a Self-Microemulsifying Drug Delivery System is mainly the composition of the containing substances. The self-emulsifying property of SMEDDS is a pre-requisite for dispersion and why are so important for this reliably reproducible drug delivery properties and release.[33]

Oils

In SMEDDS oils provide the solubilising effect for lipophilic drugs and they contribute to the characteristic formulation data such as drug loading capacity. Both medium chain triglycerides (MCTs) and long chain triglycerides (LCTs) can be used. Medium chain triglycerides such as caprylic/capric triglycerides (eg. Miglyol 812, Captex 355) used have high solubilisation potential, are readily absorbed, and form stable emulsions. Long chain triglycerides such as soybean oil, olive oil, or corn oil. These LCTs elicit a more controlled release but may have slower emulsification. Semi synthetic oils are also available such as Labrafac lipophile WL and Maisine 35-1 which provide a combination of versatility and solubilisation potential. Selection of the oil depends on the physico-chemical properties of the drug and release requirements.[34]

Surfactants

SMEDDS require surfactants to decrease the oil-water interfacial tension to so that spontaneous production of a microemulsion occurs. Non-ionic surfactants are commonly employed because they are more biocompatible than ionic based surfactants. The most common are polysorbates, polyoxyl castor oils, and PEG (polyethylene glycol) esters of fatty acids. Surfactants with high hydrophillic lipophillic balance (HLB '12) are normally used to give an oil in water microemulsion which rapidly disperses and remains stable**.** [35]

Co-surfactants

Co-Surfactants are added to enable a small change of the interfacial film, resulting in a lower interfacial tension and easier emulsification. aid the solubilization of the lipophilic drug and stabilize the microemulsion. Short-chain alcohols and glycols are often seen in these systems including ethanol, propylene glycol, polyethylene glycol 400, and Transcutol® P agents further resist drug crystallization upon dilution and aid the transmittance and within the microemulsion systems.[36]

Criteria for excipient selection

In the case of the excipients used in SMEDDS must be nontoxic and compatible for regulatory. reasons. Excess surfactant or co-surfactant can cause irritation therefore GRAS listed materials are most likely be selected. Suitable excipients need to maintain appearance, thermodynamic stability, excipients interfere with drug degradation, and can aid it's function. Regulatory authorities such as the FDA and EMA possess lists of permitted excipients for oral applications; thus the excipient must balance solubilization capabilities with safety and the matters of application.[37]

Mechanism Of Self- Microemulsifying Drug Delivery System

SMEDDS is defined by how easily they spontaneously form microemulsions when fourfold dilution along with gentle agitation in GI fluids. A copy of the mechanistic basis involves the phenomenon of self-emulsification is primarily driven by thermodynamic considerations. Microemulsions, unlike conventional emulsions, are thermodynamically stable systems. Their spontaneous formation results from the reduction in free energy when a mixture of oil, surfactant, and co-surfactant disperses in an aqueous medium.

The Gibbs free energy of an emulsion system can be expressed as

$\Delta G = \sum(N\prod r^2\sigma) - T\Delta S$

Where, ΔG is the free energy of the system, N is the number of droplets, r is the droplet radius, σ is the interfacial tension, T is the temperature, and ΔS represents the entropy change. [38]

If self-emulsification is to occur spontaneously, then the free energy change must be zero or preferably negative. This is achieved by the surfactant and co-surfactant providing an interface with ultra-low surface tension and therefore a negligible free energy barrier to change; the formation of billions of small oil droplets with an enormous change in entropy is energetically favourable. A thermodynamic balance exists between these two opposing factors.

Mechanism for reducing Interfacial Tension

The forming of the microemulsion depends on a high interfacial tension in the oil-water system. This is kept low by surfactant and co-surfactant molecules themselves, that modify the weak forces that tend to hold the oil and water together into a distinction, producing a very flexible interfacial film which can accommodate many ballasts using surfactants with appropriate HLB values. Sometimes, a co-surfactant such as a short-chain glycol or alcohol may be added to further aid the flexibility of this film, by inserting itself between the surfactant molecules thereby lowering the free energy of the film allowing millions of oil droplets to be formed of nano-size dimension. It is then possible for self-dispersion of the phase to be achieved by even the low energy currents that are naturally present in the duodenal and ileal area, e.g. peristalsis.[39]

Formation of Microemulsion Droplets in the GI Tract

Following oral administration, SMEDDS are exposed to the aqueous environment of the stomach and intestine, initiating the emulsification. The irritation of gastric motility allows dispersion the isotropic mixture very quickly to small microemulsion droplets. The size of these splendid droplets are usually between 100 and 250 nm which is a very large surface area for drug dissolution.

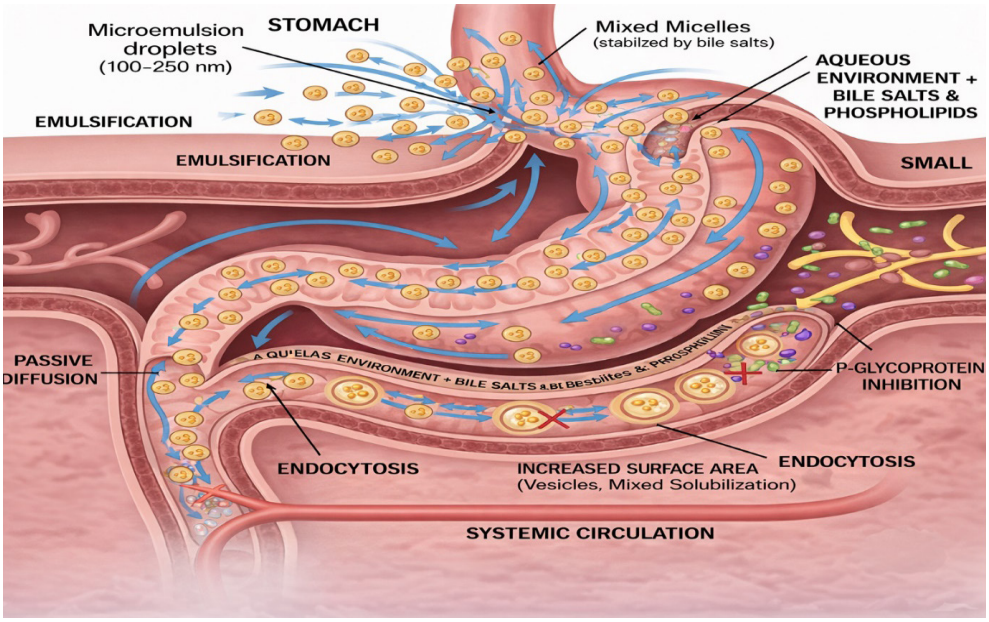

Fig no. 1: SMEDDS on microemulsion and drug absorption in GI SMEDDS: Microemulsion properties and drug absorption

The bile salts and phospholipids in the intestine additionally serve to stabilize the microemulsion. Surfactant properties of bile salts assist the excipients in the formulation to reduce interfacial tension between themselves and oil phase, thereby reducing surface tension. Surfactant properties of bile salts assist the excipients in the formulation to reduce interfacial tension [40] between themselves and oil phase, thereby reducing surface tension. These micelles are important for solubilization of lipophilic drugs to facilitate passage through the unstirred water layer in close proximity to the intestinal enterocytes.

The lipid digestion also leads to the formation of colloidal particles, for example vesicles and mixed micelles that carry the drug and promote absorption. Drugs contained in microemulsion droplets may be partitioned into the aqueous medium and then permeate through intestinal mucosa by paracellular transport as well as endocytosis or passive diffusion. In addition, the surfactants used in SMEDDS could inhibit transiently may increase gut membrane permeability by changing fluidity and inhibiting efflux transporters (e.g., P-gp). The combination of these effects retains the drug in a solubilised form throughout its journey through the gut, with little opportunity for precipitation and maximum opportunity reasonable chance of absorption into the systemic circulation.[41]

Method Of Preparation Of Smedds

Conventional Methods

Simple Mixing Method

- Oils, surfactants/co-surfactants are weighed carefully and mixed gently with heating if necessary.
- The drug is solubilised into the mixture, forming a clear isotropic system.
- It is the simplest and frequently employed for preliminary evaluation of formulations

Aqueous Titration Method

- Excipients are mixed and titrated with water or buffer to produce a clear, or slightly blue-green microemulsion.
- The method is used to establish the optimum region of self-emulsification on pseudo-ternary phase diagram.
- It assists in the identification of proper surfactant to co-surfactant ratios and formulating robustness.[42]

Dilution Method

- The preconcentrate of oil, surfactant, and drug is diluted with aqueous medium under mild agitation.
- Upon dilution, spontaneous emulsification occurs, producing fine oil-in-water dispersions.
- This simulates in vivo conditions and is useful for assessing self-emulsification efficiency.

Phase Diagram Construction

- Pseudo-ternary phase diagrams are developed by varying oil, surfactant, and co-surfactant ratios with water.
- The diagrams identify microemulsion domains and provide insight into stability regions.[43]
- This method is essential for rational selection of excipient ratios.

Solvent Evaporation Method

- Drug is initially dissolved in a volatile solvent containing lipid excipients, then the solvent is evaporated under reduced pressure.
- The product is an isotropic mixture that comprises the

drug incorporated in the lipid-surfactant system.
- It can be useful for incorporating drugs with poor solubility in oils. .

Sonication Method

- The excipients and drug are mixed and subjected to sonication to obtain a uniform distribution.
- Sonication aids in breaking the droplets down in size and increase the clarity of the system.
- It is also used for thermolabile drugs requiring remote heating. It is often employed for thermolabile drugs to avoid prolonged heating.[44]

Novel Approaches

Spray-drying to produce S-SMEDDS

Atomize the liquid SMEDDS (drug + oil + surfactant/co-surfactant) into a heated chamber in the presence of a solid carrier so solvent/volatile fraction evaporates and a free-flowing powder form.

Procedure

- Prepare liquid SMEDDS by dissolving or dispersing the drug in an optimized oil–surfactant–co-surfactant mixture; use ethanol if needed to reduce viscosity.
- Select an appropriate solid carrier (e.g., porous silica, dextran, mannitol) based on compatibility and desired drug release behavior.
- Mix the liquid SMEDDS with the carrier to form a uniform slurry and homogenize to ensure even distribution.
- Filter the mixture to remove large or undispersed particles.
- Spray-dry the slurry under optimized temperature and flow conditions to produce solid SMEDDS powder.
- Collect and sieve the dried powder to eliminate agglomerates and improve flow.
- Characterize the final product for particle size, drug content, self-emulsification efficiency, reconstitution behavior, and residual solvent levels. Advantages/ Disadvantages: scalable and industry-friendly, good loading possible; may alter droplet size or reduce some excipient content due to thermal exposure.[45]

Lyophilization (freeze-drying) of SMEDDS

Freeze the liquid system (can be with or without cryo/lyo-protectants dispersed) then sublimate the ice in a vacuum. Results in a porous reconstitutible solid which maintains the micro-structure.

Procedure

- Prepare liquid SMEDDS and if necessary dilute or solublize in water-miscible solvent system suitable for freezing (or emulsify in aqueous cryoprotectant if the SMEDDS is not water miscible).
- Add cryo/lyo-protectants (e.g. trehalose, mannitol, sucrose) and bulking agents to maintain structure.
- Fill vials/trays aseptically/control conditions and then pre-freeze rapidly (snapfreeze in liquid nitrogen or controlled shelf freezing) to determine the size of ice crystals and porosity.
- Primary drying, keep the shelf temperature low and sublimate the ice under vacuum.(pressure and shelf temperature determined by formulation thermal properties.)

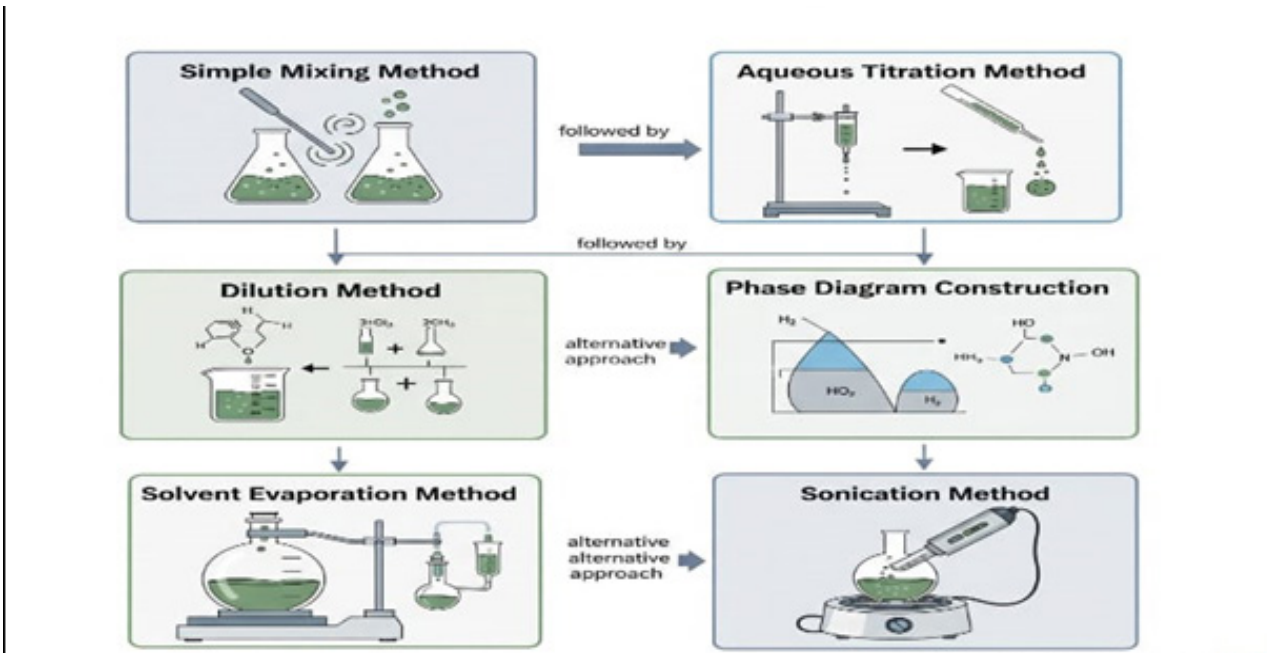

Fig 2: Method of Preparation of SMEDDS using conventional methods:

- Secondary drying, raise the shelf temperature (below drug/excipient decomposition) to remove excess moisture.
- End cycle when residual moisture is in specification and seal vials under inert gas if necessary.
- Characterize, the appearance of the cake, residual moisture, reconstitution time, droplet size distribution on dilution and stability.[46]

Adsorption onto porous solid carriers (liquid-to-solid conversion)

Physically adsorb the liquid SMEDDS onto a porous solid carrier (e.g. high surface area MCC or silica, Neusilin®) until a flowable powder is obtained (may require tableting).

Procedure

- Choose a suitable highsurface area carrier (pore volume and size, Neusilin®, porous silica, MCC)
- Titrate on a small scale to see how much will adsorb onto a fixed mass of agent (add SMEDDS gradually until flow or sticking).
- Add liquid to carrier in a planetary mixer/mortar/mill slowly to make a uniform wet mass of the desired die size.
- Dry (tray, oven) if necessary to remove excess solvent/moisture and optionally granulate (to improve flow).
- Sieve/mill if necessary to desired particle size;
- Add glidants/flow agents (e.g. Colloidal silica). Characterize % absorption, flow, tablet ability (if compressing), time & droplet size on dispersion. [47]

Hot-Melt Extrusion (HME)/melt extrusion for S-SMEDDS

Mix lipid/surfactant/drug with a polymer or lipid excipient and extrude using heat & shear to make a continuous solid dispersion/extrudate & then mill/print into dosages.

Procedure

- Choose a thermally stable API/excipient mix (lipids, plasticizers, PEG or PEO polymers), etc.
- MixAPI +lipids+polymer powders homogeneously; pre-heat blender if necessary
- Set extruder temperature profile to above melting point, keep residence time short (above grease for plasticizer).
- Feed the mixture at fixed rate; check and optimize screw speed/torque/rate to make homogeneous extrudates;
- Quickly cool (chill roller), pelletize/mill to desired size.
- Additional drying if necessary; compress or coat as necessary.
- Characterize: solid state (DSC/XRD), dispersion of drug, reconstitution, dissolution & stability, etc.[48]

Fluid-bed granulation and melt/granulation processes

Impregnate a fluid bed with SMEDDS (liquid or melted) on to carrier beads or granules to produce granules with improved flow and controlled drug release.

Process

- Load inert cores/granules (e.g. saccharides, MCC pellets) into a fluid-bed granulator.
- Spray liquid SMEDDS (or molten lipid SMEDDS) onto the fluidised cores/granules using a nozzle whilst controlling spray rate and air temperature in order to avoid over wetting.
- Continue until the desired content has been delivered and dry in place by gradually increasing inlet air temperature or decreasing spray rate.
- Optionally deposit a topcoat to modify release or protect the lipid.
- Characterise granule size, flow, packing, drug titers and in vitro dissolution/emulsification.[49]

Spray-congealing / spray-cooling (encapsulation)

Atomise a molten lipid/SMEDDS directly into a cooled chamber to produce droplets that immediately congeal to form lipid micro-particles capable of melting/dissolving in the GI tract and releasing the SMEDDS.

Process

- Melt the lipid matrix and add the drug and liquid SMEDDS components, ensuring the mixture is above melting point.
- Keep the molten feed at a controlled temperature and allow atomisation into a cold chamber (cold air supply or cooled bath) so droplets instantly congeal.
- Collect the micro-particles, pass through a sieve and optional polish coat.
- Characterise particle morphology, melting point, in vitro release and self-emulsification of the reconstituted SMEDDS.[50]

Extrusion–spheronization / multiparticulate pellet formation

Incorporate SMEDDS into extrudates that are converted into pellets or beads through spheronization to generate a flexible multiparticulate dosage form.

Process

- Prepare a wet mass containing the required SMEDDS, binder(s) and filler(s) until a uniform extrudable mix is achieved.

Extrude the wet mix through an appropriate die to form cylindrical strands.
Spheronize extrudates using a spheronizer to produce spherical pellets; dry and size fraction.
Coil pellets for long-term release or entricity.
Characterise pellet size, homogeneity of drug content and self-emulsification on dispersion.[51]

3D printing (additive manufacturing) of S-SMEDDS dosage forms

Load a printable formulation (SMEDDS and a polymer) into a 3D printing platform such as semisolid extrusion or fused

deposition controlled by HME to generate customised geometries.

Process

- Determine printing process: semisolid extrusion for paste-like SMEDDS variants, FDM for filament fed by HME using SMEDDS.
- Develop a shape control platform by adjusting rheology (viscosity, yield stress) and adding rheology modifiers if appropriate.
- Print test articles and nally post-process to stabilize shape (e.g. cooling).
- Characterise test shape for dose uniformity, mechanical integrity, disintegration and emulsification performance.[52]

Supercritical fluid (CO2-based) processing

Use supercritical CO2 as an antisolvent, drying medium or impregnation vehicle that provides extremely fine control over particle (re)precipitation or loading of SMEDDS in to polymeric matrices with very low residual solvent and residual stress.

Process

- Mix drug and/or SMEDDS components in to a suitable solvent, and attempt to contact supercritical CO2 in order to precipitate particles or load SMEDDS into porous solid supports.
- Adjust temperature and pressure to achieve desired solubility and nucleation trajectory.
- Separate precursor from the excess SCF and recover particle or impregnated solid; remove residual phase by pressure reduction.
- Characterise particle form, loading and shelf-life stability in reconstitution and emulsification assessments.[53]

Electro spraying / electrospray-drying & nanoencapsulation

Form nano- to micro-particles by electrostatic charging of a solution/emulsion (containing SMEDDS) through a gold coated needle under high voltage; solvent evaporation results in particles of defined size and morphology.

Procedure

- Dissolve SMEDDS and polymer/excipient (to form shell) in a volatile solvent.
- Set electrospray flow rate (low microliter/min range), voltage, tip-to-collector distance and room conditions.
- Collect the particles on a grounded collector and post dry under vacuum to eliminate residual solvent.
- Determine size, encapsulation efficiency, surface morphology and dilution behavior. [54]

High-energy / micro fluidic emulsification (micro fluidization, ultrasonication, high-pressure homogenization)

Apply intense shear or forced passage over ridges/trenches in micro channel system to reduce droplet size of pre-emulsions and produce SNEDDS/SMEDDS with narrow PDI; frequently used as a pretreatment before solidification.

Procedure

- Make a coarse emulsion of SMEDDS and water phase (if needed) or pre-emulsify the liquid SMEDDS in a solvent.
- Repeatedly pass the pre-emulsion through a high pressure homogenizer or microfluidizer (adjust pressure and passes to get optimum droplet size).
- Use ultrasonication for laboratory scale droplet size reduction (adjust amplitude and time to prevent heating).
- Characterise droplet size (DLS) and stability; acquire to waste elimination processing. Critical parameters: maintain temperature control; repeatedly passing lowers droplet size but adds energy input and contamination chance. Critical parameters**:** control temperature during processing; multiple passes reduce size but increase energy input and possible degradation. [55]

Co-processed excipients & engineered carriers (engineered silicas, mesoporous solids)

utilize engineered carriers using known or designed surface chemistry and pore configuration to anchor SMEDDS and increase loading, stability and controlled release.

Procedure

- Select/make carrier of desired pore size, pore surface chemistry or mesoporosity (engineered silica, functional silicas).
- Incipient wetness, spray-drying or vacuum impignoate the liquid system.
- Remove solvent under gentle conditions.
- Characterize loading, pore filling (BET), release characteristics and emulsification[56]

Pseudoternary Phase Diagram in Self-Microemulsifying Drug Delivery Systems

Basic Concepts and Significance

Self-microemulsifying drug delivery systems (SMEDDS) require an exact balance between their three components oil and surfactant and co-surfactant to achieve stable microemulsion creation through aqueous dilution. Pseudoternary phase diagrams serve as essential graphical tools to accomplish this goal. The pseudoternary system uses surfactant and co-surfactant combination (Smix) as a single pseudo-component to display oil and Smix and water compositional relationships. The method uses microemulsion creation thermodynamics because suitable surfactant and co-surfactant combinations reduce the interfacial free energy that exists between oil and water. The diagrams show the zones which produce stable microemulsions that maintain their thermodynamic equilibrium whereas turbid or phase-separated systems remain identifiable.

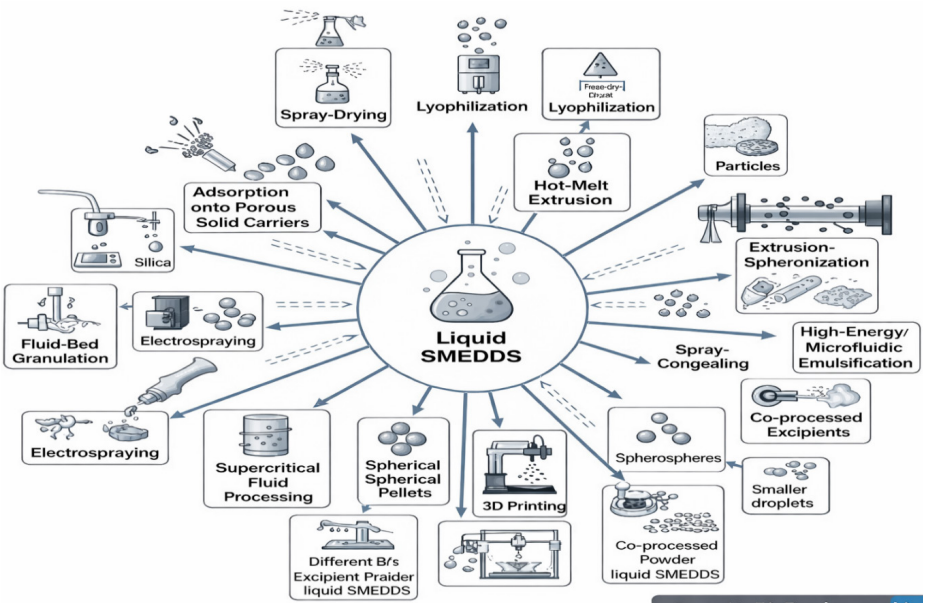

Fig 3: Method of preparation of SMEDDS by using Novel techniques

The development of formulations depends on pseudoternary phase diagrams which help researchers test different excipients and evaluate self-emulsification capacity and maintain consistency in their formulation process. The study provides details about microemulsion classification and stability regions and droplet dimension patterns which play a crucial role in improving the solubility and oral bioavailability of drugs that have low water solubility**.**

Construction Methods

Scientists create pseudoternary phase diagrams through systematic experiments which use water titration or dilution methods for their research. The general steps are

- Selection of Components: Based on solubility studies, suitable oils, surfactants, and co-surfactants are chosen. The selection of oils depends on their ability to dissolve the drug while surfactants and co-surfactants need to show biocompatibility and emulsification properties.[57]
- Preparation of Smix: The mixture uses predefined weight ratios to combine surfactant and co-surfactant materials (e.g., 1:1, 2:1, 3:1). Multiple diagrams are created because each ratio produces distinct phase behavior.
- Sample Preparation: The team prepares oil and Smix mixtures using different ratios which typically range from 9:1 to 1:9. The team conducts water titration on each blend using small increments to observe the mixture's progress toward clarity, turbidity, or phase separation.
- Identification of Regions: The researchers observed the system boundaries which separate clear microemulsions from emulsions and phase-separated systems. The researchers created triangular coordinates which show these regions that connect the three points of oil, Smix, and water.
- Software Support The advanced methods use software-based construction together with dynamic light scattering and rheological measurements to confirm the microemulsion areas and droplet size distributions.

Optimization of SMEDDS Formulation

The optimization process begins after the pseudoternary phase diagram has been created because scientists will study the identified microemulsion areas. The process involves the following aspects

- Selection of Microemulsion ZoneThe selection process chooses the wide stable microemulsion area because products created in this area will likely result in immediate emulsification together with small droplet sizes that occur during dilution.
- Droplet Size and Polydispersity Index (PDI): The optimized formulations will produce nano-sized droplets which have a narrow size distribution. This process improves drug dissolution together with biological membrane absorption.
- Thermodynamic Stability Testing: The formulations undergo three tests which include centrifugation and freeze-thaw cycles together with heating-cooling stress tests to verify their capacity to maintain stability over time while preventing phase separation.[58]
- Drug Loading and Solubilization Efficiency: The system's ability to dissolve the drug without causing precipitation represents a vital measurement. The optimization process aims to achieve maximum drug loading capacity while keeping the system stable.
- Self-Emulsification Efficiency: The researchers assess how easily the product disperses in water through

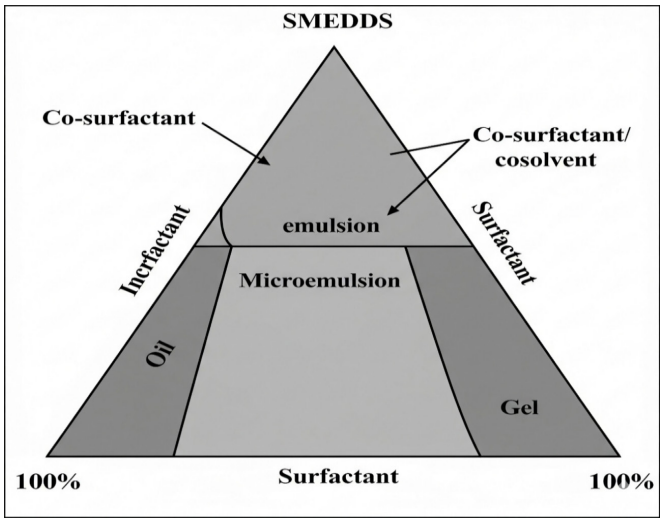

Fig 4: Pseudoternary Phase Diagram of SMEDDS:

mild agitation tests. A strong SMEDDS formulation should disperse quickly and evenly throughout the gastrointestinal tract to create conditions that match the digestive system.

- In vitro and In vivo Evaluation: The researchers use optimized formulations to assess drug release patterns together with permeability and pharmacokinetic properties. The diagram-guided method improves oral bioavailability results when compared to traditional formulation methods.

Characterization of SMEDDS

Self-microemulsifying drug delivery systems (SMEDDS) consist of lipid-based formulations which enhance the solubility and oral bioavailability of drugs that have low solubility. Proper functioning requires both proper excipient selection and microemulsion system creation, which requires complete testing to verify product stability and security and uniformity and therapeutic function.[59]

Visual Assessment

The visual assessment method serves as an elementary technique to evaluate SMEDDS performance. The formulation undergoes evaluation for its ability to maintain clear appearance and rapid emulsification while preventing any development of turbidity or phase separation after it gets diluted with water. The microemulsion formation process achieves efficient results when the material shows a clear appearance with a slight bluish tint, which helps to identify between fine dispersions and coarse emulsions.

Droplet Size and Polydispersity Index (PDI)

Droplet size acts as a crucial element which determines how drugs get released and absorbed into the body and their overall bioavailability, because smaller droplets create more surface area which leads to quicker dissolution. The scientific techniques of Dynamic Light Scattering (DLS) and Photon Correlation Spectroscopy (PCS) serve as standard methods for determining droplet size and distribution. The typical size of droplets produced by SMEDDS ranges from 20 to 200 nanometers. The Polydispersity Index (PDI) measures size distribution; values under 0.3 indicate systems which have identical particle sizes while higher values mark systems which experience particle clumping and loss of stability. Accurate assessment of droplet size and PDI measurement is vital, because these specific factors determine both product stability in physical form and its performance during actual use.

Zeta Potential

The zeta potential value determines the surface charge of droplets and their electrostatic repulsion forces, which control the stability of the formula. Higher absolute values of a zeta sizer measurement indicate stronger repulsive forces between particles and reduced risk of droplet aggregation or coalescence. In SMEDDS, zeta potential values greater than ±30 mV generally signify good physical stability. However, systems stabilized by non-ionic surfactants may remain stable even at lower values due to steric hindrance. Overall, zeta potential serves as a key indicator of dispersion stability and potential shelf life.

Emulsification Time:

The researchers assess emulsification time to measure the rate at which self-emulsification progresses after the substance contacts aqueous gastrointestinal fluids. The evaluators conduct their testing process by introducing the formulation into a beaker that contains simulated gastric or intestinal fluid which they stir at a slow pace until they achieve complete dispersion. The ideal SMEDDS formulation should achieve complete emulsification within a one-minute time frame which creates a uniform product that contains no visible oily particles.[60] The testing process requires extended emulsification time which indicates poor product performance and results in unpredictable drug release during actual bodily testing. The test creates a simulation of the human body and shows how well the product functions in real-world situations.

Cloud Point Measurement

The cloud point represents the temperature at which a clear microemulsion transforms into a turbid state because of phase separation that occurs when non-ionic surfactants lose their hydrophilic polyoxymethylene chains. The determination involves heating the diluted SMEDDS under controlled conditions until visual cloudiness appears. The high cloud point value protects the formulation because it maintains both stability and clarity throughout both physiological conditions and storage conditions. The system will experience phase separation during actual body processes if the cloud point measurement falls below body temperature 37 °C which will result in decreased drug solubility and lower bioavailability. The measurement

of cloud point serves as an essential stability assessment method for products that use surfactant-based formulas.

Thermodynamic Stability Studies

Thermodynamic stability testing distinguishes SMEDDS from conventional emulsions. Microemulsions maintain their stable thermodynamic state which enables them to withstand all stress tests including centrifugation and temperature changes and freeze–thaw cycles without any phase separation or drug precipitation.

- Centrifugation test: Formulations undergoare centrifuged at high-speed centrifugation which reaches speeds (e.g., 3500 to –5000 rpm for) to accelerate phase separation testing.. An SMEDDS should maintain its isotropic and homogeneous properties throughout its stable state.
- Heating–cooling cycles: The method uses multiple temperature alternations between 4 °C and 45 °C to determine which formulations will develop instability.
- Freeze–thaw cycles: The system undergoes multiple freezing and thawing sessions which demonstrate the possibility of component crystallisation or precipitation.
- Only formulations that pass this rigorous stability tests are considered suitable for further development.

In Vitro Drug Release Studies

The in vitro release studies show how SMEDDS dissolve and release their drugs. The testing uses dialysis bags or diffusion chambers or dissolution apparatus to test the formulation which is released in a proper dissolution medium that simulates gastric or intestinal fluid.

SMEDDS will demonstrate a higher drug release rate than traditional formulations because their nano-sized droplets provide better solubilization. The release data may be fitted into kinetic models (zero-order, first-order, Higuchi, Korsmeyer–Peppas) to understand the mechanism of drug release. The studies predict how substances will behave inside the body while they establish bio-relevant dissolution behavior.

Lipolysis Model

The lipolysis model creates an in vitro system which imitates gastrointestinal digestion processes for lipid-based formulations through the use of pancreatic lipase and bile salts and phospholipids. The system tests how drugs move between three different sections which include aqueous and micellar and precipitated states after the digestion process. The system predicts drug solubility for absorption through his tests which measure oral bioavailability and connect laboratory findings to real-world results.[61]

Solid Smedds

Solid SMEDDS are self-microemulsifying drug delivery systems that have been converted from liquid to solid form using various solidification techniques. They retain the self-emulsifying properties of liquid SMEDDS but in a solid, more stable, and user-friendly dosage form.

Need for Solidification of Liquid SMEDDS

While liquid SMEDDS improve the solubility and bioavailability of poorly water-soluble drugs, they have several drawbacks:

Stability issues

Liquid formulations can suffer from leakage, phase separation, and chemical degradation.

Handling difficulties

They may require specialized packaging and are not always suitable for patient use.

Poor patient compliance

Unpleasant taste and inconvenient administration (e.g., liquid-filled capsules) can reduce adherence.

Incompatibility with solid dosage forms

- Liquid systems can't be directly formulated into tablets or capsules without special handling.
- Solidification addresses these limitations by transforming the system into a more robust and convenient dosage form.[62]
- Solid SMEDDS are self-microemulsifying drug delivery systems that have been transformed from liquid to solid dosage forms using different solidification methods. They possess the self-emulsifying characteristics of liquid SMEDDS but in a solid, more stable, and convenient dosage form.

Need for Solidification of Liquid SMEDDS

Although liquid SMEDDS can enhance the solubility and bioavailability of poorly water-soluble drugs, they have some limitations

- Stability problems: Liquid SMEDDS are prone to leakage, phase separation, and chemical instability.
- Handling problems: They require special packaging and are not ideal for patient administration.
- Poor patient compliance: They are unpleasant to take and inconvenient to administer (e.g., liquid-filled capsules).
- Incompatibility with solid dosage forms: Liquid SMEDDS cannot be easily formulated into tablets or capsules without special handling.
- Solidification can overcome these problems by converting the system into a more stable and convenient dosage form.

Techniques for Preparing Solid SMEDDS

Several techniques are used to transform liquid SMEDDS into solid dosage forms

- Adsorption on Solid Carriers
- Liquid SMEDDS is adsorbed on porous carriers such as silica or magnesium aluminometasilicate.
- Free-flowing powders can be encapsulated in capsules or tabletted.

Several methods are employed to convert liquid SMEDDS into solid dosage forms

Adsorption onto Solid Carriers

- Liquid SMEDDS is adsorbed onto porous carriers (e.g., silica, magnesium aluminometasilicate).
- Free-flowing powders can then be filled into capsules or compressed into tablets.

Spray Drying

- Liquid SMEDDS is sprayed in a hot chamber, resulting in the formation of dry, solid particles.
- Large-scale production is possible.
- The liquid SMEDDS is atomized into a heated chamber, forming dry, solid particles.
- Suitable for large-scale production.[63]

Freeze Drying (Lyophilization)

- Water or other solvents are removed by sublimation under low temperature and pressure.
- Porous, stable particles are formed.
- Water or another solvent is removed by sublimation under low temperature and pressure.
- Produces porous, stable particles.

Melt Granulation / Melt Extrusion

- The lipid component is melted and mixed with solid carriers.
- The mixture is granulated or melt-extruded into solid dosage forms.

Palletisation

The liquid system is transformed into spherical pellets using extrusion-spheronization.

Supercritical Fluid-Based Methods[64]

- Supercritical CO_2 is used to remove solvents and create solid dispersions.
- The lipid phase is melted and mixed with solid carriers.
- The resulting material is granulated or extruded into solid forms.

Palletisation[65]

Converts the liquid system into spherical pellets using techniques like extrusion-spheronization.

Supercritical Fluid-Based Methods

Use of supercritical CO_2 to remove solvents and form solid dispersions.[66]

Advantages of Solid SMEDDS over Liquid SMEDDS

IN -VIVO AND IN- VITRO PERFORMANCE

Self-microemulsifying drug delivery systems (SMEDDS) have attracted significant attention as enabling technologies for improving the oral delivery of poorly water-soluble drugs. There in vitro and in vivo evaluations are central to establishing their therapeutic advantages over conventional formulations. The following subsections summarize comparative studies, bioavailability enhancement, and in vitro–in vivo correlation (IVIVC) in the context of SMEDDS.

Self-microemulsifying drug delivery systems (SMEDDS) have received considerable attention as enabling technologies for enhancing the oral delivery of poorly water-soluble drugs. There are in vitro and in vivo assessments of SMEDDS that play a pivotal role in ascertaining their therapeutic benefits over conventional formulations. The following subtopics will briefly describe the comparative studies, bioavailability enhancement, and in vitro-in vivo correlation (IVIVC) in relation to SMEDDS.[68]

Comparative Studies with Conventional Formulations

The performance of SMEDDS is typically compared with conventional dosage forms such as suspensions, tablets, or simple oil solutions of poorly soluble drugs. There are several obvious trends that emerge from such comparative studies:

Solubilization and Dissolution

In vitro studies have clearly indicated that SMEDDS exhibit significantly faster dissolution and higher apparent solubility than conventional formulations. The spontaneous formation of fine oil-in-water microemulsions offers a large interfacial surface area, thus accelerating the release of drugs.

Drug Precipitation Risk

Conventional formulations are often prone to the risk of drug precipitation upon dilution, especially in supersaturated systems. However, SMEDDS keep the drug in a solubilized form owing to the stabilizing action of surfactants and co-surfactants.

Absorption Efficiency

In vivo studies have Conventional formulations can have irregular or incomplete absorption patterns because of solubility issues, whereas SMEDDS overcome the solubility barrier and ensure efficient absorption throughout the gastrointestinal tract.

Consistency in Pharmacokinetics

Liquid SMEDDS have been found to have less variability in pharmacokinetic parameters than suspensions, ensuring consistency in pharmacokinetics.

- Taken together, these comparative studies clearly establish that SMEDDS are superior to conventional formulations in terms of in vitro release and in vivo absorption**.**
- The performance of SMEDDS is generally benchmarked against conventional dosage forms such as suspensions, tablets, or simple oil solutions of poorly soluble drugs. Several consistent trends emerge from these comparisons[69]

Solubilization and Dissolution

In vitro studies demonstrate that SMEDDS achieve much faster dissolution and higher apparent solubility compared to conventional formulations. The spontaneous formation

Table 2: missing caption

Feature	*Solid SMEDDS*	*Liquid SMEDDS*
Stability	More stable, less prone to degradation	Sensitive to temperature and light
Convenience	Easier to handle, store, and transport	Requires special containers
Patient Compliance	Tasteless, easier to swallow (tablets/capsules)	May have unpleasant taste
Dosage Form Flexibility	Can be formulated as tablets, powders, pellets	Mainly limited to soft/hard gelatin capsules
Scalability	Suitable for industrial manufacturing	Complex filling operations
Reduced Leakage Risk	Solid form prevents leakage	Risk of leakage from capsules
Improved Drug Loading	Better control over content uniformity	Sometimes limited by solubility in oils/surfactants[67]

of fine oil-in-water microemulsions provides large interfacial surface area, enhancing the rate of drug release.

Drug Precipitation Risk

Conventional formulations often face challenges of drug precipitation upon dilution, particularly for supersaturated systems. In contrast, SMEDDS maintain drugs in a solubilized state due to the stabilizing role of surfactants and co-surfactants.

Absorption Efficiency

In vivo studies reveal superior intestinal absorption for SMEDDS. Conventional formulations may exhibit erratic or incomplete absorption due to poor solubility, whereas SMEDDS bypass dissolution limitations and promote efficient absorption across the gastrointestinal tract.

Consistency in Pharmacokinetics

Liquid SMEDDS generally show reduced variability in pharmacokinetic parameters compared to suspensions, ensuring more predictable therapeutic outcomes.

Collectively, these comparative studies confirm that SMEDDS outperform conventional formulations in both in vitro release and in vivo absorption.[70]

Bioavailability Enhancement Studies

One of the main aims of SMEDDS is to enhance the oral bioavailability of Biopharmaceutics Classification System (BCS) class II and IV drugs. Both preclinical and clinical studies have confirmed the effectiveness of SMEDDS in the following ways:

Increased Cmax and AUC

SMEDDS formulations result in a substantial increase in peak pl0asma concentration (Cmax) and overall drug exposure (AUC) compared to conventional formulations. This is due to increased solubilization, prevention of drug precipitation, and stimulation of lymphatic transport.

Rapid Onset of Action

The rapid emulsification and reduction in droplet size of SMEDDS result in faster absorption of the drug, thereby decreasing Tmax (time to reach maximum concentration).

Mechanisms of Improvement

The improved bioavailability can be ascribed to several mechanisms, which include (i) avoidance of the dissolution step, (ii) improvement in membrane permeability, (iii) inhibition of efflux transporters such as P-glycoprotein by surfactants, and (iv) stimulation of lymphatic transport of lipophilic drugs, thus avoiding the hepatic first-pass effect.

Examples

Cyclosporine, ritonavir, and tacrolimus have demonstrated significant improvement in systemic exposure when developed as SMEDDS, thus emphasizing their potential applications.

- Thus, bioavailability enhancement is the most appealing advantage of SMEDDS over conventional dosage forms.
- One of the primary objectives of SMEDDS is to improve the oral bioavailability of Biopharmaceutics Classification System (BCS) class II and IV drugs. Both preclinical and clinical investigations have consistently validated their potential

Enhanced Cmax and AUC

SMEDDS formulations often lead to significant increases in peak plasma concentration (Cmax) and overall drug exposure (AUC) compared to conventional formulations. This enhancement arises from increased solubilization, protection of drugs from precipitation, and promotion of lymphatic transport.

Rapid Onset of Action

Due to their rapid emulsification and droplet size reduction, SMEDDS accelerate drug absorption, resulting in shorter Tmax (time to reach maximum concentration).

Mechanisms of Improvement

The enhanced bioavailability can be attributed to multiple mechanisms, including (i) bypassing the dissolution step, (ii) increasing membrane permeability, (iii) inhibiting efflux transporters such as P-glycoprotein through surfactants, and (iv) promoting lymphatic uptake of lipophilic drugs, thereby avoiding hepatic first-pass metabolism.

Examples

Drugs such as cyclosporine, ritonavir, and tacrolimus have shown marked improvement in systemic exposure when formulated as SMEDDS, highlighting their clinical relevance.

Thus, bioavailability enhancement remains the most compelling advantage of SMEDDS over traditional dosage forms.[71]

In Vitro–In Vivo Correlation (IVIVC)

The development of IVIVC is essential for the extrapolation of in vivo performance from in vitro results, thereby minimizing the need for comprehensive animal and human studies. In the case of SMEDDS, the relationship is more complex than that of conventional dosage forms because of their distinct digestion and absorption mechanisms.

Models of In Vitro Dissolution

The conventional dissolution test has limited predictive ability because the SMEDDS formulation's performance is not solely dependent on dissolution, but also on dispersion, droplet formation, and enzymatic digestion in the gastrointestinal tract.

Lipolysis Models

In an attempt to enhance IVIVC, in vitro lipolysis models have been designed, whereby SMEDDS formulations are exposed to enzymatic digestion by pancreatic lipase in the presence of bile salts and phospholipids. These models attempt to replicate the physiological environment of the intestine and estimate the amount of drug that remains solubilized versus precipitated following enzymatic digestion.

Correlation with In Vivo Data

It has been found that there is a reasonable correlation between the results of in vitro lipolysis and in vivo absorption. Formulations that keep the drug in a solubilized form during in vitro lipolysis tend to have higher plasma concentrations in vivo.

Challenges in IVIVC

Although significant progress has been made, the development of a general IVIVC for SMEDDS is still difficult because of individual differences in the secretion rate of bile salts, enzyme activity, and gastrointestinal transit times. Hence, IVIVC may be developed for a particular drug, but it may be case-specific.

Establishing IVIVC is critical for predicting in vivo performance from in vitro tests, thereby reducing reliance on extensive animal and clinical studies. For SMEDDS, this correlation is more complex compared to conventional formulations due to their unique digestion and absorption pathways.

In Vitro Dissolution Models

Standard dissolution testing provides limited predictive power because SMEDDS performance depends not only on dissolution but also on dispersion, droplet size formation, and enzymatic digestion in the gastrointestinal tract.

Lipolysis Models

To improve IVIVC, in vitro lipolysis models have been developed, where SMEDDS are subjected to enzymatic digestion by pancreatic lipase in the presence of bile salts and phospholipids. These models simulate the intestinal milieu and help determine the proportion of drug remaining solubilized versus precipitated after digestion.

Correlation with In Vivo Data

Studies have shown that in vitro lipolysis results align reasonably well with in vivo absorption trends. Formulations that maintain the drug in solubilized states during in vitro lipolysis generally exhibit higher plasma concentrations in vivo.

Challenges in IVIVC

Despite progress, achieving a universal IVIVC for SMEDDS remains challenging due to interindividual variability in bile salt secretion, digestive enzyme activity, and gastrointestinal transit times. Therefore, while IVIVC can be established for specific drugs, it is often case-dependent.[72]

APPLICATION OF SMEDDS

Self-Microemulsifying Drug Delivery Systems (SMEDDS) enhance the oral bioavailability of poorly water-soluble drugs by creating fine microemulsions in gastrointestinal fluids. They are extensively used for improving drug bioavailability, targeted drug delivery, and developing appropriate drug delivery systems for pediatric and geriatric patients.

Oral Delivery of Poorly Water-Soluble Drugs

One of the primary applications of SMEDDS lies in enhancing the oral bioavailability of lipophilic drugs with poor aqueous solubility, which constitute a significant proportion of new chemical entities. Drugs such as cyclosporine, ritonavir, and fenofibrate have shown limited absorption when administered in conventional formulations due to solubility-limited dissolution and erratic gastrointestinal absorption. SMEDDS improve solubilization by maintaining the drug in a dissolved state throughout gastrointestinal transit, thus enhancing its absorption.

The unique self-emulsifying property of SMEDDS ensures rapid dispersion in the gastrointestinal tract, leading to the formation of fine oil droplets with a large surface area for drug absorption. This mechanism bypasses the dissolution step, which is often the rate-limiting factor for lipophilic drugs. Moreover, SMEDDS can promote lymphatic transport, thereby avoid first-pass hepatic metabolism and improve systemic availability. Their ability to protect the drug from enzymatic degradation in the gut further contributes to improved therapeutic efficacy.[73]

Delivery of Peptides and Proteins

Oral delivery of peptides and proteins is limited by enzymatic degradation and low intestinal permeability.

Table 3:

Product Name	*Drug*	*Indication*	*Company*	*SMEDDS Role*	*Reference*
Neoral®	Cyclosporine A	Immunosuppressant (e.g., post-transplant)	Novartis	Enhanced and consistent oral bioavailability	77
Sandimmune®	Cyclosporine A	Immunosuppressant	Novartis	Earlier formulation with variable bioavailability; replaced by Neoral®	78
Fortovase®	Saquinavir	HIV protease inhibitor	Roche	Improved solubility and absorption compared to conventional capsules	79
Norvir®	Ritonavir	HIV protease inhibitor	AbbVie	Liquid formulation developed using SMEDDS for better absorption	80

Self-Microemulsifying Drug Delivery Systems (SMEDDS) provide a protective lipid-based environment that helps shield these macromolecules from gastrointestinal enzymes while enhancing mucosal permeability and drug transport across the intestinal barrier. Although challenges remain in maintaining peptide stability within lipid matrices and achieving consistent bioavailability, SMEDDS offer a promising and non-invasive platform for advancing oral delivery of peptide and protein therapeutics.[74]

Targeted Drug Delivery:

Self-microemulsifying drug delivery systems (SMEDDS) have emerged as promising carriers for targeted drug delivery due to their capacity for site-specific release and selective tissue accumulation. By altering the composition of oils, surfactants, and co-surfactants, the physicochemical properties of SMEDDS can be tailored to direct drugs toward specific tissues or organs. Upon emulsification, SMEDDS produce small droplets that enhance membrane penetration, supporting targeted intracellular delivery. In oncology, SMEDDS have been applied to deliver chemotherapeutic agents, exploiting the enhanced permeability and retention (EPR) effect for tumor-specific accumulation while reducing systemic toxicity. Furthermore, surface modifications using ligands such as folic acid, peptides, or antibodies improve cancer cell targeting. SMEDDS can also be designed for lymphatic targeting, which is valuable in managing lymphatic disorders or enhancing vaccine efficacy. Their lipid content and particle size significantly influence lymphatic uptake, allowing for precise formulation adjustments based on therapeutic goals. Thus, SMEDDS offer versatile platforms for advanced targeted therapies.[75]

Pediatric and Geriatric Formulations

Formulating drugs for pediatric and geriatric populations presents distinct challenges related to swallowing difficulties, taste masking, and variable gastrointestinal physiology. SMEDDS provide a patient-friendly alternative to conventional solid dosage forms by enabling the development of liquid or soft-gel formulations that are easier to swallow and administer. This is particularly advantageous in pediatric care, where patient compliance is often compromised due to the unpalatable taste or inconvenient dosage forms.

The inherent solubilizing capability of SMEDDS ensures uniform drug distribution and predictable pharmacokinetics, which is essential in populations with altered absorption profiles, such as neonates or elderly individuals. Furthermore, SMEDDS formulations can be dispersed in small volumes of water or juice without compromising stability, facilitating dose flexibility and ease of administration.

In the geriatric population, issues such as polypharmacy, decreased salivary flow, and dysphagia can be addressed through SMEDDS-based formulations that do not require chewing or extensive fluid intake. Additionally, the enhanced bioavailability provided by SMEDDS can potentially reduce the required drug dose, thereby minimizing side effects and drug interactions.[76]

CASE STUDIES

Commercially Marketed SMEDDS Products

These formulations are designed to improve the bioavailability of poorly water-soluble drugs by forming microemulsions upon contact with gastrointestinal fluids.

Research Case Studies of SMEDDS for Specific Drugs:

Several studies have investigated SMEDDS to enhance drug delivery and targeting

REGULATORY ASPECTS

FDA and EMA Perspectives: FDA and EMA Perspectives

SMEDDS are assessed as a part of lipid-based oral drug delivery formulations. Both FDA and EMA demand in-depth formulation characterization, such as composition, droplet size, stability, and efficiency of emulsification. Bioavailability and bioequivalence studies are critical, especially for generic formulations. FDA guidelines for NDAs/ANDAs include manufacturing, stability, and safety of excipients, whereas EMA focuses on pharmacokinetics, risk management, and scientific rationale for excipients and processing.

Excipients and GRAS Status

Excipients commonly used in SMEDDS, such as MCTs, polysorbates, PEG, and propylene glycol, are generally

Table 4: Different research studies showing SMEEDS for various treatment studies.

Drug	*Therapeutic Use*	*Study Highlights*	*Reference*
Paclitaxel	Anticancer	SMEDDS formulation showed enhanced tumor targeting and oral bioavailability; utilized P-gp inhibitors to overcome drug efflux.	81
Curcumin	Anti-inflammatory / Anticancer	Curcumin-loaded SMEDDS improved oral bioavailability and demonstrated better anti-tumor activity in animal models.	82
Tamoxifen	Breast cancer	SMEDDS with folic acid surface modification showed enhanced uptake by cancer cells and improved cytotoxicity.	83
Docetaxel	Anticancer	SMEDDS enhanced lymphatic transport and systemic exposure, reducing the need for toxic solubilizers like polysorbate 80.	84
Valsartan	Antihypertensive	SMEDDS-based formulation significantly improved solubility and oral absorption.	85
Artemether and Lumefantrine	Antimalarial	Co-loaded SMEDDS achieved synchronized release and enhanced bioavailability in preclinical models.	86

considered to be GRAS.[87] New excipients or excipients used at high concentrations must be fully evaluated for safety. GRAS status is not a guarantee of approval, as the excipient's suitability for the proposed formulation, route of administration, and patient population must be taken into account.

Excipients and GRAS Status

Excipients commonly used in SMEDDS, such as MCTs, polysorbates, PEG, and propylene glycol, generally have GRAS status. Novel or high-concentration excipients require thorough safety evaluation. GRAS status alone does not ensure approval; suitability for the intended formulation, administration route, and patient population must be considered.

Guidelines for Lipid-Based Formulations

Specific SMEDDS There are no specific guidelines for SMEDDS are limited, but the following ICH guidelines are followed: developers follow broader documents like ICH Q8 (pharmaceutical development), Q9 (quality risk management), and EMA's Quality by Design (QbD).) recommendations. Technical resources such as tools like the Lipid Formulation Classification System (LFCS) assist inhelp guide excipient selection choice and the prediction of predict in vivo performance.[88]

Research Gaps And Future Perspectives In Smedds Development

SMEDDS improve solubility and oral bioavailability of poorly soluble drugs in water, but their use in the clinic is hindered by knowledge gaps. Future breakthroughs could come from new excipients, nanotechnology, personalized formulations, and new solidification techniques.

Research on New Lipids and Surfactants

One of the most important issues in SMEDDS formulation is the lack of suitable excipients with optimal safety and emulsifying properties. Most existing formulations are based on traditional excipients such as medium-chain triglycerides, oleic acid, polysorbates, and polyethylene glycol derivatives. However, these excipients may not always possess the desired properties of stability, drug-carrying capacity, and compatibility with certain drug substances.

To address this issue, there is an increasing need to investigate new biocompatible lipid excipients of natural or synthetic origin. Structured lipids, amphiphilic phospholipids, and esters with defined hydrophilic-lipophilic balance (HLB) values are promising alternatives. Green surfactants, which are biodegradable and of renewable origin, can also provide eco-friendly alternatives with preserved performance. Further studies are needed to assess the long-term safety, metabolism, and regulatory status of these new excipients

SMEDDS enhance solubility and oral bioavailability of poorly water-soluble drugs, yet clinical application is limited by research gaps. Future advancements may arise from novel excipients, nanotechnology integration, personalized formulations, and improved solidification methods.

Exploration of Novel Lipids and Surfactants

A critical challenge in SMEDDS formulation is the limited range of pharmaceutically acceptable lipids, surfactants, and co-surfactants with optimal safety and emulsification properties. Most current formulations rely on conventional ingredients such as medium-chain triglycerides, oleic acid, polysorbates, and polyethylene glycol derivatives. However, these excipients may not always provide the desired stability, drug loading capacity, or compatibility with certain drug molecules.

To overcome this, there is a growing need to explore novel, biocompatible lipid excipients derived from natural or synthetic sources. Structured lipids, amphiphilic phospholipids, and esters with tailored hydrophilic-lipophilic balance (HLB) values are potential candidates. Additionally, green surfactants—biodegradable and derived from renewable sources—can offer eco-friendly alternatives while maintaining functional performance. Further research is required to evaluate the long-term safety, metabolic fate, and

regulatory acceptance of these new excipients.[89]

Integration with Nanotechnology

The integration of SMEDDS with nanotechnology provides new opportunities for the targeted and controlled delivery of drugs. The addition of nanostructures such as solid lipid nanoparticles (SLNs), nanocrystals, or nanoemulsions to the SMEDDS matrix could improve the encapsulation efficiency of drugs, their uptake by cells, and their ability to cross biological barriers.

Nano-based SMEDDS could also provide opportunities for the simultaneous delivery of multiple drugs, including small molecules, peptides, and nucleic acids, with synergistic effects. In addition, the modification of SMEDDS droplets with targeting ligands or stimuli-sensitive materials could further improve the targeted delivery of drugs, especially in cancer and inflammatory diseases. However, the development of such nanotechnology-based SMEDDS is still in its infancy.[90]

Approaches to Personalized Medicine

Given the current focus on personalized medicine, the concept of formulating SMEDDS on a personalized basis is an area of great potential in the future. Differences in gastrointestinal physiology, enzyme expression, and genetic polymorphism among individuals can impact the performance of lipid-based formulations.

Personalized SMEDDS can be formulated on the basis of individual parameters such as age, disease status, metabolism, or microbiota. Technologies such as pharmacogenomics, artificial intelligence, and machine learning could be particularly important in the development of personalized systems. However, much research is required to understand how these technologies can be leveraged in formulation science.

The convergence of SMEDDS with nanotechnology opens new avenues for achieving targeted and controlled drug delivery. Incorporation of nanostructures—such as solid lipid nanoparticles (SLNs), nanocrystals, or nano emulsions—within the SMEDDS matrix can enhance drug encapsulation efficiency, improve cellular uptake, and facilitate passage through biological barriers.

Nano-enabled SMEDDS may also allow for the co-delivery of multiple therapeutic agents, including small molecules, peptides, and nucleic acids, with synergistic effects. Moreover, functionalization of SMEDDS droplets with targeting ligands or stimuli-responsive materials can further enhance site-specific delivery, particularly in oncology and inflammatory disorders. However, the development of such hybrid systems is still in its infancy, and challenges remain in terms of large-scale manufacturing, physicochemical stability, and reproducibility.[91]

Personalized Medicine Approaches

With the growing emphasis on personalized medicine, tailoring SMEDDS formulations to individual patient needs represents an important future direction. Inter-individual variability in gastrointestinal physiology, enzymatic activity, and genetic polymorphisms affecting lipid metabolism can influence the performance of lipid-based formulations.

Personalized SMEDDS could be developed based on patient-specific parameters such as age, disease state, metabolic profile, or microbiome composition. Technologies such as pharmacogenomics, artificial intelligence (AI), and machine learning may play a key role in designing and optimizing such individualized systems. However, significant research is needed to understand how to integrate these tools into formulation science and regulatory frameworks.

Advanced Solidification Techniques

Although liquid SMEDDS offer several biopharmaceutical advantages, their liquid nature poses challenges in terms of stability, handling, and patient acceptability. Transforming liquid SMEDDS into solid dosage forms—such as tablets, capsules, or pellets—can overcome these limitations while retaining the benefits of microemulsion-based delivery.

Conventional solidification methods, such as spray drying and adsorption onto solid carriers, often suffer from limitations in scalability and drug loading. Emerging techniques like hot-melt extrusion, freeze-drying, and supercritical fluid processing offer promising alternatives, enabling the production of stable, high-drug-load solid SMEDDS with improved mechanical properties. Nonetheless, issues related to process optimization, excipient compatibility, and regulatory acceptance need further investigation.[92]

Conclusion

Self-microemulsifying drug delivery systems (SMEDDS) have recently been recognized as a promising approach for improving the oral bioavailability of poorly water-soluble drugs. Consisting of oils, surfactants, and co-surfactants, SMEDDS can spontaneously generate a fine oil-in-water emulsion in the gastrointestinal tract, which helps to improve solubilization and absorption. Several commercial products, including Neoral®, Sandimmune®, and Norvir®, have already demonstrated the success of SMEDDS in the clinical delivery of lipophilic drugs. Besides improving bioavailability, SMEDDS also have some other advantages, such as lymphatic targeting, reduced interindividual variability, and the possibility of site-specific delivery by surface modification with targeting ligands.

Recent studies have broadened the application of SMEDDS to more advanced areas, combining nanotechnology and researching solidified dosage forms for improved stability and patient compliance. Moreover, their flexibility matches the increasing need for personalized medicine. With the continuous development of new excipients and formulation technologies, SMEDDS have great potential for future innovations in drug delivery.

Self-microemulsifying drug delivery systems (SMEDDS) have emerged as a promising strategy for enhancing the

oral bioavailability of poorly water-soluble drugs. Comprising oils, surfactants, and co-surfactants, SMEDDS spontaneously form fine oil-in-water emulsions in the gastrointestinal tract, facilitating improved solubilization and absorption. Several marketed formulations, such as *Neoral®*, *Sandimmune®*, and *Norvir®*, exemplify the clinical success of SMEDDS in delivering lipophilic drugs effectively. Beyond bioavailability enhancement, SMEDDS offer additional advantages, including lymphatic targeting, reduced inter-individual variability, and the potential for site-specific delivery through surface modifications with targeting ligands.

Recent research has expanded the scope of SMEDDS toward advanced applications, integrating nanotechnology and exploring solidified dosage forms for enhanced stability and patient compliance. Furthermore, their adaptability aligns with the growing demand for personalized medicine. As novel excipients and formulation techniques continue to evolve, SMEDDS hold considerable potential for future innovations in drug delivery. Continued interdisciplinary research and regulatory alignment will be crucial to unlocking their full therapeutic capabilities across a broader range of therapeutic areas.

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