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Novel Approach in Solid SMEDDS

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ABSTRACT

Around 40-60% of potential drugs in the pharmaceutical industry are lipophilic in nature, which means they have limited water solubility and permeability, causing formulation issues. The self-micro emulsifying drug delivery framework is one of the approaches for increasing the solubility of hydrophobic drugs. Self-micro emulsifying formulations (droplet size < 100 nm) improve oral bioavailability of hydrophobic drugs by facilitating solubilization and presenting the drug in a soluble form, bypassing the dissolution process. The formulation of these dosage forms includes a number of components, such as lipids, surfactants, and co-surfactants, which enhance oral bioavailability by increasing lymphatic transport and overcoming hepatic first pass metabolism.

The review article provides a thorough analysis of the formulation, characterization, and recent trends in SMEDDS in the pharmaceutical industry. Various formulation techniques are described in detail, including adsorption onto solid carriers, spray drying and melt granulation. Case studies of the different drugs manufactured into Solid SMEDDS are highlighted to show their practical applicability and efficacy enhancements. Overall, the purpose of this article is to provide a critical review of current research trends, as well as insights into future directions and potential breakthroughs in the field of drug delivery by SMEDDS.

Keywords: *Solid SMEDDS, hepatic first-pass metabolism, lymphatic transport, melt granulation.*

INTRODUCTION

Most new drug candidates employed in formulation development nowadays are sparingly soluble and have low bioavailability. In order to solve these issues, a variety of formulation techniques are proposed, including the use of lipid complexes, pH change, nanoparticles, Solid dispersions, surfactants, β-cyclodextrin, and permeation enhancers. Lipid-based careers are gaining popularity for developing self-emulsifying drug delivery systems (SEDDS) to improve oral bioavailability of lipophilic drugs, overcoming challenges like specialized equipment and manufacturing processes. [1)] Self-micro emulsifying drug delivery system (SMEDDS) is best and most preferable technique to increase oral bioavailability. SMEDDS are a category of emulsion that has drawn special interest as a way to improve the oral bioavailability of drugs with poor absorption. When combined with water, an oil and non-ionic surfactant mixture can create self-emulsifying systems, which are transparent and clear isotropic solutions. These compositions create a fine oil-in-water emulsion that is gently agitated, possibly due to gastrointestinal motility. However, the liquid form of SMEDDS

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requires the usage of expensive soft gelatin capsules. Additionally, the oil material may leak out of the capsules. Furthermore, drug precipitation and chemical instability may be observed in liquid SMEDDS (L-SMEDDS). Therefore, it has been suggested that using solid SMEDDS (S-SMEDDS) is a better strategy because it lowers production costs and improves stability, patient compliance, and dose accuracy.[2)] The solid self-micro emulsifying drug delivery systems (S-SMEDDS) are a new approach to overcome the above-mentioned problems. Using a variety of methods such as adsorption on solid carriers, wet granulation by high-shear mixer, spray drying extrusion and spheronization, etc. the liquid self-emulsifying agents in this formulation are combined with the powder to create solid dosage forms, such as tablets and capsules.

S-SMEDDS Overcoming the Need of Liquid SMEDDS

- Stability: In general, solid SMEDDS are more stable and reproducible than liquid SMEDDS. The formulation is shielded from degradation by the solid form from sources like oxidation, hydrolysis, and microbial contamination. This may result in a longer shelf life and increased medication effectiveness.
- Dosing accuracy: Solid SMEDDS offer better dosing accuracy compared to liquid formulations. They can be precisely formulated into unit doses, such as tablets or capsules, ensuring consistent and accurate dosing for patients. This is particularly important for drugs with narrow therapeutic windows where precise dosing is critical.
- When S-SMEDDS (solid micro-emulsion pre-concentrate) comes into contact with water, it easily forms Microemulsion.[3)]
- Patient compliance: When it comes to oral medication, solid SMEDDS may be more patient-complied with than liquid versions. Solid dosage forms, like tablets or capsules, are often more convenient for patients to consume than liquid versions, which can result in higher adherence of prescribed treatment regimens.
- Reduced variability: When compared to liquid formulations, solid SMEDDS provide less variation in drug release. Better control over drug release kinetics, reduced variances in absorption patterns, and stable medication plasma concentrations over time are all made possible by the solid dosage form.
- Better handling and storage: Compared to liquid formulations, solid SMEDDS are simpler to handle and store. They are more convenient to transport and store because they are less likely to leak, spill, or evaporate—especially in situations where temperature control is required.

Advantages of SMEDDS

1) The solubility of hydrophobic drugs is facilitated by SMEDDS, which offers the same benefit as emulsions. When compared to SMEDDS, which are thermodynamically stable and can be readily stored, macroemulsions undergo creaming over a period of time. [6)]
2) SMEDDS are more stable than emulsions due to their reduced energy consumption and simplified manufacturing procedure. SMEDDS can be prepared with basic mixing equipment, and it takes less time to make than emulsions. [4)]
3) The formulation of SMEDDS allows for the efficient absorption of poorly soluble drugs with limited absorption rate due to dissolution rate, resulting in a consistent plasma-time profile. It's possible that the drug's constant plasma levels are the result of the drug being presented in dissolved form rather than the poorly soluble form, bypassing the crucial dissolution step in drug absorption. [4)]

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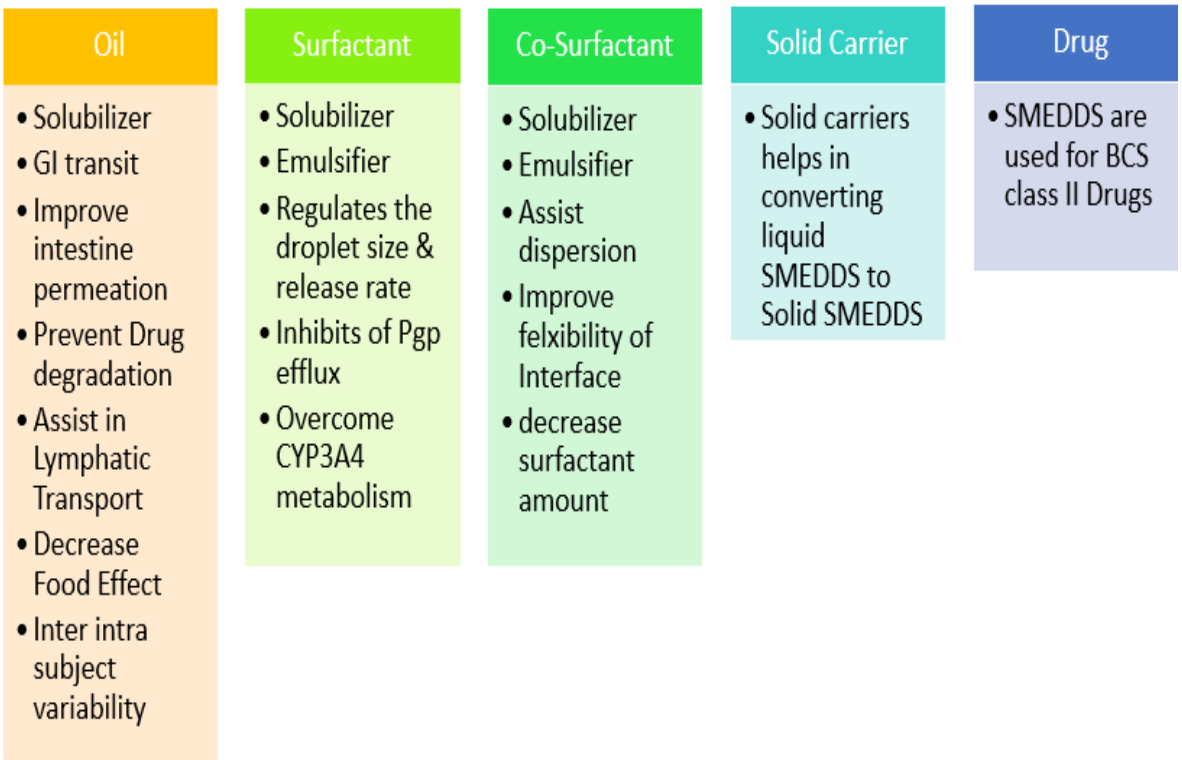
4) As SMEDDS are designed to give drugs to the body in the form of oil droplets, they can protect drugs that are prone to degradation by chemical and enzymatic processes in the gastrointestinal tract.[5)]
5) Due to their reduced volume, ease of administration, and superior patient care, the majority of SMEDDS formulations are in the form of tablets or capsules. [6)]
6) Quick onset of effect is achieved by the drug's capacity to be absorbed quickly through oral administration, facilitated by SMEDDS.[7)]
7) Simple, low-cost manufacturing facilities, like a basic mixer with an agitator and volumetric liquid filling equipment, are all that are needed to make SMEDDS, making it easy to manufacture at large scale. [6)]

Disadvantages of SMEDDS

1) Require a significant amount of surfactants, which can be harmful in certain instances.[5)]
2) Storage and handling: Liquid SMEDDS cause challenges with storage, stability, and handling. SSMEDDS appears to be an appropriate remedy to these difficulties.[8)]
3) Drug precipitation during dilution: Diluted SMEDDS precipitate drugs in gastrointestinal fluid. A fundamental criterion for lipid formulations is that they can retain the drug once solubilized in the gastrointestinal tract (GIT). The advantage of the lipid-based formulation technology is nullified by drug precipitation from the system.[5)]
4) Lack of efficient in vitro predictive models for formulation assessment is a significant obstacle to the development of SMEDDS and other lipid-based formulations.[9)]
5) Validating formulations with several components is more challenging.[9)]



Role played by Components of S-SMEDDS

COMPOSITION

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1) **Lipids (Oil):** Oils are a crucial part of SMEDDS because the kind and concentration of oil used in the formulation determines how well the drug is dissolved and how easily it enters the lymphatic circulation for poorly soluble drugs.[4)]. Lipids, mostly in their oil form, play a prominent role in the enhancement of intestinal permeation and protection of drugs from degradation in the gastrointestinal tract. By making formulations containing digestible lipids, triglycerides, diglycerides, fatty acids, phospholipids, cholesterol, and other synthetically derived lipids, it not only improves drug bioavailability because of enhanced absorption but also the role these lipids play in shielding the drug from harsh conditions inside the gut. These protection mechanisms help in maintaining the integrity of the drug until it hits its target site. In regard to SMEDDS, food effects on the absorption of drugs will be reduced by the utilization of lipids.

   The delivery of drug throughout the fed and fasted states becomes more consistent. This formulation strategy will also reduce the inter- and intra-subject variability, hence guaranteeing a more predictable and reliable therapeutic outcome. In particular, natural oils and fats composed of triglycerides with varying chain lengths and degrees of unsaturation are potent. The degree of unsaturation can, however, be reduced by synthetic hydrogenation, which would also alter the melting point and sensitivity to oxidation; this might have a bearing on the stability and performance of dosage form pharmaceuticals.

2) **Surfactant:** A surfactant compound needs to be amphiphilic because it comprises of both nonpolar hydrophobic (lipophilic) and polar or charged hydrophilic moieties. In the formulation of SMEDDS, emulsification is mainly imparted by surfactants. This can be mainly achieved by a combination of various surfactants having different HLB values. The HLB value is high for hydrophilic surfactants and thus provides very good solubilization in an aqueous medium, while for lipophilic surfactants, it is low and is thus easily dissolved in oils. The balance of this guarantees to formulate stable microemulsions with the required droplet size. Surfactants reduce interfacial tension; hence, excellent conditions are created during the formation of small droplets, further increasing the surface area for drug absorption.

   Some surfactants used in SMEDDS formulations have been reported to be capable of inhibiting P-gp and CYP3A4, specific enzymes involved in drug efflux and metabolism, respectively. It inhibits these pathways, increasing the bioavailability of the encapsulated drug. Secondly, some surfactants may even be able to modulate the intestinal epithelial cell permeability by opening tight junctions and further promote drug absorption. It is how these surfactants are carefully selected and combined in SMEDDS to maximize drug solubility, stability, and bioavailability. Surfactants used in SMEDDS are mainly (i) non-ionic, (ii) anionic, (iii) cationic or zwitterionic Surfactants.

- Non-ionic surfactants are those in which the highly polar groups, such as polyoxyethylene or hydroxyl, provide the hydrophilic group with its water solubility without carrying any charge. Examples include polysorbates (Tweens) and sorbitan esters (Spans).
- Anionic surfactants are those in which the hydrophilic group—such as carboxyl (RCOO-), sulphonate (RSO3 -) or sulphate (ROSO3 -) carries a negative charge. Examples include sodium lauryl sulphate and potassium laurate.
- Cationic surfactants: these have a positive charge on the hydrophilic group. Quaternary ammonium halide is one example.

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- Zwitterionic Surfactants: Both a positive and a negative charge are present in ampholytic surfactants, also known as zwitterionic surfactants. For instance, sulfobetaines
- Polymeric Surfactants: Macromolecular surfactants called polymerics can provide SMEDDS formulations special qualities including enhanced stability and controlled release. As examples, consider: Pluronics are ethylene oxide and propylene oxide block copolymers.

Cosurfactant: Co-surfactants with HLB (value-10-14) are used alongside surfactant to lower oil phase tension, expand interface, and enhance fluidity, thereby increasing system entropy. [10]

Cosurfactants play a major role in enhancing solubilization and emulsification properties of SMEDDS. The cosurfactants further aid in developing a more stable microemulsion by enhancing the solubilization of poorly soluble drugs. Additionally, it has been shown that the presence of a cosurfactant can significantly reduce the amount of surfactant required to generate effective emulsification, which often minimizes potential toxicity created by a high concentration of the surfactant in a formulation.[11)]

Co-solvents like diethyl-glycol-monoethyl ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate etc, may help to dissolve large amount of hydrophilic surfactants or hydrophobic drug in the lipid base. These solvents sometimes play role of co-surfactant in microemulsion systems.[1)]

Adsorbents / solidifying agents: Adsorption of liquid SMEDDS to a solid carrier or the use of several solidification techniques, such as spray drying, spheronization, melt extrusion, nanoparticle technology, supercritical fluid-based technologies, etc., are the usual processes for converting liquid SMEDDS to S-SMEDDS. However, the adsorption method for these is straightforward and only entails adding liquid formulations to carriers by blending them together in a blender.[12)] Adsorbents such as cellulose, aerosil, neusilin US2, and fujicalin are utilized.[1)]

FACTOR AFFECTING SMEDDS

(a) API dose: For the formulation of SMEDDS, medications with low therapeutic doses are typically preferred. However, these drugs have significant solubility in all SMEDDS components, particularly in the lipid phase. A drug with a low Log P-value (around 2) and poor solubility in both oil and water is not a suitable contender for SMEDDS.[8)]

(b) Solubility of the Drug in the Oil Phase: The drug's solubility in the oil phase often has an impact on SMEDDS's capacity to maintain the drug in solution. Assume that a surfactant or co-surfactant has a greater effect on the drug's solubilization. Then, there is a chance of precipitation since the surfactant or cosurfactant's solvent capacity will be reduced due to the dilution of SMEDDS.
[9)]

(c) The polarity of lipophilic phase: The polarity of lipophilic phase: Drugs release from the microemulsion is governed by one of the factors that are the polarity of the lipid phase. HLB, the molecular weight of the micronized drug, the chain length and degree of unsaturation of fatty acid govern the polarity of the droplet.[14)]

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(d) Temperature: Temperature affects nucleation rate and drug-polymer binding, due to increased drug solubility and weakening intramolecular interactions at higher temperatures.[6)]

e) Impurities: Impurities in the solution promote the nucleation process. Impurities lower the energy barrier for nuclei to develop, which eventually results in the creation of crystals. Consequently, compared to homogeneous nucleation processes, the critical cluster size is substantially less.[6)]

f) Degree of supersaturation: By accelerating up the nucleation rate, a higher degree of supersaturation in the SMEDDS formulation promotes drug precipitation. The following processes can lead to supersaturation: (a) the solvent evaporates from the solution; (b) the solution cools if the solute has a positive heat of solution; (c) a chemical reaction forms a new solute; (d) a substance with a higher solubility in solvent than the solid to be crystallized is added; and d) addition of solvent that lowers the solubility of the solute.[6)]

METHOD OF PREPARATION

Phase Titration Method

- The spontaneous emulsification method (also known as the phase titration method) is used to generate microemulsions, which can be represented using phase diagrams.
- Studying the complex series of interactions that can happen when several components are combined can be accomplished with the use of a phase diagram.
- formed in conjunction with different association structures (emulsion, micelles, laminar, hexagonal, cubic, and other gel and oil dispersions) based on the concentration and chemical composition of each component. Determining the phase boundaries and comprehending the phase equilibrium are crucial; each corner of the diagram represents 100% of the component under consideration. The region can be classified as either w/o or o/w microemulsion based solely on its composition, meaning it can be classified as being rich in water or oil. In order to exclude metastable systems, careful assessment is necessary.

Phase Inversion Method

These techniques involve modifying the surfactant's spontaneous curvature. This can be accomplished in the case of non-ionic surfactants by raising the system's temperature, which causes a transition phase inversion—a change from a low-temperature O/W micro-emulsion to a W/O micro-emulsion at higher temperatures. A point with less surface tension and no spontaneous curvature is reached by the system as it cools, which promotes the development of small oil droplets. The process is referred to as the phase inversion temperature (PIT).[9)]

Solidification Techniques

Spray Drying: Spray drying is one of the methods most frequently used to solidify SMEDDS. The liquid SMEDDS formulation is atomized into tiny droplets and injected into a hot air chamber during the spray drying process. Solid particles, such as drug-loaded microemulsion droplets contained within a solid matrix or particles covered with solid carriers, are formed as the solvent rapidly evaporates. A variety of solid carriers have been used for preparation of S-SMEDDS e:g Dextran 40 (water soluble solid carrier, Aerosil®200 (non-porous and hydrophilic solid carrier).[3)]

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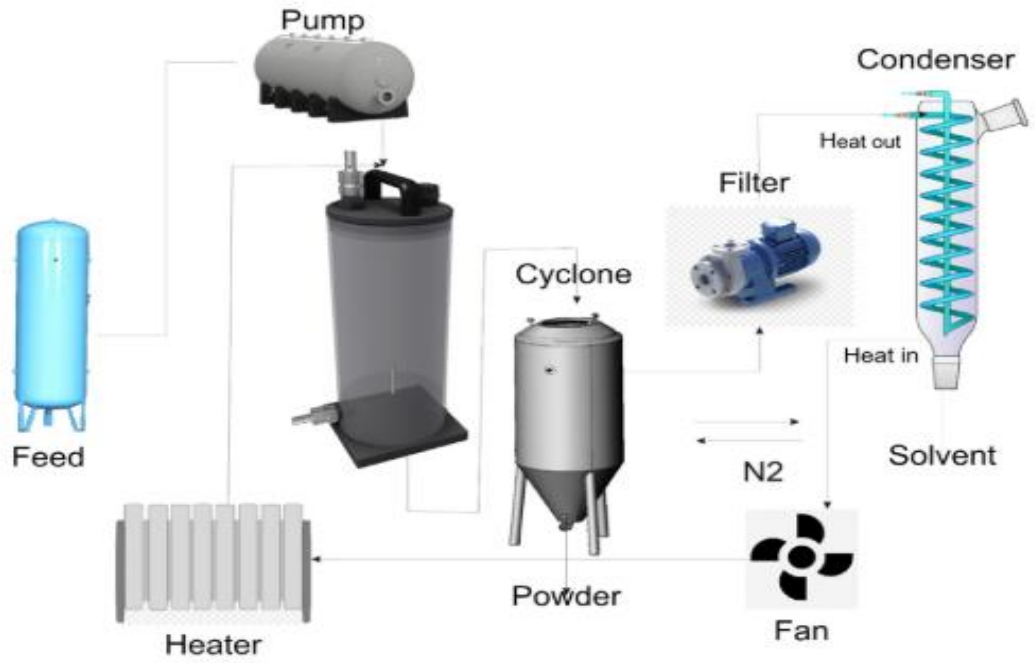

Method for preparation of S-SMEDDS (Hot Melt Extrusion Method) [16)]

Spherical Crystallization: Drug and/or excipients in the SMEDDS formulation may crystallise into spherical particles using this technique. Anti-solvent precipitation and liquid-liquid dispersion are two techniques that can accomplish this. As an alternative to traditional crystalline forms, the resulting spherical crystals can offer better flow properties, an increased dissolution rate, and controlled release characteristics. [17)]

Hot Melt Extrusion (HME): With hot melt extrusion (HME), active pharmaceutical ingredients (APIs) and polymer matrices are melted and mixed to create a homogenous melt that is then extruded through a die to create solid dosage forms. For SMEDDS, HME can be used to melt-process the liquid formulation with appropriate excipients to create solid extrudates or pellets. This process has benefits including increased drug stability, enhanced bioavailability, and controllable release of the drug. [2)]

Liquid and semisolid self-emulsifying formulations for capsule filling

The most popular simple method for encapsulating liquid or semi-solid SE formulation for oral delivery is capsule filling.

The procedure for semisolid formulations consists of four steps:

- Heating semisolid excipients to a minimum of 208° C, which is above their melting temperatures.
- Incorporation of active substances (with stirring).
- Capsule filling with molten mixture.
- Cooling to room temperature. [3)]

Adsorption on Solid Carriers: The final solid product is obtained by adsorbing liquid formulation on solid carriers. This allows the product to flow freely and be compressed or directly put into hard gelatin capsules. Good content uniformity and the possibility for high lipid exposure are two important advantages of the adsorption approach. Solid carriers that can be used are e:g Neusilin US2, Avicel PH 101, Spray dried lactose.[3)][1)]

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Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: Two kinds of submicron particles (50–1000 nm) made of lipid components that are physiologically acceptable are called SLN and NLC. The process of producing SLN involves homogenizing the solid matrix and drug under high pressure using an aqueous solution containing poloxamers 188 or polysorbates 80 as surfactants and glyceryldibehenate as the solid lipid matrix. Together with the traditional SLN components, they usually comprise a liquid lipid excipient, such as medium chain triglycerides. Their primary applications have been in controlled-release formulations administered orally, intravenously, or topically. [1)]

Cryogenic Grinding: The majority of formulations that use Gelucire® 44/14 as a self-emulsifying excipient employ this technique. Due to gelucire's low melting point, only semi-solid dosage forms may be created; gelucire must first be melted and then combined with the drugs. Therefore, the process of cryogenic grinding can be used to create solid dosage forms such as tablets and pellets.[18)]

Fluid bed granulation:
The goal of fluid bed granulation is to better understand how to optimize the granulation process variables (such as the type of solid carrier and granulation dispersion) and formulation variables (such as high drug loading and suitable product characteristics).

For each stage the process yield (η) was calculated by Eq. (1):

η = × mass dry product dry entering substance / 100 %.

Fluid-bed granulation facilitates the generation of S-SMEDDS that exhibits full drug release. Binder type, concentration, and binder/SMEDDS ratio are significant factors. S-SMEDDS tablets with quick release of drugs and maintained self-emulsifying properties.[19)]

Spray Cooling: Droplets of molten droplets are sprayed into a cooling chamber, where they solidify and re-crystallize into spherical solid particles. These particles settle to the chamber's bottom and are collected as fine powder. The fine powder is then directly filled into hard shell capsules or used for making solid dosage forms. To atomize the liquid mixture and produce droplets, a variety of equipment is available, including pressure, rotary, two-fluid, and ultrasonic atomizers.[3)]

Characterization of SMEDDS

Visual Evaluation: The development of a macroemulsion is indicated by an opaque and milky white appearance after diluting SMEDDS with water, while the formation of a microemulsion is indicated by a clear, isotropic, transparent solution. Visual inspection can also be used to assess drug precipitation in diluted SMEDDS. In cases where drug precipitation is not apparent the formulations can be regarded as stable. Increasing the concentration of surfactant helps prevent precipitation, which is common if the formulation consists of water soluble cosolvents.[4)]

Size of the Emulsion Droplet: As it controls the rate and extent of drug release and absorption, it is a critical component of self-emulsification/dispersion performance. The Coulter nano-sizer can be utilised to obtain a comparative measurement of the average particle size for this type of system since it automatically provides Photon Correlation analysis on scattered light. This instrument. Measure the dynamic variations in laser light

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scattering intensity caused by Brownian motion-induced particle oscillation. This method is applied in cases when the range of particle sizes is smaller than 3μm; the size range of SMEDDS is 10 to 200 nm.[21)]

Emulsion Droplet Polarity: Emulsion droplet polarity is a key component in determining emulsification efficiency. The polarity of the oil droplets is greatly influenced by the hydrophilic portion's molecular weight, the emulsifier concentration, the chain length and degree of unsaturation of the fatty acid, and the HLB. Polarity refers to the drug compound's affinity for oil /or water, as well as the types of forces created. Drug polarity promotes rapid drug release into the aqueous phase.[22)]

Zeta Potential Measurement: Zeta potential is often measured using a zeta metre system or a zeta potential analyser. After the proper dilution, the zeta potential value reflects the stability of the emulsion. A higher zeta potential suggests that the formulation is stable. Zeta potential is typically negative since fatty acids are present, but when cationic lipids like oleyl amine are employed, the positive charge develops. Because the positive charge droplets have the ability to connect with the GIT mucosal surface effectively, high adherence and improved absorption are predicted as a result of these electrostatic interactions.[4)]

Self-emulsification Time: Time for self-emulsification, which is typically measured with a USP Type II dissolution device. In short, the formulation was added to distilled water that was kept at 37 °C, and the amount of time it took for a clear solution to develop was noted while the water was gently agitated at 100 rpm [20)].Grade I emulsions are those that quickly take on a clear look in less than a minute. Grade II denotes a little hazy opacity of the emulsion after two minutes. If an emulsion forms in three minutes and is dazzling white in colour, it might be categorized as grade III. Grade IV has a dingy, greyish-white emulsion that looks slightly oily for longer than three minutes. On the other hand, grade V shows inadequate emulsification and big oil droplets on the surface.[23)]

Cloud Point Determination: Typically, spectrophotometric measurement of the formulation's cloud point is performed by progressively raising the water bath's temperature. The temperature at which the clear solution turns cloudy is known as the cloud point, and it is shown by the point where the transmittance percentage drops. Body temperature is 37 ∘C, hence in order to maintain the self-emulsification property, formulations should show a higher cloud point than body temperature. Due to the surfactant's susceptibility to dehydration, phase separation and decrease in drug solubilization are frequently seen at temperatures higher than the cloud point. Drug lipophilicity and other formulation components affect cloud point.[4)]

Viscosity Measurements: Rheometers such as the Brookfield cone and plate rheometers equipped with rotating spindle or cone spindle Brookfield viscometers are typically used to measure the viscosity of diluted SMEDDS formulations, which are microemulsions. The formation of an O/W microemulsion from a W/O microemulsion with an intermediate bicontinuous phase is indicated by the initial increase in viscosity during titration, which is followed by a decrease, and an increase in water volume, which is attributable to the water percolation threshold.[4)]

Transmittance test: The transparency of the diluted SMEDDS formulation is indicated by this test. After diluting the formulation with water, it is measured spectrophotometrically,

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with water serving as the blank. The formation of a clear and transparent microemulsion is indicated by a percentage transmittance value that approaches 100%.[4)]

In Vitro Dissolution Profile: The drug release from a hard gelatin capsule can be studied using USP XXIII apparatus I at 100 rpm or USP XXIII apparatus II at 50 rpm, or dialysis method at 37 ± 0.5∘C. At regular intervals, samples should be collected from the medium, and the drug content measured and compared to the control. The polarity of the oil droplet affects drug release from the diluted SMEDDS.The higher the polarity, the faster the drug leaves the oil droplet and enters the aqueous phase.[4)]

Differential Scanning Calorimetry: Differential Scanning Calorimetry determined the physical state of the drug in the solid SMEDDS formulation. About 2 mg of pure drug, excipients, and the solid SMEDDS were weighed and placed individually in sealed standard aluminium pans. These were then scanned over a temperature range from 25°C to 300°C at 10°C/min under a nitrogen atmosphere. A reference of an empty aluminium pan was used. The thermograms gave information about the thermal behaviour of the drug and the drug crystallinity upon dispersion of the drug in a solid SMEDDS and possible interactions with the excipients.[1)]

X-ray Diffraction: XRD was carried out to investigate the crystallinity of the pure drug and solid SMEDDS formulation. The powder samples were placed in an aluminium sample holder, and the analysis was conducted using the help of an XRD-6000 diffractometer. Cu Kα radiation was created at 30 mA and 40 kV. Scanning of samples was done for a 2θ range of 10°-90° with a speed of 10°/min. This method helped detect any changes in the crystalline structure of the drug while it was incorporated in the solid SMEDDS, which is critical to understanding its formulation stability and characteristics of drug release.[24)]

Scanning Electron Microscopy (SEM): The particle shape and surface morphology of the solid SMEDDS were studied by scanning electron microscopy. The solid SMEDDS samples were lyophilized to remove moisture completely, mounted on aluminium stubs with adhesive tapes, and then coated with a thin layer of gold using a sputter coater to enhance conductivity. The morphological observations were done on the surfaces at an acceleration voltage of 20 kV and have minutely revealed to show the surface characteristics, particle distribution within the solid SMEDDS formulation.[24)]

Transmission Electron Microscopy (TEM): TEM was used for the evaluation of the internal nanostructure of SMEDDS. The samples were prepared by applying the formulation on a carbon-coated copper grid and observed under the TEM at an acceleration voltage of 80-120 kV. This technique afforded clear images with details on droplet size and distribution or structural arrangement in SMEDDS, thus providing insight into its character. [24)]

Drug-excipient Compatibility Studies: As the drug is mixed with excipients such as oils, surfactants, co-surfactants, etc. in these formulations, it is crucial to understand that the characteristics of the drug remain unchanged upon the addition of these excipients, which makes this study significant in the context of solid self-micro emulsifying drug delivery systems. Typically, an FTIR spectrophotometer with the diffuse reflectance principle is used to take the FTIR spectra of solid SMEDDS, a physical mixture of the drug and oily excipients, and pure drug substances. Then, any spectral alterations are looked for in the resulting spectra.[1)]

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Stability Studies

1. Thermodynamic Stability Studies

- **Heating Cooling Cycle**
  Samples are heated to temperatures ranging from 4°C to 45°C in many cycles, often done in hexaplicate. If SMEDDS remained stable at these temperatures, centrifugation testing was performed.
- **Centrifugation Test**
  Passed SMEDDS were centrifuged at 3500 rpm for 30 minutes using a digital centrifuge. If SMEDDS indicated no phase separation, freeze-thaw stress testing was performed.
- **Freeze-thaw cycle**
  Freeze-thaw cycles are typically performed three times between -21°C and +25°C. For at least 48 hours, every formulation is maintained at each temperature. In order to determine the effectiveness of self-emulsification, the formulation that passes the thermodynamic stress tests is then subjected to the dispersibility test.[22)]

FUTURE ASPECTS

Techniques are now being used to turn liquid/semi-solid SEDDS and SMEDDS formulations into powders and granules, which can then be further processed into conventional "powder-fill" capsules or even compressed into tablets, with regard to the formulation development of poorly soluble drugs in the future. Moreover, there is growing interest in the use of inert adsorbent agents to turn liquids into powders that can be further processed to create powder fill capsules or tablets. Colloidal silicon dioxide, also known as Aerosol 200, is chosen as a gelling agent for oil-based systems with the potential to reduce the quantity of solidifying excipients needed while also helping to slow the release of the drugs. Hot melt granulation is a granule or pellet production technology that allows up to 25% solubilizing agent to be added to a formulation by employing it as a binding agent for waxy solubilizing agents.[24)]

Supersaturable SMEDDS: Reduced surfactant content and a water-soluble polymer that functions as a precipitation inhibitor or supersaturated promoter are the two main components of supersaturable SMEDDS. Traditionally, SMEDDS have been used extensively to improve the oral absorption of poorly soluble medicines. However, drug precipitation may happen when traditional SMEDDS formulations are administered in the GI area, which could prevent intestinal absorption from improving. Conversely, GI discomfort may result from SMEDDS's high surfactant content. In order to counteract these undesirable consequences, supersaturable SMEDDS, a novel method to thermodynamically stable formulation, have been created. [1)]

Advanced Formulation Techniques: As formulation techniques continue to be researched, more effective and stable SMEDDS formulations should be developed. In order to maximise medication solubility and stability within the microemulsion, this involves investigating innovative excipients, surfactants, and co-solvents.

Customised Drug Delivery: Upcoming SMEDDS formulations could be made to fit the pharmacokinetic characteristics of particular medications, enabling the development of unique drug delivery plans. To maximise therapeutic efficacy while reducing side effects, this may entail targeted administration to particular tissues or cells or controlled release formulations.

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Combination Therapy: By enabling the delivery of several medications at once, SMEDDS creates opportunities for combination therapy. Subsequent investigations might concentrate on refining drug combinations in SMEDDS formulations to attain synergistic effects, boost treatment outcomes, and increase patient compliance.

RECENT TRENDS IN SMEDDS

Supersaturable SEDDS (S-SEDDS)

Supersaturated drugs formulations may be able to increase drug absorption, according to Higuchii T. When working with several poorly water-soluble drugs, polyvinylpyrrolidone and water-soluble cellulosic polymers such hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), and hydroxyl propyl MC phthalate are helpful for generating a supersaturatable state. HPMC was used as a precipitation inhibitor. [25)]

Self-microemulsifying Floating Dosage Form

The floating system prolongs the release of drugs in the stomach by increasing their residence time. Furosemide's innovative floating formulation involves adsorbing it onto a blend of high functionality excipients, matrix forming polymers (HPMC E50 LV and HPMC K4M), and NaHCO3 (a gas-generating agent) to create a floating matrix with controlled drug release.[26)]

Self-nanoemulsified Drug Delivery System

SEDDS was used to develop a self-nanoemulsified drug delivery system (SNEDDS) for ubiquinone. The study found that SNEDDS surpassed traditional emulsified systems in terms of solubility and drug precipitation of the active drug in the vehicle with time.[27)]

Self-microemulsifying Mouth Dissolving Film (SMMDF)

Xiao L, et al. developed a self-microemulsifying mouth-dissolving film (SMMDF) for poorly water-soluble drugs. Indomethacin was produced by fusing self-microemulsifying segments with solid carriers containing microcrystalline cellulose, low-substituted hydroxypropyl cellulose, and hypromellose. The SMMDF is a promising dosage structure that offers excellent accommodation, rapid onset of activity, and improved oral bioavailability for poorly water-soluble drugs. [28)]

Sustained Release Dosage Form

Formulating SEDDS with ketoprofen in a sustained release dosage form resulted in improved drug release. Silicon dioxide was utilised as a gelling agent, which may aid in solidification and delay drugs release. The effect of cosurfactant and gelling agent concentrations on emulsification and drug diffusion in vitro was investigated using a 3(2)-factorial design. [29)]

Dry Emulsions

To increase the bioavailability and photostability of amlodipine, which is poorly water-soluble and photosensitive, a dry emulsion (DE) was created by spray-drying the oil-in-water emulsion. DE formulation significantly increased amlodipine's photostability while also enhancing the physical stability of emulsion systems. Consequently, DE formulation resulted in 2.6- and 2.9-fold greater Cmax and AUC0-24 h of amlodipine compared to oral administration of amlodipine powder in rats. [30)]

Self-Microemulsifiyng Suppository

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Self-micro emulsifying suppositories (SMES) of β-artemether have been developed for rectal administration to enhance the onset and duration of action. SMES for β-artemether were compared to traditional PEG-based suppositories. The study found that SMES has all the necessary physicochemical properties of suppositories. In vivo investigations showed that SMES has better antimalarial activity than PEG-based suppositories. [31)]

CONCLUSION

The development of Solid SMEDDS (Solid Self-Micro emulsifying Drug Delivery Systems) offers a new and hopeful way of circumventing the shortcomings in conventional drug delivery techniques for poorly water-soluble drugs. Solid SMEDDS are an attractive choice for addressing drug delivery issues because of their advantages, which include increased solubility, stability, and bioavailability.

The majority of commercially available SMEDDS formulations come in soft gelatin capsules, which makes handling problematic and raises the product's cost. The development of solid SMEDDS might thereby reduce handling concerns, lower the product's cost, and solve the liquid product's stability issue. By providing more efficient and patient-centered solutions, these advancements have the potential to overcome the difficulties associated with traditional delivery. A new era of accuracy and effectiveness in medical treatment is about to begin with SMEDDS, which are poised to transform drug delivery systems as research on these methods expands and improves.

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