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SOLID SUPERSATURABLE SMEDDS: A POLYMERIC PRECIPITATION INHIBITOR TO ENHANCE SOLUBILITY AND BIOAVAILABILITY

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ABSTRACT

More than 60% of drugs are poorly water-soluble, and it has less bioavailability. There are many techniques to overcome these problems, like Cyclodextrins, salt formation, lipid-based formulation, and solid dispersion. Amongst all approaches, supersaturable self micro emulsifying drug delivery system has been demonstrated to enhance oral solubility and bioavailability effectively. Supersaturable formulations are exposed to gastrointestinal fluids, the medication concentration exceeds equilibrium solubility. High medication concentrations improve oral absorption of poorly water-soluble medicines in this way. Nevertheless, since many drugs are thermodynamically unstable at high concentrations, they precipitate rapidly in vivo before getting absorbed, resulting in poor bioavailability. Precipitation inhibitors are widely valuable for enhancing solubility, absorption rate, and bioavailability in various formulations. This review article provides information about various polymers used in supersaturation effects on self-micro emulsifying drug delivery systems (SMEDDS).

Keywords: Supersaturable, SMEDDS, solubility, bioavailability, solid SMEDDS

Background

Supersaturable SMEDDS

The active medication must stay solubilized at a high concentration after dispersion as the significant criteria for generating a stable SMEDDS. In particular, high apparent drug concentrations in colloidal micelles are

susceptible to fast precipitation in vivo, resulting in unpredictable bioavailability **[1-7]**. This results in a supersaturated state that is thermodynamically unstable (spring effect). Thus, a high surfactant concentration is customarily required to avoid precipitation, which can cause significant toxicity issues. In addition, the use of a polymer-based precipitation inhibitor (PPI), a hydrophilic macromolecule, to treat a supersaturated formulation primarily reduces crystallization and increases systemic medication absorption **[8, 20-21]**.

Additionally, a Precipitation Inhibitor can keep the medication in a kinetically stable supersaturable state, allowing for effective absorption **[20]**. These properties are obtained by slowing drug precipitation/crystallization by nucleation inhibition, crystal growth, or combining the two. Furthermore, supersaturable SMEDDS with PPI eliminate the need for high surfactant concentrations and delay drug precipitation, allowing for maximum supersaturation. Physical instability provides a challenging obstacle for designing an elegant and stable oral medicinal product due to the liquid nature of the formulation. In this case, supersaturation solidification has been frequently exploited to overcome physical stability difficulties in microparticulate oral lipid formulations **[9]**. The use of specific processes like spray drying to make solid supersaturable SMEDDS (solid SS SMEDDS) has several advantages, including scalability, robustness, storage/handling concerns, and improving the overall stability profile of the final oral product **[10-13]**.

Main text

Supersaturable SMEDDS Formulations

Supersaturable SMEDDS exposed to the aqueous environment of the gastrointestinal tract, supersaturable formulations can cause supersaturated drug concentrations. For medications to be absorbed at the desired moment, this mechanism must be generated and maintained. Many factors influence the creation of Supersaturable SMEDDS, including the processing procedures utilized, the compound's physicochemical qualities, and the tendency to create and sustain a supersaturated drug solution. The "spring & parachute" notion has been used to dissolve profiles that indicate rapid initial supersaturation of the medication and subsequent slowing of precipitates **[22, 39]**.

Figure 1 shows Types of solutions (Saturated, Supersaturated, Unsaturated).

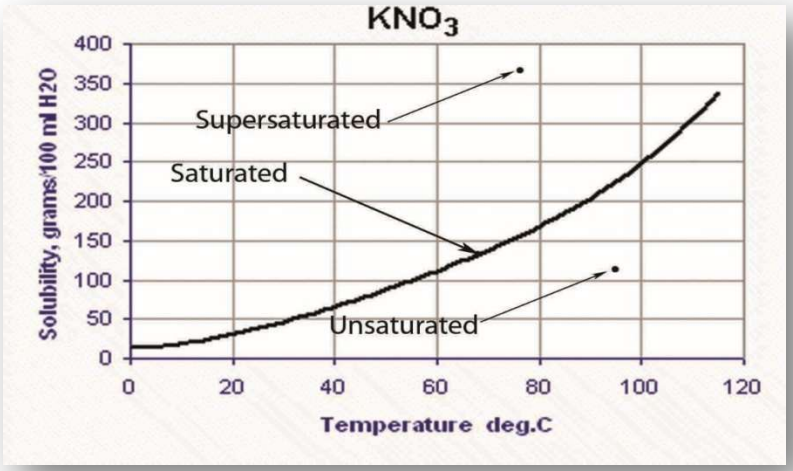

Figure 1: Types of solutions (Saturated, Supersaturated, and Unsaturated)

Drug Precipitation Inhibitors

Polymers

Polymers with low concentration (0.01-0.05%) could significantly affect drug nucleation and/or crystal growth rates and crystal morphology, leading to drug precipitation inhibition. For example, hydroxypropyl methylcellulose (HPMC), hydroxypropyl methylcellulose acetate succinate (HPMCAS), methylcellulose (MC), HPC, which are cellulose derivatives and vinyl polymers, for example, polyvinyl pyrrolidone, PVA, Poly (acrylic acid), polyvinyl pyrrolidone vinyl acetate (PVPVA) have been studied most.

Surfactants

Surfactants are used to enhance solubility and reduce the degree of supersaturation. For instance, Pluronic, tween 20, cremophore can delay precipitation from a supersaturated solution.

Cyclodextrins (CDs)

Cyclodextrins, for example, are widely known for their solubility and capacity to increase bioavailability. It will form inclusion complexes with a range of hydrophobic medicines, improving their solubility and lowering the degree of supersaturation, resulting in a slower nucleation rate and crystal formation.

Mechanisms of precipitation inhibition

Crystallization includes two stages: the first nucleation, solute molecules gather into two or three-dimensional clusters within the solution. If they are large than the critical size, then clusters continue to grow. The second stage is crystal growth, where the molecules periodically arrange themselves to form the crystal structure. Crystallization

effects on various properties of inhibitor, the drug, and the medium. Thermodynamic precipitation can be used to prevent medication precipitation. Increased drug solubility inhibits drug precipitation by lowering the degree of supersaturation, nucleation rate, and crystal formation. Surfactants, solvents, and cyclodextrin are only a few examples of solubilizers. By preventing or delaying drug precipitation in the supersaturated state, kinetic inhibition of drug precipitation is accomplished. Various polymers, for example, HPMC 5% and PVP 0.01 percent w/w.

Mechanism of self micro emulsifying drug delivery system:

When the entropy shift favoring dispersion is more significant than the energy necessary to increase the surface area of the dispersion, self-emulsification happens. The energy required to establish a new surface between the oil and water phases determines the free energy of a typical emulsion. Equation 1 can be used to describe this.

$\Delta G = \Sigma N \pi r2 \sigma$

G denotes the interfacial energy; the number of droplets with radius r is denoted by N, and E. denotes the free energy. The emulsification process can occur spontaneously in self-emulsifying systems because the energy required to produce an emulsion is low. According to Wakerly et al., introducing a binary combination (oil/non-ionic surfactant) to water generated an interface between the oil and water phases, which was then penetrated by water dissolution inside the oil phase. This process will continue until the surface's solubility limit is reached.

Components of SMEDDS formulation

Drug

SMEDDS can increase oral medication bioavailability, mainly for drugs that are in BCS classes II and IV. The drug contender should be a weakly water-soluble medication with an intermediate partition coefficient (log P between 2-4). The physicochemical parameters of the produced SNEDDS, such as log P, PKa, molecular weight, ionization group, number of medicines, phase behavior, and final droplet size, impact their performance. It was also agreed that a medication candidate with a low melting point and a low dosage would be acceptable for generally preparing the SMEDDS **[13, 14]**.

Oils

Oil is the essential excipient in SMEDDS formulation to enhance solubility and provide a fraction of lipophilic drug transported through the intestinal lymphatic system, thereby enhancing absorption from the GI

tract depending on the molecular nature of triglycerides **[13-16]**.

Surfactants

An anionic surfactant, for example, is one in which the hydrophilic groups have negative charges, such as carboxyl (RCOO-) or sulphonate (RSO3-). Sodium lauryl sulfate, potassium laurate are two examples. Second, cationic surfactants, such as quaternary ammonium halide, positively charge the hydrophilic group. Third, both negative and positive charges are present in ampholytic surfactants (also known as zwitterionic surfactants). Sulfobetaine, for example. Fourth, there are nonionic surfactants, which have no charge but do have water solubility. Surfactants with negative and positive charges are called ampholytic surfactants (also known as zwitterionic surfactants) **[17]**.

Co-surfactants/ Co-solvents

Co-surfactants and solubilizers are added to the SMEDDS to increase drug loading, improve self-emulsification time, and modulate microemulsion droplet size. Including co-surfactants and solubilizers in the SMEDDS might result in a phase diagram with a larger self-micro emulsification zone. Propylene glycol, polyethylene glycol, polyoxyethylene, Lauroglycol^{TM}, Transcutol®, and other co-surfactants and solubilizers are commonly used in the production of SMEDDS **[17]**.

Aqueous Phase

The properties of the aqueous phase in which the SMEDDS are administered determine the droplet size and stability of the microemulsions. As a result, the pH and ionic content of the aqueous phase should be addressed during the creation of the SMEDDS. In addition, the SMEDDS microemulsions' self-micro emulsification property and features in varied pH and electrolyte concentrations of the aqueous phases should be investigated in accordance with their administration manner **[18]**.

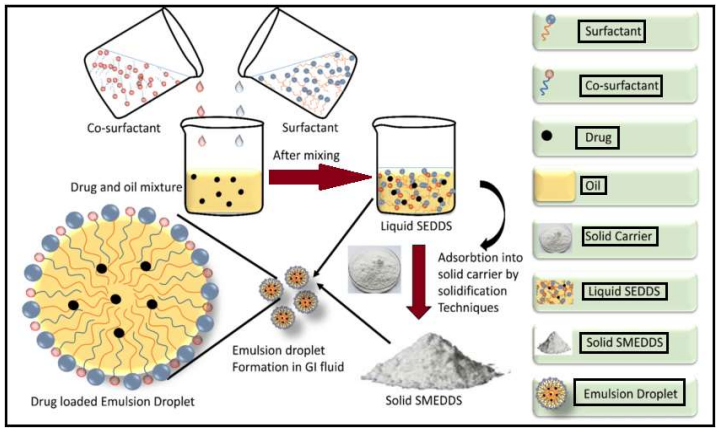

Figure 2: Method of Preparation of Solid SMEDDS

Ternary Phase Diagram

The ternary phase diagram between the surfactant, oil, and solubilizer must be plotted to determine the self-emulsification area after selecting the suitable excipients for the formulation of the SMEDDS. After diluting the different compositions of the ternary phase diagram with a constant amount of water, the droplet size of the emulsions or microemulsions is measured to determine the self-microemulsification area in the ternary phase diagram. The self-micro emulsification area is defined by locations with spontaneous microemulsions and droplet sizes smaller than 200 nm. The ternary phase diagram is a three-dimensional plot shown in a two-dimensional format for easy explanation and comprehension. The relative proportion of the three components is displayed in the ternary phase diagram to indicate that all three components have a total of 100 percent or are normalized to 100 percent. The effect of several variables on the features of the SMEDDS, such as droplet size, self-microemulsification time, and in vitro dissolution, can also be studied using a statistical experimental design or response surface methods to optimize the SMEDDS. The response surface methodology can generate the desired product with tiny droplet size, reduced self-emulsification time, and high in vitro dissolution rate once the mathematical correlation between the factors and the response is discovered **[19]**.

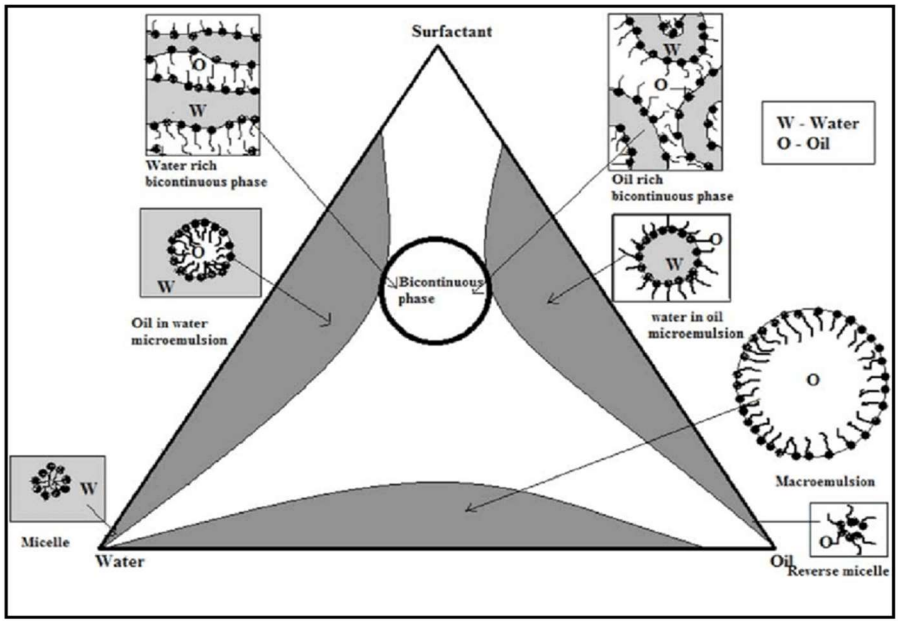

Figure 3: Pseudo Ternary Phase Diagram

Characterizations of Supersaturable SMEDDS

Droplet size and Zeta Potential

The Smoluchowski theory can be used to determine the particle charge of produced microemulsions. The zeta potential indicates the colloidal dispersion's stability. If the formulation has a high zeta potential, it will remain stable, especially if the zeta potential is more than 30 mV **[24]**.

Morphology

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) can be used to examine the morphology of microemulsion droplets (SEM). The TEM technique would provide information on the vesicles' inner structure, while the SEM approach would provide information on the vesicles' surface shape. Before the measurement, the sample may be diluted to a sufficient concentration **[24-28]**.

Self microemulsion time

A dissolution apparatus is used to evaluate the efficacy of self-microemulsification. 1 mL of SMEDDS is dissolved in 250 mL of water at 370.5°C in general. A paddle rotating at 50 rpm provides gentle agitation. The rate of emulsification and the final look of the emulsion is used to evaluate SMEDDS. The time it took to emulsify is recorded. After the emulsification is complete, the samples are taken for particle size using photon correlation spectroscopy and other characterizations **[29]**.

Refractive Index

The refractive index (RI) is a valuable tool for determining whether or not a formulation is precise. A refractometer is used to determine the system's RI by dropping a drop of the solution onto a slide and comparing it to water, which has a RI of 1.333. The formulation is transparent if the RI of the system is similar to the RI of water. The RI is also used to determine the formulation's thermodynamic stability. For example, the SMEDDS' constant structure and thermodynamic stability would be indicated by minimal changes in the RI at various storage time points.

Percentage transmission

The % transmittance of the system is determined using a UV spectrophotometer and water as a blank after dilution of the formulation at 638 nm wavelength. The formulation would be clear and transparent if the percentage transmittance value were closer to 100 percent.

Viscosity

A viscometer, such as a Brookfield cone or plate viscometer, is used to determine the viscosity of liquid SMEDDS. The viscosity is

measured in centipoises and is proportional to the shear rate.

X-ray diffraction

For solid-state interaction studies of supersaturable SMEDDS, the diffraction studies, solid-state, physical mixture, diffraction technique will be obtained by X-ray diffractometer.

Invitro dissolution study

The SMEDDS in vitro dissolution profile should be investigated in several dissolution media associated with the intended route of administration, such as pH 1.2 and pH 6.8 for oral application, using dissolution equipment Type II. The dissolved medication in the dissolution media would be collected and analyzed using an acceptable analytical method over a predetermined period. In comparison to the pure drug, cumulative amounts of drug dissolved against SMEDDS timings would be displayed **[40]**.

Thermodynamically stability study

A thermodynamic stability test would be performed during the development phase to overcome the problem of the metastable formulation. First, the liquid SMEDDS would be centrifuged for 30 minutes at 3,500 rpm. Next, the heating-cooling cycle would be applied to the formulation that did not demonstrate any phase separation. Six 48-hour cycles between 4°C and 45°C would be carried out. The freeze-thaw stress test would then be performed on the formulation that is still stable, with three cycles between -21°C and 25°C lasting 48 hours. The formulation that passes the thermodynamic stability test is chosen to be the stable formulation for further research **[34-39]**.

Stability Study

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use recommends that stability studies of nanomedicines, including the SMEDDS, be carried out according to their recommendations (ICH). Non-targeted nanomedicines, exempt from biotechnological product rules, should follow the processes outlined in the ICH Q1A(R2) and Q1C guidelines. Meanwhile, the ICH Q5C guideline processes should be followed by the targeted nanomedicines, which are generally incorporated with biotechnological goods. SMEDDS should also be tested for heat stability and moisture sensitivity under storage circumstances. The ICH standards prescribe storage temperatures of 25°C ± 2°C/ 60% ± RH 5% RH and 40°C ± 2°C/ 75% RH ± 5% RH for long-term and accelerated storage, respectively. In addition, an appropriate intermediate storage condition is indicated (30°C ± 2°C/ 65% ± RH 5%

RH). Furthermore, if any drug items have to be stored in a refrigerator, long-term and accelerated storage settings of 5°C ± 3°C and 25°C ± 2°C/ 60% RH ± 5% RH is recommended, respectively. In addition, the features of the samples should be determined, such as appearance, color, drug content, and dissolving profile. If these features match the initial formulation, the formulation is said to be stable. Other metrics that can be used to characterize the s-SMEDDS include micromeritic properties such as bulk density, tapped density, angle of repose. Dissolving the s-SMEDDS in a suitable solvent and assessing the drug content in the solvent extract using an appropriate analytical method should be used to determine the drug content in the s-SMEDDS. Hardness, friability, weight variation, disintegration, and dissolution are other properties that the s-SMEDDS produced tablets might be examined **[33]**.

Factors affecting SMEDDS

Drug Dose

SMEDDS is not suited for drugs provided at substantial doses unless they have excellent solubility in at least one of the self-micro emulsifying drug delivery system components, ideally the lipophilic phase. This is because the drugs are water-insoluble, and lipids (usually log P values of around 2) are the most challenging to deliver via SMEDDS **[40]**.

Solubility of the drug in the oil phase

The drug's solubility largely determines the capacity of SMEDDS to keep the drug in a soluble state in the oily phase. Therefore, there may be a risk of precipitation if the surfactant or co-surfactant contributes to a greater extent of drug solubilization, as dilution of SMEDDS reduces the solvent capacity of the surfactant or co-surfactant **[2]**.

Equilibrium solubility:

It can be used to predict potential cases of gastrointestinal precipitation. In the solubilizing environment of the gut, however, crystallization may be slow. According to Poutons' research, it can take up to 5 days for such a formulation to reach equilibrium, and the medicine can stay hyper-saturated for up to 24 hours after the initial emulsification event **[1]**.

The polarity of lipid phase

One of the elements that govern microemulsion release is the polarity of the lipid phase. The polarity of droplets is determined by HLB, fatty acid chain length and degree of unsaturation, lipophilic part molecular weight, and emulsifier content. In reality, the polarity of medicine indicates its attraction for oil and water and the types of forces involved. Because of the strong

polarity, the medication will be released quickly into the aqueous phase **[2]**.

Droplets charge of emulsion

The droplet charge of emulsion is the most promising parameter of absorptive cells, and other cells in the body are negatively charged concerning the mucosal solution in a lumen. On the other hand, positive charge emulsion droplets undergo electrostatic interaction **[31-34]**.

CONCLUSIONS:

Supersaturable self micro emulsion has cardinal approach to enhance oral solubility and bioavailability. It maintains drugs in the supersaturated states *in-vivo* is a necessity in this formulation to ensure adequate absorption. In order to attain enhanced bioavailability, polymer precipitation inhibitors have been utilized to extend supersaturated drug concentrations *in vivo*. Understanding precipitation inhibition processes is one of the issues now facing formulation scientists in identifying acceptable and efficient polymer precipitation inhibitors in supersaturable formulations. For the formulation of therapeutic molecules with low water solubility, self-micro emulsifying drug delivery devices offer a potential option. In addition, SMEDDSs can help in the oral distribution of hydrophobic medications. Despite extensive research into precipitation inhibitors and supersaturable formulations, little is known about the mechanisms of inhibition, particularly at the molecular level. Drug precipitation inhibitors are generally identified and selected empirically, requiring considerable formulation screening and in vivo research. Selecting the appropriate precipitation inhibitor(s) for a specific molecule of interest requires a better knowledge of the working mechanism of precipitation inhibitors.

List of Abbreviations

sSMEDDS: Self-microemulsifying drug delivery system

SEDDS: Self-emulsifying drug delivery system

S-SMEDDS: Solid Self-microemulsifying drug delivery system

API: Active pharmaceutical ingredients

GI: Gastrointestinal

MCC: Microcrystalline cellulose

PEG: Polyethylene glycol (PEG)

PG:Propylene glycol

PDI:Polydispersity index

PI- Precipitation inhibitors

HLB: Hydrophilic-lipophilic balance

MCT: Medium-chain triglycerides

LCT: Long-chain triglycerides

BCS: Biopharmaceutical classification system

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