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INVESTIGATING ADVANCES IN SELF-EMULSIFYING DRUG DELIVERY SYSTEM

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Abstract : The solubility of orally administered pharmaceuticals is a major challenge for the pharmaceutical industry because around 35–40% of newly approved drugs have low water solubility, which causes poor dissolution and high intra- and inter-subject variability. and inadequate bioavailability results in an imbalance in dosage proportionality. This could rise as a result of various processes such the formation of salt, solid dispersion, and complicated construction. The Self-Emulsifying Drug Delivery System (SEDDS) is being more widely used to improve the solubility of lipophilic medications. G1 fluids are an example of an aqueous medium. SEDDS are described as isotropic mixtures of one or more hydrophilic solvents, co-solvents, and/or surfactants that, when gently shaken and then diluted in water, have the unusual ability to generate fine oil-in-water (o/w) micro emulsions. SEDDS are defined as isotropic mixes of one or more hydrophilic solvents, co-solvents, and surfactants that, when gently stirred and then diluted in water, have the remarkable capacity to create fine oil-in-water (o/w) micro emulsions. GI fluids are an example of an aqueous medium. Typically designed in liquid or solid dosage forms like tablets, capsules, or pellets, SEDDS provide a number of benefits, such as increased drug permeability, better drug solubility, and protection against drug degradation in the gastrointestinal tract. Additionally, they offer versatility in terms of choosing lipids, surfactants, and co-surfactants, enabling the formulation to be tailored to the unique physiochemical characteristics of the medication. A broad variety of pharmacological classes, including lipophilic, poorly soluble, and low bioavailability medications like immunosuppressant, lipid-lowering medicines, anticancer treatments, and antiviral products, have been effectively treated using SEDDS.
Keywords:- Aqueous solubility**,** Self-emulsifying drug delivery system (SEDDS, Isotonic mixtures

INTRODUCTION

Drugs that are more readily absorbed throughout the gastrointestinal tract (GIT) have strong oral bioavailability, but there are a few possible drawbacks. These consist of suitable intestinal permeability, resistance to metabolism in the enterocyte and the liver, and proper stability and solubility in the GI fluid **Sharma V., et al. 2012**. The discovery that co-administering poorly soluble, lipophilic medications with a high-fat meal can increase their oral bioavailability has sparked renewed interest in the formulation of these treatments in lipids to improve drug solubilization in the gastrointestinal tract **Sachan r et al, 2010**. Drug absorption is improved and even normalized by lipid-based formulations, which is especially advantageous for medications with low therapeutic index **Patil P et al, 2007.** By a variety of ancillary mechanisms, such as (a) inhibiting P-glycoprotein-mediated drug efflux and resorptive metabolism by gut membrane-bound cytochrome enzymes, (b) promoting lymphatic transport, which carries drugs directly to the systemic circulation without undergoing hepatic first-pass metabolism, and (c) by increasing GI membrane permeability, these formulations can also improve drug absorption **Bhargava P et al,2011**. Improving the compound's physicochemical characteristics, such as salt formation and particle size reduction, could be one strategy to increase the medication's rate of solubility. These techniques do have certain restrictions, though. Lipid-based formulations have received a lot of attention lately as a means of increasing the oral bioavailability of poorly soluble medications. The most common method, in fact, is to include the drug ingredient into inert lipid vehicles, with a focus on self emulsifying drug delivery systems (SEDDS), oils, surfactant dispersions, self-emulsifying formulations, emulsions, and liposomes **Binita S et al 2004**. In order to help formulation scientists create stable, safe, and effective self-emulsifying formulations, this review of self emulsifying drug delivery systems (SEDDS) is written because these drug delivery systems have the potential to improve the bioavailability of low soluble drugs in the biopharmaceutical classification. An extensive and updated description of literature reports on various types of self-emulsifying formulations, techniques employed, characterization, optimization, and application strategies are discussed comprehensively. The figures are self-designed to demonstrate the concept, mechanism, and meaning of SEDDS **Mistry R et al 2011.**

AIMS:

To assess recent advancements in the formulation and design of Self-Emulsifying Drug Delivery Systems (SEDDS) for enhanced drug solubility and bioavailability.

To evaluate the potential of SEDDS in improving the oral delivery of poorly water soluble drugs, with a focus on overcoming formulation challenges and optimizing drug release kinetics.
To explore novel strategies for tailoring SEDDS formulations to specific drug molecules and therapeutic applications, including targeting specific absorption sites and facilitating controlled drug release.
To investigate the mechanistic insights into the self-emulsification process and the physicochemical factors influencing the stability and performance of SEDDS formulations.

Methods:

Capsule filling with Liquid and Semisolid Self emulsifying formulations: Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid SE formulations for the oral route. For semisolid formulations, it is a four-step process:
a. Heating of the semisolid excipient to at least 20°C above its melting point
b. Incorporation of the active substances (with stirring).
c. Capsule filling with the melt cooling to room temperature. For liquid formulations. it involves a two-step process.
d. Filling of the formulation into the capsules followed by sealing of the body and cap of the capsule, either by banding or by micro spray sealing (Pouton C.W et al.,1997)
1. Spray Drying: This method entails preparing a formulation by combining the medication, solid carriers, lipids, and surfactants, then solubilizing the mixture before spray drying. The liquid composition that has been dissolved is subsequently atomized into a droplet spray. When the droplets are placed in a drying chamber, the volatile solvents evaporate and leave behind tiny solid particles that can be crushed and put into pills or capsules, for example. The spray drying method was used to create the nimodipine self micro emulsifying formulation, which used dextran as a solid carrier 32. The development of self-emulsifying curcumin 33 and dexibuprofen has also made use of this technology.
2. Spray Cooling: Another name for this method is spray congealing. It includes combining drugs, surfactants, and lipids to generate a molten formulation. After that, it is sprayed into a room for chilling. The melted droplets solidify and congeal again into spherical solid particles, which gather as fine powder at the chamber's bottom. Then, the fine powder can be utilized to create solid dosage forms like pills, capsules, and so forth. A variety of atomizers can be used to atomize the liquid mixture and produce droplets, but the ultrasonic atomizer is the most recommended. This method uses polyoxyl glycerides as excipients, particularly steroylpolyoxyl glycerides (gelucire 50/13 36, for example). Spray cooling has been used to prepare the SEDDS for prazoquantel 35 and diclofenac 36 (Devarajan V et al.,2011).
3. Adsorption to Solid Carriers: To achieve adsorption to solid carriers, merely blend liquid SEDDS onto the solid carriers. Solid carriers include microporous inorganic materials, colloidal inorganic materials with a high surface area, cross-linked polymers, and nanoparticle adsorbents. Examples of these include silica, silicates, magnesium hydroxide, trisilicate, talc, and crosspovidone (Rege,RD khan et al.,2002). The resulting free powder can then be filled into capsules or, alternatively, combined with appropriate excipients before being compressed into tablets. Good content homogeneity is one of the adsorption technique's main advantages.

PROPERTIES OF SEDDS:

1. They may quickly self-emulsify intestinal fluids, and when the peristaltic and other motions of the digestive system cause mild agitation, they produce a fine o/w emulsion. **2.** They are able to successfully mix drugs—whether hydrophilic or hydrophobic with the oil surfactant mixture.

3. Both liquid and solid dose forms can be utilized with them.

4. They need medication protection from the harsh environment in the stomach and a lower dosage of the drug than is required for a window in the gastrointestinal tract. Tinum, these synthetic systems may provide an enhancement in the rate and extent of absorption and lead to more repeatable blood time profiles for lipophilic medicinal compounds that show dissolution rate limited absorption.

5. One of the most significant advantages that sets SMEDDS apart from other drug delivery methods, such as solid dispersions, liposomes, nanoparticles, etc., is its ease of manufacture and scaling up. These methods require relatively basic and affordable manufacturing facilities, such as a simple mixer with an agitator and volumetric liquid filling machinery. This clarifies the pharmaceutical industry's involvement in the SMEDDS .

Advantages:

1. Improved solubility and bioavailability: SEDDS can improve the intestinal fluids' solubility and bioavailability of weakly water-soluble medications. The reason for this is that fine oil in-water droplets develop on their own and enhance the surface area available for drug absorption.

2. Increased stability: SEDDS can help medications remain stable by shielding them from chemical reactions that could break them down in the gastrointestinal system, such as oxidation and hydrolysis. This is because an oily, protective covering has formed around the medication.

3. Simple formulation: SEDDS is readily formed using a range of lipophilic excipients and surfactants, providing flexibility in component selection and formulation optimization. This is especially helpful for medications that are challenging to convert into traditional oral dose forms.

4. Better patient compliance: SEDDS can increase patient compliance by lowering dosage frequency and lowering the requirement for large dosages of medication. This is because the drug's higher bioavailability enables therapeutic levels to be reached with less dosages.

Disadvantages:

1. Complex formulation: SEDDS formulations can be intricate and need for the optimization of several different elements, including oils, co-solvents, and surfactants. The formulation becomes more complex, and it becomes more difficult to maintain the same composition and quality of the reference sample when references are used to compare the performance of several SEDDS formulations.

2. Interference with drug release: The inclusion of references in SEDDS may cause problems for the medication to come out of the formulation since the reference sample may have various co-solvents or surfactants that have an impact on the drug's solubility and dissolution. 3. Incompatibility problems: Using references may also result in incompatibilities, particularly if the reference sample is poorly described or has contaminants that may interact with the medication or other SEDDS formulation ingredients.

Biopharmaceutical Classification system:

Drugs are categorized using the Biopharmaceuticals Classification System (BCS) according to their permeability and solubility properties, which might affect their oral bioavailability. One kind of lipid-based formulation that can improve the solubility and bioavailability of poorly soluble medications is the self-emulsifying drug delivery system (SEDDS). Drugs are categorized by the BCS into four groups (BCS classes 1 through 4) according to their permeability and solubility

1. BCS Class I: High permeability and solubility. This class of drugs has very soluble and permeable compounds, which typically lead to good oral bioavailability. They have a high systemic exposure and are well absorbed.

2. BCS Class II: High permeability, low solubility. This class of drugs has strong permeability through the gastrointestinal barrier but limited solubility in the digestive juices. Their bioavailability may be impacted by their restricted gastrointestinal tract dissolution and/or precipitation. Danazol, ketoconazole, and griseofulvin are a few medications in this.

3. BCS Class III: Low permeability and high solubility. This class of drugs has minimalpermeability across the gastrointestinal barrier but significant solubility in the digestive juices. Their low permeability may limit their absorption, which could affect their bioavailability. Medications in this category include ranitidine, nadolol, and atenolol.

4. BCS Class IV: Low solubility, low permeability. Drugs in this category have low solubility in the gastrointestinal fluids and low permeability across the gastrointestinal membrane. They may have poor bioavailability due to both limited dissolution and low permeability**.** Examples of drug in this category are diazepam, digoxin, and paclitaxel.

Factors affecting SEDDS:

1. **The nature and dosage of the medication**: medications that are taken at very high dosages shouldn't be used with SMEDDS unless they have exceptionally high solubility in at least one of the components, ideally the lipophilic phase. Drugs having restricted solubility in lipids and water, usually with log p values of about 2, are the hardest for SMEDDS to administer.3. The drug's solubility in the oil phase has a significant impact on SMEDDS's ability to keep the drug in a soluble form.

2. **Concentration of Surfactant or Co-Surfactant**: Lowering the solvent capacity of the surfactant or co-surfactant due to SMEDDS dilution may result in precipitation if surfactant or co-surfactant is contributing to a greater extent to drug solubilisation .

3. **Lipophilic phase polarity**: One of the variables controlling drug release from micro emulsions is the lipid phase's polarity. The HLB, the fatty acid's chain length and degree of unsaturation, and the drug's micronized molecular weight all influence the droplet's polarity.

The Emulsification Process:

1] **Mechanism of Self-emulsification**: When there is a change in entropy (energy), self emulsification takes place. The energy needed to construct a new surface between the two phases determines the free energy of traditional emulsion formation, which is expressed by the following equation. where N is the number of droplets with radius r, o is the interfacial energy with time, and A.

2] G is the process free energy (ignoring the mixing free energy). To decrease the interfacial area and, thus, the system's free energy, the two phases of the emulsion will naturally tend to separate. Consequently, typical emulsifying agents stabilize the emulsions produced by aqueous dilution by forming a monolayer surrounding the emulsion droplets, which lowers the interfacial energy and acts as a barrier to coalescence. When an emulsion forms spontaneously in a self-emulsifying system, the free energy needed to do so is either very low, positive, or negative. Emulsification is a process that requires very little energy input and destabilizes the environment by contracting particular interfacial regions. The interfacial structure must not oppose surface shearing in order for emulsification to take place (Singh AK etal.,2009)..

The ease with which water permeates the different liquid crystals or phases that form on the droplet's surface is known as emulsification. When an oil/non-ionic surfactant binary mixture is added to water, an interface between the oil and aqueous continuous phases forms. Water then dissolves in the oil phase as a result of aqueous penetration through the interface, and this process continues until the solubility limit is reached in the vicinity of the interface. Additionally, the creation of the scattered liquid crystalline phase will be the outcome of water penetration. Once formed, rapid water penetration into the aqueous cores, assisted by the gentle agitation of the self-emulsification process, causes interface disruption and droplet formation. Eventually, all materials near the interface will be liquid crystal, with the exact amount depending on the surfactant concentration in the binary mixture. These self-emulsified systems' exceptional solubility to coalescence is thought to be caused by the liquid crystal interface that surrounds the oil droplets (Xiaole Qi et al.,2011).

3] Ternary Phase Diagram Construction: This is the initial stage prior to initiating the formulation. Finding the optimal emulsification area for a mixture of oil, surfactant, and cosurfactant is useful. The oil, co-surfactant, and surfactant tertiary phase diagrams each show an apex of the triangle 13. The techniques for ternary phase diagrams are the water titration method and the dilution method.

a) **Dilution technique:** Ternary mixes of oil, cosurfactant, and surfactant in different proportions were made. Based on the requirements, the percentage of oil, surfactant, and co surfactant. Compositions are assessed for the potential to create nano emulsions by dilution with the proper volume of double-distilled water area of nano-emulsion formation for each system, allowing for the production of nano emulsions with the desired globule size.

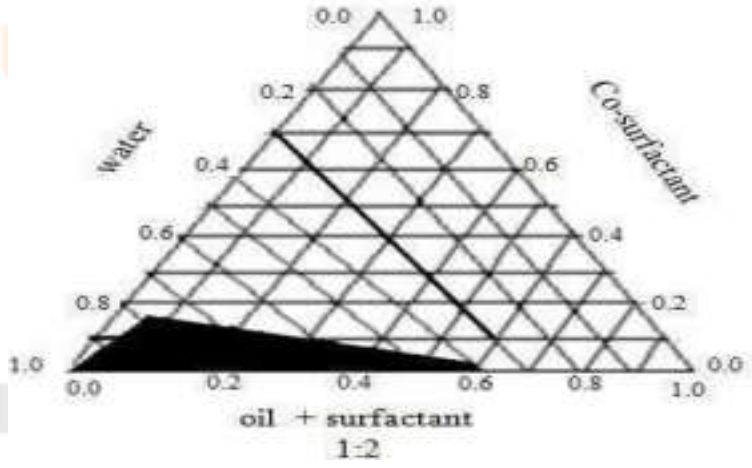

Fig:(2) Ternary phase diagram evaluation of SEDDS

b) Water Titration Method: As illustrated in figure 2b, homogenous liquid mixes of oil, surfactant, and co-surfactant were titrated with water at room temperature in order to further restrict the pseudoternary phase diagrams. Surfactant, the cosurfactant, and the Od phase. Oily solutions of oil, surfactant, and co-surfactant were created with ratios ranging from 9:1 to 1:9, weighed in the same screw-cap glass tubes, and vortexed eight times at Km values of 1.5 and

1. To achieve equilibrium, each combination was then gradually swirled at room temperature while aliquots of distilled water were added

5. CONCLUSION

Self-emulsifying drug delivery systems are actually mixtures of drog, lipid phase,emulsifier and/or co-solvent. SEDDS are apromising approach for drugs with poor aqueoussolubility and hence can be more useful for BCS Class II and IV drags as upon administration. When the dosage form reaches G.LT, the SEDDSsystem take water from its surroundingenvironment and spontaneously forms oil in wateremulsion which disperse into fine droplets. Thefiner droplets provide higher surface area for thedrug to dissolve or permeate in surroundingmedium. SEDDS are prepared generally in liquiddosage forms but solid SEDDS (tablets, capsules, beads microspheres etc.) are preferred due to easein handling, transportation and better stability. Also it avoids GI irritation and controlled andsustained release of drug release is achievable. Absence of suitable in vitro models explaining thestate (whether dissolved or not) in G.I.T (in vivo) for evaluation of SEDDS are major hurdles. Further, with solid SEDDS, compatibility andinteraction studies between the excipients such asadsorbent, capsule shell & formulation components can be carrierout in order to effectively harness itspotential for the benefit of mankind. The SEDDSshould be suitably exploited to develop platformtechnologies for improving bioavailability of BCSclass II and IV drugs.

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