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

AIM & OBJECTIVES

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.
- To examine the biopharmaceutical and pharmacokinetic implications of SEDDS-based drug delivery systems, including their impact on drug absorption, distribution, metabolism, and excretion.

OBJECTIVES:

- Review recent literature on the formulation development and characterization of SEDDS, including studies on excipient selection, formulation optimization, and stability evaluation.
- Investigate the influence of formulation parameters such as oil phase composition, surfactant/co-surfactant ratio, and emulsification methods on the self-emulsification efficiency and in vitro/in vivo performance of SEDDS.
- Explore innovative approaches for enhancing the oral bioavailability and therapeutic efficacy of poorly water-soluble drugs using SEDDS, including co-delivery of synergistic compounds, solidification techniques, and nanostructured lipid carriers.

INTRODUCTION

3. 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 preabsorptive 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**

3.1 SELF EMULSIFYING DRUG DELIVERY SYSTEMS (SEDDS)

Lipid-based formulations include SEDDS. Lipid formulations include liposomes, oils, solid lipid nanoparticles, emulsions, and surfactant dispersions. SEDDS are isotropic combinations of surfactants, lipids, and drugs that typically include one or more co-solvents or co-emulsifiers that are hydrophilic. These systems can instantly create a fine (oil in water) emulsion with modest agitation and dilution with aqueous media. The term "SEDDS" is wide and generally refers to emulsions that have droplet sizes between a few nano-meters to several microns. SMEDDS stands for "self-micro-emulsifying drug delivery systems," which refers to formulations that produce transparent microemulsions with oil droplets that are between 100 and 250 nm in size. A more contemporary term, "self-nano-emulsifying drug delivery systems" (SNEDDS), refers to globule sizes that are smaller than 100 nm **Choukesy R et al, 2011**. Patients and manufacturers alike most readily accept oral formulations for the treatment of various medical conditions. As a result, oral medication delivery systems make up the bulk of those on the market for healthcare products today. Pharmaceutical research scientists face significant obstacles when developing oral drug delivery systems because over 50% of novel molecular entities (NMEs) have inconsistent and low bioavailability **Pouton CW et al, 1997.**. Poor aqueous solubility, a significant hepatic first-pass effect, acid lability in gastric fluid, limited intestinal permeability, gut wall metabolism by the cytochrome P450 (CYP450) family of isozymes, and high P-glycoprotein (P-gp) efflux are some of the apparent causes of these variable bioavailability problems. Various formulation techniques, including solid dispersions, cocrystals, inclusion complexes, micronation, and suspensions, have consistently been used to increase the oral bioavailability of pharmaceuticals. However, as these methods merely improve the drug's dissolving capability, their effectiveness is generally restricted. Due to their exceptional merits, such as a notable increase in dissolution performance, solubility, and permeability, decreased gut wall metabolism by the CYP450 group of enzymes, circumvention of the extensive hepatic first-pass effect, decreased P-gp efflux, and lowering intra-/inter-subject inconsistencies in gastrointestinal (GI) absorption, the potential of lipid-based self-emulsifying drug delivery systems (SEDDS) has recently been explored for this purpose. The inception of self-emulsifying (SE) systems dates to the early 1960s, when chemicals and insecticides with low water solubility were dissolved using mixtures of hydrophilic and lipidic excipients **Sunitha R et al, 2011**. Later, in 1985, Pouton revealed for the first time that SEDDS had been developed to overcome the different challenges that lipophilic medicines face. Several researchers have been using SEDDS's

potential to improve bioavailability since the 1990s, which has led to some laboratory research work moving into industrial settings and eventually into clinics. Under the terms of U.S. patent 4388307, Sandimmune (Sandoz), which contains cyclosporine A, was the first SE formulation approved by the FDA for transplant rejection in 1983, setting new standards in the field of SEDDS **Singh S et al, 2020**. Subsequently, several foreign patents covering SE formulations of various medication kinds have been awarded. Table 1 shows a list of recently marketed SEDDS formulations along with their final dosage form, composition of excipients, patent, and marketing status.

Since the commercialization of oral lipid-based drug products in 1981, over a hundred approved items have been made available on the market, according to the updated list of marketed goods in Table 1. These products, which are often packaged in soft or hard gelatin capsules, are mostly based on type III lipid-based self-emulsifying systems, which contain lipids, surfactants, and/or cosurfactants. Additionally, type I formulations—which solely comprise lipids—and type IV formulations—which include **Pouton CW et al, 1997.** Here, the emphasis has only been on current discoveries and cutting-edge technologies. a comparison of several patents on oral and non-oral SEDDS that have been submitted with important regulatory agencies across the globe. These patents undoubtedly demonstrated the adaptability of SEDDS in enhancing the bioavailability of medications belonging to BCS classes II and IV as well as in overcoming the difficulties associated with BCS classes I and III medications' drug delivery **Rege RD et al, 2002**. Examples of medications falling within these headings are anti-infectives, NSAIDs, immune suppressants, anticancer, antiretrovirals, and cardiovascular medicines. Furthermore, it is reasonable to assume that certain SEDDS have been investigated for non-oral drug administration, generating stomach discomfort and/or undergoing substantial hepatic first-pass metabolism after oral ingestion. Furthermore, these new studies support the use of SEDDS in enhancing the bioavailability of biological products, phytochemicals, bioactive herbal medicines, and nutraceuticals **Muller et al, 1998**. The more in-depth information about the formulation and development of SEDDS, their composition, characterization mechanistic elements, and applications has already been covered in length in the prior review study that our team put together. In light of earlier publications and patent literature, the current review study aims to present a comprehensive account of the latest advancements in SEDDS technology, with a focus on the formulation features of various types of innovative SE formulations for oral and non-oral drug

administration **Sunitha R et al, 2011. System for Self-Nano Emulsifying Drug Delivery** SNEDDS: SEDDS forms SNEDDS, which are nanoemulsions. Regardless of the manufacturing method, they are heterogeneous dispersions of two immiscible liquids (oil-in-water [O/W] or water-in-oil [W/O]) with a mean droplet size in the nanometric scale (usually 20-200 nm). This is especially crucial for medications that increase solubility, including atorvastatin and simvastatin **(Kumar S et al.,2012).**

3.2 System for Self-Micro Emulsifying Drug Delivery

SMEDDS: The SEDDS forms micro-emulsions known as SMEDDS. It creates an optically transparent emulsion and is thermodynamically stable. The primary distinction between conventional emulsions and micro-emulsions is mostly caused by the size of the droplets. The usual emulsion droplets have a size range of 0.2 to 10 µm, while the micro-emulsion droplets created by the SMEDDS typically have a size range of 2 to 100 nm. Since the particles are tiny, there is a greater surface area available for absorption and dispersion compared to solid dosage forms **(Nigade P M et al.,2012).**

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 **(Sharma V et al.,2012).**

3.3 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 **(Bhargava P et al.,2011).**

3.4 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.

LITERATURE REVIEW

4. REVIEW OF LITERATURE

Sunitha R et al.,2011: Reviewed the excipients create good emulsification systems with several surfactants approved for oral administration and exhibit enhanced drug solubility qualities, modified or hydrolysed vegetable oils have found widespread application. They have physiological and formulative benefits, and the byproducts of their destruction are like those that are naturally produced by intestine digestion.

Singh G et al.,2012): Reviewed A variety of substances with surfactant characteristics can be used to create self-emulsifying systems, although the number of suitable surfactants for oral use is small. The most advised ones are nonionic surfactants, which have a lower toxicity and a comparatively higher hydrophilic-clipophilic balance (HLB) than ionic surfactants. However, they may cause temporary alterations to the intestinal lumen's permeability. One important consideration when selecting a surfactant is safety. Therefore, natural emulsifiers are chosen over synthetic surfactants, but their ability to self-emulsify is restricted. The size of the droplets and the concentration of the surfactants being utilized are related. In certain instances, a decrease in mean droplet size may result from raising the surfactant content.

Rajinikanth P S et al..,2012: Reviewed the stability of the oil droplets brought about by the surfactam molecules' localization at the oil-water interface. Conversely, if surfactant concentrations decrease, the mean droplet size could rise. This effect may be explained by the improved water penetration into the oil droplets, which is mediated by the higher concentration of surfactant, causing an interfacial disruption and the ejection of oil droplets into the aqueous phase. These formulations' surfactants are known to promote bioavailability through a variety of processes, including as enhanced drug solubility and greater intestinal epithelial permeability. enhanced permeability at tight junctions and reduced/inhibited the drug efflux of p-glycoprotein. On the other hand, the high surfactant content could irritate the gastrointestinal system or result in mildly reversible changes in intestinal wall permeability.

Sachan R et al.,2010: studied about surfactant, they irritate the glands, co-surfactants are necessary in relatively large concentrations (usually greater than 30%w/w) to produce an ideal SMEDDS. Therefore, co-surfactant is employed to lower surfactant concentration. The cosurfactant's and surfactant's combined function is to reduce interfacial tension to an extremely low, even momentary negative value. At this point, the interface would enlarge to create finely dispersed droplets. These droplets would then absorb additional surfactant and

surfactant/cosurfactant until their bulk conditions were sufficiently reduced to restore a positive interfacial tension. The micro emulsions are created by this "spontaneous emulsification" process. Although alcohol-free self-emulsifying micro-emulsions have also been reported in the literature, organic solvents suitable for oral administration (ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc.) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base and can act as co-surfactant in the self-emulsifying drug delivery systems. Since alcohol and other volatile co-solvents in conventional self-emulsifying formulations are known to migrate into the shells of soft gelatin or hard sealed gelatin capsules, resulting in the precipitation of the lipophilic drug, such systems may have some advantages over the other formulations when incorporated into capsule dosage forms. However, the alcohol-free formulation's capacity to dissolve lipophilic drugs may be restricted. Therefore, while choosing a component, the right decision must be made.

Patil P et al.,2007: Reviewed Viscosity Enhancers, By adding extra materials, such as acetyl alcohol, tragacanth, beeswax, and stearic acids, among others, the viscosity of the emulsions can be changed.

4.1 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 **(Kumar A et al.,2008).**

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 minimal

permeability 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 **(Patel P A et al,2008).** Examples of drug in this category are diazepam, digoxin, and paclitaxel.

Table . 1 List of examples of drug

Class 1 Highly Soluble Highly permeable	**Class 2** Poorly soluble Highly permeable	**Class 3** Highly soluble Poorly permeable	**Class 4** Poorly soluble Poorly permeable
Metoprolol Propranolol L-dopa Captopril Glucose	Danazol Ketoconazole Griseofulvin Folic acid Dapsone	Atenolol Nadolol Rantidine Hydrochloride Metaformin	Diazepam Digoxin Paclitaxel Terfenadine Acetazolamide

4.2 Composition of Self Emulsifying Drug Delivery System

1] Active Pharmaceutical Ingredient (API): BCS class II medications, such as itraconazole, nifedipine, vitamin E, simvastatin, danazol, ketoconazole, mefanimic acid, naproxen, and carbamazepine, are recommended since SEDDS are used to boost the solubility of poor water-soluble pharmaceuticals.

2] Excipients are utilized in SEDDS; the choice of excipients is very important because of toxicity concerns and pharmacological acceptability. Therefore, there are tight guidelines regarding the usage of excipients. The temperature at which self-emulsification takes place, the type and concentration of the oil/surfactant ratio, and the surfactant/co-surfactant ratio all affect the self-emulsification process. For this reason, while choosing excipients for SEDDS, the whole aspect needs to be taken into account **(Revathi S et al.,2013).**

a) Oils: Depending on the molecular makeup of the triglyceride, oils can solubilize the

b) necessary dosage of the lipophilic drug, aid in self-emulsification, and increase the percentage of lipophilic drug transported via intestinal lymphatic system, thereby boosting absorption from the gastrointestinal tract. 7.

c) Different degrees of saturation in long and medium chain triglyceride (MCT) oils have been employed in the creation of self-emulsifying formulations. Amphiphilic molecules possessing surfactant characteristics, such as novel semisynthetic MCT, are gradually and efficiently substituting the standard MCT oils in the SMEDDS. In comparison to LCT, MCT are more soluble and mobile at lipid/water interfaces, which is linked to a quicker rate of MCT hydrolysis.

d) Generally speaking, compared to MCT, a larger concentration of chromophore RH40 is needed when utilizing LCT to create micro-emulsions. Because edible oils have a limited capacity to dissolve significant quantities of lipophilic medicines, they are not often chosen.

4.3 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 (Chen Y et al.,2009).

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 (Taha E et al.,2007).

4.4 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 sohibility 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 nanoemulsions 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.

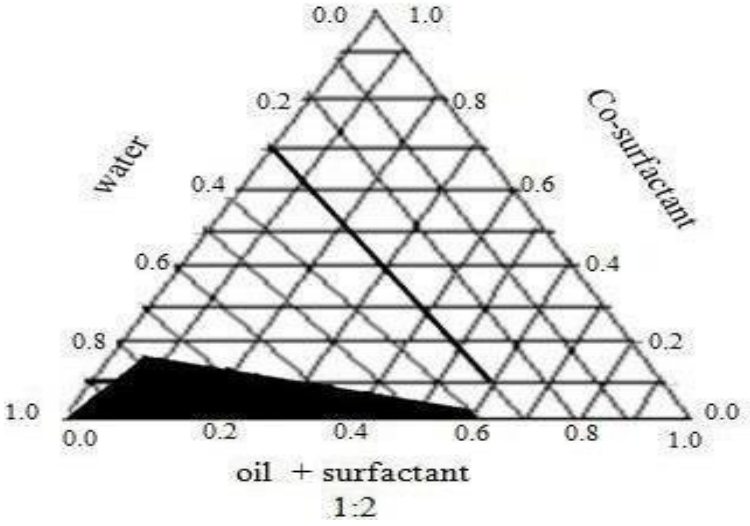

Fig:(2) Ternary phase diagram evaluation of SEDDS

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 (Kyatanwar AU et al.,2011).

4.5 Evaluation of SEDDS:

A number of tests are carried out for characterization and evaluation of SEDDS.

1] **Drug Content**: The drug is extracted from pre-weighed SEDDS by dissolving it in an appropriate solvent. The solvent extract's drug content is examined using an appropriate analytical technique 14

2] **Dispersibility Test**: The purpose of the dispersibility test for SEDDS is to determine how well it can disperse into an emulsion and classify the size of the resulting globules. A typical USP dissolving device 2 (Paddle Type) is used to carry it out. 500 ml of water are mixed with 1 ml of each formulation at 37 +/-0.5°C while the paddle is spinning at 50 revolutions per minute. The SEDDS formulation produces a variety of mixtures or gels upon titration with

water, from which the formulation's in vitro performance can be evaluated using the grading system listed below: 1–5.

Grade A: A transparent or bluish nanoemulsion that forms quickly (in less than a minute).

Grade B: A bluish white emulsion that forms quickly and is slightly less clear.

Grade C: A fine, two-minute-old milky emulsion.

Grade D: A dull, grayish white emulsion that takes longer than two minutes to emulsify and has a slightly greasy appearance.

Grade E: Formulation with big oil globules visible on the surface and either weak or little emulsification. Once distributed in the GIT, the Grade A and Grade B formulations will stay as nano-emulsions. Although a Grade C formulation might be suggested for the SEDDS formulation. From micro emulsion to emulgel, the formulation loses stability (Chen Y et al.,2011).

3] **Determining the rheological properties**: The SEDDS system may also be used to soft gelatin capsules; in this case, it must have measurable flow characteristics for processing. Viscosity, flow, thixotropy, static yield, and creep value of the formulation (diluted to 5% v/v water) are measured using digital instruments called rotational viscometers, which are connected to either a cup and bob or a coaxial measurement device. The viscosity of new SEDDS formulations as well as other formulations that have been held for extended periods of time has also been measured using a particular kind of rotational viscometer. Since low viscosity systems are typically ow and high viscosity systems are typically w/o in nature, the viscosity determination of liquid SEDDS also w) reveals whether the system is o/w or w/o. The relationship between dilution and viscosity of formulation is inverse (Mishra N et al.,2009).

4] Thermodynamic stability studies: Precipitation of the medication in the excipient matrix can negatively impact a formulation's performance, hence physical stability is crucial. The bioavailability and therapeutic efficacy of a formulation might be impacted by phase separation of the excipients caused by poor physical stability. Additionally, if the formulation is placed into a capsule, the incompatibilities between the formulation and the capsule's gelatin shell could result in brittleness, softness, delayed disintegration, or insufficient drug release. The cycles that follow are completed for these investigation.

a) **Heating cooling cycle 17**: This involves six cycles of beating and cooling between the temperature of a refrigerator (4°C) and an increased temperature (45°C), with the product

being exposed to each temperature for at least 48 hours. The centrifugation test is thereafter performed on those formulations, which show stability.

b) **Centrifugation:** Formulas that successfully complete the heating-cooling cycle are centrifuged for 30 minutes at 3,500 rpm.

For the freeze-thaw stress test, formulations that don't exhibit phase separation are chosen.

c) **Freeze-thaw stress cycle:** Three cycles of freezing and thawing between -21°C and 25°C are conducted, and the formulations that pass this test exhibit good stability with no phase separation, cracking, or creaming. They are stored at room temperature for at least that long. The formulations that pass this test are then subjected to a dispersibility test to see how well they self-emulsify (Pouton CW et al.,2000).

5] Robustness to Dilution: Emulsions that exhibit no phase separations or drug precipitation even after 12 hours of storage are deemed resilient to dilution when diluted with different dissolving media.

6] Turbid Metric Evaluation: The parameter of turbidity is used to calculate droplet size and self-emulsification time. A turbidimeter is used to measure the turbidity when a fixed amount of SEDDS is added to a fixed quantity of a suitable medium (0.1 N HCL or Phosphate Buffer) while being continuously stirred at 50 rpm on a magnetic stirrer at the ideal temperature. The rate of turbidity change, or the rate of emulsification, cannot be monitored because the time needed for complete emulsification is too short. Following emulsification, turbidimetric assessment is used to track droplet growth.

7] Measurements of particle size and droplet size analysis: The droplet size of the emulsion is determined using laser diffraction techniques, dynamic light scattering (DLS), or photon correlation spectroscopy (PCS). There are several tools available for measuring particle size, such as the Zetasizer, Mastersizer, and Particle Size Analyzer, which can measure sizes ranging from 10 to 5000 nm (Singh S et al.,2020).

8] Time for Self-Emulsification: Using the USP Dissolve Apparatus 2 at 50 rpm, 0.5 g of SEDDS formilations are added to 250 ml of 0.1NHCL or 0.5% SLS (Sodium Lauryl Sulphate) solution to evaluate the self-emulsification time. The self-emulsification time for the formulation is the amount of time needed for emulsification at room temperature.

9] In vitro Diffusion research: This investigation uses a dialysis technique, where phosphate buffer (pH 6.8) is typically utilized as the dialyzing medium (20), to examine the release behavior of the formulation. The dialysis membrane has one end secured with thread, and it

is filled with 0.5 ml of dialyzing media and 1 ml of the SEDDS formulation. Using a magnetic stirrer or dissolving device, the other end of the membrane is similarly knotted with thread and allowed to rotate at 100 revolutions per minute in the dialyzing solvent. Samples are taken out at various intervals and tested following an appropriate dilution. New dialyzing medium is added to the volume of samples that were removed (Gursoy RN et al.,2004).

10] In vitro Dissolution Technique: Using a USP type 2 dissolution apparatus and 500 ml of simulated gastric fluid containing 0.5% w/v of SLS at 50 rpm and maintaining a temperature of 37±0.5°C, quantitative in vitro dissolution studies are conducted to evaluate drug release from oil phase into aqueous phase. Samples are taken out in aliquots at regular intervals, and the volume taken out is replenished with new media. After that, samples are examined using a UV spectrophotometer or any other appropriate method.

11] Liquefaction Time: This test measures how long it takes for the solid SEDDS formulation to dissolve in simulated stomach fluid in vivo without agitation. The mixture is wrapped in a clear polyethylene sheet and fastened to the thermometer's bulb. Next, the thermometer is inserted into a round-bottom flask filled with synthetic stomach fluid devoid of pepsin. The heating mantle keeps the temperature at 37±0.5°C (Mistry R et al.,2011).

12] Refractive index (R.I.) & Percent Transmittance: These metrics are calculated to assess the formulation's transparency. By placing a drop of solution on a slide and comparing the result to water, the refractive index of the formulation (R.I=1.333) is determined using a refractometer. Using distilled water as a blank, the % transmittance of the formulation is determined at a certain wavelength using a UV spectrophotometer. A formulation is considered transparent if its R.I. is comparable to that of water and its percent transmittance is more than 99%. SEDDS in dosage form:

4.6 Dosages form of SEDDS

1. Self-Emulsifying Capsules: When a capsule containing a traditional liquid self-emulsifying formulation is used, it spontaneously forms microemulsion droplets that spread throughout the gastrointestinal tract and increase absorption. They do have certain drawbacks, though, in that medication absorption is reduced if the microemulsion undergoes irreversible phase separation. In these situations, super-saturable SEDDS is prepared by adding sodium dodecyl sulphate to SE formulations in order to increase absorption. This prevents drug precipitation by creating and preserving a supersaturated condition in vivo. These formulations minimize

any gastrointestinal side effects and contain less surfactant.

2. Dry Emulsion: This type of emulsion is primarily o/w and is made solid by spray drying, freeze drying, or solid carrier adsorption. Before using, the dry emulsion can be re-dispersed in water. In reality, these are powders that emulsify on their own in vivo or following exposure to an aqueous solution. Dry emulsion technology successfully eliminates the stability issues (such as phase separation, creaming, and microorganism contamination during storage) connected with traditional emulsion in addition to avoiding the use of hazardous or poisonous organic solvents. For these formulations, medium chain triglycerides, or MCTs, are typically utilized as the oil phase. Tablets and capsules can be further prepared with the use of dry emulsions.

3. Self-Emulsifying Solid Dispersion: Although stability is a key problem during their fabrication, solid dispersions have been frequently employed to boost the rate of dissolution and bioavailability of weakly water soluble medicines. One method that is frequently used to prepare solid dispersions is hot-melt granulation (Chuksey r et al.,2011).

4. Self-Emulsifying Tablets: To prepare self-emulsifying tablets, a nano-emulsion was first adsorbed on granular materials and subsequently compressed to create tablets. In 45 minutes, the improved self-emulsifying tablet's dissolving profile revealed 80–90% drug release.

5. Self-Emulsifying Beads: In SE systems, solid dosage forms can be created by forming beads with a reduced amount of excipient. Solvent evaporation was the method employed by Paradkar and Patil (31) to deposit the SE system into microporous polystyrene beads. Polystyrene beads with pores have intricate internal void formations. The copolymerization of the monomers divinyl benzene and styrene results in these beads. It is biocompatible, stable, and chemically inert throughout a broad pH, temperature, and humidity range. The loading effectiveness and in vitro drug release from SES loaded porous polystyrene beads are determined by geometric properties of porous materials, such as bead size and pore architecture (Shukla J B et al.,2010).

6. Self-Emulsifying Nanoparticles: These can be made using sonication, emulsion diffusion-evaporation, or solvent injection techniques. Molten lipid mass including drug, surfactant, and lipid is injected dropwise into a non-solvent system in the solvent injection method. After filtering out larger particles, the filtrate is dried to produce nanoparticles. [23/4/2024, 13:48] : Methods of solidification Semi-solid or liquid: for transforming Semisolid and liquid capsule filling Self-administering mixtures: The simplest and most

widely used method for encapsulating liquid or semisolid SE formulations for oral administration is capsule filling. The procedure for semisolid formulations consists of four steps:

4.7 Solidification techniques for Transforming.

4.7.1 Liquid/Semisolid:

4.7.1.1 Capsule filling with Liquid and Semisolid Selfemulsifying 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 (withstirring).

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 selfmicro 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. [23/4/2024, 13:49] : Particular uses for SEDDS:

4.8 Specific applications of SEDDS:

1. Improving oral bioavailability medications that are not very soluble in waterOne of the main factors limiting the bioavailability of medications that dissolve slowly is absorption rate, particularly in the case of weakly watersoluble pharmaceuticals. The capacity of SEDDS to disperse into a micro-emulsified state (globule size between!–100 mm) and release the drug into the GIT. The resulting increase in specific surface area allows for more effective drug transport through the intestinal aqueous boundary layer and the absorptive brush border membrane, which improves bioavailability because the globular size is so small. A list of all the medications (Sunitha R.,et al.,2011).

2. In the transport of peptides: By shielding macromolecules from enzymatic hydrolysis, SEDDS can distribute peptides, hormones, enzyme substrates, and inhibitors. These systems spontaneously form without the need for energy or heating, making them appropriate for thermolabile medicines like peptides 42, for example.
If Polysorbate 20 is used as an emulsifier in the micro emulsion formulation, the intestinal hydrolysis of the pro-drug by cholinesterase can be prevented.

3. Supersaturable SEDDS (S-SEDDS) to lessen surfactant adverse effects: High surfactant concentrations are employed to speed up the absorption of poorly soluble drugs, which may irritate the glands. S-SEDDS formulations stabilize the drug in a super saturated state by combining a polymeric precipitation inhibitor with a lower concentration of surfactant. The purpose of HPMC and other cellulose polymers is to prevent crystallization and keep the medication in a supersaturated state for an extended period of time. The toxicity/safety profile of the S-SEDDS formulation is superior to that of the traditional SEDDS formulation. Further explanation is required for the process underlying the usage of polymers to stabilize super saturation and restrict crystal formation. For example, salicylic acid and docetaxel 8–44

SEDDS formulation use HPMC as a precipitation inhibitor. Using PNU-91325 as a precipitation inhibitor in place of propylene glycol has been shown to boost bioavailability fivefold (Morty R B et al.,2008).

In reality, self-emulsifying drug delivery systems are blends of co-solvent, lipid phase, emulsifier, and/or medication.

As a promising method for medications with low water solubility, SEDDS may prove more beneficial for BCS Class II and IV drags when administered. As soon as the dosage form reaches G.LT, the SEDDS system absorbs water from the surroundings and creates an oil-in-water emulsion that disperses into tiny droplets on its own. The medicine can dissolve or penetrate the surrounding media more easily.

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.

Future Prospectives of SEDDS

1. Advanced Formulations for Enhanced Bioavailability

Future advancements in SEDDS will likely focus on optimizing formulations to further enhance the bioavailability of highly lipophilic and poorly soluble drugs. This includes exploring novel excipients that can stabilize the emulsion and increase drug loading capacity.

2. Nanotechnology Integration

Integrating nanotechnology into SEDDS could lead to the development of nanoemulsions and solid lipid nanoparticles, offering even smaller particle sizes and potentially better bioavailability and stability. Nanoscale SEDDS can provide targeted drug delivery, reduced side effects, and controlled release patterns.

3. Hybrid Drug Delivery Systems

Combining SEDDS with other drug delivery technologies, such as polymeric nanoparticles, liposomes, or hydrogels, to form hybrid systems could address multiple delivery challenges at once, such as simultaneous delivery of hydrophilic and lipophilic drugs, or the targeting of specific tissues or cells.

4. Application in Nutraceuticals

The principles of SEDDS can be applied to improve the bioavailability of nutraceuticals, which often face similar solubility and stability challenges as pharmaceuticals. This could enhance the therapeutic effects of dietary supplements and functional foods.

5. Personalized Medicine

Advances in biotechnology and pharmacogenomics may lead to the development of personalized SEDDS formulations, tailored according to an individual's genetic profile. This could optimize drug efficacy and minimize adverse effects.

6. Enhancing Patient Compliance

SEDDS can be developed into more patient-friendly forms, such as chewable tablets, effervescent tablets, or transdermal patches, which may enhance patient compliance, particularly among children and elderly patients who might have difficulty swallowing capsules.

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