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SELF-EMULSIFYING DRUG DELIVERY SYSTEM: A NOVEL APPROACH TO AVOID FIRST PASS METABOLISM.

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Abstract: Self- emulsifying drug delivery system has received attention for its capacity to enhance the solubility and bioavailability of drugs that are poorly water-soluble drugs. Self-emulsifying drug delivery systems are isotropic mixtures of drug, lipids and surfactants, usually with one or more hydrophilic cosolvents or co-emulsifier with droplet size ranging from few nanometres to several micrometers. SEDDS belong to lipid-based formulations. Lipid formulations can be oils, surfactant dispersions, emulsions, SEDDS, solid lipid nanoparticles and liposomes. SEEDS are ranging in size from approximately 100 nm (SEDDS) to less than 50 nm for self-micro-emulsifying drug delivery systems (SMEDDS), on dilution with physiological fluid. This article provides an overview of self-emulsifying drug delivery system and their applications, as well as their ability to resist first-pass metabolism.

Index Term: Self-emulsifying drug delivery system, needs, mechanism, applications, future aspects.

I. INTRODUCTION

[1] The most commonly prescribed drugs are taken by mouth. However, more than 40% of new chemical substances have a low aqueous solubility, resulting in adversity in oral therapy delivery. These drugs poor solubility and, in the end, low dissolution rate in the gastro-intestinal fluids results in a poor bioavailability. The bioavailability of BCS class ii drugs can be enhanced by increasing the solubility and dissolution rate of these drugs in the gastro-intestinal fluids. By modifying pharmacokinetic profiles, the effectiveness of these can be enhanced by increasing its gastrointestinal solubilization. [2] The oral route is the most popular, because it is noninvasive, cost-effective, and does not cause pain at the site of injection. It is the most cost-effective way to treat chronic illnesses. [3] Problems relating to the drug's physicochemical properties, such as poor solubility, low permeability, instability, and rapid metabolism, are all contributing to a decrease in oral bioavailability. [4] To solve these problems, various formulation techniques are employed, including the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrins, nanoparticles, and solid dispersions. Recently, much attention has been paid to lipid-based products, with a particular emphasis on self-emulsifying drug delivery systems (seeds) to improve lipophilic drug oral bioavailability.[5] To address these challenges, various formulation techniques are being used, including the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrins, nanoparticles, and solid dispersions. recently, much attention has been Given to lipid-based formulations, with a particular emphasis on self-emulsifying drug delivery systems (seeds). [6] Recently, much attention has been paid to self-emulsifying drug delivery systems in an attempt to improve the oral bioavailability of poorly aqueous soluble drugs. Sedds are isotropic mixtures of oil, surfactants, solvents, and co-solvents/surfactants. These systems have a primary ability to produce fine oil in-water (o/w) emulsions or microemulsions upon mild agitation following dilution by an aqueous phase through the gastrointestinal tract for lipophilic drugs, which have a dissolution rate limited absorption, and sedds may be a promising strategy to increase the rate and extent of oral absorption. This paper provides an overview of the various sedds developments and their biopharmaceutical applications. [7] Sedds is also However, conventional sedds are mainly made in liquid form, which has some drawbacks. Solid sedds (s-sedds), which are made up of liquid/semisolid self-emulsifying (se) ingredients, have gained in popularity as

a result of solid sedds (s-sedds). discussed in detail, with particular emphasis on the development of a solid self-emulsifying delivery system and the dosage form of sedds. [8] Sedds typically produce emulsions with a droplet size between 100–300 nm. These systems, which dissolution rate-limited absorption, can result in a reduction in the absorption rate and intensity, resulting in more reproducible blood-time profiles. [9] Sedds has been shown to increase absorption of drugs by rapid self-micro emulsification in the stomach, with the micro-emulsion droplets dispersing in the gastrointestinal tract to reach absorption sites. [10] The resultant small droplet size of sedds provides a large interfacial surface area for drug release and absorption, and the specific components of sedds promote drug transport through the intestinal lymphatic system. Sedds has enhanced the oral absorption of many drugs.

1.1. BIOPHARMACEUTICAL ASPECT:

[11] It is well known that lipids or food can improve the bioavailability of poorly water-soluble drugs. There are a variety of potential mechanisms by which lipids can improve bioavailability including:

1. **Alterations (reduction) in gastric transit:**

This would slow down delivery to the absorption site and shortening the time available for dissolution.

2. **Increase in effective luminal drug solubility:**

The presence of lipids in the GI tract results in an increase in the secretion of bile salts (BS) and endogenous biliary lipids, including phospholipid (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the GI tract solubilization ability. However, intercalation of administered (exogenous) lipids into these bs structures either directly (if sufficiently polar), or secondary to digestion results in micellar swelling and a further increase in solubilization ability.

3. **Stimulation of intestinal lymphatic transport:**

Lipids can increase the speed of lymphatic transport and bioavailability for drugs that are highly lipophilic, either directly or indirectly by reducing first-pass metabolism.

4. **Changes in the biochemical barrier function of the GI tract:**

It is clear that certain lipids and surfactants can attenuate the activity of intestinal efflux transporters, as shown by the p glycoprotein efflux pump, and may also reduce the rate of enterocyte-based metabolism.

5. **Changes in the physical barrier function of the GI tract:**

Several combinations of lipids, lipid digestion products, and surfactants have been shown to have permeability enhancing properties. However, passive intestinal permeability is not thought to be a significant obstacle to the bioavailability of the majority of poorly water-soluble, and in particular lipophilic, drugs, for the most part.

6. **Effect of oils on the absorption:**

Such formulations result in a fine oil in water emulsion with gentile agitation, which can be provided by gastro motility. A self-emulsifying system also increases the reproducibility of the plasma level-time relationship. Oils have been implicated in increased lymphatic absorption of water insoluble substances, including altered gastrointestinal motility, increased bile flow and drug solubilization, increased mucosal permeability, increased mesenteric lymph flow, and increased lymphatic absorption of water insoluble substances, as well as increased hydrophobic compounds.

1.2. NEED OF SELF-EMULSIFYING DRUG DELIVERY SYSTEM

[12] To pre-dissolve the compound in a suitable solvent and place the capsules on the stomach, the oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and place the capsules on top. This method has the major benefit of redissolving the substance, eliminating the initial rate-limiting step of particulate dissolution in the GI tract. However, a potential problem is that the drug will precipitate out of solution as it disperses in the GI tract, particularly if a hydrophilic solvent is used (e.g. acetone). Polyethylene glycol (polyethylene glycol) is a synthetic polyethylene glycol. There is less chance of precipitation in the GI tract if the drug can be dispersed in a lipid vehicle, since partitioning kinetics Favor the drug staying in the lipid droplets. To improve the solubility of the drug compound, one way to make it in a solid solution is to use a water-soluble polymer. For making solid solutions with poorly soluble substances, polyvinyl pyrrolidone (pvp) and polyethylene glycol (peg 6000) have been used, for example. With this method of preparation, a potential problem is that the drug may have a more thermodynamically stable state, which could result in the

compound crystallizing in the polymer matrix. Therefore, the chemical stability of such formulations must be investigated using techniques such as differential scanning calorimetry or x-ray crystallography. In this situation, the sedds scheme a viable option.

II. SELF- EMULSIFYING DRUG DELIVERY SYSTEM

[13] A self-emulsifying drug delivery system refers to a combination of natural or synthetic oils, solid or liquid surfactant, and one or more hydrophilic cosolvent or cosurfactant. SEDDS undergoes self-emulsification when gently stirred and diluted in water, like in the GI tract. The self -micro emulsifying formulations expand outward in GI tract, benefiting from the natural movement of the stomach and intestines for agitation needed for emulsification. For drugs that have poor absorption due to slow dissolution, this system may enhance both the speed and amount of absorption.

2.1.1. [14] Self-emulsifying therapeutic system

1. Self-emulsifying formulation (SEF'S)
2. Self-micro emulsifying formulation (SMEF'S)
3. Self-nano emulsifying formulation (SNEF'S)

Table 2.1: Features of different self-emulsifying formulations

SEF'S	SMEF'S	SNEF'S
Oil droplet size 200nm	Oli droplet size is 100-250nm	Droplet size >100nm
Appearance is turbid use	Appearance clear to translucent use	Optical clear use
Surfactant of HLB<12	Surfactant of HLB >12	Surfactant of HLB >12
Concentration of oil is 40-80%	Concentration of oil is less than 20%	

2.1.2. Factors affecting self-emulsifying drug delivery system

1. Nature and dose of the drug:

[15] Sedds should be used with drugs that are Given at a very high dose unless they have a high solubility in at least one of the sedds components, preferably in the lipophilic phase. Sedds is the most effective at delivering the drugs with a limited solubility in water and lipids (typically with log p values of about 2). The ability of Sedds to maintain the drug in its solubilized state is greatly influenced by the drug's solubility in the oil phase. As mentioned above, if a surfactant or co-surfactant is involved in the drug solubilization in a greater degree, there could be a risk of precipitation, as the surfactant or co-surfactant's dilution will reduce the solvent capacity. To anticipate potential cases of precipitation in the gut, equilibrium solubility tests can be carried out. However, crystallization can be slow in the gut's solubilizing and colloidal stabilizing environment. According to pouton's report, such formulations can take up to five days to reach equilibrium, and the drug can remain in a super-saturated state for up to 24 hours after the initial emulsification process. It could therefore be argued that such products are not likely to precipitate the drug in the stomach before it is absorbed, and that super-saturation could actually increase absorption by increasing the drug's thermodynamic activity. There is a clear need for practical strategies to predict the fate of drugs after dispersion of lipid systems in the gastro-intestinal tract

2. Polarity of the lipophilic phase:

The polarity of the lipid phase is one of the factors that determines the drug release from the microemulsions. The HLB, the chain length and degree of unsaturation of the fatty acid, the molecular weight of the hydrophilic portion, and the emulsifier's concentration determine the droplet's polarity. The polarity in the chart above indicates the drug's affinity for oil and/or water, as well as the type of forces formed. The high polarity will promote a rapid release of the drug into the aqueous phase. This is confirmed by the findings of sang-Cheol chi, who found that the rate of release of idebenone from sedds is dependent on the polarity of the oil phase used. With a formula that had an oil phase with the highest polarity, the highest release was achieved.

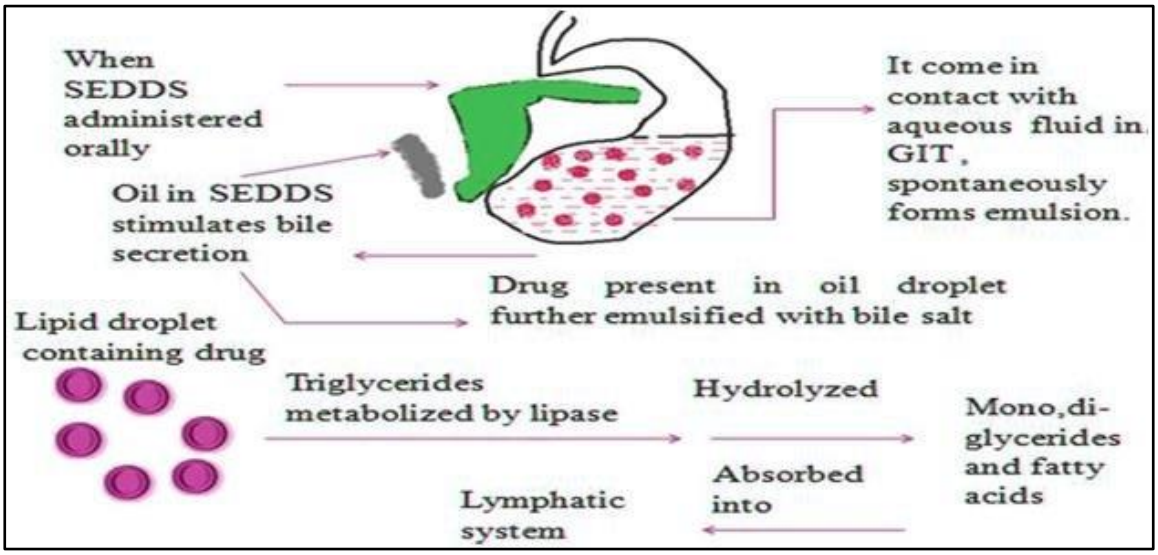
III. MECHANIAM OF SEDDS

[16] In the literature, various approaches have been proposed. There is no single method for describing all aspects of micro emulsion formation. Schulman et al., 2002. The spontaneous formation of micro emulsion droplets was due to the formation of a complex film at the oil-water interface by the surfactant and cosurfactant, according to the report. The thermodynamic model of micro emulsion formation explains that emulsification occurs when the entropy difference favouring dispersion is greater than the energy required to increase the surface area of the dispersion and the free energy (ΔG) is negative. The free energy in the micro emulsion formation is a direct result of the energy required to create a new surface between the two phases, and can be expressed by the following formula:

$$\Delta G = \Sigma N_л r2 \sigma$$

Where, ΔG is the free energy associated with the process (ignoring the free energy generated by the mixing). The interfacial energy is represented by n and. With time, the two phases of the emulsion tend to separate, reducing the interfacial space, and consequently, the system's free energy decreases. The emulsions formed by aqueous dilution are therefore stabilized by conventional emulsifying agents, which form a monolayer around the emulsion droplets, reducing the interfacial energy and acting as a barrier against coalescence.

Fig. 3.1. Mechanism of action of self-emulsifying drug delivery system



IV. COMPOSITION OF SEDDS

[17] SEDDS belong to lipid-based formulations. Lipid formulations can be oils, surfactant dispersions, emulsions, SEDDS, solid lipid nanoparticles and liposomes. Typically, self-emulsifying drug delivery system are comprised of :

1. Oil
2. Surfactant
3. Cosolvent

The self-emulsifying process is depending on

1. The nature of the oil–surfactant pair.
2. The surfactant concentration.
3. The temperature at which self-emulsification occurs

1. **Oil:**

Oils can solubilize the lipophilic drug in a specific amount. It is one of the most important excipients because it can aid self-emulsification and increase the amount of lipophilic drug transported by the intestinal lymphatic system, increasing absorption from the GI tract. In the construction of sedds, long-chain triglyceride and medium chain triglyceride oils with different saturation levels have been used. Sedds' success has been largely due to their composition and physiological benefits, as shown by modified or hydrolysed vegetable oils. Novel semi-synthetic medium-chain triglyceride oils have surfactant properties and are increasingly replacing traditional medium-chain triglyceride oils.

2. **Surfactant**:

In the preparation of sedds, non-ionic surfactants with high hydrophilic–lipophilic balance (HLB) values are used (e.g., tween, labrasol, labrafac cm 10, Cremophor, etc.). In order to produce a stable sedds, the usual surfactant strength is between 30–60% w/w of the formulation. Surfactants have a high HLB and hydrophilicity, which allows for the immediate formation of o/w droplets and/or rapid diffusion of the product in the aqueous environment. Surfactants are amphiphilic in nature, and they can dissolve or solubilize very large amounts of hydrophobic drug compounds. This will prevent precipitation of the drug within the GI lumen and prolongation of drug molecules. Emulsifiers made from natural ingredients are supposed to be safer than synthetic ones and are recommended for SDLF (self-dispersed lipid formulation). Non-ionic surfactants are generally less harmful than ionic surface-active agents, but they can result in small reversible changes in intestinal wall permeability. To avoid the potential toxicological problems associated with a high surfactant content, he developed a new vehicle made of a fine emulsion with only a minimum surfactant content (3%). The formation of self-micro emulsifying formulations (smedds) is facilitated by lipid mixtures with higher surfactant and co-surfactant/oil ratios. Formulations consisting only of the surfactant mixture may result in emulsions or micro emulsions (when surfactants have different low and high HLB), micelle solution, or, in some cases, niosomes, which are non-ionic bilayer vehicles made of surfactant-based bilayers

3. Cosolvent:

Cosolvents such as diethylene glycol monomethyl ether (transcutol), propylene glycol, polyethylene glycol, tetrahydrofurfuryl alcohol polyethylene glycol ether (glycofurol), etc., can help to dissolve large amounts of hydrophilic surfactants or the hydrophobic substance in the lipid base. In microemulsion processes, these solvents can act as the cosurfactant.

V. ADVANTAGES

1. [18] Maximum bioavailability with a minimum dose.
2. Temporal profile of drug absorption is more consistent
3. Selective delivery of medication to specific area in gastrointestinal tract.
4. Safeguarding medication in the digestive system
5. Delivery profile has been controlled.
6. Enhanced drug loading capacity.
7. Enhanced patient convenience and compliance.
8. Reduction in health care cost.
9. Reduction in dosing frequency

VI. Disadvantages of SEDDS

1. [19] Insufficient reliable invitro model's for evaluating formulation effectiveness.
2. Conventional dissolution methods are ineffective for formulation require digestion before drug release.
3. More work is required to develop and validate the in vitro model.
4. Various lipid-based formulations must be created and assessed in live subject.
5. The potential for irritation in GIT may increase with drug instability and high levels of surfactants in the formulation, typically ranging from 30-60%.
6. Poor systemic availability in general.
7. Reduced potential for dosage adjustment.

VII. APPLICATIONS OF SEDDS

1. [20] Sedds have potential applications as devices for the administration of lipophilic drugs
2. After incorporation of polymer in the composition1, it allows for a long time of release of drugs
3. Fine oil droplets drain quickly from the stomach and aid in the spread of the drug throughout the intestinal tract, minimizing irritation that can occur as a result of prolonged contact with drugs and gut wall trough.
4. reduction of inter-subject and intrasubject variability.
5. Sedds offer reproducibility of the plasma profile.
6. They can disguise the bitter taste and order of the drug, e.g., morphine. Chlorpromazine is a form of chlorpromazine.
7. In food industry, multiple emulsions are used.
8. They can be used to prolong the drug's release, resulting in a long-term release effect.
9. Essential nutrients such as fats, proteins, and vitamins can all be emulsified and given to a bedridden patient by way of sterile intravenous injection.
10. Emulsions protect drugs that are susceptible to oxidation or hydrolysis.

11. To aid in diagnosis, intravenous emulsions of contrast media have been developed.
12. A hydrophilic as well as hydrophobic drug can be entrapped

VIII. FUTURE ASPECTS

1. [21] supersaturable SMEDDS (S-SMEDDS):

The toxic effects of surfactants are well known, and the use of these surfactants at such high levels, which are often used in SMEDDS formulations, can cause gastrointestinal side effects, thus overcoming this problem and minimizing GI side effects when uses the new class of formulations. oversaturated dosage forms called saturated SMEDDS (S-SMEDDS) were developed and developed. The S-SMEDDS approach is to produce a long-term supersaturated solution of the drug by releasing the drug from a suitable dosage form into an aqueous medium. The purpose of supersaturation is to increase the thermodynamic activity of the drug above its solubility limit and thus increase transport in and through the biological\fluid. S-SMEDDS preparations contain less surfactant. and a polymeric precipitation inhibitor to produce and stabilize the drug in a transient supersaturated state. Hydroxypropyl methylcellulose (HPMC) and related polycellulose. A supersaturated self-micro emulsifying drug delivery system (S-SMEDDS) of paclitaxel was developed utilizing HPMC as a precipitation inhibitor with a conventional SMEDDS formulation. In vitro dilution of the S-SMEDDS formulation resulted in the formation of a microemulsion followed by slow crystallization of paclitaxel on standing. This result indicated that the system was supersaturated with crystalline paclitaxel, and the HPMC in the formulation prolonged the supersaturated state. In the absence of HPMC, the SMEDDS formulation rapidly precipitated, resulting in a low concentration of paclitaxel solution. A pharmacokinetic study showed that the Paclitaxel S-SMEDDS formulation produced approximately 10-fold higher peak concentration (Cmax) and 5-fold higher oral bioavailability (F 9.5%) compared to the orally administered Taxol formulation (F ~ 2.0%)) and SMEDDS formulation without HPMC (F ~ 1%). When applying the supersaturated SMEDDS method, a smaller amount of surfactant can be used with HPMC to create a temporarily supersaturated state, with a lower degree of dissolution. Thus, a high concentration of free drug would be achieved in life by creating and maintaining a supersaturated state and increasing the driving force for absorption. It is worth emphasizing that the significantly lower amount of surfactant used in the S-SMEDDS formulation provides a better toxicity/safety profile than conventional SMEDDS formulations. However, the mechanism underlying crystal growth inhibition and stabilized supersaturation is poorly understood, although several studies have been done to investigate this.

2. Solid SMEDDS:

SMEDDS are usually prepared in liquid dosage forms that can be administered in soft or hard gelatin capsules, which have a number of disadvantages, particularly the fragility and leakage problems of hard gelatin capsules. An alternative method is to add liquid self-emulsifying ingredients to the powder to obtain a solid dosage form (tablets, capsules). The progesterone pellet formulation in SEDDS is made using an extrusion/Spheronization process to achieve good in vitro drug release (100% within 30 minutes, T50% after 13 minutes). The same dose of progesterone (16 mg) in granules and liquid SEDDS produced similar AUC, Cmax and Tmax values. A method for producing self-emulsifying pellets by wet granulation of a powder mixture consisting of microcrystalline cellulose, lactose and nimesulide with a mixture containing mono- and diglycerides, polysorbate 80 and water as a model drug was studied. Granules made with an oil to surfactant ratio of 1:4 (w/w) showed better results in penetration tests.

IX. CONCLUSION

A novel method for overcoming the first pass metabolism has been developed using a self-emulsifying drug delivery method in the formulation of drug compounds with a low aqueous solubility. Sedds are a safe alternative to poorly water-soluble drugs. Sedds have been shown to significantly improve oral bioavailability in order to facilitate the delivery of hydrophobic drugs in the oral cavity. By this method, the drug's release can be extended by the incorporation of polymer in the body. Sedds seems to be a novel and economically feasible option. Sedds will continue to be used in novel ways in drug delivery and solve problems associated with the delivery of poorly soluble drugs with future research.

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