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SELF EMULSIFYING DELIVERY SYSTEM –MOSTLY DISCUSSED BUT STILL REMAINED CHALLENGING ASPECT TO ENHANCE THE ORAL ABSORPTION OF LIPOPHILIC DRUG

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ABSTRACT: Oral route of drug delivery is the simplest and most accepted way of administration of drugs due to greater stability, high patient compliance, accurate dosage, cost effectiveness and high patient compliance of drugs. But with oral formulations bioavailability is the major problem for newly discovered drug because 40 percent are lipophilic compounds. There are several factors responsible for low oral absorption of hydrophobic drugs and one very particular one is poor absorption due to slow and/or incomplete drug dissolution and precipitation in the gastro-intestinal lumen or other aqueous media. Therefore in order to be delivered orally and to achieve acceptable bioavailability, lipophilic drugs require a co-administered drug delivery system. This article mainly gives overview of technologies available with special emphasis on mechanism of SEDDS and potential for commercialization of formulation as compared to other technologies along with examples. But there are certain disadvantages of SEDDS like lack of good predicative in vitro models for assessment of the formulations and higher concentrations of surfactant used may cause some allergic reactions. So it requires more development and still remained challenging aspect to enhance oral absorption of lipophilic drugs.

INTRODUCTION: To increase oral bioavailability of hydrophobic drugs Lipid-based drug delivery systems are usually studied. Recent approaches have included the lipid vehicles such as oils, liposomes and self-emulsifying formulations to administer various drug entities [1, 2]. Due to the lack of guidance for formulation and knowledge these systems are not commercially used.

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However Self-emulsifying drug delivery systems (SEDDS), can surely be used to enhance oral bioavailability of low-solubility compounds.

SEDDS can be easily mixed with gastrointestinal fluid with low agitation [1] and having minimum droplet sizes ranging from a few nanometers to hundreds of nanometers. For example, SEDDS of Tipranavir (TPV), which is used as anti- HIV drug increases the bioavailability of drug two times in rats when compared with solid powder [3]. Kommuru et al [4] increased bioavailability of Coenzyme Q10, 150 % by developing SEDDS.

There are many examples in literature indicating use of self emulsifying drug delivery systems to

increase bioavailability [5-9], but mostly do not discuss [2] how this formulation was developed. Current SEDDS is formulated and developed by trial and error basis. In the development of SEDDS, ability to emulsify [7, 9] is most important aspect of formulation and also property of formulation to interact with biological environment must be studied for its optimization.

Although vast study is done on function of emulsions [10-13], fundamental aspects of emulsion are not studied for development of formulation [10-13]. But some studies indicates predictive models that relate emulsion properties with formulation parameters [14-17].

There is no experimental design developed for analysis and optimization of emulsion function across a broad range of formulation parameters. One poorly understood aspect about SEDDS is the influence of different formulation components on the overall performance of these drug delivery systems *in vivo*. Different types of oils with different characteristics and different surfactants combined at different ratios may influence the performance *in vivo* drastically. There is no guidance currently available for formulating a drug with specific properties with self emulsifying drug delivery formulations. It is therefore necessary to investigate the influence of formulation components with a quantitative and statistically designed and analyzed manner.

The mechanism of how self emulsifying drug delivery systems act to increase bioavailability of poorly soluble drug is unknown.

Suggested mechanisms responsible of functioning of SEDDS in the GI tract environment includes the increased drug solubilization in the aqueous lumen phase due to alterations in the composition and character of colloidal environment in the GI tract fluid and increased drug absorption due to enhanced permeability (e.g. widening of tight junctions, changes to cellular processing) and lymphatic transport [18]. Important mechanisms that would influence drug solubilization in the lumen is the rate and extent of digestion of lipidic formulation components. Another one is the rate at which the drug is released from oil droplets especially during the process of "degradation" of the emulsified drug carriers by the digestive enzymes *in vivo*. It is essential to investigate the rate of digestion of self emulsifying formulation lipids, rate of drug release, as well as the rate and amount of drug transport across.

Intestinal monolayer incorporated with SEDDS in order to understand and predict formulation functioning in GI tract. Knowledge gained from these mechanistic understandings can be used as quantitative expressions which then can be incorporate into a pharmacokinetic model that will predict oral bioavailability of a drug administered with self emulsifying drug delivery systems. To define and understand challenges involved with oral delivery of hydrophobic drug compounds it is necessary to present an overview of current technologies.

Oral delivery of hydrophobic compounds:

With oral formulations bioavailability is the major problem for newly discovered drug as 40 percent are lipophilic compounds [5]. There are several factors responsible for low oral absorption of hydrophobic drugs and one very particular one is poor absorption due to slow and/or incomplete drug dissolution and precipitation in the gastro-intestinal lumen or other aqueous media [19]. Therefore in order to be delivered orally and to achieve acceptable bioavailability, lipophilic drugs require a co- administered drug delivery system.

Oral drug delivery systems for hydrophobic drugs:

Compounds that have low aqueous solubility are class II and class IV drugs classified by BCS. These drugs get eliminated by the biological environment either as metabolites or unchanged forms [20]. Critical steps in oral drug absorption are intestinal transit, gastric emptying, dissolution, permeability, metabolism by liver or intestinal lymphatic route. In order to enable oral bioavailability of a water insoluble drug, one common approach is the use of a carrier that can enhance the amount and the time of dispersed drug in the gastrointestinal fluid. In order to increase the amount of drug administered orally, excipients that solubilize high amounts of hydrophobic drug are being used. By selecting the optimum liquid

vehicle composition, it is possible to eliminate or at least minimize drug precipitation [19]. Drug delivery systems that alter the drug solubilization in the biological environment will be discussed in the following sections.

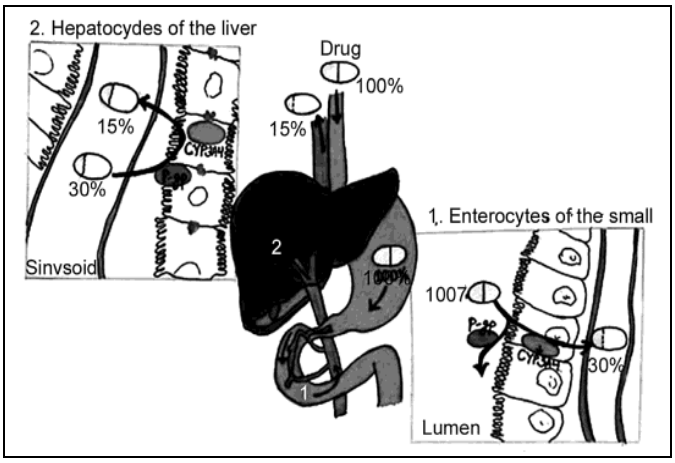

FIG.1: PHYSIOLOGICAL PATHWAYS LEADING TO REDUCING IN DRUG BIOAVAILABILITY THROUGH ORAL CONVENTIONAL DOSAGE FORMS

Overview of technologies:

In order to increase oral solubility of conventional dosage forms like tablets, capsules, syrups or solutions various excipients such as surfactants, organic solvents, triglycerides , cyclodextrins and phospholipids are used [21].

Ethanol, PEG 400, propylene glycol, glycerin non-ionic surfactants are the most commonly used commercially as a water soluble organic solvents. Solubility of Ritonavir, an HIV protease inhibitor, is increased by using a co-solvent mixture of ethanol, water, glycerin, surfactant Cremophor RH 40, and peppermint oil from 1 µg/ml to 20 mg/ml in oral dosage forms. Another example is the solubility of Sirolimus, used as an immunosuppressant which was solubilized using the surfactant polysorbate 80 (Tween 80), and a proprietary solution Phosal 50 PG, that is composed of phosphatidylcholine, propylene glycol, mono- and diglycerides, 1.5- 2.5 % ethanol, soy fatty acids, and ascorbyl palmitate. The resultant drug's oral bioavailability was 14% [22, 23]. Another approach to formulate lipophilic drugs is the use of water insoluble solvents for the solubility enhancement. Such solvents include; long-chain triglycerides, peanut oil, hydrogenerated vegetable oils, hydrogenerated soybean oil, beeswax, Vitamin E, oleic acid and the medium-chain triglycerides derived from coconut oil and palm seed.

Drugs solubilized into these solvents are usually encapsulated in gelatin capsules [21]. Liposomes for instance, are amphilic phospholipid molecules that are arranged in a closed spherical bilayer which are utilized to increase the bioavailability of lipophilic compounds. A drug with a basic functional group can be solubilized in acidic solutions with pKs lower than the drug's and pH can be controlled adjusting the salt forms used, a hydrochloric acid, tartaric acid, benzoic acid, or citric acid. An example of the pH modified drugs is Loratadine, a drug for allergic treatments. The drug is soluble in citric acid, water, glycerin and propylene glycol mixture at 1 mg/ml where as it is not soluble in neutral pH water [21].

Another approach to increase oral bioavailability of water insoluble drugs is to use cyclodextrin complexation. Cyclodextrins are cyclic oligosaccharides of a -D-glucopyranose containing a hydrophilic outer surface and a hydrophobic central cavity [24]. In the past years, there have been a tremendous amount of research done on cyclodextrins and currently there are more than 21 commercial formulations available. Most commonly used solid form of cyclodextrins is "-cyclodextrin. Even though its solubility is limited to 18 mg/ml in water it is possible to alter this value with covalent modifications which will also result with a biologically safer formulation. Surfactants are also utilized to solubilize hydrophic drug compounds.

However due to biological toxicity issues they have been avoided most of the time. Surfactants are structures that have both a hydrophobic head and a hydrophilic tail. These structures self-assemble to form micellar structures at above critical micellar concentration that varies with the type of the surfactant. Thus, drugs can be solubilized in monomers, in micellar structures, or in both. Micelles, once formed, are known to have a capacity of capturing higher amounts of compounds compared to monomers. A significant bioavailability enhancement is enabled by 20% d- -tocopherol polyethylene glycol 1000 succinate (TPGS) containing formulation of drug

Amprenavir. The bioavailability of Amprenavir in conventional capsule or tablet formulations is nearly zero.

However when formulated with TPGS, the bioavailability was increased up to 70% in beagle dogs. The reason to this significant increase in bioavailability was showed to be due to the TPGS potent inhibitor structure of an active flux which was tested across Caco-2 cellmonolayers [25]. This effect indicates that surfactants not only enhance bioavailability by solubilizing high amounts of drug but also play an important role in efflux inhibition and overall permeability enhancement. Surfactants can also be utilized as components of self- emulsifying drug delivery systems, other than being a direct co-solvent for the drug. In self-emulsifying drug delivery system formulations surfactants are incorporated with an oily component to form low surface energy oil droplets as drug carriers [21]. There are similar approaches to those explained above for injectable formulations for the bioavailability enhancement of water insoluble drugs.

Microemulsions or Self-Emulsifying Drug Delivery Systems (SEDDS):

Emulsions in general are thermodynamically unstable systems. The droplets of the dispersed phase are large. Microemulsions on the other hand are emulsion systems that have a droplet size of a few to hundreds of nanometers and are typical complex fluids that consist of three essential components: two immiscible fluids and a surfactant. Typically these are water-in-oil or oil-in-water microemulsions where the rheological properties of these two liquids and microstructure of the surfactant strongly affect the resulting microemulsion.

Microemulsions and micellar solutions are distinguished from emulsions by the fact that the average drop size does not grow with time, which is a manifestation of thermodynamic un stability. Micellar solutions and microemulsions on the other hand are assumed to be thermodynamically stable [26]. Reasons why there is tremendous attention on SEDDS include industrial trend towards the discovery and development on hydrophobic drugs and the resolution of technology transfer, stability and regulatory issues by SEDDS and the fact that they have proven pharmaceutical benefit with commercially available compounds of up to 5 fold increase in bioavailability (cyclosporine, lipid soluble vitamins, HIV protease inhibitors etc.) [27]. Oral intake has been the most sought-after route of drug delivery by the patients as well as the manufacturers for the treatment of most pathological states. Despite tremendous strides made in novel non-oral drug delivery systems (DDS) till date, majority of the drug formulations available in the commercial world today are the oral ones [28].

Due to high lipophilicity and poor water solubility, nearly about one half of drug components loses its oral delivery through gastrointestinal (GI) tract. It ultimately affect the inadequate oral bioavailability of such drugs which is primarily a function of their solubility and dissolution, [29, 30]. Besides, oral bioavailability also depends upon a stability in GI fluids, [29, 30] intestinal permeability, [31] resistance to metabolism by cytochrome P450 enzymes, [32, 33] and interaction with efflux transporter systems like P-glycoprotein [34, 35].

In order to improve the oral bioavailability of diverse drugs many formulation approaches have been employed. Out of that lipid based DDS is having great potential to improve absorption of poorly soluble drug after meals [36, 37]. These include various types of lipid suspensions, solutions and emulsions [38-41]. With applications in specific domains, the lipidic formulations, thus, have carved a significant niche in oral drug delivery.

Self-emulsifying drug delivery systems (SEDDS) are newly developed and are having promising approach to improve oral bioavailability of drugs.
With these formulations slow and incomplete absorption of drug is reduced, transportation of via lymphatic system is increased and absorption from GI tract is facilitated [42, 43].

The following points should be considered in the formulation of a SEDDS:

1. The solubility of the drug in different oil, surfactants and surfactant and co solvents.

2. The selection of oil, surfactant and co solvent based on the solubility of the drug and the preparation of the phase diagram.

3. The preparation of SEDDS formulation by dissolving the drug in a mix of oil, surfactant and surfactant or co solvents.

4. The addition of a drug to a SEDDS is critical because the drug interferes with the self emulsification process to a certain extent, which leads to a change in the optimal oil surfactant ratio. So, the design of an optimal SEDDS requires pre formulation solubility and phase diagram studies.

Drugs with low aqueous solubility present a major challenge during formulation as their high hydrophobicity prevents them from being dissolved in most approved solvents. The novel synthetic hydrophilic oils and surfactants usually dissolve hydrophobic drugs to a greater extent than conventional vegetable oils. The addition of solvents including ethanol, Propylene Glycol and Polyethylene glycol, also contribute to the improvement of drug solubility in the lipid vehicle [44].

Recent advancement and future prospects [45]:

Dry emulsions: Dry emulsions are powders from which emulsion spontaneously occurs in vivo or when exposed to an aqueous solution.

Self-emulsifying Capsules: After administration of capsules containing conventional liquid SE formulations, micro emulsion droplets form and subsequently disperse in the GI tract to reach sites of absorption.

Self-emulsifying sustained/controlled release tablets: Combinations of lipids and surfactants have presented great potential of preparing SE tablets that have been widely researched.

Self-emulsifying sustained/controlled release pellets: Pellets as a multiple unit dosage form, possess many advantages over conventional solid dosage forms, such as flexibility of manufacture, reducing intrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability.

Self-emulsifying beads:

Self-emulsifying sustained release microspheres:

Self-emulsifying nanoparticles:

Self–emulsifying suppositories:

Self-emulsifying implants:

Self-emulsifying fast dissolving tablets:

These are the novel techniques or advancement used in the formulation of SEDDS.

Advantages of SMEDDS:

- Spontaneous formation
- Ease of manufacture
- Thermodynamic stability
- Improved solubilization of bioactive materials
- More consistent temporal profiles of drug absorption
- Greater bioavailability
- Less drug need to be used
- These systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles

Limitations of SMEDDS:

- Chemical instabilities of drugs and high surfactant concentrations
- The large amount of surfactant in self-emulsifying formulations (30-60%) irritates GIT
- Moreover, volatile co solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft

or hard gelatin capsules, resulting in the precipitation of the lipophilic drug [46-48].

CONCLUSION: In this review, the current technologies along with examples and limitations for successful lipid based drug delivery system have been discussed to provide a platform for more development in the field. The true potential of Self Emulsifying Drug Delivery System is yet to be recognized and further research need to be done to know absorption enhancing mechanism of lipids to develop better co relation between *in vivo* and *in vitro* behavior of formulations.

As for different types of drug molecules for development and for characterization of lipid based formulations and also to increase the stability of lipid based systems, higher concentrations of surfactant can be used but may also causes some allergic reactions. So on these areas more work should be done to overcome the drawbacks and to understand the mechanism. This article gives basic platform to understand it in a better manner.

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