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Review self Emulsifying Drug Delivery System

MS. Gauri V. Wagh and Mr.Shubham P. Jaiswal
[1]B-pharma student Ishwar Deshmukh Institute Of Pharmacy, Digras.Maharashtra, India.
[2]Assistant professor, Department of Pharmaceutics, Ishwar Deshmukh Institute Of Pharmacy,Digras. Maharashtra, India.

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ABSTRACT: Oral route is the easiest and most convenient route for drug administration. Oral drug delivery systems being the most cost effective and leads the drug delivery market. Self emulsifying drug delivery systems (SEDDS) possess unparalled potential improving oral bioavailability of poorly water soluble drugs. Following their oral administration ,these systems rapidly disperse in gastrointestinal fluids, yielding micro or nanoemulsions containing the solubilized drug.Self emulsifying drug delivery systems are a vital tool in solving low bioavailability issues of poorly soluble drugs. Hydrophobic drugs can be dissolved in these systems ,enabling them to be administered as a unit dosage form for per oral administration. This article presents an exhaustive account of various literature reports on diverse types of self emulsifying formulations with emphasis on their formulation, characterization and in vitro analysis, with examples of currently marketed preparations. .

KEYWORDS: Self emulsifying drug delivery systems, isotropic, emulsions ,bioavailability. oral delivery ,composition and application.

I. INTRODUCTION

Oral intake has been the most sought after route of drug delivery by both patients and drug manufactures for the treatment of most pathological states. Nevertheless, with oral delivery, over one half of the compounds are diminished in the gastrointestinal (GI) tract because of their high lipophilicity and consequently poor aqueous solubility. Oral bioavailability of such drugs , being primarily function of their solubility and dissolution. Further, bioavailability also depend upon a multide of other drug factors such as stability in GI fluids ,intestinal permeability, resistance to metabolism by cytochrome P450 family of enzymes present in gut enterocytes and liver hepatocytes and interactions with efflux transporter system such as P-glycoprotein (P-gp). Figure 1 illustrates the mechanisms of the physiological pathways through which the bioavailability of drug from the conventional formulations tends to get impeded. This approaches include various types of lipid suspensions, solutions and emulsions. Self emulsifying drug delivery systems are relatively newer, lipid based technological innovations with immense promise in enhancing the oral bioavailability of drugs. These formulations can been shown to reduce the slow and incomplete dissolution of drug , facilitate the formation of solubilized phase .

Self emulsifying drug delivery systems (SEDDS) are isotropic mixtures of drug, lipids and surfactant. SEDDS is a broad term, typicallyau producing emulsions with a droplet size ranging from few nanometers to several microns . approximately 40% of new drug candidates have poor water solubility and the oral delievery of such drugs is associated with low bioavailability ,high intra and inter subject variability and lack of dose proportionately. An additional advantage of SEDDS over simply oily solutions is that they provide a large interfacial area for partitioning of drug between oil and water. The potential of SEDDS for lipophilic compound as well understood long ago with the introduction of cyclosporine. The SEDDS system was further modified to self micro emulsifying (SMEDDS) or self nanoemulsifying (SNEDDS) drug delievery system classified as type 3a and type 3b ,which additionally contain one or more surfactant or hydrophilic cosolvents. From these aspects objective of this review is to identify and analyze the potential controversies reported by pharmacokinetic studies of orally administered SEDDS. Self nanoemulsifying drug delievery systems is a recent term constructing the globule size range less than 100 nm. Self micro emulsifying drug delievery systems indicates the formulations forming transparent micro emulsions with range between 100 and 250 nm.

ADVANTAGES :

1) Control of delivery profiles.
2) SEDDS can be formulated into liquid dosage form and solid dosage form.
3) Reduced variability including food effects.

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4) Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT.
5)The main advantage of SEDDS is that it enhances the bioavailability of oral lipophilic drug.

DISADVANTAGE :

1) Cosolvents which are volatile in nature and can migrate on hard or soft gelatin capsule shell leading to the precipitation of lipophillic drug.
2)Production cost is expensive.

LIMITATIONS : One of the barrier for the development of self emulsifying drug delivery system (SEDDS) and other lipid based formulation is the lack of good predicative invitro models for estimation of the formulation.Traditional dissolution method do not work, due to these formulations potentially are dependent on digestion prior to release of the drug. To devasted this, an invitro model simulating the digestive processes of the duodenum has been developed. This invitro model needs further development and validation before its strength can be evaluated . Further development will be based on invitro -invivo correlation and therefore different prototype lipid based formulation needs to be developed and tested in vivo in a suitable animal model. Future studies will addressed the development of the invitro model.

MECHANISM Of SEDDS :

Different approaches have been the reported in the literature. No single theory explains all aspects of microemulsion formation. Schulman et al considered that the spontaneous formation of micro emulsions droplets was due to the formation of a complex film at the oil water interphase by the surfactant and cosurfactant . According to reiss ,self emulsification occur when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phases and can be described by the equation.

$\Delta G = Sni\ pri2S$

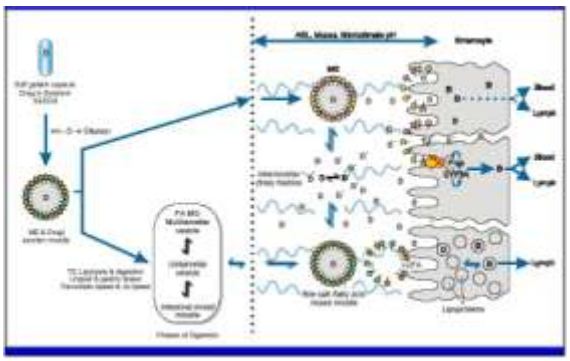
Where Δ G is the free energy associated with the process, L is the number of droplets of radius r and S represent the interracial energy. The two phases of emulsions tend to separate with a time to reduce the interracial area and, subsequently, the emulsion is stabilized by emulsifying agents, which form a monolayer of droplets, and hence reduces the interfacial energy as well as providing a barrier to prevent coalescence.

Mechanism for absorption enhancement

Composition:

The self emulsifying process based on

- The nature of the oil and surfactant
- The concentration of the surfactant
- The temperature at which self emulsification occurs.



Oil

Both long and medium chain triglycerides (MCT) oils with various degrees of saturation have been used for the design of self dispersing formulations. Oil represent one of the most important excipients in the SEDDS formulation not only because it can solubilize the required dose of the lipophillic drug or facilitate self emulsification but also and mainly because it can increase the fraction of lipophillic drug transported via the intestinal lymphatic system. Unmodified edible oils provide the most 'natural' basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drug and their relative difficulty in efficient self emulsification.

Surfactant :

Compounds exhibiting surfactant properties may be employed for the design of self emulsifying system but the choice is limited as for very few surfactant are given by orally. Non ionic surfactant with a relatively to

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hydrophillic+lipophillic balancefor the design of self dispersing systems, the commonly used emulsifiers are various solid and liquid ethoxylatedand poyglycosylyzed glycerides and tween 80 are the mostly used in excipients. Theusual surfactant concentration in self emulsifying formulationsrequiredto form and maintain an emulsion rate in the GI tract. A large quantity of surfactant may irritate the GI tract.

Thefour groups of surfactants are as following-

A) Anionic surfactant
B) Cationic surfactant
C) Non ionic surfactant
D) Ampholytic surfactant

Anionic surfactant :

Surfactants where the hydrophillic group carries negative charge such as carboxyl (RCOO-),Sulphonate(RSO3-)or sulphate (ROSO3-)Examples: Sodium lauryl sulphate,Potassium laurate.

Cationic Surfactant :

Surfactant where the hydrophiliic group carries positive charge. Examples : Quaternary ammonium halide.

Non ionic Surfactant :

Surfactant where the hydrophillic group carries no charge but derives it's water solubility from highly polar group such as hydroxyl or polyethylene (OCH2CH2O). Examples : Sorbitan esters (Spans), Polysorbates (Tweens).

Ampholytic surfactant

Surfactant contain both positive and negative charge,also called as (zwitterion) surfactant. Examples:sulfobetaines.

Cosolvents :

The production of SEDDS contain high concentration of surfactants, thus the concentration of surfactant can be reduced by incorporation of surfactant. Organic solvents, suitable for oral administration (ethanol, propylene glycol) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in lipid base. Addition of an aqueous solvent such as Triacetin (an acetylated derivative of glycerol) for example glyceryl triacetate or other suitable solvent such as cosolvents. These solvents play the role of cosurfactantin the microemulsion systems, although alcohol free self emulsifying micro emulsions have also been described in the literature.Tricetin ismiscible in in the lipid phase and it can be solubilize to hydrophobic drug.

Factors Affecting SEDDS :

- **Polarity of the lipophillic phase**

The polarity of the lipid phase is one of the main factors that govern the drug release from the micro emulsions. The polarity of the droplet is managed by the HLV, the chain length and degree of unsaturation of the fatty acid, the molecular weight of the hydrophillic portion and the concentration of the emulsifier. The high polarity will promote a rapid rate of release of the drug into the aqueous phase.

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- **Nature and dose of the drug**

Drugs which are administered at very high dose are not suitable for SEDDS unless they have extremely good solubility in at least one of the components of SEDDS preferably lipophilic phase. The ability of SEDDS to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in oil phase. The drugs which have limited solubility in water and lipids are more difficult to deliver by SEDDS. As mentioned above if surfactant or cosurfactant is contributing to the greater extent in drug solubilization then their could be a risk of precipitation ,as dilution of SEDDS will lead to lowering of solvent capacity of the surfactant or cosurfactant.

Formulation :

Oils, surfactant and cosolvent based on the solubility of drug. The preparation of SEDDS formulation by dissolving the drug in mixture of oil, surfactant and cosolvents. The addition of the drug to SEDDS is difficult because the drug interferes with the self emulsifying process, which leads to a change in optimal oil surfactant ratio so design of optimal SEDDS require preformulation Solubility and phase diagram study. The SEDDS formulation forms a clear dispersion instantaneously in the GI tract that remains stable on dilution. Such dispersions are either micro or nanoemulsion, depends on the globule8 size of the SEDDS formulation. Recently synthesized drug that are being discovered are lipophillic in nature and have poor aqueous solubility, there by posing problems in their formulation into delivery system. The hydrophobic agent remains solubilized until the time relevant for its absorption Silva et al. Found that two main factors, small particle size and polarity ofoil droplets, determine the efficient release of the drug compounds from SEDDS.In o/w microemulsion ,theimpact of polarity of oil droplets is not consider because the drug compound incorporated within the oil droplets reaches the

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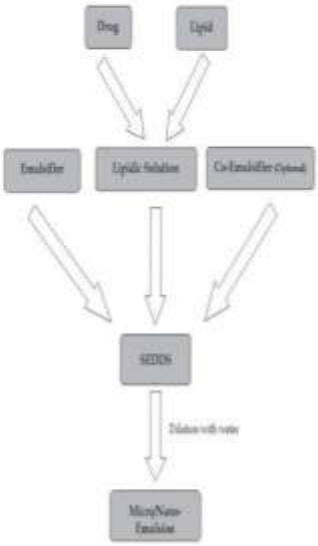
capillaries.Figure illustrates the usual methodology pathwaysto prepare SEDDS formulations and the eventual formation of themicro/nano-emulsions following their dilution. These SEDDS have to be formulated as an oral solution in soft gelatin capsules or as solid dosage forms in hard gelatin capsules, depending on the final physicalnature of the system as liquid or semisolid/solid,respectively.



FigureSchematic flow chart on the general strategy of formulating self emulsifying systems and their subsequent conversion to micro/nano emulsions.

The SEDDS have been classified as Type 1,2,3A,3B and 4. Type 1 which contains only mixtures of lipidic constituents but without surfactant and cosurfactant, all the SEDDS formulations tend to result in globule size in the nanometer ranges.When the type 1 is the devoid of surfactant and cosurfactant, all the rest of the categories contain different percentage of these constituents. Type 1 SEDDS have been found to be of limited utility, as the rate governing phenomenon determining their efficacy is lipid digestibility. When type 1 SEDDS have employ long chain fatty acids. Type 2 to 4 SEDDS are better suited for various kind of drugs.

The Self Dispersing Lipid Formulations(SDLFs) is one of the most important approaches to overcome the formulation difficulties of various hydrophillic/lipophillicdrug to improve the bioavailability of poorly soluble drugs. The (SDLFs) contain oil and surfactant of mixture into which the drug is incorporated. The SDLFs are of two things namely Self EmulsifyingDrug Delivery System (SEDDS)formed using surfactants of HLB <12 and Self Micro Emulsifying Drug Delivery System formed surfactants of HLB >12 . Both SEDDS and SMEDDS are stable preparations and improve the dissolution of the drug due to increased surface area of dispersion.

e.g. : Cyclosporin A[17⁄8],Coenzyme Q10 [14].

EVALUATIONPARAMETERS :

Droplet Size- The droplet size of the emulsions is determined by photon correlation spectroscopy using a zetasizer instrument able to measure sizes between 10 and 5000 nm. Light scattering is observing at 25 °c at 90° angle, after external regularity with spherical polystyrene beads. The nanometric size of the particle is reserve after 100 times dilution with water which proves the system's compatibility with excess water.

Zeta potential measurement –This measurement is used to identify the charge of droplets. In prevalent SEDDS, the charge on an oil droplet is negative due to presence of free fatty acids. Zeta potential of dispersionis measuredby applying an electric field across the dispersion.

Turbidimetric evaluation- Nephaloturbidimetric evaluation is done to regulate the growth of emulsification. In self emulsifying system,(0.1 N of hydrochloricacid) is addedto fixed quantity of suitable medium under continuous stirring(50 rpm)

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on magnetic plate at ambient temperature and increase in turbidity is measured by using turbidimeter.This apparatus is connected to a dissolution appratus and optical clarity of formulation taken every 15 s to determine the drug of nano/micro emulsion. The timerequired for complete emulsification was too chart, it was impossible to monitor the rate of change of turbidity.

Viscosity Determination-The viscosity determination check whether the system is o/w or w/o. If this system has low viscosity then it is o/w or the system hashigh viscosity then it is w/o type of system. The SEDDS systemis generally administered in soft gelatin or hard gelatin capsules So it can be easily spill out into capsules and system should not too thick to create a problem. The rheological properties of the microemulsion are evaluated by Brookfield viscometer.

Dispersibilty Test :

The efficacious of self emulsification of oral nano or micro emulsions is assessed using a standard USP XVII dissolution apparatus II. One milliliter ofeach formulation was added to 500 ml of water at 37±0.5 °c. A standard stainless steel dissolution paddle rotating at 50 rpm provided by the gentle agitation.

GradeA : Rapidly forming (within 1 min) nanoemulsion having a clear or bluish appearance.

GradeB : Rapidly forming slightly less clear emulsion, having a bluish white appearance.

Grade C : Fine milky emulsion that formed within 2 minutes.

Grade D : Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).

Grade E : Formulation exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. White formulation falling in grade C could be recommend for SEDDS formulation.

Method Of Preparation :

A) Solidification techniques for transforming liquid /semisolid

Different types of solidification techniques are as below :

A) Spray Drying

In this type of technique, it involves the formulation by mixing of lipids, surfactants, solubilization of the mixture, drug, solid carriers before spray drying process. The solubilized liquid formulation is then atomised into a spray of droplets.Thedroplets are introduced into a drying chamber, where the volatile phase (e.g the water contained in an emulsion)evaporated and drying chamber are selected according to the drying characteristic of the product and powder specification. Such particles can be further prepared into tablets or capsules.

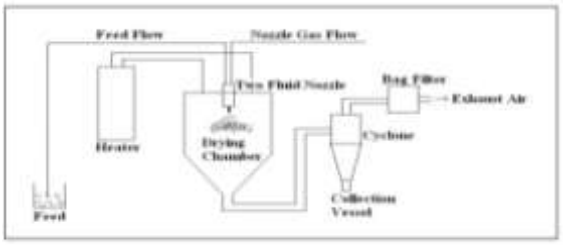

Fig 1 -Spray Drying.

B) Adsorption to solid carriers :

Soild carriers can be microporous inorganic adsorbent substances, cross linked polymers, nanoparticle adsorbents, high surface area colloidal inorganic adsorbents. (e.g. silicates,magnesium hydroxide, cross linked polymethyl methacrylate). SEDDS can be adsorbed at high levels up-to 70% (w/w) onto suitable carriers. Free flowing powders may be obtained from liquid self emulsifying formulation by adsorption to the solid carriers. In the adsorption process, it involves the addition of liquid on the carriers by mixing in a blender. It is one of the simplest method of self emulsifying formulation. The adsorption technique has been successfully applied to gentamicin and erythropoietin with caprylocaproyl polyoxylglycerides formulations that maintain their bioavailability and enhancing effect after adsorption.

C) Melt granulation :

Melt granulation is one step process and it allowing the transformation of powder mix into granules or spheronized pellets. The process in which powder agglomeration is obtained through addition of binder that melts or softens at relatively low temperatures. The technique needs high shear mixing in presence of meltable binder. This is

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referred to as " pump on" technique. The binder may be blended with powder mix in the form of solid or semisolid state and allowed to melt by heat generated from the friction of particles during high shear mixing referred to as "melt in" process. This proves is also known as pelletization process.

D) Capsule filling with liquid and semisolid self emulsification formulations :

Capsule filling is the simplest and one of the most common technology for the encapsulation of liquid or semisolid self emulsifying formulation for oral route. A primary consideration in capsule filling is the compatibility of the excipient with the capsule shell. The advantages of the capsule filling are simplicity of manufacturing, suitability for low dose and highly potent drugs and high drug loading. Upto 50% potential.

For semisolid formulations, it consist of four step process :

A) Heating of the semisolid excipient at least 20° above it's melting point.
B) Incorporation of the active substances
C) Capsule filling with molt cooling to room temperature. For liquid formulations, it involves two step process.
D) Filling of the formulations into capsule followed by sealing of the body and cap of the capsule, by binding or by micro spray sealing.

Melt extrusion :

It is solvent free process that allows drug high loading (60%) as well as content uniformity.Extrusionis a procedure of product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions. Applying extrusion spheronization, self emulsifying pellets of diazepam and progesterone and bilayerd cohesive. Self emulsifying pellets have been prepared.

Application :

Solid SEDDS

SEDDS are prepared as liquid dosage form that can be administered in soft gelatin capsules have some disadvantages in the manufacturing process. The alternative method is the incorporation of liquid self emulsifying ingredients into a powder in order to create a solid dosage form.

Super saturable SEDDS :

The high surfactant level is present in SEDDS formulation and can lead to GI side effects and new class of supersaturable formulations, including supersaturable SEDDS have been designed to reduced the surfactant side effects and achieve rapid absorption of poorly soluble drugs.

Super saturation is to increase the thermodynamic activity to the drug beyond it's solubility limit to result in an increased driving force for transit into and across the biological barrier.

II. CONCLUSION :

Solid dosage form of SEDDS is established as advantageous from formulation aspects and stability but in terms of pharmacokineticsbenefits, it cannot be concluded that solid SEDDS is much better than liquid SEDDS filled capsule. Self emulsifying drug delivery system are promising approach for the formulation of drug compounds with poor aqueous solubility. Development of this technology, SEDDS will continue to enable novel application in drug delivery system. SEDDS have been shown to improving the oral bioavailability of poorly water soluble drug and traditional preparation of SEDDS involves the dissolution of drug in oils and their bending with suitable solubilizing agents.

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