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An Updated Review on Self Emulsifying Drug Delivery System

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Review Article

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Abstract

Solubility of orally administered drug is major obstacle of pharmaceutical industry as nearly 35-40% of newly discovered drugs substancehave low aqueous solubility which results in their poor dissolution and bioavailability, which results in high intra & inter subject variations & lack of dose proportionality. The dissolution and bioavailability of drug substances can be enhanced by various methods like salt formation, solid dispersion and complexion. Self-Emulsifying Drug Delivery System (SEDDS) is getting popularity for enhancing solubility of lipophilic drugs. SEDDS is a combination of aqueous solvents and co-solvents/surfactants that have an ability of forming fine oil-in-water (o/w) micro emulsions upon gentle agitation after dilution in aqueous media, such as GI fluids. This review provides an updates in the advancements in SEDDS with regard to its composition, evaluation, and also various pharmaceutical applications.

Keywords: SEDDS; Self-emulsifying; Drug delivery system

Introduction

The oral route of administration is the most favorable route of drug delivery. Near about 35 to 40% of new drugs has low water solubility which leads to their poor dissolution which results in low bioavailability, collectively resulting in high intra & inters subject variability & lack of dose proportionality. There are various methods are used to overcome these issues i.e. less solubility and bioavailability, which may result into improved therapeutic efficacy of corporate drugs. Self-Emulsifying Drug Delivery System are helps to solve low bioavailability problem of less soluble & more permeable chemical compounds [1,2]. Aqua phobic drugs can be solubilizing in this systems which allow them to be prepare as a unit dosage form for per-oral administration. When Self Emulsifying Drug Delivery System's formulation is reached and release in the lumen of the gastrointestinal tract, Then there is a contacts between GI fluid and dosage form and forms a micro/ Nano emulsion which is called as self-emulsification or in-situ emulsification which further categories to solubilisation of drug that can be absorbed by lymphatic pathways, which bypass the hepatic first-pass metabolism. The process of self-emulsification occurs through the formation of liquid crystals (LC) and gel phases. The release of drug from Self Emulsifying Drug Delivery System is dependent on LC(liquid crystal) formed at the oil-water interface, as long as it is likely to act on the angle of curvature of the droplet formed and the resistance developed for separation of drug into aqueous medium [3].

Influence of liquid crystals will be more prominent for semisolid or solid Self Emulsifying Drug Delivery System because liquid crystals phases are formulates in-situ, and the drug disperses through liquid crystals phases into aqueous medium [4].

This bioavailability improvement characteristic has been linked with a number of in- vivo characteristics of

lipids containing formulation including: The formulation of fine dispersions and micellar suspensions to resist the recrystallization and precipitation of the drug. The capacity of certain lipid molecules and their metabolites to start small changes in the gastro-intestinal fluid to facilitate improvement in drug absorption. Inhibition of cellular outflows mechanism, which retain drugs out of circulation. Some lipid excipients are correlated with the selective drug uptake into the lymphatic system, consequently reducing the effect of first-pass metabolism.

Properties of Seeds

As name indicates they are able to self-emulsify shortly in gastro-intestinal fluids under the influence of light agitation provided by the Peristaltic movements of gastro intestinal tract, they forms a fine oil in water emulsion [4,5]. They can effectively incorporate drug (hydrophobic or hydrophilic) in the oil surfactant mixture. They can be utilized for liquid and solid dosage forms. They require minimum dose of drug as compare to conventional dosage forms

Types of Seeds

Based on the aqueous solubility of incorporated substance Self Emulsifying Drug Delivery System categories in following two types:

A. Water soluble Component Systems: These systems are formulated by using hydrophilic surfactants with HLB value more than 12 with co solvents such as Ethanol, Polyethylene glycols and Propylene Glycol. Type III Self Emulsifying Drug Delivery System is commonly known as self-micro-emulsifying drug delivery systems (SMEDDS) [6].

Type III formulations can be further classified into Type III A & Type III B, to identify more hydrophilic forms. In Type IIIB, the mixture of hydrophilic surfactants and co solvents (Ethanol, Polyethylene glycols and Propylene Glycol) is increased and lipid content is minimized.

B. Non-water soluble Component Systems: These systems contains the lipids & lipophilic surfactants having HLB value lower than 12 that self emulsifies to form fine O/W emulsion in hydrophilic medium. Self-emulsification is generally done at the concentration higher than 25% of surfactant w/w. But at a surfactant concentration between 50-60% w/w the emulsification process may be gambled with formation of viscous liquid crystalline gels at the oil-water interface. This system is also called as Type-II Self Emulsifying Drug Delivery System according to lipid formulation classification System (LFCS). As shows in figure.1 [7]. Less water soluble drugs can be incorporated in Self Emulsifying Drug Delivery System & encapsulated in capsules (hard or soft gelatine) to formulate convenient single unit dosage forms.

Advantages [8]

- Improves oral bioavailability that permits dose reduction.
- More compatible temporal profiles of drug absorption.
- Target selective drug toward specific absorption window in gastro-intestinal track,
- Protection of drug from the hostile environment in GIT.
- Better management of delivery profiles.
- Consistency in drug absorption profile.
- Reduced variability including food effects.
- Protection of more sensitive drug compounds.
- High drug payloads.
- Versatility of dosage form as can be used with solids or liquid.

Disadvantages

Lack of good predicative in vitro models for assessment of the formulations in development of Self Emulsifying Drug Delivery System [9,10]. These formulations potentially are dependent on digestion prior to release of the drug therefore traditional dissolution methods does not work.

Mechanism of Self-Emulsification

The process of self-emulsification is not yet fully understood. Although, according to Reiss, self-emulsification proceed when the change in entropy that promotes dispersion is higher than the energy needed to expand the surface area of the dispersion [11]. Additionally, the free energy of a traditional emulsion formation is a direct function of the energy needed to create a new surface area between the two phases and can be described by following equation [11].

Self-emulsifying processes are related to the free energy, ΔG [10] given by:

$$\Delta G = \sum N \pi r2 \sigma$$

Where,
N = Number of droplets
r = Radius of droplet
σ = Interfacial energy

Emulsification requires very small amount of energy involves destabilization by contraction of local interfacial regions. For emulsification to occur, it is compulsory for the interfacial structure to have zero resistance to surface shearing [12]. Previously, it was suggested that the capacity of emulsification could be associated with the ability through which water penetrates into the various liquid crystals or gel phases formed on the surface of the droplet [13,14].

According to Wakerly, et al. the introduction of a binary mixture i.e. Oil/non-ionic surfactant to water results in formation of interface between the oil and water-continues phases, after which solubilisation of water within the oil phase owing to water penetration through the interface takes place [13].

This will proceed until the solubilisation limit is touches close to the interface. Furthermore water penetration will results in formation of the dispersed liquid crystals phase. As the water penetration occurs, at the end all material goes close to the interface will be liquid crystal, the real amount depends on the concentration of surfactant in the binary mixture. When formed, rapid penetration of water in the aqueous cores, assisted by the smoothly agitation of the self-emulsification process, causes interface disturbance and formation of droplet. The high stability of this self-emulsified systems to coalescence is considered to be because of the liquid crystals interface surrounding by the oil droplets. The involvement of the liquid crystal phase in the process of formation emulsion was extensively studied by Pouton, et al. [13,15-17].

Groves & Mustafa developed a method of quantitative estimation of the quality of emulsification by monitoring the turbidity of oil-surfactant system in aqueous system, by using phosphate fatty alcohol ethoxylate (PFE) and phosphate nonyl-phenoxylate (PNE) in n-hexane and recommended that emulsification process may be correlates with the ease with which the water penetrates in the oil-water interface, with the help of formation of liquid crystalline phase resulting in swelling at interface, resulting in the greater ease of emulsification [14].

Pouton has cleared that the emulsification capacity of surfactant may be correlate to the phase inversion behavior of the system. If increases in temperature of the oil/water system which is stabilized by non-ionic surfactants, the cloud point of the surfactant will be reached after phase inversion [18].

The surfactant is highly mobile at the time of phase inversion temperature because of which the interfacialenergy of oil/water is minimized which leads to a reduction in energy needed for process of emulsification. Pouton has cleared that the specificity of surfactants combination required to allow continuous emulsification is related with a minimization of phase inversion temperature, when increasing the ease of emulsification. For systems which contains co-surfactant, components separation between the oil and aqueous phases, may take place which leads to mechanism, described as “Diffusion &Standing” because of which oil is solubilized, which promotes it’s immigration into the aqueous phase [12,19,20].

Formulation

It contains large varieties of liquid or waxy excipients which are produced in large quantities from cationic, anionic hydrophobic and hydrophilic surfactants, to water-soluble co-solvents, oils through biological lipids, there are number of different combinations are formed for encapsulation in hard or soft gelatine or mixtures which disperse for giving fine colloidal emulsions [18].

- The following points should be considered in the formulation of a self-Emulsifying Drug Delivery System. The drug solubility in different surfactants, oil and co-solvents.
- The selected surfactants, oils and co-solvents have high compatibility for incorporation of drug substance and the preparation of the phase diagram.
- The self-Emulsifying Drug Delivery System preparation are formulate by dissolving the drug substance in a mixture of surfactant, oil and co-solvent [21].

The incorporation of a drug substance to a self-Emulsifying Drug Delivery System is someway critical because the drug interferes with the process of emulsification to some extent, which starts the change in the optimal oil-surfactant ratio. So, the design of an optimal self-Emulsifying Drug Delivery System needed the pre-formulation-solubility and phase-diagram studies. In the case of prolonged self-Emulsifying Drug Delivery System, formulation is formulate by addition of polymer or gelling agent [22].

Excipients Used in seeds Formulation

Oil: A large number of excipients are used in the process of formulation of self-Emulsifying Drug Delivery System. Oil in surfactant are most important components, although, co-surfactants can also be used. Addition of other excipients in SEDDS is depends on the type of dosage form. Various types of natural, synthetic or semi synthetic oils have used in formulation of self-Emulsifying Drug Delivery System of various drugs substances [23]. Normally oils having long & medium triglycerides chain with varying in number of double or triple bonds are used for formulation of self-Emulsifying Drug Delivery System. Edible oils provides “Natural” base for lipid containing compounds, but they are no longer used in preparation of self-Emulsifying Drug Delivery System because of their low solubility and low efficiency of self-emulsification, Therefore, modified or hydrolysed vegetable oils are preferred for preparation Self Emulsifying Drug Delivery System formulation [4,24]. The most commonly used oils with drug substances for the preparation of self-Emulsifying Drug Delivery System are given in table 1.

Oils	Drugs
Polyoxy castor oil	Simvastatin [25]
Maisine oil	Lercanidipine [13]
Soya bean oil	Probucol [26] Ibuprofen [27]
Oleic Acid	Puerarin [28]
Peanut oil	Griseofulvin [29]

Table 1: Oils with drug substances for the preparation of seeds.

Surfactants

Non-ionic surfactants with high hydrophilic ± lipophilic balance (HLB value) were recommended for the preparation of self-Emulsifying systems, where the tween 80 and numbers of liquid or solid ethoxylated polyglycolyzed glycerides are the mostly used as excipients. Non- ionic surfactants are less toxic as compared to ionic surfactants, but they can cause reversible change in permeability of intestinal lumen. The optimum surfactant concentration in self- Emulsifying system is 30% to 60% w/w surfactant to maintain the stability of emulsifying system [13,30].

Higher concentration of surface active agents may cause gastrointestinal tract irritation. Thus, the safe side of the surfactant vehicle should be carefully considered in all cases. The high HLB value and optimum hydrophilicity of surfactants is required for the rapid formation of o/w droplets and/or immediately spreading of the formulation in the hydrophilic environment, providing a good self-emulsifying activity. The surface-active agents are amphiphilic in nature; therefore they have higher affinity of dissolving hydrophobic drugs substances. Various surfactant used with drugs in Self Emulsifying system are shown in table 2.

Surfactants	Drugs
Tween 85	Indomethacin [31]
Cremophor EL	Loratadine [32]
Labrafil M 1944 CS	Probucol [33]
TPGS	Tacrolimus [34]
Tween 80	Ketoprofen [27] Carvedilol [35]

Table 2: Surfactant Used With Drugs in Self Emulsifying System.

Co-Solvents

Many organic solvents are suitable for oral use. Some examples are polyethylene glycol, ethanol and propylene glycol, which help to dissolve large concentration of hydrophilic surface active agents or drug in liquid base. Addition of a hydrophilic solvent such as Triacetin, for example glyceryl triacetate or other suitable solvents act as co- solvents. Triacetin is mostly used since it is miscible in the oil or lipid phases and it can also be used to dissolve a hydrophobic drug [36]. Uses of alcohol & other volatile solvents are prohibited in self-Emulsifying system because it results in precipitation of hydrophilic drug substances [22]. Therefore, Alcohol and other volatile solvents free Self Emulsifying Drug Delivery System can also been studies. Some examples of co-solvents used in marketed products are mentioned in table 3.

Co-Solvents	Marketed Products
Glycerine	Sandimmune soft gelatine capsule
Poly Ethylene Glycol	Targretin soft gelatine Capsule, Gengraf hard gelatine capsule
Ethanol	Neoral Soft gelatin & Neoral oral, sandimmune soft gelatine capsules
Propylene glycol	Neoral soft gelatin, Neoral oral solution, Gengraf hard gelatin, Lamprene soft gelatin capsule

Table 3: Co-solvents used in marketed products.

Evolutionary Parameters

- Self-Emulsification Time
- Liquefaction time
- In vitro Diffusion Study
- Turbidimetric Evaluation
- Robustness to dilution
- Zeta Potential Determination
- Electro conductivity study
- Dispersibility Test

Self-Emulsifying Time: The self-emulsification time is calculated by USP dissolution apparatus II (paddle type) at 50 r/ min, where 0.5 g of Self-Emulsifying systems formulations is put into 250 ml of 0.1N HCL or 0.5% SLS solution. The time of occurrence of emulsification at room temperature is determined as self-emulsification time for the formulation [37].

Liquefaction time: This test is use to determine the time required by solid Self Emulsifying Drug Delivery System formulation to melt in-vivo without agitation in simulated gastric fluid. The formulation is packed in a transparent polyethylene film and tied to the bulb of thermometer [38]. The thermometer is then placed in round bottom flask in which simulated gastric fluid without pepsin is filled. The temperature is maintained at 37+ 0.5°C.

In vitro Diffusion Study

In this test the ability of the formulated products to release the active component present in formulation is studied by using dialysis technique where phosphate buffer (pH 6.8) is generally used as dialyzing medium. One end of the dialysis membrane is tied with a thread and 1 ml of the self-emulsifying drug delivery system formulation along with 0.5 ml of phosphate buffer (pH 6.8) is filled in the membrane. The other end of dialysis membrane is also tied with thread and then rotates in dialyzing medium at 100 r/ min using magnetic stirrer or dissolution apparatus. Samples are withdrawn at different interval of time and then after suitable dilution are analyzed. Same volume of samples withdrawn is replaced with fresh dialyzing medium [39].

Turbid metric Evaluation

Turbid metric evaluation is done to monitor the growth of process of emulsification. Determinate quantity of Self-emulsifying system is added to determinate quantity of suitable medium i.e. 0.1N hydrochloric acid with continuous stirring on magnetic plate at atmospheric temperature, and then increase in turbidity is measured using a turbid meter. The rate in of change of turbidity (rate of emulsification) is not possible to determine because the emulsification process occurs in very short period of time [35].

Robustness to dilution

Emulsions on dilution with number of dissolution media does not show any type of phase inversions or precipitation of drug substances even after a long storage, that formulation products is considered as robust to dilution [38,40].

Zeta Potential Determination

The stability of emulsion is directly linked with the charge present on mobile surface, which is termed as zeta potential. Zetasizer, Mastersizer etc. are generally used to determine zeta potential. The Zetasizer uses light scattering techniques to determine the size of globule, zeta potentialand molecular weight of Nano particulate systems. The instrument determines size and zeta potential for optimization of stability and shelf life and speeding up the formulation development The SEDDS formulation is diluted in a ratio of 1: 2500 (v/v) with distilled water with constant stirring with stirrer for determination of zeta potential [41]. Zeta potential is calculated according to Helmholtz-Smoluchowski equation

$$U=\varepsilon\xi Ex/\mu$$

Where,

U =Electrophoretic velocity ε = permittivity

ξ = Zeta potential μ = Viscosity

Ex = Axial electric field

Electro conductivity study

The Self Emulsifying Drug Delivery System contains ionic or non-ionic surfactant, oil, and water. Accordingly, this test is used to measure the electro conductive nature of system. The electro conductivity of formulated system is measured by electro conduct meter.

Dispersibility Test

The dispersibility test of SEDDS is performed to determine its ability to disperse into emulsion and the size of formed globules to categorize them as SNEDDS. It is performed by using a standard USP dissolution apparatus-II i.e. Paddle Type [19,42]. 1 ml of each formulated emulsions is added to 500 ml of water at 37 + 0.5 °C and the paddle is rotated at a speed of 50 r/ min. On titration with water the Self Emulsifying Drug Delivery System formulation forms a mixture or gel which is of different type (given in table 4) depending upon which the in vitro performance of formulated product can be determined [43].

Mixture/Gel	Type of formulation
Milky gel	Emulgel
Milky or cloudy mixture	Emulsion
Transparent mixture	Micro-Emulsion
Transparent gel	Micro emulsion gel

Table 4: Type of formulation depending upon visual observation.

Factors Affecting Seeds

Polarity of the Lipophilic Phase [44]

The polarity of the lipophilic phase is one of the main factors that affect the release of drug substances from micro-emulsions. The polarity of the droplet is controlled by the HLB scale, the chain length and the numbers of double or triple bond present in fatty acid, the molecular weight of the hydrophilic side and the concentration of the emulsifying agent. In fact, the hydrophilicity of the drug reflects its affinity for oil and/or water, and the type of bonding formed. The higher polarity will leads a rapid rate of release of the drug substances into the aqueous phase. This is cleared after observations of Sang-Cheol Chi, who observed that the rate of release of idebenone from SEDDS is depends on the polarity of the oil phase used. The highest drug release was obtained with the formulation that had an oil phase with higher polarity.

Nature and Dose of the Drug

Drugs substances which are administered at very high amount are not suitable for SEDDS unless they have extremely better solubility in at least one component of SEDDS, ideally lipophilic phase. The drugs substance with limited or less solubility in water and lipids are more difficult to prepare by SEDDS. The ability of SEDDS to maintaining the drug substance in solubilized form is highly influenced by the solubility of the drug substance in lipophilic phase. As mentioned above if surfactant or co-surfactant is contributing in drug solubilisation in higher extent there could be a chance of precipitation, as dilution of SEDDS will lead to lowering of solvent capacity of the surfactant or co-surfactant. Equilibrium solubility measurements can be carried out to forecast potential cases of precipitation in the gut. But, crystallisation could be slow in the solubilising and stabilized. Colloidal environment of the gut. Pouton's study reveal that such formulations can takes five days to reach equilibrium and at that the drug can remains in a super-saturated state for up to 24 hours after the initial emulsification occurs. It could thus be argued that these formulated products are doesn't cause precipitation of the drug in the gut before the drug is absorbed from GIT, and indeed that super-saturation of drug substance could actually enhance absorption by increasing the thermodynamic activity of the drug substance. There is a requirement for practical methods to predict the fate of drugs after the dispersion of lipophilic systems in the GIT.

Applications

Supersaturable seeds (S-Seeds): Supersaturable-SEDDS formulations have a low level of surfactant along with polymeric precipitation inhibitors which makes more stabilized the drug in a super saturated state. HPMC & other cellulose polymers are used to inhibit crystallization and for maintaining supersaturated state of drug for longer time. S-SEDDS are formulated to reduce the side effects of surfactants & to achieve better absorption of poorly soluble drug because high surfactant level may cause GI irritation [43]. It has been observed that the remarkably reduction in concentration of surfactant used in the S-SEDDS formulation gives a better safety profile than the other conventional SEDDS formulation. The mechanism of inhibition of crystal growth and stabilization of super saturation by means of polymers needs further explanation [43-45]. Indocetaxel and salicylic acid [46]. SEDDS formulation, HPMC is used for inhibition of precipitation in formulation. A five times increase in bioavailability has been observed with PNU-91325 when HPMC is placed at the place of propylene glycol, as a precipitation inhibitor [47].

Improvement in Solubility and Bioavailability: If drug is formulated in SEDDS, then it increases the solubility of drug substances because it circumvents the dissolution step in case of Class-II drug i.e. Low solubility/high permeability. In SEDDS, the lipid matrix interacts rapidly with water, to forms a fine particulate oil-in-water (o/w) emulsion. The emulsion droplets will release the drug substance in the gastrointestinal tract in a dissolved state readily available for absorption. Therefore, increase in AUC i.e.a bioavailability and Cmax is observed with many drugs when presented in Self Emulsifying Drug Delivery System [8].

Protection against Biodegradation: The capacity of self-emulsifying drug delivery system to reduce degradation as well as it improves absorption, for which both low solubility and degradation in the GI tract contribute to a low oral bioavailability. Many drugs are degraded in physiological system and become in effective, may be because of PH lower than 7 in stomachs, hydrolytic degradation, or enzymatic degradation etc. Such drugs when presented in the form of SEDDS can be protected against these types of degradation processes as liquid crystalline phase in SEDDS might be an act as barrier between this environment and the drug [7].

Conclusion

From the above review we can conclude that Self-emulsifying drug delivery systems is a step towards the manufacturing of formulation containing drug compounds which having low aqueous solubility profile(BCS class-II and IV). The oral drug delivery of hydrophobic drugs can make possible by Self Emulsifying Drug Delivery System, which have been shown to enhance oral bioavailability of drug. The efficiency ofthe Self Emulsifying Drug Delivery System formulation is case specific in most instances thus, the formulation contains should determine carefully. Since a high concentration of common surfactants use in the Self Emulsifying Drug Delivery System formulation, toxicity of the surfactant being used should be considered. With future development of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the administration of poorly soluble drugs substance.

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