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Self Emulsifying Drug Delivery Systems: Progress till now

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Abstract

Over 40 % of the new age drugs have poor hydrophilicity. This causes issues in formulation and thereby limiting its dissolution and bioavailability, forcing them to be given intravenously resulting in increased production cost, poor patient compliance, and toxicity in long term therapy. Self Emulsifying Drug Delivery System (SEDDS) is a pharmaceutical formulation aimed at increasing the dissolution of orally administered drugs, mainly BCS II class of drugs in GIT. The approach overcomes the problem of dissolution limited absorption of hydrophobic drugs and therefore minimum effective concentration of drug in plasma is attained. SEDDS consists of different proportions of oil, surfactant, and cosurfactant which modify the solubilising capacity of the drug and thereby varying the drug release profile. The aim of this review is to summarise the potential applications of SEDDS for increasing the oral bioavailability of BCS class II drugs. This review details about the selection of lipid system, surfactants and cosolvents. The review provides the overview of potential application of self emulsified system, and effectively summarizes the progress made till now in this domain.

Key Words: Biosurfactants, Bioavailability, Poorly soluble drug, QbD, SEDDS,

INTRODUCTION

Oral drug delivery systems including tablets and capsules are the most conventional and widely used dosage forms due to their relative safety, stability in storage and ease of production in bulk. They also have better patient compliance and enables self-administration compared to parenteral dosage forms. But recently their formulation has become increasingly difficult as the majority of these drugs have poor aqueous solubility (BCS Class II), which is one of the prerequisite factor to formulate any drug as oral dosage forms, thus leading to poor dissolution and bioavailability.

A number of techniques are used to overcome this problem including micronization, solid dispersions, liposomes etc. Self Emulsifying Drug Delivery System or SEDDS is one such method, which is used to enhance the dissolution and bioavailability of lipophillic drugs (BCS II and IV) [1,2], which have poor aqueous solubility [3]. In SEDDS formulation, drugs are incorporated in soft or hard gelatin capsules with inert liquid vehicles containing oil, surfactant and co-surfactant.

Unlike emulsions, in SEDDS, only the dispersed phase is formulated and administered orally, while the continuous phase is the GI fluid. The GI fluid with mild agitation disperses the drug to form an oil-in -water emulsion, to present the drug in solubilised form thus eliminating dissolution rate limiting processes.

SEDDS is associated with the production of emulsions with a particle size ranging from a few nanometers (nm) to several micrometers (µm). Depending upon the droplet size, SEDDS can be classified as Self Micro Emulsifying Drug Delivery Systems (SMEDDS) and Self-Nano Emulsifying Drug Delivery Systems (SNEDDS) [4]. SMEDDS form transparent microemulsions with oil droplets ranging between 100 - 200 nm, whereas SNEDDS can produce microemulsions with droplet size lesser than 100 nm [5].

Even though the mechanism by which they enhance solubility is not clearly known, as the average droplet size of the emulsion decreases, zeta potential increases; hence the repulsive forces prevents coalescence and stability is attained without phase separation. Also as the droplet size reduces, surface area exposed to the dissolution media increases [6]. In addition, the co-surfactants along with surfactants decrease the interfacial surface tension between oil droplet and aqueous media and thereby increase the solubilisation, hence enhancing the dissolution rate and their ability to enter into lymphatic circulation; thereby bypassing first pass metabolism, enhancing their bioavailability.

FORMULATORY ASPECTS OF SEDDS

SEDDS are the isotropic mixtures of oil, surfactant and cosurfactant, which emulsifies spontaneously in presence of GI fluids under mild agitation to form oil in water (O/W) emulsion (nano/micro).Nano/Micro emulsion region is characterized by the ternary phase diagram. The three major components which represent the ternary phase diagram are oil, surfactant and aqueous phase. If cosurfactant is used, it will represent as single component by mixing at a fixed ratio with surfactant and treated as single pseudo component. The apex of the triangle represents the individual component of the system, and the corresponding volume fraction is 100 %.The loading of drug to SEDDS formulation is very crucial because the drug obstructs with the self-emulsification process. So, the development of an optimal SEDDS formulation proceeds with the preformulation-solubility studies for further screening of excipients to develop ternary phase diagram[7]. The water titration method can be used to investigate concentration range of oil, surfactant and cosurfactant, which could give the boundaries for nano/micro emulsion region in pseudo ternary phase diagram.

The formulation development proceeds with the proper selection of oil, surfactant, and cosurfactant. While formulating, it is necessary to have correct ratio of the drug, oil, surfactant and co-surfactant for better and

optimum SEDDS preparation. The effective drug absorption from SEDDS after oral administration depends upon the ratio of oil/surfactant and the HLB value of surfactant. These factors will also determine the self-emulsification and droplet size of the emulsion.

The conventional method of preparation involves one factor at a time (OFAT) approach. But given the complexity of the formulation and the ingredients involved, design of experiments and risk assessment techniques based on Quality by Design (QbD) methodologies are increasingly used in the formulation of SEDDS. Given the diversity of excipients available in this space and the multitude techniques adopted QbD techniques lend a controlled and reproducible results thereby resulting in the better optimised formulation which will meet its therapeutic goals [8]. Majority of the work that happens in this space are aided with the application of QbD. The most commonly used experimental design paradigms during the formulation development are mixture design with several procedural variants and screening design primarily used in the earlier part for exploratory purposes. The DoE methods typically involve identification of the parameters to be optimized (responses) and the formulatory inputs of the problem (factors) [9].

Selection of excipients

Oils

Oils are the primary lipophilic excipients which are used to formulate SEDDS. They provide the base in which the drug is solubilised and also promote self-emulsification. Lipids exert their action in self emulsified system through several complex mechanisms which leads to alteration in the biopharmaceutical properties of the drug, such as increased dissolution rate of the drug and solubility in the intestinal fluid, protection of the drug from chemical as well as enzymatic degradation and the formation of lipoproteins which promotes the lymphatic transport of highly lipophilic drugs. The triglycerides present in oils enhance the uptake of lipophilic drug via the intestinal lymphatic system [10].

Selection of oil is based on the solubilising capacity for the drug. The physicochemical properties of the oil like polarity, water-solubility, interfacial tension, viscosity, density, phase behaviour and chemical stability play an important role in the stability and dispersion characteristics of the prepared SEDDS [11]. Along with the physicochemical characteristics the regulatory aspects such as irritancy, toxicity, purity, chemical stability, capsule compatibility and cost also plays an important role in the selection of lipids. Ability of the oil to dissolve large amounts of the drug substance is taken into consideration and hence majority of edible oils are not preferred due to low uptake to the therapeutic substance. Some of the most commonly used edible oils are coconut oil, castor oil, palm seed oil, olive oil, peanut oil, soybean oil, corn oil, cinnamon oil, sesame oil etc. The most common lipid used in the SEDDS system are triglyceride vegetable oils. This class of oils does not present any safety issues since they get easily digested and absorbed. Triglycerides can be classified into short chain triglycerides (SCT), medium chain triglycerides (MCT) and long chain triglycerides (LCT).LCTs are the triglycerides with the lipid chain length of more than C_{10}, where as MCTs are the mixtures of mono and diglycerides of fatty acids with a carbon chain length of C_8-C_{10}.The solvent capacity of triglycerides for the drugs depends upon the effective concentration of the ester group. Both long chain triglycerides and intermediate chain triglyceride oils with a diverse degree of saturation have been used for the formulation of SEDDS. Where the MCT have higher solvent capacity than LCT and they are less prone to oxidation. For the preparation of SNEDDS, MCTs are more preferred than LCTs because of their good solubilization properties, better chemical stability of the drug and self emulsification properties [12]. LCTs are preferred in the preparation of self emulsified formulations for drugs such as antiviral, antiretroviral and antineoplastics, which are supposed to be absorbed through lymphatic system. Table 2 gives the information about the most commonly used oils in the SEDDS preparation.

Surfactants

Surfactants are amphiphilic compounds which are used to increase the solubility of the drug. They have a hydrophilic head and a hydrophobic tail which makes them soluble in both polar and non-polar solvents. They act by reducing the surface tension between the drug and the solvent and thereby enabling the emulsification of the drug. The surfactants improve the intestinal permeability by improving the affinity between the biological membrane and the lipid system. The surfactant which gets partitioned into the lipid bilayer, will improve the permeability of the drug by membrane disruption and helps the drugs to get absorbed by passive transcellular mechanism[13]. The droplet size obtained after invivo emulsification of SEDDS formulation is directly influenced by the amount of surfactant incorporated in the formulation. Higher the amount of surfactant, smaller the droplet size obtained after emulsification. The large amount of surfactant may cause GI irritation. The surfactant concentration in the range of 30-60 % of the total formulation gives stable emulsion. The smaller droplets obtained in the self emulsified formulation promotes the fast emptying of stomach and wide dispersion in the GIT, facilitating minimum exposure to higher amount of surfactant and reduces the GI irritation. The natural emulsifiers like lecithin, alkaline medium chain monoglycerides are best preferred than the synthetic surfactants due to their higher level of safety. However because of their limited self emulsification properties the natural surfactants are less preferred than synthetic surfactants.

There are different types of surfactants available namely non-ionic, cationic, and anionic surfactants [14]. Non-ionic surfactants like Tween 80, Tween 20, and Cremophore RH40 are extensively used in SEDDS. In recent years a combinations of ionic and non-ionic surfactants are also used, as they increase the microemulsion region. The stability of SEDDS at different

pH and temperature depends upon the surfactant used. Non-ionic surfactants are less toxic and the stability of the formulation remains unaffected with altered pH and ionic strength. Amphiphilic surfactants have been known to prevent the precipitation of drug in the Gastro intestinal tract [1].

HLB stands for hydrophilic-lipophilic balance that expresses the relationship between the hydrophilic and lipophilic components of a surfactant. HLB value categorizes surfactants as lipophilic when the HLB value is lesser than or equal to 10 and hydrophilic when the value is greater than 10 (Table 3). Surfactants with low HLB value (3-6) are used in w/o microemulsions while those with high HLB values (8–18) are used in o/w microemulsions. The surfactants used in the SEDDS formulation should have higher HLB value to obtain fine O/W emulsion with good self emulsification process [15]. It is preferred to go for combination of surfactant to obtain required HLB value than the single surfactant.

Biosurfactants

From past few decades, biosurfactants have gained considerable interest in the field of agriculture, food, cosmetics and pharmaceutical industries. Biosurfactants are the surface active metabolites of microorganisms. When they are grown in a water miscible or oily substrate culture broth, and remain adhered to microbial surfaces or secreted into the culture broth. Biosurfactants are the promising alternatives to synthetic surfactants because of their lower toxicity, biodegradability, good environmental compatibility and greater stability at different pH and temperature [16]. The lipophilic portion of the biosurfactant is composed of saturated, unsaturated, linear, branched or unbranched long chain fatty acid and hydrophilic part of the molecule can be a carbohydrate, cyclic peptide, amino acid, phosphate carboxyl acid or alcohol. Based on the chemical composition and microbial origin, biosurfactants are classified into five different types[17,18].They can be used as emulsifiers, solubilizers and as wetting agents and finds application in enhancing the bioavailability of poorly water soluble drugs. The research related to application of biosurfactants in the preparation of emulsified products is in earlier stages of fruition. Table 4 summarizes about most common examples of biosurfactants and the microorganisms utilized in the production.

Co-surfactants

Ideally higher concentrations of surfactants (ranging from 30-60% w/w) are required for optimised SEDDS production [20]. Hence, the addition of co-surfactants can reduce the concentration of surfactants to be incorporated in the formulation.

Co-surfactants are usually alcohols or amines chemically with carbon chain length C-4 to C-10.They acts by reducing the interfacial tension (transient negative value), producing dispersed droplets and adsorbing more surfactant into the bulk, therefore stabilising micelle formation. This process is 'spontaneous emulsification' producing microemulsion. The solubility limit of the co-surfactant is considered as the CMC of the co-surfactants. When the concentration exceeds CMC, new phase due to aggregation is formed.

However, the addition of co-surfactants may not be essential for many of the non-ionic surfactants. The choice of surfactant and co-surfactant is crucial for SEDDS and solubilisation of emulsion. A co-surfactant of HLB 10-14 is ideal to lower O/W surface tension

Co-solvents

The role of co-solvents in SEDDS includes

1. Solubilisation of the drug
2. Increase the dispersibility of hydrophilic surfactant in the oil phase
3. Homogeneity and stability of the formulation

The various co-solvents are ethylene glycol, glycerol, propylene glycol, Transcutol HP or medium chain length alcohols (C8-C12) may be sufficient [21]. However, co-solvents lose their solvent capacity post dilution, which leads to drug precipitation. Higher concentrations of co-solvents are immiscible with the oil and lower concentration may be incompatible.

The choice between co-surfactants and co-solvents depends on the nature of drug and the type of emulsion. Lower solubilisation capacity is to be considered for hydrophobic drugs diluting in co-solvents containing SEDDS formulation with aqueous phase .if otherwise, large amount of co-solvents are needed which results in precipitation of drug when the formulation is dispersed in aqueous media. However, alcohols and other volatile solvents may interact with the primary packaging (gelatine capsules), Hence SEDDS without alcohols and related compounds are preferred.

Mechanism of self emulsification

Self-emulsification depends on Gibbs free energy (ΔG), where the change in enthalpy (ΔH) is greater than the energy required to increase the surface area between the oil and water phases [22].

$(\Delta G) = (\Delta H) - T\Delta S$

Where T is the constant temperature and ΔS is the entropy. The value of Gibbs energy determines the spontaneity of the dispersion process. The free energy is direct function of the energy required to create a new surface area during the process of dispersion. The equation is represented by:

$$r^2\sigma = \Sigma Ni4m^2\ \sigma$$

N is the number of droplets of radius r

σ is the interfacial energy

m^2 is the surface area of the O/W dispersion

Emulsification occurs spontaneously with SEDDS, when the value of free energy is low, irrespective of positive or negative. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing. The addition of a binary mixture (oil/ non-ionic surfactant) to water results in interface formation between the oil and surfactant, aqueous penetration through the interface; this tends to occur until the solubilization limit is close to the interface.

To reduce the interfacial area, the O/W emulsion may separate with time, therefore, the emulsion is to be stabilized by the addition of emulsifying agents, which forms a monolayer of emulsion droplets, and hence reduce

the interfacial energy, as well as providing a barrier to prevent coalescence.

Selection of Drug

SEDDS offers a potential platform for the improvement of oral bioavailability of poorly water soluble drugs especially BCS Class II and Class IV drugs. BCS Class II drugs suffers from poor water solubility issues where they have good permeability charecteristics.BCS Class IV drugs are having poor solubility and permeability characteristics. Hence BCS Class II and IV are the suitable candidates for the SEDDS development. Apart from the solubility issues, the drug candidate selected should have higher log P (> 4).The drugs having a log P value greater than 5 are the strong candidates for SEDDS. For the development of lipoid system the drugs should have low melting point and dose.

SUPERIORITY OF SEDDS COMPARED TO OTHER SOLUBILITY ENHANCING TECHNIQUES

Even though many different techniques are available to improve the solubility of drugs, SEDDS has proved to be one of the most effective techniques as it provides better results with the use of minimum ingredients and provides optimum control of drug release [23,24] SEDDS are having greater market value and Some of the marketed products are summarized in table 5. The bioavailability of Nimodipine (NM) in various forms like SEDDS, NM suspension, NM oily solution and miscellar solution has been studied by Kale AA and Patravale VB. Nimodipine has poor oral bioavailability less than 12%. SEDDS were prepared by using Gelucire 11/14, Labrasol, TranscutolP and Pluralolique CC 497. The *in-vitro* dissolution studies showed drug release of 80% in the first 10 mins and a bioavailability of 460.74% as compared with 194.3% and 153.85% as seen with the suspension and miscellar solution. The formulation was further assessed for changes during shelf life for 3 months, which showed no changes in clarity and dissolution efficiency [25].

ADVANCED TECHNIQUES IN SELF EMULSIFIED DRUG DELIVERY SYSTEM

Solid SEDDS

Several recent researches were focused on converting liquid-SEDDS to solid-SEDDS in order to enhance its reproducibility and to overcome stability related problems associated with liquid SEDDS. Solid SEDDS are prepared by incorporating liquid SEDDS preconcentrate into powdered particles to improve the oral bioavailability of sparingly soluble drugs. SSEDDS are capable of maintaining self emulsification property and be able to form a fine oil-in-water emulsion under gentle agitation provided by the gastrointestinal motion. Some of the techniques employed were spray drying, adsorption onto a solid carrier, eutectic mixtures melt granulation and melt extrusion etc[26,27and 28]. Solid-SEDDS of Ketoprofen, a BCS 2 drug prepared by the adsorption of liquid-SEDDS onto Aerosil 200. The liquid–SEDDS prepared by using Cinnamon oil, Cremophore RH 40, PEG 600 and Ethanol. *In- vitro* drug release studies showed that 98.1536% of drug was released in 6 hrs as compared to the 40% of the pure drug [29].Table 6 overviews about enhancement of dissolution characteristics of BCS class II drugs Solid SEDDS formulations in comparison with the respective pure drug compound.

Preparation of Solid SEDDS

The various methods for the preparation of S-SEDDS formulation are available. The most preferred and commonly used methods for the preparation of solid SEDDS is adsorption onto solid carriers and spray drying as these are very simple and no additional instruments are needed and they further enhance the solubility of drugs by converting the crystalline form of drug to its amorphous form [35].

Spray drying

Spray drying method is most suitable for liquid SEDDS formulation containing thermo labile drugs. In this method the drug solution prepared by using organic solvent or water is sprayed into a hot air chamber, where water or organic solvent evaporates to give solid microparticles of the drug. During this process the lipid excipient is spray dried along with inert solid carriers. Spray drying helps in reducing the average particle size to an optimum to achieve maximum solubilisation in the aqueous media [36,37]. Solid dispersions of Atorvastatin prepared by spray drying technique by Czajkowska A et al. Atorvastatin is insoluble at pH<4 and poorly soluble in water. It`s bioavailability is 12% in a dose of 40 mg. The two different SEDDS formulations were prepared by dissolving the drug in Oleic acid and Tween 80 to give one liquid SEDDS and Capryol 90 and Tween 80 to give second SEDDS. The mean droplet size was found to be 200nm. It was then subjected to spray drying process to get solid SEDDS with droplet size of 330 nm. Even though the drug release was faster in liquid SEDDS, the Solid-SEDDS showed better solubilisation properties [38].

Adsorption of liquid SEDDS on to solid carrier

Adsorption of liquid SEDDS is aided by the incorporation of various inert solid carriers such as Avicel or aerosol 200.The method of preparation involves mixing of liquid SEDDS with carriers in a blender. The carriers can be micro porous/colloidal inorganic substances (magnesium trisilicate, magnesium hydroxide, and talcum) and cross linked polymers (cross linked sodium carboxy methyl cellulose, cross linked poly methyl methacrylate). The cross linked polymers helps in sustaining the release of the drug and assist in slowing down the process of drug precipitation. Bakhle SS and Avari JG prepared liquid SEDDS formulation of Cilnidipine, a poorly soluble drug by using Capryol 90, Tween 80 and Transcutol HP, resulting in an emulsion droplet size of 200nm. *In vivo* dissolution studies showed optimum dissolution and absorption of 99.9% in 90 minutes compared to pure drug at 42.2% in the same condition. The converted solid SEDDS of Clinidipine with Nesulin UP at the ratio of 1:1 showed good flow characteristics and content uniformity [39].

Melt granulation techniques

In the melt granulation technique, powder agglomeration can be obtained by the addition of lipid (binder) that melts relatively at low temperature. The liquid addition and subsequent drying phases are not involved in the melt

granulation. Solid and semisolid lipid binders including Gelucire, lecithin, polysorbates etc are available in the market. The lipid excipients used must be semisolids at room temperature and 15-25% can be incorporated in the formulation. Seo A and his team prepared solid agglomerates of Diazepam by using meltable binders like Gelucire and Polyethylene glycol 3000 (PEG).The agglomerates prepared with Gelucire showed better dissolution characteristics as compared to PEG 3000 agglomerates [40].

Hot Melt Extrusion

Melt extrusion is a solvent free process that converts a raw material into a product of uniform shape and density by forcing it through a die at controlled temperature and pressure. Aperture size of the extruder determines the shape and size of the spheroids. Luis Antonio D Silva and his co-workers prepared enteric Solid SMEDDS of Cardevidol (CARV) by hot melt extrusion technique (HME).L-SMEDDS prepared with Capric/Caprylic triglycerides, Pluro Isostearique and Transcutol HP, upon gentle agitation gave rise to a clear, translucent microemulsion. HME technique was utilized for the incorporation of L- SMEDDS in to an enteric polymeric matrix. The Box- behnken and ANOVA analysis showed the extrudates with the lowest CARV concentration and highest temperature and recirculation time during HME, led to a rapid and complete microemulsions reconstitution and drug release in pH 6.8. The research concludes HME is one of the versatile, industry viable and solvent free process [41].

Super saturable SEDDS

The main concept involved in the development of SEDDS for poorly soluble drug is preventing the precipitation of drug on *invivo* dilution with the gastrointestinal fluid. The invivo dilution of SEDDS formulation in the intestinal aqueous medium results in the partitioning of drug within the o/w emulsion droplets. Incase, the partition coefficient of the drug for the SEDDS microemulsion droplets is such that the solubility of drug is more in aqueous phase the drug will start precipitating followed by water dilution. This will have a major impact on the *invivo* performance of the drug. Hence the supersaturable SEDDS could be a promising approach for improvement of oral absorption of poorly water soluble drugs. Super-saturated SEDDS are formulations that contain decreased amount of surfactant than SEDDS and contain precipitation inhibitors usually polymers that slowdown precipitation. These formulations are prepared to reduce the discomfort and side effects caused due to the usage of excessive surfactants and to eliminate possible toxicity on long term consumption [42,43].

The supersaturated state of the drug in the GIT is prolonged by the presence of cellulosic polymers. The cellulosic polymer acts as an excellent crystal growth inhibitors in SEDDS formulation. The presence of HPMC in the Supersaturated SEDDS prevents the nucleation as well as the crystal growth by getting adsorbed on to the surface of crystal or to the nucleus surface. Guilan Quan and his team prepared an optimized Solid SEDDS (SSEDDS) for water insoluble drug Fenofibrate by using mesoporous silica Santa Barbara Amorphous-15 as inert carrier. The optimized SSEDDS have been converted into super saturable solid SEDDS by using precipitation inhibitor called Soluplus. The pharmacokinetic study conducted in beagle dogs concluded, the area under the concentration-time curve of the super- saturable solid SEDDS is 1.4 times greater than that of SSEDDS. Hence the study proved that the combining SSEDDS with Soluplus as a super saturation stabilizer constitutes a potential tool to improve oral absorption of poorly water soluble drug. Zadeha BS and his co-workers prepared Super-saturated SEDDS of Griseofulvin, an anti-fungal drug belonging to BCS class II by using a precipitation inhibitor hydroxyl propyl methyl cellulose. The particle size of the resultant emulsion found to be 310-834nm. The drug release percentage reported as 22.38-46.95 after 24hrs and the permeability ratio was 3.25 times greater than that of conventional saturated solutions of Griseofulvin. This shows that, supersaturated SEDDS can act as an alternative to decrease the concentration of surfactant in long term therapy for maximum efficacy[44].

POTENTIAL APPLICATIONS OF SEDDS

Dissolution enhancement of BCS Class II drug: SEDDS undergo self-emulsification process where microemulsion or nanoemulsions of oil-in-water type are instantaneously formed when introduced into GI fluid, which undergoes rapid dissolution [45,46]. El-Sayyad and coworker improved the dissolution property of Leflunomide, a BCS II class drug by incorporating the self-emulsifying form of drug onto liquisolid system in the form of tablets. The self-emulsified system was prepared by using Sesame oil/Liquid paraffin oil, Tween 80 and PEG 300. The self-emulsified mixture was adsorbed on powder excipient to form liquisolid powder. Hence SEDDS technique and liquisolid technology can be a promising technique to enhance the dissolution of leflunomide [47].

Prevention of entero hepatic circulation: Post dissolution, the hydrophobic drug is rapidly absorbed by the lymphatic system[48] and hence bypasses hepatic metabolism leading to maximum bioavailability of the drug on oral administration[49,50]. Darunavir (DRV) is BCS Class II, HIV–I Protease inhibitor.DRV is reported as poor oral bioavailable therapeutic compound. Pokale R and Bandivadekar M improved bioavailability of Darunavir by formulating into a SEDDS by using Imwittor 988 (oil), Tween 20, and Span 20 (surfactants). The bioavailability of the compound improved by enhancing the solubility as well as by promoting the lymphatic uptake of the drug molecule [51].

Dose reduction: Dose of many lipophilic drugs can be substantially reduced; this in turn decreases toxicity and drug-induced adverse drug reactions. Tamoxifen citrate is an antiestrogen for peroral breast cancer treatment. The drug delivery encounters problems of poor water solubility and enzymatic degradation both in intestine and liver. Yosra SR et al prepared SNEDDS of Tamoxifen Citrate by using Maisen 35-1, Caproyl 90, Cremophor RH 40 and Propylene glycol. Optimized SNEDDS formulations showed higher drug release than the drug suspension.

Hence the drug loading into an optimized SNEDDS could be a promising approach to improve oral efficacy of the Tamoxifen citrate [10].

Peptide drug delivery: Peptides unstable in GI can be administered by SEDDS preparation and their activity is retained [52]. Li P et al proved that the bioavailability of insulin can be enhanced by loading into lipid based drug delivery system by complexing with bio surfactants. The insulin complex was prepared by using distearyl dimethyl ammonium bromide (DSAB) and or soybean phospholipid (SPC).The FT-IR studies showed no significant change in the structure of insulin after complexation with the surfactants [53].

Dosage regimen: SEDDS decreases frequency of drug administration and improves patient compliance. Subudhi BB and Mandal S prepared Ibuprofen loaded Self Micro Emulsified Drug Delivery System (ISMEDDS). ISMEDDS was investigated for its intestinal transport behaviour using Single-Pass Intestinal Perfusion (SPIP) method in rats. The permeability behaviour of Ibuprofen over three concentrations (20, 30, and 40 µg/ml) was studied in each isolated region of rat intestine by SPIP method at a flow rate of 0.2 ml/min. The estimated human absorption of Ibuprofen for SMEDDS was higher than that of drug suspension and the marketed formulation. Hence the developed SMEDDS for Ibuprofen would possibly be advantageous in terms of minimized side effects, increased bioavailability and hence the better patient compliance [54].

ADR reduction: Recent studies have shown that formulating drugs as SEDDS can also minimise side-effects. Lornoxicam is a new nonsteroidal anti-inflammatory drug of the oxicam class having analgesic, anti-inflammatory and antipyretic properties. Aparna C and co-worker prepared Lornoxicam SEDDS to decrease the side effects associated with lornoxicam. SEDDS were prepared using different ratios of excipients (capryol 90, tween 20 and tween 80 and transcutol P). Optimum release of 87.12% was attained and the effect was sustained for 24 hrs and there was a significant reduction in paw-edema in rats was observed in comparison to the conventional tablet formulation [55].

Prevention of therapeutic incompatibilities: Drugs that cause IV incompatibilities can be formulated as SEDDS. The ability of SEDDS to optimize dissolution and bioavailability of docetaxel and its ability to decrease the side effects associated with IV formulations in comparison to taxotere has been investigated by Valicherla GR and coworkers. SEDDS were formulated using Vitamin E TPGS, Gelucire 44/14 Capryol 90 and Transcutol HP. The drug tested in rats showed 3.19 times increase in oral bioavailability compared to taxotere and also increased anti-tumour activity by 24 times due to better adherence at the tumour site in breast cancer for up to 72 hrs [56].

Table 1: Advantages and disadvantages of SEDDS

Advantages	Disadvantages
SEDDS formulations reduce the dose of the drug by increasing solubility and bioavailability of the drug.	Interaction of liquid or semi-solid SEDDS preparation with excipients of soft gelatine capsules on long period of storage.
Targeting drugs to selective site in GIT	Leakage of formulation contents from soft gelatine capsules
Peptides that are prone to enzymatic hydrolysis in GIT can be delivered in this formulation	When the liquid formulation is introduced into the GI fluid, it may lead to cracking
Post dissolution, the hydrophobic drug is rapidly absorbed by the lymphatic system	Quality control tests for SEDDS is cumbersome and exhaustive
Control of delivery profiles	Liquid SEDDS are relatively unstable due to microbial degradation
Onset of action is quick.	Higher concentration of surfactant in the formulation causes GI irritation
Lipid digestion process has no influence on SEDDS	

Table 2: Oils used in SEDDS formulation

Oils	Chemical Name	Manufacturer/ Supplier
Captex 200P	Propylene Glycol Dicaprylocaprate	Abitec Corporation, USA
Captex 355 EP/NF	Glycerol Tricaprylate/ Caprate	Abitec Corporation, USA
Labrafac	Triglycerides of caprylic and capric acids	Gattefosse, Saint-Priest, France
Acrysol- k- 150	Polyoxyl 40-hydrogenated castor oil	Corel pharma chem.
Acrysol-k-160	Polyoxyl 60-hydrogenated castor oil	Corel pharma chem.
Maisine CC	Glyceryl monolinoleate	Gattefosse, Saint-Priest, France
Peceol	Glyceryl monooleate	Gattefosse, Saint-Priest, France
Capryol PGMC	Propylene Glycol Monocaprylate	Gattefosse, Saint-Priest, France
Labrafac lipophile WL 1349	Medium Chain Triglycerides	Gattefosse, Saint-Priest, France
Labrafil M 2125 CS	Corn oil PEG - 6 esters	Gattefosse, Saint-Priest, France
Gelucire 44/14	Hydrogenated coconut oil PEG 1500 esters	Aikon International limited
Aconon MC 8-2 EP/NF	Caprylocaproylmacrogolglycerides	Abitec Corporation, USA
Capmul PG-8 NF	Propylene Glycol Monooctanoate	Abitec Corporation, USA

Table 3: Surfactants used in SEDDS formulation

Surfactant	Chemical name	HLB -Value
Tween 20	PEG-20 sorbitan monolaurate	17
Tween 60	PEG-20 sorbitan monostearate	15
Tween 80	PEG-20 sorbitan monooleate	15
Span 80	Sorbitan monooleate	4.3
Cremophor RH 40	PEG-40 hydrogenated castor oil	13
Cremophor-EL	PEG-35 castor oil	12-14
Labrasol	PEG-8 caprylic/capric glycerides	14
Transcutol P	Diethylene glycol monoethyl ether	4
Labrafil WL 2609 BS	PEG-8 corn oil	6-7
Labrafil M 1944 CS	Oleoyl polyoxyl-6-glyceride	9
Gelucire 44/14	Lauroyl macrogol-32 glycerides	11

Table 4: Biosurfactants types and the producing microorganisms with the examples [19]

Biosurfactant type	Microbial source	Examples of biosurfactants
Glycolipids	*Nocardioides sp. Pseudomonas aeruginosa, Candida antartica, Acinetobacter calcoaceticus,*	Rhamnolipids, Sophorolipids, Trehalolipids
Polymeric Surfactants	*Acinetobacter calcoaceticus, Bacillus stearothermophilus, Candida lipolytica*	Emulsan, lipomanan, alasan, liposan
Lipopeptides	*Bacillus licheniformis, Bacillus pumilus, Bacillus subtilis, Candida lipolytica*	Surfactin, Lichenysin
Fatty Acids and Phospholipids	*Corynebacterium lepus, Nocardia erythropolis, Penicillium spiculisporum, Aspergillus, Corynebacterium lepus*	Corynomycolic acid, Spiculisporic acid
Particulate Surfactant	*Acinetobacter calcoaceticus, Cyanobacteria, Pseudomonas marginalis*	Whole cells, Vesicles

Table 5: Marketed products

Brand name	Drug	Dose	Dosage form
PaninumBioral®	Cyclosporine	50mg,100mg	Soft gelatin capsule
Lipirex®	Fenofibrate	10mg	Hard gelatin capsule
L-Ors Soft Captm Alza®	Guaiphenesin	200 mg	Osmotic pump
Convulex®	Valproic acid	150,300,500 mg	Soft gelatin capsule
JuvelaN®	Tocopherol nicotinate	200 mg	Soft gelatin capsule
Agenerase®	Amprenavir	50 mg	Soft gelatin capsule
Rapamune®	Sirolimus	0.5,1,2 mg	Oral solution
Targretin/ Bexarotene®	Bexarotene	75 mg	Soft gelatin capsule
Gengraf®	Cyclosporin A	25,100 mg	Hard gelatin capsule
Zipsor®	Diclofenac potassium	25 mg	Soft gelatin capsule
Kaletra®	Lopinavir, Ritonavir	20,80 mg/ml	Oral solution
Fortovase®	Saquinavir	200 mg	Soft gelatin capsule
Aptivus®	Tipranavir	250 mg	Soft gelatin capsule
Accutane®	Isotretinoin	10,20,40 mg	Soft gelatin capsule
Sandimmune®	Cyclosporin	25,50,100 mg	Soft gelatin capsule
Solufen®	Ibuprofen	-	Hard gelatin capsule
Neoral®	Cyclosporin	25,100 mg	Soft gelatin capsule and Oral solution
Depakene®	Valproic acid	250,500 mg	Soft gelatin capsule
Vesanoid®	Tretinoin	10 mg	Soft gelatin capsule
Norvir®	Ritonavir	80mg/ml	Oral solution
Rocatrol®	Calcitriol	0.25,0.5 µg	Soft gelatin capsule

Table 6: The drug release profile of pure drug powder compared with S-SEDDS

Drug	Pure drug powder	Solid SEDDS	Reference
Olmesartan medoxomil	11.23% in 60 minutes	>90% in 60 minutes	26
Erlotinib	20% in 60 minutes	70% in 60 minutes	30
Dexibuprofen	<50% in 30 minutes	>90% in 30 minutes	31
Nateglinide	42% in 120 minutes	98% in 120 minutes	32
Simavastatin	14.53% in 60 minutes	84.86% in 60 minutes	33
Glipizide	21.04% in 20 minutes	>85% in 20 minutes	34

CHARACTERIZATION OF SEDDS

Thermodynamic stability studies

The performance of the SEDDS formulation depends upon the stability of the product. SEDDS are thermodynamically stable systems where the capability of SEDDS to withstand various stress conditions can be checked through thermodynamic stability studies. The stressed thermodynamic studies involve subjecting the formulations into freeze thaw cycle, centrifugation and heating cooling cycle [57].

Heating cooling cycle: It involves cooling and heating (six cycles each)at refrigerator temperature (4^{o}C) and at elevated temperature (45^{o}C) with an exposure period of not less than 48 hrs. The stable formulations are further subjected to centrifugation study[39]**.**

Centrifugation test: The SEDDS formulations are subjected to centrifugation test to observe phase separation. The formulations are centrifuged at 3500 rpm for 30 min at different temperatures. The formulations are further subjected to freeze thaw cycle, if there is no phase separation observed after centrifugation [58].

Freeze thaw cycle: The formulations are stored for not less than 48 hrs at the temperature between 21^{o}C and 25^{o}C. The formulations which show no phase separation, cracking and creaming re determined as having good thermodynamic stabilities [32].

Rheological properties

The rheological properties like viscosity and flow of SEDDS has to be checked to characterize the system physically and to control its stability. The SEDDS are filled into either hard gelatine capsules or soft gelatine capsules; hence SEDDS should have good flow characteristics in order to ensure uniform filling into the capsules [59].

Self-emulsification

The self-emulsification property of SEDDS formulation can be checked by subjecting to aqueous dilution under mild agitation. The SEDDS should disperse rapidly and completely. The role of surfactants is to reduce the interfacial tension and facilitate the formation of emulsion [60].

The efficiency of self-emulsification of oral nano or micro emulsion is evaluated by standard USP XXII dissolution apparatus for. Based on the visual appearance and self-emulsification time, self-emulsifying systems can be graded as the following [61].

Grade I**:** Emulsion formed with in one minute, clear bluish appearance and emulsion with droplets in nano range

Grade II**:** Emulsion with bluish white appearance, less clarity and formed rapidly.

Grade III**:** A fine milky white emulsion formed within two minutes

Grade IV**:** Emulsification takes more than 2 min and dull greyish in appearance.

Droplet size

The droplet size of the emulsion is an important factor to evaluate the stability and release of drugs. Because droplet size governs the intestinal absorption and oral bioavailability of the drug, smaller the droplet size, higher the surface area and this results in better release characteristics [62]. The droplet size will have a profound influence on the permeability of drug through intestinal mucosa. The droplet size can be determined by diffraction technology [63].

Zeta Potential

The charge of the droplet can be determined by checking the zeta potential. The degree of electrostatic repulsion between particles in a dispersion system depends on the value of zeta potential. Zeta potential helps in predicting the stability of emulsion [64]. The stable SEDDS formulations will have zeta potential greater than -30 mV. In conventional SEDDS, the charge of an oil droplet is negative because of the presence of free fatty acids. It was also observed that addition of surfactant led to decrease in the particle size which leads to an increase in the zeta potential value.

CONCLUSION

The progress made till now has made it possible to formulate SEDDS in bulk, thus decreasing the production cost and enhance therapeutic benefits. SEDDS also has been proven to reduce side effects due to less drug accumulation and enhances the therapeutic activity which is beneficial for long term therapy. With the advent of biosurfactants its benefits and application of numerical optimization and DoE methods to SEDDS has far enhanced the capability as an effective drug delivery platform than it was envisioned earlier. Application of these newer concepts in SEDDS as noted, has improved the viability and manufacturability of these formulations, thus offering a potential solution to one of the formulators primary requirement of safety and bioavailability.

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