A review on Self Emulsifying Drug Delivery System, Their preparatory methods and role in biomedical applications

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Abstract

The oral route of drug administration is still considered as most preferred and favorable route. However, this route of administration causes some problems related to drug solubility and deliverance of proteins and peptides. To overcome these issues different dosage forms were formulated and characterized to enhance oral bioavailability of lipophilic drugs. Techniques that include salt formation, liposomes, and complexation were employed but the Self-emulsifying drug delivery system (SEDDS) gained more importance as it is considered to improve the oral bioavailability of active pharmaceutical ingredients (API) that are insoluble in water. This dosage form formulates oil in water (O/W) emulsions as it gets diluted in the gastrointestinal tract (GIT). Agitation provided by GIT enables them to formulate emulsion upon dilution with GIT contents. Approximately 40% of the new APIs were lipophilic in nature which decreases their aqueous solubility and ultimately their bioavailability was decreased. Formulations prepared by SEDDS hence, improve solubility and bioavailability of drugs. Another use of SEDDS is that it can be used to bypass first-pass metabolism and proteins, and peptides can easily be delivered through the oral route.

Keywords: Bioavailability, First pass effect, SEDDS, lipophilic, drug delivery, Oral route

1. INTRODUCTION

The oral route of drug administration is even now considered as the most favored route for the delivery of drugs, due to the highest patient compliance. Meanwhile, the bioavailability of some drugs becomes the rate-limiting step for this route of administration[1]. One of the major problems in development of different dosage forms would be the solubility profiling of drugs. For more than 40% of the active constituents are not water soluble which ultimately causes poor water solubility and poor

bioavailability. Different strategies were present to develop new dosage forms so, that the solubility profiling of these drugs could possibly be enhanced. These techniques include the use of surfactants, salt formation, liposome manufacturing, microemulsion, nanoparticles, and the use of permeation enhancers to increase drug permeation.

Recently, a new dosage form prepared by using lipid as base which definitely improves the solubility and hence increases oral bioavailability. Two such techniques were named as the Self-emulsifying drug delivery system (SEDDS), and self-emulsifying system (SES)[2]. SES is considered as most widespread and commercially feasible oil based formulations for the deliverance of such drugs that represents dissolution as speed limited absorption. It is an isotropic combination of surfactants, oils, and cosurfactants. The role of cosolvents was to emulsify the dosage form into water in oil (W/O) or oil in water (O/W) emulsion when administered orally[3]. However, in the last decade, SEDDS has gotten more attention from researchers. SEDDS was formulated as an isotropic mixture of surfactants, oils with or without the addition of cosolvents, that spontaneously formulates an O/W nano emulsion upon agitation with water. SEDDS is a very promising nano-systems. The system can rapidly and easily formed by simple mixing with used ingredients[4]. SEDDS were formulated to minimize the solubility issue of lipophilic agents which affects their bioavailability[5]. This system retains for a prolonged extent in GIT and hence improves cellular uptake of drugs[6]. SEDDS has proved to be effective in the delivery of proteins and peptides to bypass the gastric environment and improve their bioavailability in the intestine[7]. Upon its introduction into aqueous media, it forms fine oil-in-water emulsions with only gentle agitation such as GI motility, because the free energy required to create a new surface between the oil and water is lower than the entropy change that favors dispersion[8,9]. SEDDS based on their droplet size was further classified into, SEDDS having a droplet size range between 100–300 nm and droplet size less than 50 nm were termed as self-micro emulsifying drug delivery systems (SMEDDS)[3].

SEDDS were considered a new dosage form that improves the slow or complete dissolution of drugs, facilitates the formation of solubilized phases, it by passes the p-glycoprotein efflux, increasing the rate of absorption through the intestinal system hence, it increases the absorption of drugs in GIT[10].

FORMULATION ASPECTS OF SEDDS

SEDDS forms clear dispersion as it gets exposed to GIT. Such dispersions vary in size they may be either nano or micro emulsions. SEDDS carry drug molecules with them. As they, meet GIT drug molecules releases, the hydrophobic part must remain solubilized for that time as the formulation remains for GI absorption. SEDDS contains an emulsifier, essential lipids, and a co-emulsifier. Final product may be dispense in capsule or a tablet depends on formulation[11].

Pouton theory for SEDDS

Pouton by 2000 introduced a lipid formulation classification system (LFCS). By 2006 LFCS was reconstructed by Pouton himself. As per the LFCS classification system, SEDDS were treated as type II as they are an isotropic mixture of simple oil or a mixture of surfactants and oils which when exposed to the media of the gastric zone; get emulsified. Consequently, it can be concluded that the SES improves the absorption of drugs and thus improves their distribution. As the drug avoids gastric irritation the process of slow dissolution enhances the bioavailability of lipophilic-based drugs. The major reason behind high demand for the availability of lipid based excipients is that they dissolve poorly aqueous drugs in suitable solvents, thus enhances their absorption and bioavailability[12]. Pouton classifies them into four categories as shown in Table 1.

Table 1. Classification system for lipid formulations suggested by Pouton[13,14]

Significance / composition	Type I	Type II	Type III A	Type III B	Type IV
Percentage of mixed glycerides or triglycerides	100	40-80	20	<20	---
Water soluble surfactants (HLB greater than 12)		---	20-40	20-50	30-80
Water insoluble surfactant (HLB less than 12)		20-60	---	---	0-20
Co solvents that are hydrophilic in nature		---	0-40	20-50	0-50
Particle size	Coarse	100-250	100-250	50-100	<50
Importance of water dilution	Partial importance	Unaffected by capacity of solvent	Some solvent may be lost	Change of phase occurs and loss of solvent occurs	Change of phase occurs and loss of solvent occurs
Digestibility's significance	Vital requirement	Likely to occur	May be occurred	Not required	Not required

Type I

They consist of a solution of drugs mixed with glycerides or triglycerides which were further mixed with O/W emulsion and finally stabilized with emulsifiers like polysorbate 60 and lecithin in 1% to 1.2% respectively.

Type II

These were entitled as SEDDS, they constructed emulsion when meeting agitations of the GIT tract. In a study conducted by Shah *et, al* SEDDS appeared superior *in-vivo* profiling as compared to other dosage forms.

Type III

They were commonly known as self-microemulsifying drug delivery systems (SMEDDS). These are the formulations that have more than 12 HLB values and have hydrophilic surfactants incorporated in them other constituents include co-solvents like polyethylene glycol and ethanol. SEDDS formulations have a particle size of more than 100 nm while SMEDDS have a less than 100 nm particle size.

Type IV

These types of formulations were categorized as most hydrophilic formulations as they don't contain any natural lipids. These formulations usually produce fine dispersions which ultimately improves solubility, absorption and bioavailability[13,14].

Advantages of SEDDS

- SEDDS involves simple steps of emulsion manufacturing in comparison with conventional emulsion methods. In this process drug was dissolved in oil which were further mixed with surfactants or co-surfactant so, overall high energy was not required for the whole process.
- Emulsion un stabilities like breaking, phase inversion, coalescence and creaming were common in case of conventional type of emulsions. While SEDDS-based emulsions were clear, physically stable and can withstand a small temperature variation.
- Final products of SEDDS can be further incorporated in a capsule of other carrier system and hence improves dosage uniformity and dose size.
- Transportation and handling of SEDDS based emulsion was appeared to be easy as compared to conventional emulsions which were placed in suitable containers[3,15].
- They improve the bioavailability orally and reduces dose frequency.
- Drug targeting can also be achieved by using such type of emulsions.
- Sensitive drugs were appeared to be remained safe[16].

2. COMPOSITION OF SEDDS

SEDDS were constituted by using some components which includes surfactants, oils, solvents, and co-solvents.

Surfactants

These are one of the most important components of a formulation because they promote the process of emulsification. Surfactants are amphiphilic components and they can solubilize lipophilic drug compounds in relatively high amounts[17,18]. Definitely, the drug sustains in GIT for a longer duration[19]. Surfactant concentration and the type used that will ultimately affects its size the nano or micro sized emulsion. There are two main factors which will affects SEDDS are surfactants concentration and hydrophilic lipophilic balance (HLB)[17]. There are four types of surfactants. That are classified as anionic surfactants that carry negative charge (sodium lauryl sulfate, potassium laurate), non-ionic, which carry no charge (spans, tweens), cationic, which carries positive charge (quaternary ammonium halide) and ampholytic surfactants that carries both negative and positive charge (sulfobetaines)[1]. Amongst four classes of surfactants non-ionic surfactants were the most commonly used type because they have high HLB value[20,21]. In order to formulate a stable formulation 30-60% of the surfactants were used with in a SEDDS formulation[10,21-23]. Most used surfactants are tweens and spans. Before the selection of a surfactant, various properties of the surfactant must be considered for example the surfactant must be of natural origin and bears oral acceptance[24]. While these surfactants have less properties for emulsification so, natural based emulsifiers are relatively less used. Moreover, ionic surfactants appeared to be harmful as compared to non-ionic surfactants[10].

Biosurfactants

Concentration of the surfactants may alter the therapeutic usefulness as they alter the drug absorption at the site of action. They can also cause toxic effects depends on concentration use. So, the use of biosurfactants overcome the use of surfactants and increases the safety level while, decreasing the toxic impacts on GIT[25].

Co-surfactant

While using surfactant, co-surfactant was used to reduce the concentration of a surfactant used, because they increase the APIs loading efficiency. They decreases the toxic effects produce by the use of surfactants as well as they increases the interfacial fluidity and also enhances the process of dispersion[26]. Propylene glycol and ethanol were the most commonly used co-surfactants while a new ones were also used, which includes glycofurol and transcutol P[27]. Some other examples of co-surfactants includes poly ethylene glycol (PEG), Transcutol, glycerol and Capmul MCM[28].

Oils

One of the most common excipients used in SEDDS are oils. They not only promote self-emulsification but also solubilizes the required concentration of lipophilic material and hence, improves the transfer of formulation through intestinal lymph system. Based on molecular properties of triglycerides they also improves the secretion from GIT[29]. Different chain length of triglycerides like long and medium chains were used in different concentrations for their use in self-emulsification preparation[30]. Significant challenges like solubility issue regarding dissolution of lipophilic drugs were faced when frequently, raw, or unmodified forms of edible oils were used as base for lipid vehicles. Only modified or hydrolyzed form of vegetable oils were used for formulation purposes[31]

Co-solvents

Usually, a high concentration of surfactants was used for formulation of SEDDS which causes health issues so, their concentration of use decreases after the use of co-solvents. The simultaneous addition of co-solvents increases micelles concentration and reduces the surface tension. The most commonly used co-solvents includes PEG and ethanol[32], as these solvents increases the solubility of lipophilic drugs[33]. For optimum development of SEDDS, higher amounts of surfactant were required but this greater concentration may cause drug precipitation[34]. Consequently, this problem was solved by adding co-solvents and surfactants in a lower concentration to maintain the formulation uniformity[35,36].

3. METHOD OF PREPARATION OF SOLID SEDDS (S-SEDDS)

High pressure homogenizer

Formulations having nanosize were prepared at high pressure. While fine emulsions required a high shear under stress to be applied on them. The size of droplets could possibly be explained with the help of two theories turbulence and cavitation. Nano-emulsions could possibly be prepared by using this method having a size range of smaller than 100 nm. Size of the prepared droplets depends upon the composition of emulsion, type of homogenizer, conditions like time, intensity, temperature of the homogenizer used. Widely employed nano-emulsions for the purpose of pharmaceutical, biotechnological and food applications were prepared by using high-pressure homogenization [37].

High energy approach

Formulation of nano-emulsions required the mixing of constituents which includes surfactants, oils, and co-solvents so a high degree of mechanical energy was required[10]. Use of high mechanical energy provide a higher degree of disruptive forces that causes the large sized droplets to convert into nano sized droplets having high kinetic energy[38,39].

Spray drying

Spray drying is a process in which a liquid solution which was constituted by using water or organic solvent was sprayed into a chamber having a flow of hot air, the volatile component evaporates leaving behind the emulsion. Solid particles were prepared by using this procedure. Formulation was prepared by making a mixture of drug with excipients, which were than solubilized in an organic solvent before spray drying. Solvent was then removed from the formulation by using spray drying technology. This method was employed for the formulation of dry emulsion. Besides, the excipients were dissolved in organic solvent, O/W emulsions could be formulated and by using spray drying with in same equipment aqueous phase was removed[40].

Spray congealing or spray cooling

Spray cooling or spray congealing both are same methods. In this method formulations were converted in molten state and then sprayed in cooling chamber. Cooled air was then blown with in the apparatus, formulations got congeal or crystallize into spherical particles as they meet the air. Formed particles were then collected as fine particles from the bottom of the equipment. These particles were then formulated into dosage forms like capsules and tablets. Main point regarding the preparation of excipients was that they must be present with in the temperature range of 50-800C. This method can

further be used for improvement of bioavailability and for making sustained release formulation, depends on the behavior of drug and lipid matrix.

Melt extrusion

Melt extrusion or extrusion spheronization both are same techniques. This process is solvent free. In this process raw materials were converted into products having uniform density and shape by passing them through die under controlled pressure, temperature, and flow properties. This methodology has significantly employed for formulation of 17β- estradiol by using methyl or propyl parabens in the presence of surfactant such as poly sorbate 80 and sucrose mono palmitate[31].

Pelletisation or melt granulation

It is a one-step process, and depending upon the APIs it employs high-shear mixing. This method could be used for a high degree of drug loading of about 85%.

Direct capsule filling

Liquid of semi-solid SEDDS was then filled in soft or hard gelatin capsules. This is a simple process and is suitable for low-dose APIs. Advantages of this method include low costs for operation, good compatibility between capsule shell and capsule, and a high degree of drug loading.

Adsorption on the carrier system

SEDDS which were liquified in nature were adsorbed on some solid carriers, which were further used for capsule filling or tableting. This technique has some advantages which includes simplicity, operational cost is low, and high degree of uniformity was achieved[41].

4. EVALUATION PARAMETERS FOR SEEDS

Self-emulsification Time Determination

USP dissolution apparatus type II can be used to ensure the efficiency of the formulated SEDDS. Approximately, 250 µL of preferred SEDDS formulations were added to 500 mL of distilled water which were maintained at 37 ± 0.5°C and at rotations of 50 rpm. The rate of emulsification was than evaluated visually until the formation of final nanoemulsions.

Formulations were than assessed according to following grading system.

Grade A: were appeared to be clear nanoemulsion and formulated within 1 min

Grade B: slightly transparent nanoemulsion having bluish white appearance

Grade C: milky appearance emulsion and are formulated within 2 min

Grade D: greyish or dull white milky based emulsion formulated in more than 2 min

Grade E: these are the emulsions having poor emulsification owning large oil droplets present on the surface and no emulsion formation occurred[42].

Zeta potential, Polydispersity Index (PDI) Analysis and Particle Size

Zeta sizer was used to estimate zeta potential, PDI and particle size for selected formulated SEDDS. Sample were analyzed in triplicate manner. Photon spectroscopy was used at 25°C for the determination of size distribution and droplet size. Characterized formulations were firstly, diluted with distilled water to make clear emulsions. Value of PDI indicates the distribution profile of size. Thus, lower values of PDI values ensures a close size distribution hence offering good stability of nanoemulsions. All of the tests were conducted in triplicate manner and values of standard deviation (SD) were also calculated[43].

Solubility studies

Excipients which include oils, solvents, and surfactants, co-surfactants, and drugs solubility were carefully chosen for the formation of SEDDS. Approximately, 2 ml all the ingredients were pipetted out in reaction tubes and then mixed with dimenhydrinate in excess at 40 °C and 1000 rpm with the help of thermomixer. Amount of drug dissolved was further analyzed by using high pressure liquid chromatography (HPLC)[44].

Strength to Dilution

Phosphate buffer saline (PBS) or distilled water was used to dilute the topical SEDDSs up to approximately 100 times at different pH values. pH was adjusted to 5 by using PBS as this pH appeared to be in accordance with skin pH[45]. Prepared dilutions were than visually inspected for phase spliting for approximately 24 hours at 25 ◦C[46].

Efficacy and Self-Emulsification

Type II Distek dissolution system apparatus was used in which 1 mL of formulated SEDDSs were added to 100 ml of distilled water and was slightly agitated with the help of a paddle at 50 rpm at 32 ± 0.5 ◦C. Time which was required by the individual SEDDSs to become exposed and form into homogenous dispersions was noted[46,47].

pH and Viscosity

Brookfield Viscometer which was further equipped with temperature controller and attached with a circulating water bath was used. Water jacket temperature was maintained at 25 ± 0.5 ◦C[48]. Spindles of different sizes which includes SC4-25 LV, SC4-34 LV, T-bar E LV, and T-bar F LV were used. Torque values were maintained at 20% with 20 rpm. pH of formulated SEDDS were assessed using a suitable pH mater. Used pH meter must be calibrated at 4,7 and 10 standard pH solution prior its use[49].

Cloud Point

Distilled water was used to prepared dilutions of formulated SEDDS at 1: 100. These dilutions were placed and maintained at of 25 ◦C. Than the temperature of the dilutions was increased at a rate of 2 ◦C/min till a turbid appearance was confirmed. Which was due to dehydration of added excipients[50].

Stability Studies

Formulated preparations were than subjected to different temperatures of cold and heat. It consists of total 6 cycles during which temperature ranged between 4 ◦C and 45 ◦C, but not greater than 48 h. Formulations were than visually observed for drug precipitation and phase change[46]. Henceforth, the formulations were centrifuged at 3500 rpm for approximately 30 min. Than they were observed again by visual means for any type of instability which includes cracking, creaming and phase separation[51,52].

Droplet morphology

Transmission electron microscopy was used to study the morphology of droplets. Proper dilutions of formulations for negative staining were prepared by using 2% solution of uranyl acetate or phosphor tungstic acid. Droplets must be spherical in nature and without any signs of aggregation[53].

Drug Loading Efficiency

To determine drug loading, formulated SEDDS were diluted by using methanol in volumetric flask. Samples must be prepared in a triplicate manner and then observed by using UV- visible spectroscopy at suitable wavelength[42].

Role of SEDDS in drug delivery

Man is taking medication since its evolution. But the issues like rapid release, first pass metabolism, lipophilicity and low bioavailability causes hinderance in proper drug availability at site of action.

Different dosage form was developed to enhance the solubility and ultimately improve their bioavailability.

SEDDS is a mixture of emulsifiers, oils and aqueous phase, in which the emulsifiers transformed into nano-emulsions as they come in contact with the fluids present in GIT[4]. Easy methods of preparation and highly suitability make these formulations best to deliver through oral route[54]. Drugs from the biopharmaceutical classification system (BCS) II and IV faces issues of their low solubility, and low bioavailability. So, SEDDS improves their solubility and hence, prevent them from being precipitated in GIT[55].

5α-reductase inhibitor and SEDDS

Super saturable SEDDS (SS-SEDDS) were developed by Lee *et al* with the incorporation 5α-reductase inhibitor, dutasteride (DTS). A total number of thirteen formulations were prepared with different combinations. They were formulated to enhance DTS oral bioavailability. *In-vivo* evaluation suggest that SS-SEDDS displayed 1.3-folds higher area under the curve (AUC) values, when compared to simple SEDDS and drug suspension. It was concluded that the physico-chemical properties and oral absorption of 5α-reductase inhibitor was successfully enhanced by incorporating them in SS-SEDDS[22].

SEDDS as a muco-diffusive system

Lipophilic drug agents were employed in SEDDS to improve their drug loading volume and bioavailability by administering it through oral route[55]. Mucus which acts as a barrier is not the rate limiting step for the permeation of lipophilic agents. Sunazuka *et al.* formulate SEDDS by incorporating Fenofibrate BCS class II drug and then studied the drug permeation[56].

SEDDS for deliverance of genetic constituents

Induction of gene therapy by using oral route of administration, not only allows the production of therapeutic proteins locally at the site of disease but also establishes systemic absorption[57]. But, the oral delivery of plasmid DNA and other protein products got challenged by this route as well as their cellular processing and internalization also got disturbed[58]. Hence, the delivery of genetic material through oral delivery by using non-viral vectors incorporating in SEDDS have been studied. Therefore, the incorporation of plasmid DNA into SEDDS possibly enhances its stability and permeation which could be attributed due to presence of ultrafine oil droplets in the form of nano-emulsion.

Antibiotics and SEDDS

Zupancic *et al*. formulated SEDDS of daptomycin and than evaluated for enzyme degradation, permeability, and *in-vitro* digestion. The optimized formulation suggested to be hydrolyzed by lipase enzyme within 90 min, while it exhibits better permeation along the mucous. It showed a sustain release of the drug for approximately six hours. Bioavailability of the used drug was enhanced by 5 folds. Additionally, results of formulation suggests that it can further be used for oral use with 8% of the loaded drug[59].

Oral delivery of peptides and proteins by using SEDDS

In every field of medicine protein therapeutics plays a significant role. Though, protein therapeutics were extensively used, and they are administered through parenteral route which is not in accordance with patient compliance[60]. Therefore, there appeared an extensive interest in developing a non-invasive route of administration for deliverance of protein and peptide[61]. Regarding, the administration of protein based drugs oral route of drug administration was investigated extensively[62]. Oral delivery of peptides and proteins were challenged due to some factors which includes low cellular penetration, mucus as a barrier, enzymatic degradation in GIT and stomach acidic environment[4]. Numerous approaches were made to overcome mentioned barriers[53]. As presented in Table 2, several researches were made regarding oral administration of proteins and peptides drugs loaded in SEDDS. Numerous oils and surfactants which are employed in SEDDS development increases the permeation of the drug product;

ultimately, they increases the uptake of hydrophilic drugs at cellular ends which includes protein therapeutics. Nano size goblets provide an increase surface area for drug loading efficiency as well as their permeation at intestinal side also increases. Anhydrous form of SEDDS protects them from hydrolysis. Bioavailability of SEDDS through oral route of administration loaded with protein therapeutics increases as they contribute in opening of tight junctions and due to an enhanced lymphatic uptake[63]. Meanwhile, the loading of protein products in SEDDS were affected due to hydrophilic nature of these agents. Before protein therapeutics were loaded in SEDDS their lipophilic solubility must be increased. Their appeared various techniques by which their solubility could possibly be enhanced which includes lipophilic ion pairing[64], dual emulsification[65], with the use of solvents and co-solvents that are hydrophilic in nature[66] and modification of peptide molecules chemically[50].

Table 2. Represents research done for safe delivery of protein therapeutics

Protein	Control	Composition of SEDDS	Increase in bioavailability	Evaluation on animal species	Reference
Insulin	Solution of insulin	Co-solvent (which includes DMSO and glycerol in 1:3) (10%) Cremophor El (25%) Miglyol 840 (65%)	3.33 folds	Sprague–Dawley rats	67
Insulin	Solution of insulin	Alcohol (32.5%) Ethyl oleate (35%) Cremophor El (32.5%)	6.5 folds	Wistar male rats	68
β-lactamase	Solution of β-lactamase	Transcutol HP (25%) Cremophor EL (33.3%) Lauroglycol FCC (41.7%)	1.29 folds	Sprague rats	69

Alkaloids

One of the important classes of natural products that were found from plant origin were classified as alkaloids. Alkaloids exhibit many pharmacological activities like morphine exhibit analgesic while, taxanes and vinblastine were anti-cancer in nature[70]. As well as noscapine (N) that exhibits naturally anti-cancer activities. They potentiate death of the cancerous cells. The drug is lipophilic in nature due to which their appeared a solubility and its bioavailability issue when manufactured through oral route. Andey *et al.* solved this problem by developing and characterized N based formulation by using SES to improve its solubility and ultimately, enhancing its bioavailability. Both SMEDDS and SEDDS were prepared by using spray drying technology and formulations with or without the presence of mannosamine. Semi-synthetic polymer hydroxypropyl methyl cellulose (HPMC), tween 80, Labrasol were employed as emulsifier, surfactants, and co-surfactants in the development of formulation. SEDDS were found to be 5–6 μm while, SMEDDS were a few nanometers in size. *In-vitro* evaluation suggests that mannosamine-loaded SEDDS formulations were released for a maximum of 6 hours retaining a controlled release. Furthermore, satisfactory results from cell toxicity profiling by using H1650 SP cells were observed[71].

Anti-cancer Drugs

Docetaxel

One of the most potent ant-cancer which is a taxane derivative named as Docetaxel (DCT). DCT has a poor water solubility which is just less than 5µg/mL due to low solubility, bioavailability of the drug is just 5%.[72]. The basic reason for that low solubility of the respective drug is its bulky polycyclic structure. O enhance its oral bioavailability SEDDS were found to be a better option. Seo *et al.* formulated SNEDDS preparation to improve the bioavailability of DCT and ultimately its efficacy. Nano-emulsions of DCT-loaded SNEDDS were prepared by further using Transcutol HP, Labrasol, and Capryol as excipients. When the anti-tumor activity of SNEDDS and free drug was compared it was found that SNEDDS appeared to increase the bioavailability of the drug at the target site. Later *in-vivo* characterization confirmed that the oral bioavailability was increased up to 17% with DCT-loaded SNEDDS. Toxicity studies were also conducted to ensure any effects on the cells, and it was also found that the formulation was safe and have low cytotoxic effects as compared to standard drug. All of the results were in the support that DCT loaded SNEDDS were found to be safe and efficacious as, a dosage form can be further prepared to be used through the oral route[73].

Tamoxifen (TMX) and Naringenin (NG) based SNEDDS

NG and TMX-based SNEDDS for the treatment purposes of breast cancer were formulated by Sandhu *et al.* SNEDDS in different combination were formulated and were further evaluated for pharmacokinetic study, drug release, cell line study and *in-vivo* antitumor action. It was evaluated that good micelles were formed, the drug was released within 30 minutes and their appeared a consequent decrease in cancer cells[74].

GLM-7

One of the novel acrylamides is GLM-7, but its clinical studies have suggested that it has a very poor water solubility and its bioavailability was also disturbed[75]. Further, *Wang* and his co-workers researched a lot by making a group of researchers and formulated SEDDS formulations of GLM-7 to enhance its oral bioavailability. It was observed that the emulsion has a droplet size of 400 nm, meanwhile, the particles are spherical with uniform size and shape. Experimentally, it was found that 80% of the drug was released from SEDDS with an acidic medium. *In-vivo* studies further support the experiment, prepared SEDDS were then compared with pure drugs within the plasma of beagle dogs, it was found that a total of 9 folds of higher concentrations of SEDDS were found in the plasma of the animal. AUC of the respective drug also suggests a higher oral bioavailability[76].

3,3-diindolylmethane (DIM-14)

Another anti-tumor agent having low solubility is DIM. Patela *et al*. use cancer stem cells (CSC) for the treatment purposes of tumor by targeting with DIM-14. Poor aqueous solubility of DIM_14 restricts its pharmacological action. SES of DIM-14 showed a greater solubility and bioavailability as compared to pure compound orally. H1650 stem cell lines were further used to confirm the cytotoxic activity of the prepared formulation. While SES showed better results on cell lines. Zeta sizer confirmed that the emulsion has a negative charge on it, having a size of 250nm. Furthermore, pharmacokinetic evaluation suggested that the formulated SES of DIM-14 enhances the drug bioavailability with 3 folds. Afterwards, tumor models showed a decrease in volume up to 60% with the use of the DIM-14 dosage form[77].

SEDDS and anti-coagulants

Zupancic *et al.* developed enoxaparin low molecular weight heparin (LMWH) formulation by using different SEDDS without the presence of no lipids (NLSEDDS), which includes long-chain lipids (LCSEDDS), medium chained lipids (MCSEDDS) and short chain lipids (SCSEDDS). Further, these formulations were assessed for mucus permeability and drug release. NLSEDDA and MCSEDDS exhibit good mucus permeation. NLSEDDS depicts good stability for 90 min, while MCSEDDS were degraded by pancreatic lipase. The bioavailability of the drug was enhanced up to 2 folds[78].

Immunosuppressant

One of the most employed immunosuppressants is Tacrolimus (TC). TC exhibits variation in its oral bioavailability which ranges from 4 – 89%. The variation in its bioavailability was due to the following reasons:

i) Its poor water solubility
ii) The drug is extensively metabolized by cytochrome P450 enzyme
iii) Efflux transport of P-glycoprotein (P-gp)

Wang *et al.* then prepared SMEDDS by incorporating a sample drug as TC. The main purpose of the formulation was to improve its aqueous solubility and oral bioavailability. Which he then optimizes by using a pseudo-phase diagram. Further excipients which were included for the manufacturing of formulation includes Cremophor EL40 and Tocopheryl polyethylene glycol succinate (TPGS). Transcutol P was chosen as co-surfactant and Miglyol 840 as the oil phase, they were employed in a 2:1 within the formulation of TC-SEDDS. Solubility studies evaluated that Miglyol 840 was responsible to increase the solubility of the dosage form. To optimize the concentration of surfactant, co-surfactant and oil pseudo-ternary phase diagram was developed. SMEDDS have an average size of 20 nm. Pharmacokinetic studies support that AUC and C_{max} of the formulated TC-SMEDDS were higher which suggest that the bioavailability of the system was improved as compared to free drug. An increase in oral bioavailability of the formulation was significantly noticed as compared to free TC drug[79].

Amphotericin B (AMB)

AMB exhibits a very poor water solubility due to which its oral bioavailability is also compromised. Currently, to overcome that issue one of a new delivery system was introduced which is gaining more popularity was lipid-based drug delivery system. One of the research groups comprising of Wasan and his co-researchers, formulated and evaluated SEDDS of AMB. AMB-SEDDS were evaluated against Candida albicans–infected rats or Aspergillus fumigatus. Solvent evaporation method was used for the formulation of AMB-SEDDS. Excipients like medium chained fatty acids which includes glyceryl monooleate and triglycerides were used along with PEG phospholipids for preparation of SEDDS. Atomic fore microscopy (AFM) was used to ensure the phase stability of formulation. Droplet size of SEDDS were found to be within the range of 200-400nm. Different grades of PEG 1000, 750, 550, and 350 were used in the formulation of triglycerides which represents an excellent solubilizing property. It was found that orally formulated SEDDS loaded with AMB were prepared by using glyceryl mono-oleate PEG2000 have considerably reduced total fungal CFU (colony functional unit) intensities in the rats infected with A. fumigatus. It was concluded in the end that the formulation appeared to be effective when given in doses of 5 mg/kg and 10 mg/kg, that dose have radically decreased the fungal CFU concentrations in the kidney by > 75% and > 95%, respectively[80].

Anti-viral Drugs

One of the anti-viral drugs which is used to treat HIV-AIDS is Tipranavir (TPV). The drug acts on non-peptide protease and inhibits them[81]. TPV solubility and eventually its bioavailability was enhanced by using SES. SEDDS of TPV when compared with SES and non- SES, it was found that SEDDS formulated with SES and enclosed in soft gelatin capsule increases the bioavailability by 2 folds as compared to SEDDS filled in hard gelatin capsules (58). Another powerful anti-HIV drug that falls within the category of protease inhibitor (PI) is saquinavir (SQV). It is used in a combination regimen for the treatment of AIDS known as highly active antiretroviral therapy (HAART). Currently, the drug is available in market filled in hard gelatin capsules. The drug is insoluble in water to enhance its solubility one of the excipients named as Capmul was used. Diarrhea can be caused in the patients using that medication because the excipient was used in a higher concentration and Capmul rapidly releases the drug within the body. Finally, to overcome that typical issue new dosage forms were formulated. SQV loaded SEDDS preparations are one of the most innovative formulations used in conjugation with ritonavir to increase its bioavailability and finally reduces side effects[82].

Anti-hypertensive and Cardiovascular Drugs

A calcium channel blocker which acts an anti-hypertensive agent named as Felodipine (FP). It has a mechanism of action by blocking the signaling pathway. The drug has poor water solubility, decrease

bioavailability, and fast first pass metabolism through liver reduces its pharmacological activity. Recently, some techniques were used to increase the dissolution of FP by using wet milling or through mesoporous silica nano-particles[82]. Jing *et al*. effectively improved the oral bioavailability of FP tablets by preparing them through self-emulsifying technique. Further, both liquid and solid SES were formulated and compared. Their appeared a size comparison between SMEDDS formulated by liquid preparations and solid tablets. For characterization purposes polymorphism state of the tablets were observed through X-ray diffractometry (XRD). Lately, the formulated solid tablets were compared with marketed product in beagle dogs. *In-vivo* evaluation supports the result that a 2 folds higher bioavailability was found in tablets prepared with SES as compared to marketed product. Meanwhile, no differences between liquid or solid dosage form of FP were appeared. All of the characterizations like stability studies, dissolution studies, and bioavailability assay showed that the solid tablets were appeared to be better approach for constructing FP based emulsifying formulations because they increases the FP bioavailability[83]. One of another calcium channel blocker cilnidipine (CDP) which acts as anti-hypertensive agent have solubility issue. The drug has issue of low bioavailability which is due to low aqueous solubility. Bakhle and Avari than prepared solid SEDDS used CDP as model drug. Aim of the study was to enhance the bioavailability by increasing its aqueous solubility. Tween 80, Neusilin US2 and Capryol 90, were used as surfactant, oil phase and adsorbent in the formulation. Microemulsions were prepared by using drug and excipients. Pseudo ternary diagram was used to identify the microemulsion area. It was revealed by dissolution studies that the formulation prepared by CDP-loaded SEDDS have better solubility studies as compared to marketed CDP dosage forms. XRD studies further revealed that the CDP drug from its crystalline form was changed into amorphous form during manufacturing of dosage form, which increases the drug solubility and efficiency[84]. Regarding the prevention of cardiovascular attacks and hyperlipidemia conditions statins were used one of most potent statins is Atorvastatin (AVS). The drug is insoluble in acidic pH, and a very sparingly water soluble. Its poor solubility and low bioavailability through oral route attain due to its high pre-systemic clearance. So, the drug was formulated into lipid carrier system to enhance its solubility and consequently bioavailability. Kosnik *et al.* established liquid and solid based SES loaded with AVS to enhance its solubility. SEDDS which are liquid based consequently appeared showed some disadvantages; therefore, the researcher further prepared SEDDS formulations that are solid in nature and then compared both. Physico-chemical characterizations which include stability studies, solubility test, and size analysis and pseudo ternary phase diagram were performed on both solid and liquid formulations. Spray drying technique was employed in manufacturing of solid SEDDS. *In-vitro* dissolution studies of both solid and liquid SEDDS showed a better drug assay in case of solid SEDDS formulations. While phase diagram represents a low turbid diagram of solid SEDDS as compared to liquid ones. Therefore, the researchers have positively formulated solid SEDD loaded with AVS. They increases the BCS class II drug solubility and improves its absorption[46]. In a study conducted by Katla and Veerabrahma *et, al* they formulated losartan containing solid self-emulsifying drug delivery system (S-SEDDS) and changed it into liquid self-emulsifying drug delivery system (LSEDDS). It was inferred that the thermodynamic stability and self-emulsification efficiency of L-SEDDS were enhanced. Further *in-vivo* characterization confirmed that oral bioavailability was enhanced by 2.82 folds. SEDDS remain stable at room temperature for a period of three months[85].

5. CONCLUSION

In nutshell, it was concluded that lipophilic drugs which have a decreased aqueous solubility and hence a decreased bioavailability can easily be formulated by using SEDDS. In formulation of SEDDS a very a smaller number of surfactants were employed, and a high degree of drug loading was achieved. Hence SEDDS can furthermore be used for formulation of bioactive / drugs have low water solubility. Additionally sustained release formulations could be constructed while, using suitable composition of polymer. So, SEDDS eventually proves to increases bioavailability of poor water-soluble drugs orally.

LIST OF ABBREVIATIONS

Self-emulsifying drug delivery system (SEDDS)

X-ray diffractometry (XRD)

Oil in water (O/W)

Water in oil (W/O)

Self-micro emulsifying drug delivery systems (SMEDDS)

Gastrointestinal tract (GIT)

Hydrophilic lipophilic balance (HLB)

Area under the curve (AUC)

Nanometer (nm)

Declaration:

Ethics approval and consent to participate

Not applicable

Human and animal rights

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Funding

Not available

Conflict of interest

The authors declare no conflict of interest**.**

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