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Research Article

SELF EMULSIFYING DRUG DELIVERY SYSTEM: AN APPROACH TO ENHANCE SOLUBILITY AND PERMEABILITY

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A B S T R A C T

Self emulsifying drug delivery systems (SEDDS) are one of the novel approaches to increase the solubility and permeability of drugs belonging mainly to BCS class II (low solubility and high permeability) and IV (low solubility and low permeability). SEDDS are isotropic mixtures of lipids, surfactants and co-surfactants which are selected based on the solubility of the lipophilic drug in individual excipients. Pre-concentrate of SEDDS form oil/water emulsion in gastro-intestinal tract upon mild agitation. Thermodynamically stable micro emulsions can be achieved as a fixed ratio of surfactant and co-surfactant is used which are selected based on the pseudo ternary phase diagrams. Conversion of liquid SEDDS into solid dosage forms of SEDDS like tablets, capsules or pellets makes them more patient complaint and easy to administer. This approach increases the bioavailability of the lipophilic drugs by enhancing their solubility.

INTRODUCTION

Oral route of drug delivery is one of the most preferred routes by patients as well as the manufacturers for the treatment of several diseases. Most of the drugs are highly lipophilic in nature and thus poorly soluble in the aqueous media. Drugs belonging to BCS class II (low solubility, high permeability) and class IV (low solubility and permeability) display poor bioavailability (Samatha *et al*., 2014). Bioavailability of drugs depends on various factors like stability of the drug in GI fluids, intestinal permeability, resistance to metabolism by cytochrome P450 family of enzymes present in gut enterocytes and liver hepatocytes, and interaction with efflux transporter systems like P-glycoprotein (P-gp) (Bhupinder *et al*., 2009). The inherent behavior of drug molecules can be altered through several approaches. Particle size reduction and salt formation of the drug enhances the bioavailability without any formulation approach. Particle size reduction might not be advantageous in case of all drugs as there might be a problem in wettability and low stability. Neutral drug moieties cannot be converted into salt forms, and when salt form reaches GIT it might not be efficacious as it gets converted into acid or base. The oral drug delivery of lipophilic drugs can be increased by using a lipophilic vehicle. Along with lipophilic carrier, other excipients like surfactants, co-surfactants aid in enhancing the solubility of drug and decreasing the interfacial tension between the oil and aqueous phase (Chakraborty *et. al* 2009).

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Self-emulsifying drug delivery systems (SEDDS) are isotropic homogenous mixtures of an active compound in a combination of natural or synthetic lipids, surfactants, and co-solvents. SEDDS is a broad term typically producing emulsions with a droplet size ranging between a few nanometers to several microns. Based on the size of globules, they are classified as microemulsions, nanoemulsions or their pre-concentrates. The anhydrous liquid mixtures are commonly termed as pre-concentrates. Self-microemulsified drug delivery system (SMEDDS) indicates the formulations forming transparent microemulsions with the oil droplet size between 100 and 250 nm. Self-emulsified drug delivery system (SEDDS) is relatively a recent term indicating the globule size less than 100 nm. Upon gentle agitation in an aqueous phase, such as the upper GI lumen content, these pre-concentrates spontaneously form drug-encapsulated oil in water (O/W) micro /nano-emulsions with a particle diameter of 200 nm or less. The O/W emulsion distributes throughout the GIT and absorption of lipid and the drug occurs in the small intestine as explained in figure1.

Contrary to emulsions and suspensions, SEDDS are highly thermodynamically stable formulations. SEDDS can be converted into several solid dosage forms like tablets, pellets or even filled into soft/hard gelatin capsules or hydroxypropylmethylcellulose capsules, which makes them commercially viable and patient compliant (Cherniakov *et al*., 2015).

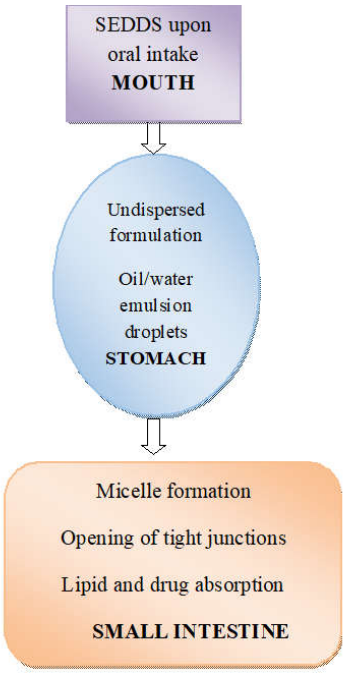

Figure 1 Explains the dispersion and absorption of SEDDS.

Formulation of cationic SEDDS can increase the penetration of the drugs through the lymphatic pathway. Addition of excipients like stearyl amine can induce a positive charge on to SEDDS which owe to higher penetration of the drug through the biological membrane as it is negatively charged.

MECHANISM OF PENETRATION

Co-administration of lipid with the lipophilic drug is advantageous because it contributes to the improvement of bioavailability of the drug by the following mechanism.

Stimulation of body secretions

Pancreatic and biliary secretions are stimulated for the digestion of lipids present in the formulation. These enzymes are water soluble in nature and act at water/lipid interface. Formation of mixed micelles is observed upon interaction of fatty acids with the bile salts which aid in solubilizing of the drug.

Prolongation of GI residence time

The co-administration of lipids along with the drugs prolongs their contact time with the GIT leading to increased drug absorption.

Lymphatic transport

The highly lipophilic drug (log*P*> 5), which has high solubility in triglycerides (>50mg/mL) can undergo lymphatic transport when co-administered with esters of unsaturated long chain fatty acids; thereby bioavailability can be improved. Restricted lymphatic transport is mainly due to low lymph-to-blood flow ratio. This enhanced lymph delivery of the drug can bypass the first pass extraction whereby the bioavailability of drugs that undergo extensive first pass effect can be improved.

Increased intestinal wall permeability

Tight junctions in the intestine open up due to lipids, leading to increased permeability of poorly permeable drugs. This mechanism favors higher/enhanced absorption of Class IV drugs which exhibit rate limited dissolution.

Reduced efflux of the drug in the GIT

Interaction of membrane lipids with anionic phospholipids (cardiolipin and phosphatidylserine) may prevent permeability of glycoprotein (P-gp). Lipid based delivery systems can increase bioavailability of the drugs which exhibit the tendency to be effluxed from the GIT through P-gp. Surfactants competitively bind with P-gp and inhibit its activity leading to membrane alteration. The residence time of the drug can be prolonged by the inhibition of efflux (Tang *et al*., 2008; Samatha *et al*., 2014).

Importance of Sedds

SEDDS offer the following advantages compared with ready-to-use emulsions, SEDDS can offer advantages such as:

1. Bioavailability can be enhanced using self emulsifying drug delivery system.
2. Large quantities of lipophilic drug can be dissolved in SEDDS and can also prevent the drug from enzymatic action making them suitable for parenteral route.
3. SEDDS possess higher/improved physical and chemical stability because of the low energy consumption even on long term storage.
4. Drug that cause irritation in GIT on prolonged contact can be formulated as SEDDS as they disperse as fine droplets which can widely distribute throughout the GIT and transported from the stomach .
5. SEDDS upon dispersion in water, produce fine droplets with large interfacial area which favors in easy partition of the drug from oil phase into the aqueous phase (Tang *et al*., 2007).
6. Formulating lipophilic drugs as SEDDS can improve their absorption as the drug is presented in its soluble form and rate limiting step of dissolution is avoided, which can lead to achievement of constant plasma -time profile.
7. Surfactants such as Tween80, Cremophors (EL and RH40), and Pluronics possess an inhibitory action on efflux transporters which help in increasing bioavailability of drugs which are substrates to the efflux pumps.
8. Surfactants of high HLB like Tween 80, Tween20 loosen the tight junctions of the intestine and thus increasing the permeability of drugs.
9. Improved physical and/or chemical stability profile upon long-term storage. Patient compliance and palatability can be improved as SEDDS can be filled into soft/hard gelatin capsules (Abhijit *et al*., 2010).
10. SEDDS can be formulated as liquids, sprays, ointments, creams, foams, and gels. It can also be used in several drug delivery systems such as topical, oral, and parenteral nutrition (Sagar, 2015).

Disadvantages of SEDDS

- Higher concentration of surfactant and their chemical stability can lead to gastric irritation.
- SEDDS are not very suitable for controlled drug release.
- Migration of volatile co-solvents in hard gelatin capsule may lead to hardening of the shell and precipitation of the lipophilic drug.

Composition of Sedds

Lipid: Lipid is one of the prime components in SEDDS formulations. They facilitate in solubilizing the lipophilic drugs or self-emulsification and also possess an ability to increase the fraction of drug transported via intestinal lymphatic system and thus leading to increased absorption from the GI tract. Digestive lipids such as triglycerides, diglycerides, phospholipids, fatty acids, cholesterol and several lipids based on synthetic origin improve the bioavailability when compared to non-digestible lipids, as there may be impairment in absorption of the administered drug itself. The degradation products of oils/lipids resemble those of natural products and thus providing advantage in terms of formulation. Both unsaturated and saturated fatty acids have been widely employed in the formulation of lipidic systems. However, the self emulsifying drug delivery system (SEDDS), in particular, comprise of saturated fatty acids like, caproic, caprylic, capric, lauric and myristic acid. Appropriate choice can be made by looking into their composition, potential utilities, physical state, and hydrophilic-lipophilic balance (HLB) (Bhupinder *et.al* 2009).

Beg *et al* (2013)., formulated SMEDDS of ondansertan hydrochloride (ONH) using several natural lipids (coconut oil, palmoline oil, olive oil, sesame oil, arachis oil, castor oil, and neem oil), and medium chain triglycerides (Captex 200, Captex 355 and Capmul MCM). Capmul MCM showed the highest solubility for ONH compared to other synthetic oils (Captex 200 and Captex 355) containing medium chain triglycerides (MCTs) and natural lipids that contain long chain triglycerides (LCTs). Capmul MCM contains a mixture of C8/C10 mono-/diglycerides which favors complete solubilization of drug in the vicinity of triglyceride chains due to shorter chain length. Captex 200/355 (C8/C10 triglycerides), have longer chain length, which is invariably insufficient for complete solubilization of ONH (Porter *et al*., 2007). Natural lipids were not selected due to low solubility of drug in these excipients, stability, and biocompatibility issues. Lipids that possessed greater number of medium chain triglycerides provided more surface area for the solubilization of the drug in comparison to the lipids with shorter or longer chain triglycerides (Beg *et al*., 2013).

Emulsifiers: The other vital component of SEDDS is the emulsifier. Surfactants are amphiphilic in nature and they can solubilize relatively high amounts of hydrophobic drug compounds. Emulsifiers of natural origin are beneficial over synthetic surfactants as they are not only less toxic but also possess a limitation in self-emulsification and hence, seldom employed for the formulation of SEDDS. Selection of surfactants is mainly dependent on HLB and safety. The HLB value of a surfactant provides information on its potential utility in the formation of SEDDS. Higher the HLB value, greater the ability to form an oil/water emulsion (Pouton, 1997; Devani *et al*., 2004). Surfactants enable in making the drug available at the site of absorption for a relatively prolonged period of time for effective absorption and it also prevents precipitation of drug compound within the GI lumen (Shah *et al*., 1994).

The most widely recommended emulsifiers include the nonionic surfactants with relatively high HLB values like solid or liquid ethoxylatedpolyglycolyzed glycerides, polyoxyethylene (20) sorbitanmonooleate (i.e., Tween 80) and poly(ethylene oxide)-poly(propylene oxide) block copolymers like Pluronic F12. Nonionic surfactants are also considered as safer than the ionic ones but the former may cause reversible change(s) in the intestinal permeability. When hydrophobic drug of higher concentration are to be dissolved, surfactants also must be used at higher concentration in order to achieve an effective SEDDS formulation. The surfactant concentration usually should range between 30 and 60% w/w for forming stable SEDDS, higher concentrations may cause irritation to the GI mucosa. The concentration of surfactant and the droplet size are inversely proportionate. This phenomenon could be attributed to the stabilization of oil droplets by localization of the surfactant molecules at the oil-water interface (Bhupinder *et al*., 2009).

Surfactants are classified into

a. ***Anionic Surfactants:*** These surfactants carry a negative charge on hydrophilic group such as carboxyl (RCOO-), sulphonate (RSO3-) or sulphate (ROSO3-). Examples: Potassium laurate, sodium lauryl sulphate.
b. ***Cationic surfactants:*** These surfactants carry a positive charge on the hydrophilic group. Example: quaternary ammonium compounds.
c. ***Ampholytic surfactants:*** (Also called zwitter ionic surfactants) these surfactants contain both negative as well as a positive charge. Example: sulfobetaines.
d. ***Nonionic surfactants:*** Surfactants that carry no charge on hydrophilic group but derive water solubility due to presence of groups such as hydroxyl or polyoxyethylene. Examples: Sorbitan esters (Spans), poly - sorbates (Tweens) (Bhupinder *et al*., 2009).

Co-surfactants: Relatively high concentrations (generally more than 30% w/w) of surfactants are employed in the formulation of optimized SEDDS. Inclusion of co-surfactants can reduce the concentration of surfactant to be used. Co-surfactants along with surfactants aid in lowering the interfacial tension between the oil and aqueous phase. They help in achieving spontaneous emulsification which forms the microemulsion. Addition of co-surfactants is not mandatory for most of the formulations with non-ionic surfactants. The selection of surfactant and co-surfactant is mainly based on their solubilizing capacity of the lipophilic drug. Organic solvents, suitable for oral administration (ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc.) aid in dissolving higher amounts of either the hydrophilic surfactant or the drug in the lipid phase and can act as co-surfactant in SEDDS. Incorporation of alcohol free systems is advantageous in capsule dosage forms, since alcohol and other volatile co-solvents are known to migrate into the shells of soft gelatin or hard sealed gelatin capsules leading to precipitation of the drug. On the other hand, the lipophilic drug dissolution ability of the alcohol free formulation may be limited (Anand *et al*., 2010).

Mechanism of Self-Emulsification

In the emulsification process, the free energy (ΔG) associated is given by the equation:

$$\Delta G = \sum \mathbf{N_i}\, \Pi r_i^2 \sigma$$

Where, N is number of droplets with radius r and σ is the interfacial energy. It is apparent from the above equation that the spontaneous formation of the interface between the oil and

water phases is energetically not favored. Spontaneous emulsion of SEDDS has not been elucidated yet in the thermodynamic sense. The ease of emulsification depends on ability of water penetrating the oil-water interface with the formation of liquid crystalline phases resulting in swelling at the interface. However, for systems containing co-surfactants, significant partitioning of components between the oil and aqueous phases may take place leading to a mechanism described as "diffusion and stranding", whereby the oil is solubilized, leading to migration into the aqueous phase (Singh *et al*., 2015). Very less energy input is required for emulsification which involves destabilization through contraction of local interfacial regions. Emulsification takes place when the interfacial structure shows no resistance against surface shearing. The mechanisms responsible for enhancement of oral bioavailability by self-nanoemulsifying drug delivery system are elucidated in Figure 2.

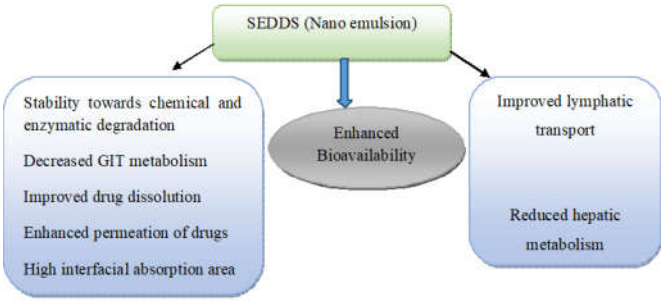

Figure 2 Mechanisms responsible for improvement in oral bioavailability in SEDDS

Method of Preparation

The method of making SEDDS is to improve the bioavailability of the drug by emulsifying the drug with the self micro-emulsifying excipients. Various steps as described below.

Phase Titration Method (water titration method)

Stepwise addition of water into solution of surfactant in oil, with mild agitation and at room temperature can produce kinetically stable nano/mciroemulsions. The spontaneous emulsification has been related to the phase transitions during the emulsification process and involves lamellar liquid crystalline phases or D-type bicontinuous microemulsion during the process. Micro emulsion prepared by this method can be depicted with the help of phase diagram. Forming a phase diagram is a useful approach to study the interaction produced by various structured components that are mixed. The understanding of their phase equilibria and demarcation of the phase boundaries are required aspects of the study. Pseudo ternary phase diagram is often constructed to find the different zones having micro emulsion zone, in which every corner of diagram shows 100% of the particular component (Abhijit *et al*., 2010; Krishnamurthy *et al*., 2014).

Phase Inversion Method

Microemulsions can be generated upon excessive addition of dispersed phase or in response to temperature. The alteration of spontaneous curvature of the surfactant forms the basis for this method. In case of usage of non-ionic surfactants, changing the temperature of the system can cause a phase transition from an o/w microemulsion (low temperature) to a w/o microemulsion (high temperature). During cooling, the system crosses a point of zero spontaneous curvature and minimal surface tension, enabling the formation of finely dispersed oil droplets. This method is referred to as phase inversion temperature (PIT) method. Various parameters such as salt concentration or pH value alteration may also lead to phase inversion. Additionally, by changing the water volume fraction a transition in the spontaneous radius of curvature can be obtained. By successive addition of water into lipid phase, water droplets are formed in a continuous lipid phase thus increasing the fraction of water volume which leads to change in the spontaneous curvature of the surfactant from initially stabilizing a w/o microemulsion to an o/w microemulsion at the inversion locus. During phase inversion, drastic physical alterations occur like change in particle size that may affect the drug release both in vivo and in vitro.

Construction of Pseudo Ternary Phase Diagram

- Pseudo ternary phase diagrams aid in characterizing the zone of micro-emulsion. These diagrams represent the alteration in phase behavior with respect to change in the composition. Ternary phase diagram comprises of three corners corresponding to 100% of each component as expressed in figure 3. When a co-surfactant is used along with a surfactant, the phase diagram is termed as pseudo-ternary.
- For pseudo ternary phase diagrams, several ratios of predetermined oil, surfactant and co-surfactant were used along with water. The oil to surfactant ratio was varied from 9:1 to 1:9 with 10 % increments. Various Smix (surfactant to co-surfactant) ratios like 1:1, 1:2 .1:3 etc were prepared. Several combination of oil to Smix ratios were titrated using water upon magnetic stirring and the samples was observed visually after 24hrs.
- Cut and weight method can be employed to determine the total area occupied by each system. The weight of each individual system and total weight of phase diagram were measured and subsequently used in calculating the percentage occupied by several regions.

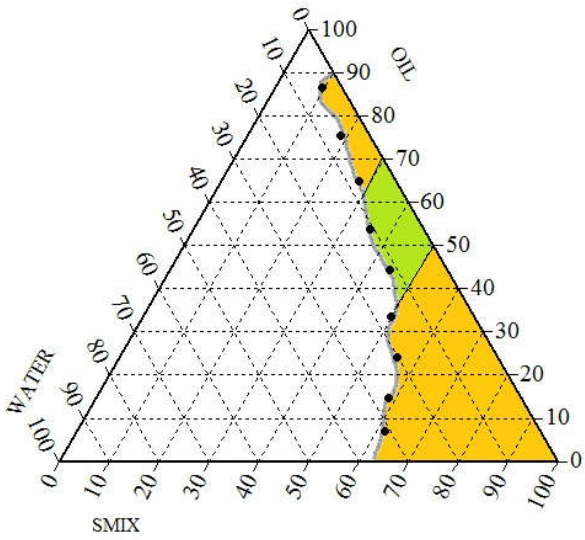

Fig 3 Pseudo ternary phase diagram

Characterization of Liquid Sedds

Solubility studies: This study is performed to find out the suitable oil, surfactant, and co-surfactant in which an excess of the drug can be dissolved. Shake flask method or an orbital shaker is used to perform this test. This method involves addition of drug in excess to the excipients of volume, 2ml which are filled in vials. The vials are shaken for 48-72 hours in orbital shaker to achieve homogenous slurry. The samples are then subjected to centrifugation at 4500 rpm for 10 minutes to obtain a supernatant followed by filtration of aliquots of supernatant using a syringe filter. The filtrate obtained is diluted with water and drug dissolved in various vehicles is analyzed by UV spectrophotometer for quantification of the drug content (Puttachari *et al*., 2014).

Visual assessment: The self-emulsification property can be assessed based on the visual appearance of the formulation when added to 100ml of distilled water at 25°C. The formation of spontaneous, clear, and isotropic solution determines the endpoint of a good micro-emulsion whereas opaque and milky appearance forms the end point of poor or no formation of micro-emulsion.

Determination of self-emulsification time: Self-emulsification time helps in determining the efficacy of self-emulsification of liquid SEDDS. This test is performed using dissolution apparatus USP type II in which 2ml of each formulation is added dropwise to the basket containing water or 0.1 N HCl maintained at 37±0.5ºC and paddle rotating at 50 rpm and observed visually for assessment of self-emulsification (Samatha *et al*., 2014).

Dispersibility test: The efficiency is assessed using a standard USP XXII dissolution apparatus type II. One mL of each formulation is added to 500 mL of water at 37 ± 0.5 ºC. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The *in vitro* performance of the formulations is visually assessed using the following grading system

Table 1 Grading for dispersibility test

Grades	Appearance
A	Rapid forming emulsion, which is clear and transparent in appearance.
B	Rapid forming, slight less clear emulsion which has a bluish white appearance.
C	Bright white emulsion or grayish white emulsion with slight oily appearance that is slow to emulsify.
D	Exhibit poor or minimal emulsification with large oil droplets present on the surface.

Grade A and B are only considered owing to their rapid microemulsion formation (Amoolya *et al*., 2018).

Transmittance test: Stability of SEDDS can be assessed based on its dilution and checked by determining transmittance using a UV Spectrophotometer (Parmar *et al*.,2012).

Droplet size determination: Spectrophotometric methods like Photon correlation spectroscopy and microscopic techniques are used for analysis of droplet size. Zetasizer is commonly used for evaluation of droplet size which works on the principle of dynamic light scattering. Mean globule size, polydispersibility index (PDI) of the emulsion of optimized liquid-SEDDS formulations are analyzed on 100 times dilution with double distilled water (Inugala *et al*.,2014; Sharma *et al*., 2010). PDI refers to the uniformity in the particle size distribution in the sample. Ideally, SNEDDS must display a wide distribution in less than 150 nm; PDI should be less than 0.5. Droplet size distribution forms one of the crucial characteristics of emulsion for stability evaluation and plays a key role in enhancing drug bioavailability.

Zeta potential measurement: Zeta potential is useful in knowing the surface charge of the particle which can determine its stability. Zeta potential can be either positive or negative, stable formulations may possess +30 to -30 mV charge. The conventional SEDDS possess a negative charge owing to the presence of free fatty acids (Gershanik *et al*., 1996). Positive charge may also be induced by addition of cationic surfactants such as stearyl amine. High zeta potential on droplets of SEDDS confers stability and long shelf life. Zeta potential at times is considered as secondary characterization parameter for SEDDS, as SEDDS are a preconcentrate mixture of the drug in oil and surfactant and emulsified in vivo only. Zeta potential can be measured by photon correlation spectroscopy using Zetasizer (Nano ZS, Malvern Instruments, UK) equipped with 4.0 mW He-Ne red laser (633 nm) which measures the potential ranged from −120 to 120 V(Gupta *et al*., 2013). Cuvette must be washed with methanol before analyzing a fresh sample. Optimized liquid SEDDS formulations are diluted with double distilled water (100 mL) for the measurement of zeta potential at 25°C (Balakumar *et al*., 2013).

Thermodynamic evaluation: Liquid SEDDS chosen from phase diagrams are subjected to this evaluation in order to avoid selection of meta-stable formulations amongst them. Centrifugation is performed to observe visually for any phase separation or drug precipitation. Formulations that are found to be stable can be further preceded to heating-cooling cycle to assess the effect of temperature variation on the formulations (Damineni *et al*., 2014). The Stability studies also help in assessing the effect of change in temperature on the L-SEDDS formulations. For centrifugation stress, the L-SEDDS formulations are diluted with aqueous phase and centrifuged at 3500 rpm for 15 min and visually observed for any phase separation. Further, the formulations must be subjected to heating and cooling cycles for about six cycles between refrigerator 4ºC and 45ºC with storage at each temperature for not less than 48 hrs (Kallakunta *et al*.,2012; Shafiq *et al*., 2007).

In vitro drug release: The in-vitro drug release of liquid SEDDS is determined using a USP Dissolution Apparatus type II-Paddle type. Dialysis membrane is used which is soaked overnight in the buffer/distilled water and the sample is placed in it by securing both the ends. Dissolution media of 900ml with an aid of rotating paddle at 50 rpm and temperature of 37ºC ±0.5º is used. Samples of 5 ml from the dissolution medium are withdrawn after specific time intervals and replaced with fresh 0.1N HCl and samples are assessed spectrophotometrically to calculate the cumulative percentage release (Ammar *et al*.,2014).

Transmission electron microscopy (TEM): SEDDS are dilute with distilled water and mixed by gentle shaking. Copper grids are allowed to stand on for 60 seconds on which one drop of sample obtained after dilution is deposited. Filter paper is used to remove excess fluid and then the grid is stained in 1% phosphotungstic acid solution for 30 seconds. Transmission electron microscopy (TEM) enables in knowing the

morphology of SEDDS by giving information on the porosity and microstructure (Ammar *et al*., 2014).

Conversion of Liquid Sedds to Solid Sedds

Liquid SEDDS possess drawbacks related to the stability of formulation, interactions between the excipients and the capsule shell, irritation of GI mucosa due to surfactants, etc. (Tang *et al*.,2007). SEDDS involve an interplay of lipidic and solidifying excipients to convert the liquid SEDDS into several solid dosage forms using diverse approaches which are mentioned in the figure 4 (Weisspapir *et al*.,2002). Solid SEDDS are advantageous as production cost is low, portability is easy, stability is high and also provides better safety, and improved patient compliance. Dose precision can be achieved and volume of drug to be administered can be reduced. Solidification techniques vary from each other in terms of drug loading capacity and recovery of the solid formulation after conversion from liquid to solid state. Thus, selection of a solidification technique would eventually depend on the nature of liquid formulation, properties of the drug, and batch size there of (Singh *et al*., 2015).

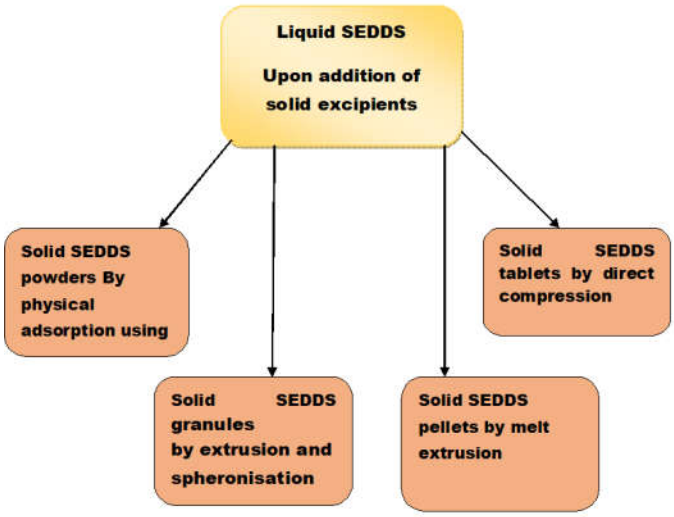

Figure 4 several approachesused for transformation of liquid SEDDS formulations into solids SEDDS

Solidification Techniques for Transforming Liquid SEDDS to Solid SEDDS

Capsule filling with liquid and semisolid self-emulsifying formulations

Capsule filling is the simplest technology for the encapsulation of liquid or semisolid SEDDS formulations for the oral route. Semi solid preparation involves (i) heating of the semisolid excipients to at least 20 ºC above its melting point; (ii) Incorporation of the drug (with stirring); (iii) filling of capsule with the molten mixture and (iv) cooling to room temperature. For liquid formulations, it involves a two-step process: either filling of the formulation into the capsules followed by sealing of the body and cap of the capsule, by banding or by micro spray sealing (Jannin *et al*., 2008). One of the major considerations that must be addressed during capsule filling is the compatibility between capsule shell and the excipients. Capsule filling is advantageous due to the ease of manufacturing and, compatibility for high potent -low-dose drug loading (up to 50% (w/w) potential (Preethi *et al*., 2012). Shailesh *et al* (2013)., prepared SMEDDS formulations containing olmesartan medoxomil (OLM) filled in capsules which have shown significant increase in the dissolution rate and *in vitro* diffusion rate when compared to plain OLM suspension (Shailesh *et al*., 2013).

Spray drying

In this technique, preparation of the formulation is done by mixing of lipids, surfactants, drug, solid carriers, and dissolution of the mixture. The solubilized liquid formulation is then atomized into a spray of droplets. The droplets are then dried, where the volatile phase (e.g. the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. These particles can be further prepared into tablets or capsules. The atomizer, the temperature, the most suitable airflow pattern, and the drying chamber design are selected according to the drying characteristics of the product and powder specification (Tao *et al*., 2008). Jayshri *et al*., 2017 prepared solid SMEDDS of Chlorthalidone (CTD) by spray drying using water-insoluble Aerosil 200 as a solid carrier. The optimized S-SMEDDS was composed of CTD, oleic Acid, Tween 20, PEG 200. Ex-vivo permeation study on chicken intestine showed that S-SMEDDS gave significant increase in the permeability of CTD compared to the powder CTD (Jayshri *et al*., 2017).

Melt granulation

Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures. It's a single step process and melt granulation is advantageous over the conventional wet granulation as there is no requirement for liquid addition and drying. The main parameters that control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder. A wide range of solid and semisolid lipids can be applied as meltable binders. Vadlamudi H.C *et al*., formulated quetiapine SMEDDS with oleic acid, Tween 80 and Glycine used at 1:1 ratio using melt granulation technique. S-SMEDDS had 1.2 years of shelf life and exhibited better anti-psychotic activity owing to enhanced biomembrane permeation in the presence of tweens as surfactants (Vadlamudi *et al*., 2019).

Adsorption onto solid carriers

Several pharmaceutical grade adsorbents are available namely grades of Neusilin US2 and Neusilin UFL 2, Feujicalin, Florite R. These free flowing powders possess large surface area and exhibits an ability to absorb around 70% w/w of their own weight. Neusilin US2 exhibits good flow property, adsorbing capacity of oils, also good Carr's index, making it an ideal adsorbent for capsule filling as well as tablet dosage form (Hentzschel *et al*.,2012; Kang *et al*, 2012). This method has an advantage of content uniformity and ease of manufacture as it involves simple addition of liquid SEDDS to adsorbent. Harshal *et al*., formulated micro-emulsifying drug delivery system (SMDDS) of fenofibrate with Tween 20, Cremophor, capmul and mixture was solidified with magnesium alumino meta silicate (NeusilinUS2). The solid SMEDDS formulation showed faster release when compared to a plain drug and conventional marketed formulation, showed a limited dissolution rate (Harshal *et al*., 2011).

Table 2 List of marketed formulations

Trade name	Drug molecule	Aqueous solubility	Type of formulation	Excipients
Fenogal --Genus Pharmaceuticals Ltd.	Fenofibrate	0.000707 mg/mL	Hard gelatin capsule	Lauryl macrogol-glycerides (Gleucire 41/44)
Infree--Eisai Co. Ltd	Indomethacin	0.00240 mg/mL	Soft gelatin capsule (200 mg)	Polyoxoy 60 hydrogenated castor oil (Cremophor RH 60), hydrogenated oil, glycerylmonooleate
Solufen-- Sanofi-Aventis	Ibuprofen	0.0684 mg/mL	Hard gelatin capsule	Lauryl macrogol-glycerides (Gelucire 44/14)
Accutane -- Roche Pharmaceuticals	Isotretinoin	0.00477 mg/mL	Soft gelatin capsule (10, 20, 40 mg)	Beeswax, BHA, EDTA, hydrogenated soybean oil flakes, hydrogenated vegetable oils, soybean oil
Norvir-- Abbott laboratories	Ritonavir	0.00126 mg/mL	Soft gelatin capsule (100mg)	Oleic acid, polyoxyl 35 castor oil (Cremophor EL)

Melt extrusion/extrusion Spheronization

The extrusion-spheronization process yield pellets. This process is devoid of solvent usage and yield produced will have high drug loading and content uniformity. This method involves four steps: (i) wet mass preparation (granulation) (ii) extrusion (iii) spheronization and (iv) drying of the pellets.

Several liquid SEDDS formulations have been converted to solid SEDDS using various approaches mentioned above and table 2 lists out few marketed formulations of solid SEDDS. Kalivoda *et al* formulated SEDDS using melt extrusion to improve dissolution behavior of poorly soluble drug fenofibrate. Blends of polymers were used as carrier: copovidone (COP), polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol copolymer (PVCL-PVAc-PEG) and hypromellose 2910/5 (HPMC). The ratio of fenofibrate to COP remained constantly 1 + 3 (weighted parts) with varying amounts of PVCL-PVAc-PEG and HPMC (Kalivoda *et al*., 2012).

CONCLUSION

This approach is advantageous as it overcomes the rate limiting step of dissolution by presenting the lipophilic drug in its soluble form with the aid of lipids and surfactants. They also help in increasing the permeability by opening of tight junctions in the intestine and even via lymphatic transport. Charged SEDDS can be more advantageous over conventional SEDDS as they can enhance permeation through the biological membrane which is negatively charged. Conversion of SEDDS to their solid form enables in increasing the patient compliance and ease of administration. SEDDS forms one of the promising approaches to increase the solubility and permeability of lipophilic drugs specially belonging to BCS class II and IV.

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