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SELF EMULSIFYING DRUG DELIVERY SYSTEM: AN APPROACH TO ENHANCE BIOAVAILABILITY AND SOLID SELF-EMULSIFYING DRUG DELIVERY SYSTEMS : A REVIEW

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ABSTRACT

Self micro emulsifying drug delivery systems are isotropic mixtures of oil, surfactant, co-surfactant and drug with a unique ability to form fine oil in water microemulsion upon mild agitation following dilution with aqueous phase. The hypothesis behind dissolution rate enhancement with SMEDDS is the spontaneous formation of the emulsion in the gastrointestinal tract which presents the drug in solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption. Article gives a complete overview of SMEDDS as a promising approach to effectively tackle the problem of poorly soluble molecules.

1.1 ORAL DRUG DELIVERY SYSTEMS

Oral route till the date has been the preferred mode of dosing because it is the easiest and most convenient mode of non invasive administration. Besides this, oral drug delivery systems (ODDS) are also being most cost effective to manufacture and thus, they have always lead the worldwide drug delivery market. The percent annual sale of overall formulation is shown in the fig.1.1.

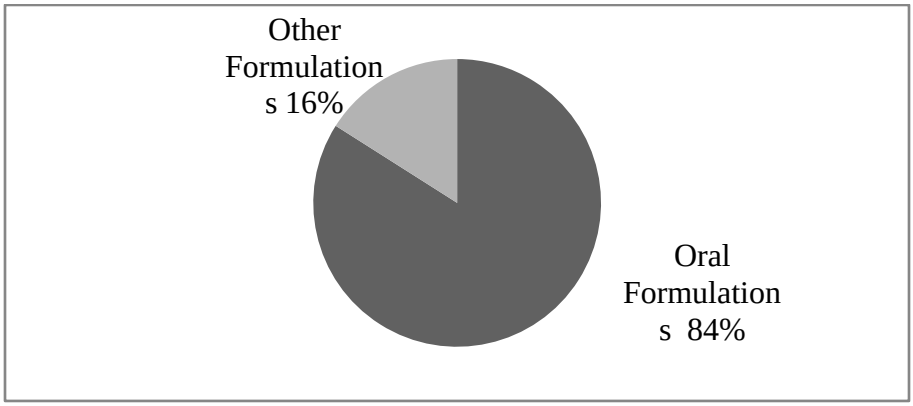

Fig.1.1: Percent sales of orally administered drugs for 50 most sold pharmaceutical products

The most commonly presented solid dosage forms in the market are tablets and capsules. All these oral dosage forms follow either an immediate or a modified drug release profile. [1]

In recent years drug bioavailability has become a subject of interest not only in drug development, but also in the early stages of drug discovery. It is a consequence of the finding that most of the candidate drugs that failed in clinical trials is because of problems with ADME (absorption, distribution, metabolism and excretion) and toxicology, rather than through of efficacy. Efforts are being made in the pharmaceutical industry to improve success rates by taking into account the ADME and toxicology aspects in drug discovery from very early period. Therefore, it is not surprising that the numbers of publications are on drug bioavailability has been increasing steadily. Thus, approaches to improve drug solubility as well as drug permeability are the two main strategies in order to enhance the bioavailability of drugs.[2]

The formulation of poorly water soluble compounds presented interesting challenge to formulation scientists in the

pharmaceutical industry. Up to 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which lead to poor oral bioavailability, high intra and inter subject variability and lack of dose proportionality. Currently, number of technologies is available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs. Various formulation strategies reported in the literature includes, incorporation of drug in oil/s, solid dispersions, emulsions, liposomes, use of cyclodextrins, co precipitates, micronization, nanoparticles, permeation enhancers and lipid solutions as mentioned in fig.1.2.[3]

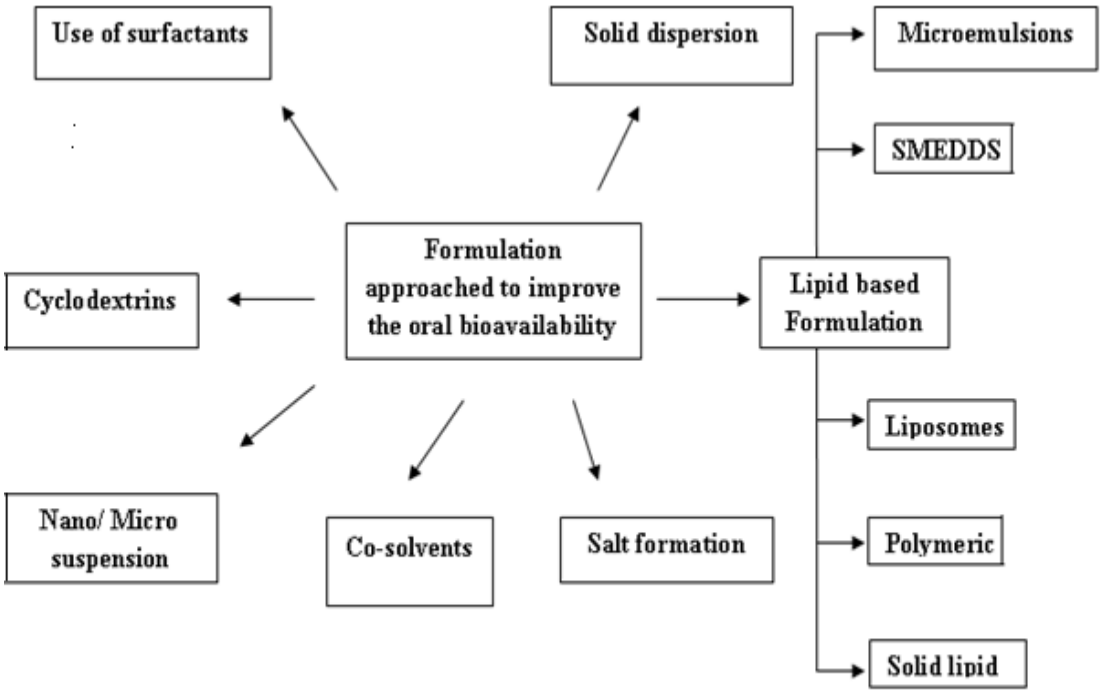

Fig.1.2: Formulation approaches for improvement of the oral bioavailability of poorly water soluble drugs

1.2.1 Biopharmaceutical Classification System (BCS classification)

BCS classification was introduced in 1995 as a basis for predicting the likelihood of *in vitro* - *in vivo* correlations

for immediate release dosage forms, based on the recognition that drug solubility/dissolution properties and gastrointestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption. According to BCS, drug substances are classified as:

Class I - High solubility high permeability
Class II - Low solubility high permeability
Class III - High solubility low permeability
Class IV - Low solubility low permeability

The FDA has set specifications regarding the solubility and permeability class boundaries used for this BCS classification.

Solubility

A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over a pH range of 1 to 7.5 (equilibrium solubility at 37 °C).

Permeability

In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on mass balance determination or in comparison to an intravenous reference dose (absolute bioavailability study).

Poorly water-soluble drug candidates often emerge from contemporary drug discovery programs and present formulators with considerable technical challenges. The absorption of such compounds when presented in the crystalline state to the gastrointestinal tract is typically dissolution rate-limited and the drugs are typically BCS class II or class IV compounds. Class IV compounds, which have low membrane permeability as well as poor aqueous solubility are often poor candidates for development, unless the dose is expected to be low. The rate and extent of absorption of class II compounds is highly dependent on the performance of the formulated product. These drugs can be successfully formulated for oral administration, but care needs to be taken with formulation design to ensure consistent bioavailability. Essentially the

options available involve either reduction of particle size (of crystalline drug) or formulation of the drug in solution, as an amorphous system or lipid formulation. The performance of amorphous or lipid formulation is dependent on their interaction with the contents of the gastrointestinal tract, therefore, a formulation exercise should involve the use of techniques which can predict the influence of gut physiology. A major consideration is the fate of metastable supersaturated solutions of drug, which are formed typically after dispersion of the formulation and its exposure to gastrointestinal digestion. A better understanding of the factors which affect drug crystallization is required and the introduction of standardized predictive *in vitro* tests would be valuable. Although many bioavailability studies have been performed with poorly water-soluble drugs, thus, far this research field has lacked a systematic approach. The use of a lipid formulation classification system combined with appropriate *in vitro* tests will help to establish a database for *in vitro–in vivo* correlation studies.[4,5] A typical representation of the BCS indicating that absorption of a class II drug can be markedly improved by attention to the formulation is mentioned in fig.1.3.

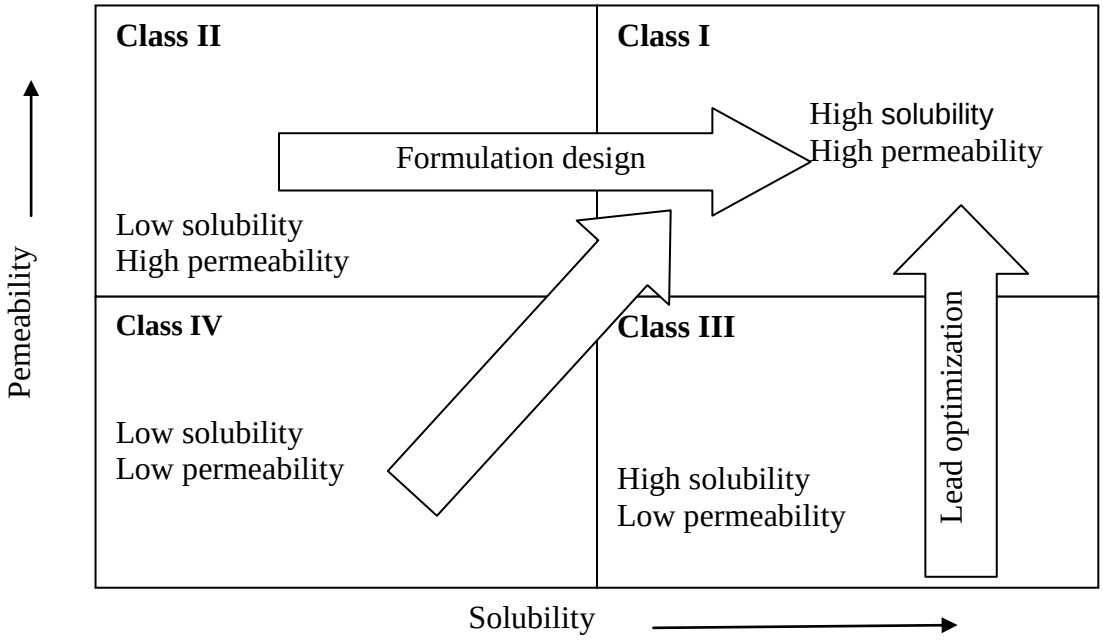

Fig.1.3: A typical representation of the BCS classification

The choice of formulation is often of critical importance in establishing a successful product for oral administration of a class II drug. If bioavailability of the drug is recognized to be formulation dependent at an early stage it is desirable to have a strategy for maximizing absorption as soon as possible. If poor formulations are used in early animal efficacy studies, the prediction of the likely human dose can be overestimated, possibly by compromising the future development of the candidate drug. Use of a poor formulation in early toxicity studies can lead to an underestimation of the toxicity due to limited exposure resulting from low bioavailability. In general terms the options for formulation of poorly water-soluble drugs include crystalline solid formulations, amorphous formulations and lipid formulations.

The dissolution rate of drug from crystalline formulations can be increased by reducing the particle size and increasing the surface area for dissolution. Lipid formulations include simple solutions, self-emulsifying drug delivery systems (SEDDS) and systems which contain very little oil and disperse to form micellar solutions. Amorphous formulations include 'solid solutions' which can be formed using a variety of technologies including spray drying and melt extrusion. Amorphous formulations may include surfactants and polymers providing surface-activity during dispersion. Inclusion of surfactants may be useful to prevent a hydrophobic barrier forming on contact with water, or agglomeration of re-crystallized drug particles after dispersion.

1.2.2 Lipid formulation classification system

The different lipid drug delivery systems available include lipid solution, lipid emulsion, microemulsion, dry emulsion. To get a clear picture of all these different systems and due to large number of possible excipient combinations that may be used to assemble these lipid-based formulations, self emulsifying systems in particular a classification systems have been established called as lipid formulation classification system (LFCS). This classification helps to better understand the fate of different lipid formulation *in vivo*, it also helps to use a systematic and rational formulation approach avoid "trial-and error" iterations. LFCS was established by Pouton in 2000 and recently updated 2006. The LFCS briefly classifies lipid-based

formulations into four types according to their composition and the possible effect of dilution and digestion on their ability to prevent drug precipitation is represented in table 1.1.

Significance

Classification aids formula by various means for assistance

- Clarify the rationale for lipid formulations development for BCS class lead candidates.
- Increase in efficacy and decrease the cost in lipid formulation development.
- Provide framework to guide regulatory agencies.

Table 1.1: Typical compositions and properties based on lipid formulations classification system (LFCS) [6]

Sr. No.	Composition	Type I Oil	Type II SEDDS	Type III		Type IV Oil free
				III A SEDDS	III B SMEDDS	
1	Glycerides (TG,DG,MG)	100%	40-80%	40-80%	<20%	-
2	Surfactants (HLB<12)	-	20-60%	-	-	0-20%
3	Surfactants (HLB>12)	-	-	20-40%	20-50%	20-80%
4	Hydrophilic co-solvents	-	-	0-40%	20-50%	0-80%
5	Particle size nm	Coarse	100-250	100-250	50-100	< 50
6	Significance of aqueous dilution	Limited importance	Solvent capacity unaffected	Some loss of solvent capacity	Significant phase changed and potential loss of solvent capacity	Significant phase changed and potential loss of solvent capacity
7	Significance of digestibility	Crucial need	Not crucial but likely to occur	Not crucial but may be inhibited	Not required	Not required

Type I: Systems consist of formulations which comprise drug in solution in triglycerides and/or mixed glycerides or in an oil-in water emulsion stabilized by low concentrations of emulsifiers such as 1% (w/v) polysorbate 60[7] and 1.2% (w/v) lecithin.[8] Generally, these systems exhibit poor initial aqueous dispersion and require digestion by pancreatic lipase/ co-lipase in the GIT to generate more amphiphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase. Type I lipid formulations therefore represent a relatively simple formulation option for potent drugs or highly lipophilic compounds where drug solubility in oil is sufficient.

Type II: Systems consist of lipid formulations constituting SEDDS and SMEDDS.[7] Self-emulsification is generally obtained at surfactant contents above 25% (w/w). However, at higher surfactant contents (greater than 50-60% (w/w) depending on the materials) the progress of emulsification may be compromised by the formation of viscous liquid crystalline gels at the oil/water interface. Type II lipid-based formulations provide the advantage of overcoming the slow dissolution step typically observed with solid dosage forms and as described above generate large interfacial areas which in turn allows efficient partitioning of drug between the oil droplets and the aqueous phase from where absorption occurs.[9]

Type III: Systems consist of lipid-based formulations, commonly referred to as self-micro emulsifying drug delivery systems (SMEDDS), are defined by the inclusion of hydrophilic surfactants (HLB>12) and co-solvents such as ethanol, propylene glycol and polyethylene glycol. Type III formulations can be further segregated (somewhat arbitrarily) into Type IIIA and Type IIIB formulations in order to identify more hydrophilic systems (Type IIIB) where the content of hydrophilic surfactants and co-solvents increases and the lipid content reduces. Type IIIB formulations typically achieve greater dispersion rates when compared with Type IIIA although the risk of drug precipitation on dispersion of the formulation is higher given the lower lipid content.[10,11]

Type IV: In order to capture the recent trend towards formulations which contain

predominantly hydrophilic surfactants and co solvents, this category was recently added. Type IV formulations do not contain natural lipids and represent the most hydrophilic formulations. These formulations commonly offer increased drug payloads when compared to formulations containing simple glyceride lipids and also produce very fine dispersions when introduced in aqueous media.[12]

Little is known however, as to the solubilisation capacity of these systems *in vivo* and in particular whether they are equally capable of maintaining poorly water soluble drug in solution during passage along the GIT when compared with formulations comprising natural oils (Type II and Type III). An example of a Type IV formulation is the current capsule formulation of the HIV protease inhibitor Amprenavir (Agenerase) which contains TPGS as a surfactant and PEG 400 and propylene glycol as co-solvents.[13,14] Characteristics, advantages and disadvantages of lipid formulations are depicted in table 1.2.

Table 1.2: Characteristics, advantages and disadvantages of lipid formulations

Sr.No.	LCFS type	Characteristics	Advantages	Disadvantages
1	Type I	Non-dispersing, require digestion	GRAS status, simple, excellent capsule compatibility	Poor solvent capacity unless the drug is highly lipophilic
2	Type II	SEDDS without water soluble components	Unlikely to lose solvent capacity on dispersion	Turbid o/w emulsion (0.25-2 µm)
3	Type IIIA	SEDDS/SMEDDS with water soluble components	Clear or almost clear dispersion, drug absorption without digestion	Possible loss of solvent capacity on dispersion, less easily digested
4	Type IIIB	SMEDDS with water-soluble components and low oil content	Clear dispersion, drug absorption without digestion	Likely loss of solvent capacity on dispersion
5	Type IV	Oil-free formulation based on surfactant and co solvents	Good solvent capacity for many drugs, disperses to micellar solution	Loss of solvent capacity on dispersion, may not be digestible

1.2 LIPID FORMULATIONS

1.2.1 Microemulsion

It is the approach of formulation of hydrophobic agents for oral drug delivery. Like an emulsion, microemulsion is a liquid dispersion of oil in water, stabilized by surfactants. The microemulsion particles are smaller than those of emulsion, rendering the micro emulsion essentially clear. Microemulsions however are thermodynamically stable and are not subject to the particle agglomeration problems of conventional emulsions. It is generally believed that microemulsions are micelle-like particles, having an essentially micellar structure that contain a distinct oil phase in the micelle core. These micelle like particles are often referred to as swollen micelles, a term which emphasizes their close relationship to true micellar particles. Despite their close relationship to micelles, microemulsion functions quite differently in drug delivery systems.

The majorities of hydrophobic agents are lipophilic and have a greater solubility in triglycerides than in surfactants. As a result, the hydrophobic therapeutic agent in microemulsion-based delivery system is preferentially solvated in triglyceride phase, which in turn encapsulated in the swollen micelle. The preferential partitioning in the triglyceride phase results in higher loading capacities than in comparable micelle-based systems, but at the cost of introducing into the delivery systems the lipolysis dependence and other disadvantages associated with the presence of triglycerides. In addition the larger size of microemulsion particles, relative to true micelles results in a slower rate of particle diffusion and thus, slower rate of drug absorption. Thus, there is a need for pharmaceutical compositions that overcomes the limitations of conventional micelle formulations, but without suffering from the disadvantages of triglyceride containing formulations.[14]

Advantages

1) Excellent thermodynamic stability
2) Longer shelf life
3) Higher drug solubilization capacity
4) Improvement in oral bioavailability
5) Protection against enzymatic hydrolysis

Disadvantages

1) Poor palatability due to lipid composition leads to poor patient compliance and acceptability.
2) Moreover due to their water content, microemulsions cannot be encapsulated in soft and hard gelatin. Therefore, a viable alternative for delivery of hydrophobic drug is SMEDDS.

1.2.2. Self-micro emulsifying drug delivery system (SMEDDS)

Self microemulsifying/emulsifying drug delivery systems are isotropic mixtures of oil, hydrophilic surfactant and/or a cosurfactant and a solubilized drug. They can be encapsulated in hard or soft gelatin capsules or can be converted to solid state (Solid SMEDDS/SEDDS). These formulations spontaneously form a fine oil-in-water emulsion in case of SEDDS and a microemulsion in the case of SMEDDS upon dilution with water. In the GI tract, they are readily dispersed, where the motility of the stomach and small intestine provides the gentle agitation necessary for emulsification. The basic difference between self emulsifying drug delivery systems (SEDDS) which is also called as self emulsifying oil formulation (SEOF) and SMEDDS is SEDDS typically produce opaque emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent micro emulsions with a droplet size of less than 50 nm also the concentration of oil in SMEDDS is less than 20% as compared to 40-80% in SEDDS.

When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles. SMEDDS formulation is comparatively simple. The key step is to find a suitable oil surfactant mixture that can dissolve the drug within the required therapeutic concentration. SEDDS produces coarse emulsions while SMEDDS produces droplets of size less than 100 nm. This property of SMEDDS makes them a natural choice for delivery of hydrophobic drugs that have adequate solubility in oil-surfactant blends.

SMEDDS improves the rate and extent of absorption of hydrophobic drugs, whose absorption is considered to be dissolution rate-limited. Upon aqueous

dilution the drug remains in the oil droplets or as a micellar solution since the surfactant concentration is very high in such formulations.[16,17] The drug in the oil droplet may partition out in the intestinal fluid as presented in fig.1.4.

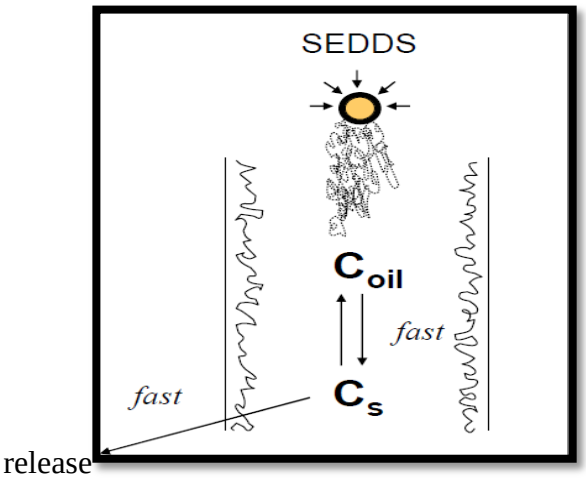

Fig 1.4: Mechanism of drug partitioning in SMEDDS

Advantages

1) SMEDDS is a novel approach to improve water solubility and ultimate bioavailability of drugs for which water is a rate-limiting step. The SMEDDS have the ability to present the drug to GIT in 100 nm globule size and subsequent increase in specific area enables more efficient drug transport through the intestinal aqueous boundary layer leading to improvement in bioavailability.
2) Many drug show large inter-subject and intra-subject variation in absorption leading to fluctuation in plasma profile. Food is major factor affecting therapeutic performance of the drug in the body. SMEDDS produce reproducible plasma profile.
3) Fine oil droplets empty rapidly from the stomach and promote wide distribution of the drug through the intestinal tract and thereby minimizing irritation frequently encountered with extended contact of drugs and gut wall.[15, 16]
4) Ease of manufacture and scale up is one of the most important advantages that make SMEDDS unique, when compared to other drug delivery system like solid dispersion, liposomes, nanoparticles, etc; dealing with improved

bioavailability. SMEDDS require very simple and economical manufacturing facility like mixer with agitator and volumetric liquid filing equipment for large-scale manufacturing.

5) SMEDDS has potential to deliver peptides that are prone to enzymatic hydrolysis in GIT.
6) When polymer is incorporated in the composition of SMEDDS, it provides prolonged release of medicaments.
7) Enhanced oral bioavailability enables reduction in dose of the drug.
8) Selective targeting of drugs towards specific absorption window in GIT.

Table 1.3: A comparative account of formulation of SEDDS and SMEDDS

SEDDS	SMEDDS
Can be a simple binary formulation with the drug and a lipidic excipient able to self-emulsifying in contact with gastrointestinal fluids (GIF) or A system comprising drug, surfactant and oil (also referred to as lipid phase).	Are composed of the drug compound, surfactant, co-surfactant and oil (or lipid phase).
SEDDS and SMEDDS form a fine oil-in-water dispersion in contact with GIF	
Lipid droplet size in the dispersion ranges from 200 nm - 5μm providing a large surface area for absorption. The dispersion has a turbid appearance.	Lipid droplet size in the dispersion is $<$200 nm providing a large surface area for absorption. The dispersion has an optically clear to translucent appearance.
SEDDS and SMEDDS have high solubilizing capacity high dispersibility capacity	
-SEDDS systems are not thermodynamically stable in water or physiological conditions. -Developed / optimization of SEDDS may require the development of ternary phase diagrams.	-SMEDDS systems are thermodynamically stable in water or physiological condition. -Pseudo-ternary phase diagram are required to optimize SMEDDS.
SEDDS and SMEDDS formulations can be prepared as liquid and semi-solid for capsule dosage forms and solid dosage forms for tabletting	

1.2.2.1 Application of SEDDS/SMEDDS formulation

Improvement of oral absorption: SMEDDS partially avoids the additional drug dissolution step prior to absorption in the GI tract. They increase the amount of solubilized drug in the intestinal fluids resulting in good drug absorption.[18] Apart from this, absorption of the drug may also be enhanced by using lipid based excipients in the formulation. There are several mechanisms through which increased absorption can be achieved. The schematic diagram describing these mechanisms of drug absorption from lipid based formulation is represented in fig.1.5.

Retardation of gastric emptying time: Surfactants are believed to play a role in retardation of gastric transit time, thereby increasing the time available for the drug to dissolve and get absorbed. Surfactants may slow down gastric emptying for a period of time by formation of viscous mass in the gastric and intestinal lumen. Labrasol (a caprylocaproyl macrogolglyceride) was shown to improve bioavailability of an investigational compound by retarding gastric emptying time.[21]

Increase in effective drug solubility in lumen: When exogenous lipid excipients are encountered in the gastric environment, they are digested by gastric lipases. Triglycerides are digested to di-glycerides and fatty acids. The duodenum secretes bile salts, Phosphatidylcholine (PL) and Cholesterol (Ch) from the gall bladder and pancreatic lipases from pancreas. These agents in combination with lipid digestion products get adsorbed to the surface of emulsion droplet and transform into small, stable droplets.

They also produce a series of colloidal particles such as micelles, mixed micelles and vesicles as given in fig.1.5. The drug contained in the oil droplet partitions into these micellar structures making them a drug reservoir at the absorption site. This results in an increased solubilization capacity of the drug in the GI tract. This capacity is dependent on the type (medium chain or long chain triglycerides) and quantity of the lipids, presence of additional lipid

excipients such as surfactants and cosurfactants and the level of endogenous BS and PL present.[22] The micelles and nanoemulsions can be absorbed through following mechanisms: pinocytosis, diffusion or endocytosis.[38] The partition of the drug from the oil droplets depends on their size and polarity. Nano sized droplets will result in faster partitioning since the drug can diffuse faster from smaller droplets.[23] In case of SMEDDS, it has been shown that digestion on the resultant microemulsion acts independently of bile salts and the polarity on the oil droplets is not significant because the drug reaches the capillaries within the oil droplets.[19]

Lymphatic transport of the drug: Most of the drugs delivered using SMEDDS are absorbed systematically via portal vein except for certain type of drugs. Lymphatic transport of the drug occurs when the drug is highly lipophilic (log P>5) and indicated high solubility in triglycerides (>50mg/ml).[37] Such drugs are absorbed via lymph vessels in the intestine which are responsible for absorption of lipids. Since the drug is cleared by the lymph vessels, they bypass the liver metabolism. This results in an increased bioavailability of these drugs. The bioavailability of Ontazolast, an extensively first-pass metabolized drug was improved when delivered in a lipid based formulation. The drug was absorbed via lymphatic pathway and thus, bypassed first-pass metabolism.[24]

Enterocyte based drug transport: Few endogenous lipid transporters have been identified which are responsible for intestinal passage of lipophilic drugs. At low lipid concentrations drugs are actively transported, while at high lipid concentrations drugs are passively permeated. P-glycoprotein (P-gp) is an efflux transporter present in enterocytes that acts as a substrate for many lipophilic drugs. Surfactants are reported to inhibit these P-gp efflux transporters resulting in an increase in permeability of poorly permeated drugs.[20] Labrasol was identified as the most effective surfactant in inhibiting the P-gp.

Improvement in membrane permeability: Lipids are responsible for

causing fluidization of intestinal cell membrane and opening of tight junctions resulting in increased membrane permeability. Labrasol has a dual property of increasing membrane permeability by both the mechanisms, while Cremphor EL and Tween 80 act by opening the tight junction barrier.[20] Surfactants also penetrate into the intestinal cell membrane and disrupt the structural organization of the membrane leading to an increased permeability.[46]

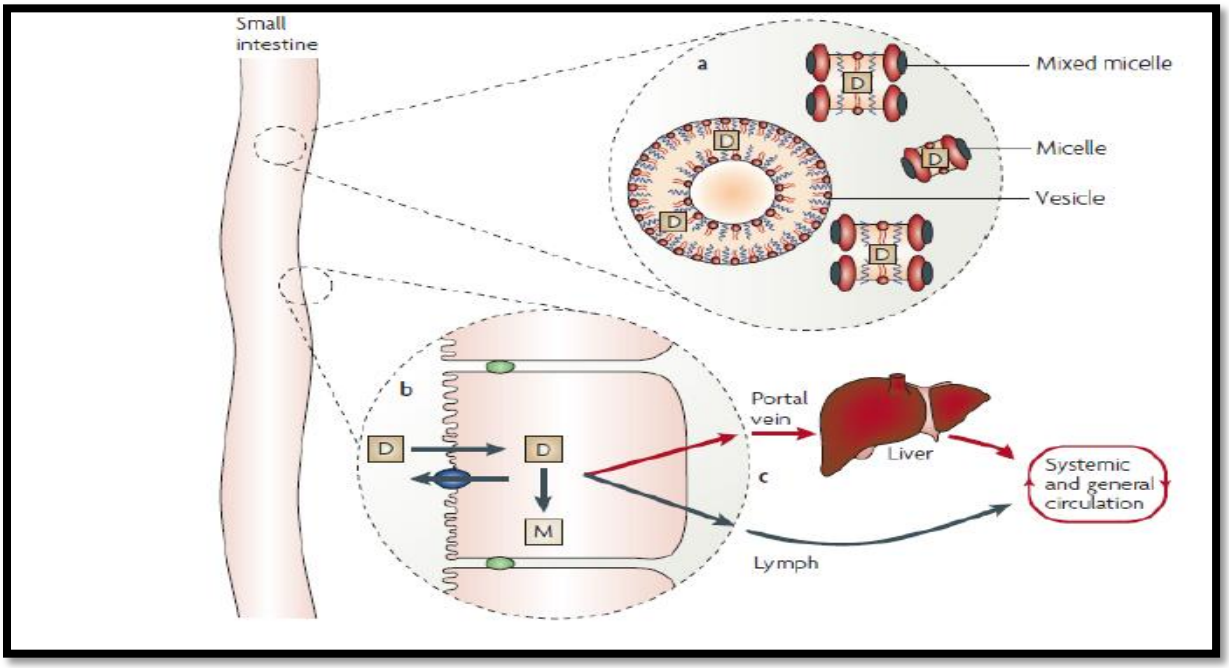

Fig.1.5: Pathways for drug absorption from lipid based formulations[31,32]

1.2.2.2 Method of formulation of SMEDDS

The method of preparing self microemulsion drug delivery system for increasing the bioavailability of a drug and/or pharmaceutical ingredient by emulsifying the drug with the self microemulsifying excipients includes various steps as described below;

1. Preparation of phase diagram
2. Solubilizing a poorly water-soluble drug and/or pharmaceutical ingredient, in a mixture of surfactant, co surfactant and co solvent. Now mix the oil phase to the

solubilized drug formulation and mix thoroughly.

3. The emulsion can then be added to a suitable dosage form such as soft or hard-filled gelatin capsules and allowed to cool.

Formulation composition

SMEDDS are composed of oil, hydrophilic surfactant and a co solvent. The process of self-emulsification is only specific to certain combinations of pharmaceutical excipients. It depends on the type of oil and surfactant pair, their ratios, the surfactant concentration and the temperature at which self-emulsification occurs. The primary step during formulation of SMEDDS is the identification of these specific combinations of excipients and construction of a phase diagram which shows various concentrations of excipients that possess self-emulsification. Mutual miscibility of these excipients is also important for producing a stable liquid formulation. Long chain triglycerides (LCT) are usually immiscible with hydrophilic surfactants and cosolvents. Polar oils such as mixed glycerides show an affinity towards hydrophilic surfactants and thus, are miscible with the surfactant and also aids in self-dispersion of the formulation. The diversity of chemical nature of lipids used may lead to immiscibility on long-term storage, so it is essential to perform physical stability tests on the formulation. If a waxy excipient is used, they should be melted before weighing and then mixed with other liquid excipients.[14]

Drug incorporation

Poorly water soluble drugs are often a choice for SMEDDS based dosage form. It is essential that the therapeutic dose of the drug be soluble in an acceptable volume of self-emulsifying mixture. The use of newer synthetic oils that are amphiphilic in nature can dissolve large quantities of the drug when compared to conventionally used pure vegetable oils or its derivatives. Surfactants also provide good solvency for the drug. Although, the cosolvent is capable of dissolving a large quantity of the drug, they may cause drug precipitation on aqueous dilution due to loss of solvent capacity. This necessitates performing

equilibrium solubility measurements of the drug in the excipients under use.

The drug may affect the self-emulsification efficiency by changing optimal oil/surfactant ratio. It may interact with the Liquid Crystalline (LC) phase of some of the mixture components causing blockage of charge movement through the system[24] or may penetrate the surfactant monolayer.[25] The incorporated drug may increase or decrease the self-emulsifying efficiency or may not affect it at all.[26,27] Hence, SMEDDS should also be evaluated for its self-emuslification efficiency in the presence of the drug. SMEDDS are known to be more sensitive towards any changes in the ratio of excipients.[28] Because of these reasons, pre-formulation solubility and phase diagrams should be thoroughly evaluated when choosing the optimized formulation.

1.2.2.3 Mechanism of self-emulsification

Conventional emulsions are formed by mixing two immiscible liquids namely water and oil stabilized by an emulsifying agent. When an emulsion is formed surface area expansion is created between the two phases. The emulsion is stabilized by the surfactant molecules that form a film around the internal phase droplet. In conventional emulsion formation, the excess surface free energy is dependent on the droplet size and the interfacial tension. If the emulsion is not stabilized using surfactants, the two phases will separate reducing the interfacial tension and the free energy.[29]

In case of SMEDDS, the free energy of formation is very low and positive or even negative which results in thermodynamic spontaneous emulsification. It has been suggested that self emulsification occurs due to penetration of water into the Liquid Crystalline (LC) phase that is formed at the oil/surfactant-water interface into which water can penetrate assisted by gentle agitation during self-emulsification. After water penetrates to a certain extent, there is disruption of the interface and a droplet formation. This LC phase is considered to be responsible for the high stability of the resulting microemulsion against coalescence.[30, 31] Self emulsification

occurs, when the entropy change occurs**,** dispersion is greater than the energy required to increase the energy required to increase the surface area of the dispersion.[25] The free energy of conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by the following equation.

$$\delta G = Ni\ \delta\ ri^2\ \delta$$

where,

δG is the free energy associated with the process (ignoring the free energy of mixing)

N is the number of droplets of radius r,

δ is interfacial energy with time

The two phases of the emulsion will tend to separate, in order to reduce the interfacial area and subsequently, the free energy of the system. Therefore, the emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents, which form a monolayer around the emulsion droplets and hence, reduce the interfacial energy, as well as providing a barrier to coalescence.[32]

On the other hand, emulsification occurs spontaneously with SEDDS because the free energy required to form emulsion is either low or positive or negative hence, the emulsion process occurs spontaneously. Moreover presence of drug may alter the emulsion characteristics, probably by interacting with LC phase.

1.2.2.4 Selection of excipients for lipid based formulations

Chemically, lipids are considered as one of the most versatile excipient class available today. There are various subcategories of lipids available and there is a constant influx of new lipid based excipients in the market. It provides

flexibility to the formulator in terms of selecting suitable excipients, but at the same time the formulator should be cautious while selecting a particular excipient. Pouton C.W. *et al*., described few factors that should be considered while selecting a lipid excipients. They are as follows

1. Regulatory issues related to irritancy, toxicity
2. Solvent capacity
3. Miscibility
4. Morphology at room temperature
5. Self- dispersibility
6. Digestibility and fate of digested products
7. Capsule compatibility
8. Purity and chemical stability and
9. Cost

a. Oil phase

Oil phase play a critical role in SMEDDS because it is responsible for solubilisation of the hydrophobic drug, aiding in self-emulsification and moreover contributes to the intestinal lymphatic transport of the drug. The emulsification property of the oil is said to be dependent on the molecular structure of the oil. Oils used in self-dispersing systems can be classified into following categories.

Triglyceride vegetable oils

They are easily ingested, digested and absorbed presenting no safety issues. Depending on the vegetable source, they can have different proportions of long chain triglycerides (LCT) and medium chain triglycerides (MCT). Generally vegetable oils are rich in unsaturated LCT with the exception of coconut oil and palm kernel oil which are rich in saturated MCT. They are highly lipophilic and their effective concentration of ester group determines its solvent capacity. MCT's are preferred over LCT's in lipid based drug delivery owing to its good solvent capacity and resistance to oxidation. Vegetable oils are not widely used in SEDDS because of their poor solubility for the hydrophobic drug and due to poor self dispersing property.

Vegetable oils derivatives

Popular vegetable oil derivatives are hydrogenated vegetable oil, mixed glycerides, Polyoxylglycerides, Ethoxylated glycerides and esters of fatty acids with various alcohols. Hydrogenated vegetable oils are produced by hydrogenation of the unsaturated bonds present in the oil.

Usually vegetable oils are hydrogenated before they are transformed into their derivatives since hydrogenation increases chemical stability. Examples of such oils are hydrogenated cottonseed oil 10 (Lubritab), hydrogenated palm oil (Dynasan), hydrogenated castor oil (Cutina HR) and hydrogenated soybean oil (Lipo).[34]

Mixed partial glycerides

They are formed by partial hydrolysis of triglycerides present in the vegetable oil resulting in a mixture of mono-, di- and tri-glycerides. The physical state, melt characteristics and the HLB of the partial glycerides depend on the nature of the fatty acid present and the degree of esterification. Glycerides with medium chain or unsaturated fatty acids are used for improving bioavailability, while ones with saturated long chain fatty acids are used for sustained-release purposes.[35] Examples of glycerides with medium chain fatty acids are Glyceryl monocaprylocaprate (Capmul MCM) and ones with long chain fatty acids are Glyceryl monoleate (Peceol) and Glyceryl monolinoleate (Maisine 35-1).

Polyoxylglycerides / Macrogolglycerides

They are formed by polyglycolysis of vegetable oil (hydrogenated or non hydrogenated) with Polyethylene glycols (PEG) of a particular molecular weight. It has a fixed composition of a mixture of mono-, di- and tri-glycerides and mono and diesters of PEG. They are readily dispersible in water making them a good choice for SEDDS. Like Glycerides, they may be composed of unsaturated long chain fatty acids such as Oleyl Polyoxylglycerides (Labrafil 1944 CS) and Linoleyl polyoxylglycerides (Labrafil M 2125CS) or medium chain fatty acids such as Caprylocaproyl polyoxylglycerides (Labrasol) and Lauroyl polyoxylglycerides (Gelucire 44/14).

Ethoxylated glycerides

They are formed from ethoxylation (etherification) of Ricinoleic acid (present in glyceride) of Castor oil. This reaction makes the oil hydrophilic. Examples of such glycerides are Ethoxylated castor oil (Cremphor EL) and Ethoxylated hydrogenated castor oil (Cremophor RH40 and Cremophor RH 60). Because of its amphiphilic nature, Cremophor are widely used as surfactants in the formulation of SEDDS.

Moreover, they can dissolve large quantities of drugs, have good self-emulsification property and their degradation products are similar to those obtained from intestinal digestion.[36, 37]

Polyalcohol esters of fatty acids

These are newer oil derivatives that possess surfactant properties because of its amphiphilic nature and are effective in replacing conventionally used oils.[37] Their composition is based on nature of alcohol used. They can be Polyglycerol (Plurol Oleique CC 497), Propylene glycol (Capryol) and Polyoxyethylene glycol (Mirj).

b. Surfactants

Surfactants are surface active molecules which concentrate at the oil-water interface and stabilize the internal phase in an emulsion. Surfactants are critical components of SMEDDS systems since they are responsible for forming a stable emulsion upon aqueous dilution. Nonionic surfactants are commonly used in this type of formulation. Proper selection of the surfactant is based on its Hydrophilic Lipophilic Balance (HLB) value and safety considerations. Nonionic surfactants with high hydrophilicity are required for SEDDS. A surfactant with an HLB value of more than 12 is necessary in SMEDDS to spontaneously form a fine oil-in-water microemulsion when dispersed in the GI tract fluids. Surfactants used in lipid based drug delivery are usually Polyethoxylated lipid derivatives. These lipids can be fatty acids, alcohols or glycerides which are linked to a certain number of repeating Polyexthylene oxide units through ester linkage (fatty acids and glycerides) and ether linkage (alcohols). The polyethylene groups provide hydrophilic characteristics to the surfactant. Examples of such surfactants are Polyethoxylated fatty acid ester (Myrj and Solutol HS 15), Polyethoxylated alkyl ethers (Brij), Polyethoxylated sorbitan esters (Tweens) and Polyethoxylated glycerides (Cremphor, Labrasol).[38] The most commonly used surfactants in SMEDDS are Tweens, Cremophors and Labrasols. Block copolymers such as Pluronics have also been used in SEDDS.[39] Emulsifiers of natural origin

are preferred due to safety considerations but are not widely used because of their poor self emulsification property.[37]

Non ionic surfactants are less toxic and possess good emulsion stability over wider range of ionic strength and pH than ionic surfactants[40], but may cause changes in intestinal lumen permeability.[41] The surfactant concentration necessary to form a stable SMEDDS ranges from 30% w/w to 60% w/w.[42] The least possible surfactant concentration should be used so as to prevent gastric irritation. Extremely small droplet size produced in case of SMEDDS promotes rapid gastric emptying and low local concentration of surfactant, thereby reducing the gastric irritation.[43] The surfactant concentration is shown to have varied effects on emulsion droplet size. Increase in surfactant concentration causes a decrease in droplet size associated with stabilization of surfactant molecules at the oil-water interface[44], while the reverse is possible due to enhanced water penetration into oil droplets leading to breakdown of oil droplets.[45] The surfactants being amphiphilic can dissolve large quantities of the hydrophobic drug. They can contribute to the total solubility of the drug in SMEDDS, thus, preventing drug precipitation upon aqueous dilution and keep the drug in solubilised state in GI tract for further absorption.[44]

c. Cosolvents

Water soluble cosolvents are widely used in lipid based dosage forms. Ethanol, Polyethylene glycol (PEG), Propylene glycol and Glycerol are examples of cosolvents used. Their role is;

a. To increase the solvent capacity of the drugs which are freely soluble in them. But this is associated with the risk of drug precipitation when SMEDDS are dispersed in water.
b. To dissolve large quantities of the hydrophilic surfactant in the oil. SMEDDS requires use of high concentration of surfactants to ensure proper dispersion of the formulation,
c. To increase the stability of microemulsion by wedging themselves between surfactant molecules.[46]

There are several key issues that have to be considered before using a particular cosolvent. The cosolvents are miscible with the oil only up to a certain limit. There are some incompatibilities of using alcohol since it may penetrate into soft and hard gelatin shell causing precipitation of the drug.

The commertial names of surfactant, co surfactant, co solvents and lipid ingredients in commercial products in which they are used are depicted in table 1.4

1.2.3 Solid self-microemulsifying drug delivery system (S-SMEDDS)

SMEDDS can exist in either liquid or solid states. SMEDDS are usually, limited to liquid dosage forms, because many excipients used in SMEDDS are not solids at room temperature. Given the advantages of solid dosage forms, S-SMEDDS have been extensively exploited in recent years, as they frequently represent more effective alternatives to conventional liquid SMEDDS. From the perspective of dosage forms, S-SMEDDS mean solid dosage forms with self-emulsification properties.

S-SMEDDS focus on the incorporation of liquid/semisolid SE ingredients into powders/nanoparticles by different solidification techniques (e.g. adsorptions to solid carriers, spray drying, melt extrusion, nanoparticles technology and so on). Such powders/nanoparticles, which refer to SE nanoparticles/dry emulsions/solid dispersions are usually further processed into other solid SE dosage forms, or, alternatively, filled into capsules (i.e. SE capsules). SE capsules also include those capsules into which liquid/semisolid SEDDS are directly filled without any solidifying excipient. S-SMEDDS are combinations of SMEDDS and solid dosage forms, so many properties of S-SMEDDS (e.g. excipients selection, specificity and characterization) are the sum of the corresponding properties of both SMEDDS and solid dosage forms. For instance, the characterizations of SE pellets contain not only the assessment of self emulsification, but also friability, surface roughness and so on.[47-50]

1.2.3.1 Carriers used for conversion of liquid SMEDDS into S-SMEDDS

Following carriers used for conversion of liquid SMEDDS into S-SMEDDS[49]

- Magnesium hydroxide
- Talcum
- Crospovidone
- Cross linked sodium carboxymethyl cellulose
- Cross linked polymethyl methacrylate
- Microporous calcium silicate (Florite® RE)
- Magnesium aluminum silicate (Neusilin® US_2)
- Silicon dioxide (Sylysia® 320)

1.2.3.2 Techniques for conversion of liquid SMEDDS to solid SMEDDS

Solid SMEDDS also offers added versatility in terms of possible dosage forms. The following description elaborates various liquid to solid SMEDDS conversion techniques;

a. Spray drying: Spray drying is the most widely used technique to convert liquid SEDDS into solid state. In this method the liquid SMEDDS is mixed with a solid carrier in a suitable solvent. The solvent is then atomized into a spray of fine droplets. These droplets are introduced into a drying chamber, where the solvent gets evaporated forming dry particles under a controlled temperature and airflow conditions.[51] The process parameters required to be controlled are inlet and outlet temperature, feed rate of solvent and aspiration and drying air flow rate. The dry particles can then be either filled into capsules or made into tablets after addition of suitable excipients. Various solid carriers that have been used for this purpose are: Aerosil 200 suspended in ethanol[48] and aqueous solution of Dextran 40.[52]

b. Adsorption: The liquid SMEDDS can be made to adsorb onto free flowing powders that possess very large surface area and are capable of adsorbing high quantities of oil material. The adsorption can be performed either by mixing Liquid SMEDDS and the adsorbent in a blender or by simple physical mixing. Adsorption is simple and just requires addition of liquid to solid.[64] The resulting powders can be either filled into capsules or can be made into tablets after addition of appropriate excipients. The adsorbents are capable of adsorbing liquid SEDDS up to 70% w/w of its own weight. Solid carriers used for this purpose can be microporous

inorganic substances, high surface area colloidal inorganic substances or cross-linked polymers.[51] Categories of solid adsorbents used are: Silicates, Magnesium tri silicate, Talcum, Crospovidone, cross-linked Sodium carboxymethyl cellulose and cross-linked Polymethyl methacrylate.[53]

c. Encapsulation: It is one of the simplest techniques for conversion of liquid SMEDDS to solid oral dosage form. Liquid SMEDDS can be simply filled in capsules, sealed using a microspray or a banding process. For semisolid SMEDDS, it is a four step process;

1. Heating the semisolid excipients to at least 20°C above its melting point.
2. Adding the drug in the molten mixture while stirring.
3. Filling the drug loaded molten mixture into the capsule shell.
4. Cooling the product to room temperature.

The compatibility of the excipients used with the capsule shell should be well investigated. Lipid excipients compatible with the capsule shell are described in the work by Cole *et al.*[53] Capsule filling of SMEDDS is suitable for low dose highly potent drugs and allows high drug incorporation.[51] The pellets are then dried and size separated. The relative quantity of water and liquid SMEDDS used in the process has an effect on size distribution, extrusion force, surface roughness of pellets and disintegration time. High drug incorporation can be achieved by using this technique.

d. Extrusion spheronization: This is a solvent free technique that converts liquid SMEDDS into pellets using extrusion and spheronization processes. In this method the Liquid SMEDDS is first mixed with a binder, followed by addition of water until the mass is suitable for extrusion. The extruded mass is then spheronized to form uniform sized pellets. The pellets are then dried and size separated. The relative quantity of water and liquid SEDDS used in the process has an effect on size distribution, extrusion force, surface roughness of pellets and disintegration time. High drug incorporation can be achieved by using this technique.[49]

e. Melt granulation: Melt granulation is another solvent free technique for converting liquid SMEDDS. In this method, liquid SMEDDS is mixed with a binder that melts or softens at relatively low temperature. This melted mixture can be granulated. This technique is advantageous since it does not require addition of a liquid binder and subsequent drying unlike conventional wet granulation. The variables to be controlled in this process are impeller speed, mixing time, binder particle size and the viscosity of the binder.[51] A mixture of mono-, di- and tri glycerides and esters of Polyethylene glycol (PEG) called as Gelucire are used as binders to prepare immediate release pellets by melt granulation and as a self-emulsifying drug delivery system by capsule moulding or as powder obtained by cryogenic grinding.[54]

1.2.3.3 Dosage forms of solid SMEDDS

Various dosage forms of S-SMEDDS are as listed below;

a. Dry emulsions: Dry emulsions are powdered solid dosage forms which spontaneously emulsify with the addition of water. Dry emulsions could be obtained by emulsifiable glass system, freeze dying and spray drying. Lipid based surfactant free emulsifiable glass system was developed by Myers *et al.,*[55] in this method a poorly water soluble drug dissolved in a vegetable oil is mixed with aqueous solution of Sucrose. The mixture is then evaporated under vacuum producing dry foam. This dry foam produces an emulsion when added to water.

b. Capsules: Solid SMEDDS prepared by various techniques mentioned above can be filled into capsule shells. This prevents physical incompatibility of liquid SMEDDS with the capsule shell. If semi-solid excipients are used in the formulation, they are first melted and then filled into capsules. Contents of the capsule then solidify at room temperature.

c. Tablets: Nazzal *et al.,*[56] formulated eutectic based self-emulsifying tablets in which irreversible precipitation of the drug within the formulation was inhibited. A eutectic forming combination of a drug and suitable semi-solid oil was

used in the formulation. Using the melting point depression method the oil phase containing the drug melts at body temperature producing emulsion droplets in the nanometer size range.

d. Solid dispersions: Availability of self-dispersing waxy semi-solid excipients has reduced the manufacturing and stability problems associated with solid dispersions. Excipients such as Gelucire 44/14 and Gelucire 50/02 are used for this purpose. These are semisolid excipients which can be directly filled into capsules in a molten state. Gelucire's have high surface activity which enhances dissolution of poorly water soluble drugs.. The bioavailability of an investigational compound was reported to have enhanced using Gelucire 44/14 relative to its conventional PEG based formulation.[57]

e. Beads: Patil *et al.,* used porous polystyrene beads for delivering self-emulsifying formulations. The formulation is incorporated into microchannels of the bead through capillary action. The beads were prepared by copolymerizing Styrene and Divinyl benzene .[58]

f.. Microspheres: Sustained release microspheres of Zedoary turmeric oil (traditional Chinese medicine) were prepared by a quasi-emulsion-solvent-diffusion method using Hydroxypropyl methyl cellulose acetate succinate and Aerosil 200.[59]

g. Nanoparticles: Self-emulsifying nanoparticles can be formulated using solvent injection technique, wherein the excipients and drug are melted together and injected into a non-solvent solution. Self-emulsifying nanoparticles of drugs were prepared using goat fat and Tween 65 using this method.[60] Glyceryl mono oleate (GMO) which has self-emulsifying property was used along with chitosan for preparation of Paclitaxel nanoparticles. Chitosan was responsible for bioadhesion of nanoparticles, while 100% drug incorporation was achieved because of self-emulsifying property of GMO.[61]

h. Implants: Self-emulsified 1, 3-Bis (2-chloroethyl)-1-nitrosourea (Carmustine,

BCNU) was incorporated into PLGA and used as an implant. The SEDDS formulation retarded the exposure of BCNU from the aqueous media and thus, improved its stability and shelf-life. The formulation comprised of Tributyrin, Cremophor RH 40, Labrafil 1944 and BCNU.[62]

i. Suppositories: Glycyrrhizin self-emulsifying suppositories were formulated using C6-C18 fatty acid glycerol ester and C6-C8 fatty acid macrogol ester. The formulation demonstrated good drug absorption as indicated by high plasma drug levels when delivered via rectal/vaginal route.[63]

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