INTRODUCTION

An overview of self emulsifying drug delivery system:

The concept of drug delivery system has emerged to minimize the toxic side effects of drug, to broaden their application, to expand modes of their administration and to solve absorption problems.. solubilization, encapsulation, and delivery of these drugs using lipid based and biocompatible systems are likely to furnish better absorption, by way of lower dose, reduced frequency of administration, and improved therapeutic index( Tenjarala S et.,al 1999).

Efforts are ongoing to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy. The most popular approach is the incorporation of the active lipophilic component into inert lipid vehicles (B.J. Aungst et al.,1993), such as oils surfactant dispersions (B.J. Aungst et al.,1994) self-emulsifying formulations, emulsions and liposomes (R.A. Schwendeneret al., 1996), with every formulation approach having its special advantages and limitations. .poor aqueous solubility leading to low absorption after in vivo administration. A part of the administered dose is absorbed and reaches the pharmacological site of action and remainder causes toxicity and undesirable side effects due to unwanted bio distribution. Enhancement in drug efficacy and lowering of drug toxicity could be achieved through encapsulation and delivery the drug in lipid based delivery system.

liposomes, niosomes, microemulsion, organogels and nanocapsules have been explored and they have emerged as prospective system for drug delivery. These self organizing systems often lead to improvement in the therapeutics index of the lipophilic drugs through increased solubilization and modification of their pharmacokinetic profiles. For fruitful uses of this system in pharmacy, tolerance towards additives, stability over wide temperature range, low viscosity, small size biodegradability, and easy elimination from the body are some of the essential criteria. Also, the size of the encapsulated particles needs to be controlled to avoid capillary blockage and hence submicron-sized entities are preferred. Development, characterization and biological studies on “biocompatible micro emulsion” have become a thrust area of research as they satisfy most of the required criteria. Development characterization and biological studies on “biocompatible micro emulsion ”as potential vehicles for drug delivery ( Kreilgaard M, et al.,2000) has become thrust area of research as they satisfy most of the required criteria (Moreno MA, et al.,2001).
Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation. Recently, SEDDS have been formulated using medium chain tri-glyceride oils and nonionic surfactants, the latter being less toxic. Upon peroral administration, these systems form fine emulsions (or micro-emulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility. Potential advantages of these systems include enhanced oral bioavailability enabling reduction in dose, more consistent temporal profiles of drug absorption, selective targeting of drug(s) toward specific absorption window in GIT, and protection of drug(s) from the hostile environment in gut. (Patil P, et al., 2004)

The process of self-emulsification proceeds through formation of liquid crystals (LC) and gel phases. Release of drug from SEDDS is highly dependent on LC (liquid crystal) formed at the interface, since it is likely to affect the angle of curvature of the droplet formed and the resistance offered for partitioning of drug into aqueous media (A.T.M. Serajuddin, et al., 1988). Effect of LC will be more prominent for semisolid or solid SEDDS because LC phases are formed in-situ, and the drug diffuses through LC phases into aqueous media. In the present topic, focus will be on lipid based drug delivery systems (e.g. Self-Emulsifying Drug Delivery systems (SEDDS)). Emulsion particles can be of either micro- or nano- size, depending on the composition of the system. These formulations circumvent the dissolution step in the gastro-intestinal tract, but are still dependent on digestion.

1.1 NEED OF SEDDS:
Oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and fill the formulation into capsules. The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used (e.g. polyethylene glycol). If the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favor the drug remaining in the lipid droplets. (Amidon, G., et.al. 1995)
Another strategy for poorly soluble drugs is to formulate in a solid solution using a water-soluble polymer to aid solubility of the drug compound. For example, polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG 6000) have been used for preparing solid solutions with poorly soluble drugs. One potential problem with this type of formulation is that the drug may favor a more thermodynamically stable state, which can result in the compound crystallizing in the polymer matrix. Therefore the physical stability of such formulations needs to be assessed using techniques such as differential scanning calorimetry or X-ray crystallography. In this type of case SEDD system is a good option.

Potential advantages of these systems include;
1. Enhanced oral bioavailability enabling reduction in dose,
2. More consistent temporal profiles of drug absorption,
3. Selective targeting of drug(s) toward specific absorption window in GIT,
4. Protection of drug(s) from the hostile environment in gut.
5. Control of delivery profiles
6. Reduced variability including food effects
7. Protective of sensitive drug substances
8. High drug payloads
9. Liquid or solid dosage forms

1.2. MECHANISM OF SELF-EMULSIFICATION:
The process by which self-emulsification takes place is not yet well understood. However, according to Reiss, self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. In addition, the free energy of a 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 equation.
\[ \Delta G = \sum_i N_i \pi r_i^2 \sigma \]

Where, \( G \) is the free energy associated with the process (ignoring the free energy of mixing), \( N \) is the number of droplets of radius, \( r \), and \( \sigma \) represents the 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 systems.

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. In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low and positive, or negative (then, the emulsification process occurs spontaneously). Emulsification requiring very little input energy involves destabilization through contraction of local interfacial regions. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing (T. Dabros, et al., 1999). In earlier work, it was suggested that the ease of emulsification could be associated with the ease by which water penetrates into the various LC or gel phases formed on the surface of the droplet. The addition of a binary mixture (oil/nonionic surfactant) to water results in interface formation between the oil and aqueous-continuous phases, followed by the solubilization of water within the oil phase owing to aqueous penetration through the interface. This will occur until the solubilization limit is reached close to the interface. Further aqueous penetration will result in the formation of the dispersed LC phase. As the aqueous penetration proceeds, eventually all material close to the interface will be LC, the actual amount depending on the surfactant concentration in the binary mixture. Once formed, rapid penetration of water into the aqueous cores, aided by the gentle agitation of the self-emulsification process, causes interface disruption and droplet formation. The high stability of these self-emulsified systems to coalescence is considered to be due to the LC interface surrounding the oil droplets. The involvement of the LC phase in the emulsion formation process was extensively studied. Later, (D.Q.M. Craig, et al., 1995) used the combination of particle size analysis and low frequency dielectric spectroscopy (LFDS) to examine the self-emulsifying properties of a series of Imwitor 742 (a mixture of mono- and di glycerides of capric and caprylic acids) /Tween 80 systems (D.Q.M. Craig, et al., 1995). The dielectric studies provided evidence that the formation of the emulsions may be associated with LC formation, although the
relationship was clearly complex (C.W. Pouton et al., 1985). The above technique also pointed out that the presence of the drug may alter the emulsion characteristics, possibly by interacting with the LC phase. However, the correlation between the spontaneous emulsification and LC formation is still not definitely established.

1.3. GENERAL FORMULATION APPROACH:

Preliminary studies are performed for selection of oil, which is an important and critical requisite for formulation of SEDDS. SEDDS consisted of oil, a surfactant and a co-surfactant. Solubility of drug is determined in various oils and surfactants. Prepare a series of SEDDS system containing drug in various oil and surfactant. Then, in vitro self-emulsification properties and droplet size analysis of these formulations upon their addition to water under mild agitation conditions is studied. Pseudo-ternary phase diagram is constructed, identifying the efficient self-emulsification region. From these studies, an optimized formulation is selected and its bioavailability is compared with a reference formulation. The efficiency of oral absorption of the drug compound from the SEDDS depends on many formulation-related parameters, such as surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge, all of which in essence determine the self emulsificationability. Thus, only very specific pharmaceutical excipient combinations will lead to efficient self-emulsifying systems. SMEDDS are distinguished from SEDDS by the much smaller emulsion droplets produced on dilution, resulting in a transparent or translucent solution. SMEDDS generally contain relatively high concentrations of surfactant (typically 40-60% w/w), and regularly contain hydrophilic cosolvents (e.g. propylene glycol, polyethylene glycols). They are often described as micro emulsion pre-concentrates, as the micro-emulsion is formed on dilution in aqueous media (Grove M., et al., 2004) When developing lipid based formulations the following parameters are believed to be important;

• The solubility of drug in the formulation as such and upon dispersion (for SEDDS),
• The rate of digestion (for formulations susceptible to digestion) and possibly
• The solubilization capacity of the digested formulation.
Oils:
Both long- and medium-chain triglyceride (MCT) oils with different degrees of saturation have been used for the design of self-dispersing formulations. Unmodified edible oils provide the most 'natural' basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-emulsification markedly reduce their use in SEDDS. In contrast, modified or hydrolyzed vegetable oils have contributed widely to the success of the above systems (D.J. Hauss, et al., 1998). Since they exhibit formulative and physiological advantages. These excipients form good emulsification systems, with a large number of non-ionic surfactants approved for oral administration, while their degradation products resemble the end products of intestinal digestion.

MCTs (Medium chain triglycerides) were preferred in the earlier self-emulsifying formulations (N. Farah et al., 1994). Because of higher Fluidity, better solubility properties and self-emulsification ability, but evidently, they are considered less attractive compared to the novel semi-synthetic medium chain derivatives which can be defined rather as amphiphilic compounds exhibiting surfactant properties. In such cases, the more lipophilic surfactant may play the role of the hydrophilic oil in the formulation. Solvent capacity for less hydrophobic drugs can be improved by blending triglycerides with mono- and di-glycerides.

Surfactants:
Non-ionic surfactants with a relatively high hydrophilic± lipophilic balance (HLB) were advocated for the design of self-dispersing systems, where the various liquid or solid ethoxylatedpolyglycolyzed glycerides and polyoxyethylene oleate (Tween 80) are the most frequently used excipients. Emulsifiers derived from natural sources are expected to be safer than synthetic ones and are recommended for SDLF (self dispersed lipid formulation) us (H. Yuasa, et al., 1994), despite their limited ability to self-emulsify. Non-ionic surfactants are known to be less toxic compared to ionic surface-active agents, but they may cause moderate reversible changes in intestinal wall permeability. (E.S. Swenson et al., 1994) proposed a new vehicle based on a fine emulsion using minimal surfactant content (3%) to avoid the potential toxicological problems associated with high surfactant concentration. (T. Amemiya et al., 1998) The usual surfactant concentration in self-emulsifying formulations required to form and maintain an emulsion state in the GI tract ranged from 30 to 60% w/w of the formulation. A
large quantity of surfactant may irritate the GI tract. Thus, the safety aspect of the surfactant
vehicle should be carefully considered in each case.

The high HLB and subsequent hydrophilicity of surfactants is necessary for the immediate
formation of o/w droplets and/or rapid spreading of the formulation in the aqueous environment,
providing a good dispersing/selfemulsifying performance. The surface active agents are
amphiphilic by nature, and they are therefore usually able to dissolve and even solubilize
relatively high quantities of the hydrophobic drug. The latter is of prime importance for
preventing precipitation within the GI lumen and for the prolonged existence of the drug
molecules in soluble form, which is vital for effective absorption. The lipid mixtures with higher
surfactant and co-surfactant/oil ratios lead to the formation of self-micro emulsifying
formulations (SMEDDS) (A. Meinzer et al., 1995). Formulations consisting only of the surfactant
mixture may form emulsions of microemulsions (when surfactants exhibit different low and
high HLB), micelle solution or, in some particular cases, niosomes, which are non-ionic,
surfactant-based bilayer vehicles(I.F. Uchegbu et al., 1998).

Co-solvents:
Relatively high surfactant concentrations (usually more than 30% w/w) are needed in order to
produce an effective self-emulsifying system. Organic solvents, suitable for oral administration
(ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc.) may help to dissolve large
amounts of either the hydrophilic surfactant or the drug in the lipid base. These solvents
sometimes play the role of the co-surfactant in the micro emulsion systems, although alcohol-
free self-emulsifying micro emulsions have also been described in the literature. Indeed, such
systems may exhibit some advantages over the previous formulations when incorporated in
capsule dosage forms, since alcohol and other volatile cosolvents comprised in the conventional
self-emulsifying formulations are known to migrate into the shells of soft gelatin, or hard, sealed
gelatin capsules, resulting in the precipitation of the lipophilic drug. On the other hand, the
lipophilic drug dissolution ability of the alcohol free formulation may be limited.

In SEDDS, the lipid matrix interacts readily with water, forming a fine particulate oil-in-
water (o/w) emulsion. The emulsion droplets will deliver the drug to the gastrointestinal mucosa
in the dissolved state readily accessible for absorption. Therefore, increase in AUC i.e.
bioavailability and Cmax observed with many drugs when presented in SEDDS.
1.4. SMEDDS (Self micro emulsifying drug delivery system)

Self micro emulsifying drug delivery system (SMEDDS) or self micro emulsifying oil formulation (SEOF) is defined as isotropic mixture of oil and surfactants or alternatively one or more hydrophilic solvents and co-solvents. (Wakerly M G et al., 1987 and Constantinides PP et al., 1995) Upon mild agitation followed by dilution in aqueous media such as the gastrointestinal (GI) fluid, these systems can form fine oil in water (o/w) emulsions or micro emulsions [self micro emulsifying drug delivery systems (SMEDDS)]. Self micro emulsifying formulations spread readily in the GI tract and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification (Shah NH et al., 1994) SEDDS typically produce emulsion with a droplet size between 100 and 300 nm while SMEDDS form transparent micro emulsion with a droplet size of less than 50 nm. When compared with emulsions which are sensitive and metastable dispersed forms, SEDDS and SMEDDS are physically stable formulations that are easy to manufacture. SMEDDS can be formulated to give sustained release dosage form by adding polymeric matrix, which is not ionizable at physiological pH and after ingestion in contact with GI fluid forms a gelled polymer making it possible to release the micro emulsified active agent in a continuous and sustained matter by diffusion (Amidon G L et al., 1995). Bases of self micro emulsifying system have been formulated using medium chain triglyceride oils and non-ionic surfactant which are acceptable for oral ingestion (JessyShaji). The lipophillic (poorly water soluble) drugs such as nifedipine, griseofulvin, cyclosporine, digoxin, itroconazole, carbamazepine, piroxicam, steroids, ibuprofen, diazepam, etc. are formulated in SMEDDS to improve efficacy and safety. It should be noted that water-in-oil version of SMEDDS has also been investigated. This system can be liquid but also semisolid depending on the excipient’s choice. These are traditionally designed for the oral route. These preparations can be given as soft or hard gelatin capsules for easy administration and precise dosage.

**COMPOSITION**

1) Oil
2) Surfactant
3) Co solvent / Co surfactant
4) Others components

OILS
The oil represents the most important excipient in the SMEDDS formulation. Indeed it can solubilize relevant amount of the poorly water soluble drug. Both long-chain triglyceride (LCT) and medium chain triglyceride (MCT) oils with different degrees of saturation have been used in the design of SMEDDS (N.H. Shah et al., 1994).

E.g. - Corn oil, olive oil, soybean oil, hydrolyzed corn oil.

SURFACHTANTS
Surfactant molecules may be classified based on the nature of the hydrophilic group within the molecule. The four main groups of surfactants are defined as follows,

1: Anionic surfactants
2: Cationic surfactants
3: Ampholytic surfactants
4: Nonionic surfactants

1: Anionic Surfactants, where the hydrophilic group carries a negative charge such as carboxyl (RCOO-), sulphonate (RSO3 -) or sulphate (ROSO3 -). Examples: Potassium laurate, sodium lauryl sulphate.

2: Cationic surfactants, where the hydrophilic group carries a positive charge. Example: quaternary ammonium halide.

3: Ampholytic surfactants (also called zwitterionicsurfactants) contain both a negative and a positive charge. Example: sulfo betaines.

4: Nonionic surfactants, where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene (OCH₂CH₂O). Examples: Sorbitan esters (Spans), polysorbates (Tweens).

Nonionic surfactants with high hydrophilic lipophilic balance (HLB) values are used in formulation of SMEDDS. The usual surfactant strength ranges between 30-60% w/w of the formulation in order to form a stable SMEDDS.

Surfactants having a high HLB and hydrophilicity assist the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature
and they can dissolve or solubilize relatively high amount of hydrophobic drug compounds (N.H. Shah et al., 1994).

**COSOLVENTS**

Organic solvents such as ethanol, propylene glycol (PG) and polyethylene glycol (PEG) are suitable for oral delivery and they enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in the lipid base. (Lambert G et al., 2002) These solvents can even act as co surfactants in micro emulsion systems. Alternately alcohols and other volatile cosolvents have the disadvantage of evaporating into the shells of the soft gelatin or hard sealed gelatin capsules in conventional SMEDDS leading to drug precipitation.

**OTHER COMPONENTS**

Other components might be pH adjusters, flavors, and antioxidant agents. Indeed a characteristic of lipid products, particularly those with unsaturated lipids show peroxide formation with oxidation. Free radicals such as ROO., RO., and OH can damage the drug and induce toxicity. Lipid peroxides may also be formed due to auto-oxidation, which increases with un saturation level of the lipid molecule. Hydrolysis of the lipid may be accelerated due to the pH of the solution or from processing energy such as ultrasonic radiation. Lipophilic antioxidants (e.g. α-tocopherol, propyl gallate, ascorbyl palmitate or BHT) may therefore be required to stabilize the oily content of the SMEDDS.

**1.5. FORMULATION OF SMEDDS**

Drugs with low aqueous solubility present a major challenge during formulation as their high hydrophobicity prevents them from being dissolved in most approved solvents. The novel synthetic hydrophilic oils and surfactants usually dissolve hydrophobic drugs to a greater extent than conventional vegetable oils. The addition of solvents, such as ethanol, PG and PEG may also contribute to the improvement of drug solubility in the lipid vehicle. (J.R. Crison et al., 1999)

With a large variety of liquid or waxy excipients available ranging from oils through lipids, hydrophobic and hydrophilic surfactant to water soluble co solvent, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixture which disperse to give fine colloidal emulsions. (N. Farah et al., 1994) The following should be considered in the formulation of a SMEDDS.
1: The solubility of the drug in different oil, surfactants and co solvents
2: The selection of oil, surfactant and co solvent based on the solubility of the drug
3: Preparation of the phase diagram.
4: The preparation of SMEDDS formulation by dissolving the drug in a mixture of oil, surfactant and co solvent (S. Nazzal et al., 2006).

**TERNARY DIAGRAM**
The use of pseudo ternary diagrams is not recent. This technique was mainly used to map the micro emulsion areas (composition ranges) (Denis J et al., 1988). Pseudo ternary phase diagram is used to map the optimal composition range for three key excipients according to the resulting droplet size following self emulsification, stability upon dilution and viscosity.

**CONSTRUCTION OF PHASE DIAGRAM**
A Titration method is employed to construct phase diagram. Mixture of oil with surfactant is prepared at different ratios (e.g. 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, 0:10) into different vials. A small amount of water in 5 % (w /w) increments is added into the vials. Following each water addition the mixture in vials is centrifuged for 2 to 3 minute and is incubated at 25°C for 48 hrs with gentle shaking. The resulting mixture is evaluated by visual and microscopy observation. For phase diagram the micro emulsion is the region of clear and isotropic solution (Gursoy N et al., 2003). Coarse emulsion is the region of cloudy dispersion.

**GENERAL PREPARATION METHOD OF SMEDDS**
The appropriate quantity of lipid and surfactant are melted together in a crucible at 40 to 60°C. The drug is added and stirred thoroughly. The mixture injected drop wise into a stirred solvent using a syringe fitted with an 18G needle at a stirring speed approx of 1000 rpm. The SMEDDS is filtered out from the solvent with aid of a filter paper (Whatmanno-1) and then dried for 72 hrs in desiccators (Gursoy N et al., 2003).

**MECHANISAM OF SELF EMULSIFICATION**
According to ‘Reiss’ self emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phases and can be described by the equation:

\[ DG = S N Pr^2 s \]
Where,
DG is the free energy associated with the process (ignoring the free energy of mixing),
N is the number of droplets of radius r and S represents the interfacial energy (Charman WN et al., 1997).

The two phases of emulsion tend to separate with time to reduce the interfacial area. The emulsion is stabilized by emulsifying agents who form a monolayer on emulsion droplets and hence reduce the interfacial energy as well as provide a barrier to prevent coalescence. In the case of self emulsifying systems the free energy required to form the emulsion is either very low or positive or negative (then the emulsification process occurs spontaneously). Emulsification requiring very little input energy involves destabilization through contraction of local interfacial regions (Porter CJ et al., 2001).

1.6. FACTORS AFFECTING SMEDDS:
1. CONCENTRATION OF DRUG: Drugs which are administered at very high dose are not suitable for SMEDDS unless they exhibit extremely good solubility in at least one of the components of SMEDDS, preferably lipophilic phase.
2. SOLUBILITY OF DRUG: The ability of SMEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oily phase. If the surfactant and co-surfactant contribute to a greater extent for solubilisation then there is risk of precipitation (. S. Nazzal et al., 2006).
3. POLARITY OF LIPID PHASE: The polarity of lipid phase is one of the factors that govern the release of the drug from the micro-emulsion. HLB, chain length, degree of un saturation of the fatty acid, molecular weight of the hydrophilic portion and concentration of the emulsifier govern polarity of the droplets.

1.7. ADVANTAGES OF SMEDDS
3. Selective targeting of drug(s) towards specific absorption window in GIT.
4. Protection of drug(s) from the hostile environment in gut.
5. Reduced variability including food effects.
7. Liquid or solid dosage forms.
8. In SMEDDS, the lipid matrix interacts readily with water, forming a fine particulate oil-in-water (o/w) emulsion. The emulsion droplets will deliver the drug to the gastrointestinal mucosa in the dissolved state readily accessible for absorption. Therefore increase in AUC i.e. bioavailability and C max is observed with many drugs when presented in SMEDDS.
9. Fine oil droplets empty rapidly from the stomach and promote wide distribution of drug throughout the intestinal tract and thereby minimizing irritation frequently encountered with extended contact of drugs and gut wall.
10. Ease of manufacture and scale up is one of the most important advantage that make SMEDDS unique when compared to other drug delivery system like solid dispersion, liposomes, nano particles etc.
11. SMEDDS has potential to deliver peptides that are processed to enzymatic hydrolysis in GIT.
12. When polymer is incorporated in composition of SMEDDS it gives prolonged release of medicament.
13. SMEDDS formulation is composed of lipids, surfactants and co-solvents. The system has the ability to form an oil-on-water emulsion when dispersed by an aqueous phase under gentle agitation. SMEDDS present drugs in a small droplet size and well-proportioned distribution and increase the dissolution and permeability.

Furthermore, because drugs can be loaded in the inner phase and delivered to the lymphatic system, can bypass first pass metabolism. Thus SMEDDS protect drugs against hydrolysis by enzymes in the GI tract and reduce the pre systemic clearance in the GI mucosa and hepatic first-pass metabolism.

1.8. SNEDDS(Self nano emulsifying drug delivery systems)

The advent of combinatorial chemistry and high-throughput screening has resulted in the rapid identification of many highly potent new chemical entities. Coincident with the increasing use of these technologies, however, has been a developing trend toward the identification of lead compounds with good therapeutic importance, but fail to elicit their maximum therapeutic effects because of poor aqueous solubility. While these attributes conspire to provide optimized drug-
receptor binding characteristics, they also tend to result in poor drug solubility and poor membrane permeability characteristics. As solubility and permeability are considered prerequisites to oral absorption, many of these drugs exhibit poor and variable bioavailability. (Amidon GL et al., 1995) Such drugs may be recognized by a high-dose-to-solubility ratio, and bioavailability is frequently increased by coadministration of food. (Dressman JB et al., 1998 and Horter D et al., 2004)

The oral delivery of such drugs is frequently associated with implications of low bioavailability, high intra- and inter subject variability, and lack of dose proportionality. (Bhatt PP et al., 2004) To overcome such problems, various formulation strategies are reported in the literature including the use of surfactants, cyclodextrins, solid dispersions, micronization, permeation enhancers, and lipids. (Aungust B et al., 1993)

Lipid-based formulations such as self-emulsifying drug delivery systems (SEDDS) have been shown to enhance oral absorption of lipophilic drugs. (Pouton C W et al., 2000) Although the exact mechanisms responsible for this enhanced absorption are not fully known, it is believed that factors including improved drug solubilization, increased membrane permeability, and lymphatic transport may make significant contributions. (Driscoll CM et al. 2002 and Porter CJ et al., 2007)

Self-nano emulsifying drug delivery systems are isotropic mixtures of oil, surfactant, cosurfactant, and drug that form fine oil-in-water nanoemulsion when introduced into aqueous phases under conditions of gentle agitation. (Nazzal S et al., 2002) This property renders SNEDDS a good candidate for oral delivery of hydrophobic drugs with adequate solubility in oils or oil/surfactant blends. (Jing-Ling T et al., 2007)

Because of self-emulsification in the stomach, the drug is presented as small droplets of oil (<5 μm) leading to improved drug dissolution through providing a large interfacial surface area for partitioning of the drug between the oil and GIT fluid. Other advantages include increased stability of drug molecules, and the possibility of administering the final product as gelatin capsules. For drugs subjected to dissolution rate-limiting absorption, SNEDDS presents a possibility for enhancement in both the rate and extent of drug absorption and the reproducibility of the plasma concentration profile. (Wei L et al., 2005 and Arida AI et al., 2007)
An example of a commercially available SEDDS is cyclosporine, Neoral, resulted in a twofold increase in its bioavailability in humans compared with other cyclosporine formulations. (Mueller EA et al., 1994) Selection of a suitable self-emulsifying formulation depends upon the assessment of the solubility of the drug in various components and the droplet size distribution of resultant emulsion following self-emulsification. (Kommuru T et al., 2001).

1.9. HYPERLIPIDEMIA

Lipid profile or lipid panel, is the collective term given to the estimation of, typically, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides. An extended lipid profile may include very low-density lipoprotein. This is used to identify hyperlipidemia (various disturbances of cholesterol and triglyceride levels), many forms of which are recognized risk factors for cardiovascular disease and sometimes pancreatitis.

Hyperlipidemia a broad term, also called hyperlipoproteinemia, is a common disorder in developed countries and is the major cause of coronary heart disease. It results from abnormalities in lipid metabolism or plasma lipid transport or a disorder in the synthesis and degradation of plasma lipoproteins. The term “dyslipidaemia” now a days is increasingly being used to describe abnormal changes in lipid profile, replacing the old term hyperlipidaemia. Hyperlipidemia means abnormally high levels of fats in the blood. These fats include cholesterol and triglycerides. These are important for our bodies to function but when they are high, they can cause heart disease and stroke. Hyperlipidemia is manifested as hypercholesterolemia and/or hyper triglycerolemia. However, hypercholesterolemia is the most common hyperlipidemia. The lipids that are involved in hypercholesterolemia are cholesterol, an essential component of cell membrane and a precursor of steroid hormone synthesis and triglycerides, an important energy source. They are transported in blood as lipoproteins. The consequence of hyperlipidaemia is that with time it can cause atherosclerosis, and thus the risk of coronary heart disease and stroke is increased. However, according to the newer scientific view, the cholesterol level alone is not the whole story. The risk of heart disease in future also depends on many other factors that influence the health of a person’s blood vessels and circulation.
Causes of Hyperlipidemia

Mostly hyperlipidemia is caused by lifestyle habits or treatable medical conditions. Lifestyle habits include obesity, not exercising, and smoking. Medical diseases that may result in hyperlipidemia are diabetes, kidney disease, pregnancy, and an under active thyroid gland. One can also inherit hyperlipidemia. The cause may be genetic if a patient has a normal body weight and other members of his/her family have hyperlipidemia. One has a greater chance of developing hyperlipidemia if he/she is a man older than age 45 or a woman older than age 55. If a close relative had early heart disease, there is also an increased risk of this disease [7]. Common secondary causes of hypercholesterolemia are hypothyroidism, pregnancy, and kidney failure. Common secondary causes of hypertriglyceridemia are diabetes, excess alcohol intake, obesity, and certain prescription medications.

Table 1: Types of hyperlipidemia

<table>
<thead>
<tr>
<th>Type</th>
<th>I</th>
<th>IIa</th>
<th>IIb</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>N, &gt;&gt;</td>
<td>&gt;&gt;</td>
<td>N, &gt;&gt;</td>
<td>N, &gt;</td>
<td>N, &gt;&gt;</td>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
<td>&gt;</td>
<td>N</td>
<td>&gt;&gt;</td>
<td>N, &gt;&gt;</td>
<td>&gt;&gt;</td>
<td>&gt;&gt;</td>
</tr>
<tr>
<td>Lipoprotein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chylomicron</td>
<td>&gt;</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>&gt;&gt;</td>
</tr>
<tr>
<td>VLDL</td>
<td>N, N, &lt;&lt;</td>
<td>&lt;&lt;</td>
<td>N, &gt;</td>
<td>&gt;&gt;</td>
<td>&gt;&gt;</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>&lt;</td>
<td>&gt;&gt;</td>
<td>&gt;&gt;</td>
<td>&gt;&gt;</td>
<td>N, &lt;</td>
<td>&lt;&lt;</td>
</tr>
<tr>
<td>HDL</td>
<td>&lt;</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N, &lt;</td>
<td>&lt;&lt;</td>
</tr>
</tbody>
</table>
'N' = Normal, '>' = slight increase, '>>' = significant increase, '<' = slight decrease, '<<' = significant decrease

**Lipoprotein Particles:**

Lipoproteins consist of a central core of hydrophobic lipid (triglycerides or cholesteryl esters) encased in a more hydrophilic coat of polar substances-phospholipids, free cholesterol and associated proteins (apoproteins). There are four main classes of lipoprotein, differing in the relative proportion of the core lipids and in the type of apoprotein. (A.Y.Kaesancini *et al.*, 1994)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Di</th>
<th>Diet, Statins, Bile Acid Sequestrants, Nicotinic Acid</th>
<th>Diet, Statins, Bile Acid Sequestrant Fibrates, Nicotinic Acid</th>
<th>Diet, Fibrates, Nicotinic Acid</th>
<th>Diet, Fibrates, Nicotinic Acid</th>
</tr>
</thead>
</table>

Table 2: **Classification of Lipoproteins**

<table>
<thead>
<tr>
<th>Chylomicrons</th>
<th>Composition</th>
<th>Density</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG &gt;&gt; C, CE</td>
<td>low</td>
<td>large</td>
<td></td>
</tr>
</tbody>
</table>

| VLDL | TG > CE | higher than chylomicron | smaller than chylomicron |
| ILDL | CE > TG | higher than VLDL | smaller than VL |
| LDL | CE >> TG | higher than ILDL | smaller than IL |
| HDL | CE > TG | highest | smallest |

The pharmacological agents which reduce the concentration of plasma lipids are called hypocholesterolemic agents or antihyperlipidemic agents or lipid Lowering Agents.
An increase in plasmalipids, particularly cholesterol, is a common feature of atherosclerosis, a condition involving arterial damage, which may lead to ischaemic heart diseases myocardial infarction and cerebral vascular accidents. These conditions are responsible for one third of all deaths from disease in industrial nations. Lipids are insoluble in water, and they are transported in the plasma as lipoproteins. An increase in the plasma concentration of these substances is termed hyperlipidemia (or hyperlipoproteinemia).

**Mechanism of Lipid Transport**

Dietary fat including cholesterol and triglycerides are absorbed in the intestine and released in the blood stream as chylomicrons. These are least dense particles having very high proportion of triacylglycerides. Lipoprotein lipase acts on these particles to release some free fatty acids that deposit in adipose tissues. The remnants of chylomicrons are picked up by the liver which has a receptor specific to chylomicron remnants. After further clean up liver releases particles called the very low density lipoproteins in the blood. These have lower triacyl glycerides than chylomicrons. Once again LPL works on these VLDL particles releasing more free fatty acids and changing the content of the particles to IDL and LDL. There are LDL receptors on the cell membranes of the extrahepatic cells which can pick up the LDL particles. This is how cholesterol reaches the interior of normal cells. Within cells, LDL particles are repackaged. Excess cholesterol is esterified and stored. Excess cholesterol suppresses the biosynthesis of LDL-receptors so that intake of cholesterol decreases. It also suppresses cholesterol biosynthesis. Repackaged LDL particles called HDL particles are then released into the blood stream. These particles are sensed by the liver through the HDL-receptors. Thus the liver gets constant information as to how much LDL and HDL are present in the blood. (Vogel G *et al.*, 1997)
Figure 1: Strategies for treating Hyperlipidemias
Control of Hyperlipidemia

There are several mechanisms by which pharmacological agents can affect the metabolism of cholesterol and the relative levels of various cholesterol carrying lipoproteins in the plasma.

(i) Inhibit synthesis of cholesterol (e.g. HMG-CoA reductase inhibition; Lovastatin).

(ii) Alter the relative levels of different plasma lipoproteins e.g. clofibrate, gemfibrozil, nicotinic acid and possibly probucol, thyroid hormone, androgens.

(iii) Sequester bile acids in the intestine, e.g. cholestyramine and colestipol.

(iv) Inhibit cholesterol absorption in the intestine, e.g. neomycin and plant steroids, such as β-sitosterol.

Figure 2: Control of Hyperlipidemia
1.10. Classification of hyperlipidemia

Hyperlipidemias are classified according to the Fredrickson classification which is based on the pattern of lipoproteins on electrophoresis or ultracentrifugation. It was later adopted by the World Health Organization (WHO). It does not directly account for HDL, and it does not distinguish among the different genes that may be partially responsible for some of these conditions. In the past it was a popular system of classification but is considered out-dated by many experts now.

Following are the five types of hyperlipidemia described by Fredrickson.

1. Hyperlipoproteinemia Type-I

Hyperlipoproteinemia Type I also called primary hyperlipoproteinaemia, or familial hyperchylomicronemia) is due to deficiency of lipoprotein lipase (LPL) or altered apo lipoprotein C2, resulting in elevated chylomicrons, the particles that transfer fatty acids from the digestive tract to the liver. Its occurrence is 0.1% of the population.

2. Hyperlipoproteinemia Type-II

Hyperlipoproteinemia Type II, the most common form, is further classified into type IIa and type IIb, which are as follows;

2.1 Hyperlipoproteinemia Type-IIa

Hyperlipoproteinemia Type-IIa may be sporadic, polygenic, or truly familial as a result of mutation either in the LDL receptor gene on chromosome 19 or the Apo B gene. The familial form of this type is characterized by tendon Xanthoma ,xanthelasma and premature cardiovascular disease.

2.2 Hyperlipoproteinemia Type-IIb

Hyperlipoproteinemia Type-IIb is caused by high VLDL levels which are due to overproduction of substrates, including triglycerides, acetyl CoA, and an increase in B-100 synthesis. They may also be caused by the decreased clearance of LDL.
3. Hyperlipoproteinemia Type-III

Hyperlipoproteinemia Type-III is due to high chylomicrons and IDL (intermediate density lipoprotein). It is also known as broad beta disease or dysbetalipoproteinemia, which is mostly due to the presence of Apo E E2/E2 genotype. It is due to cholesterol-rich VLDL.

4. Hyperlipoproteinemia Type-IV

Hyperlipoproteinemia Type-IV also known as hypertriglyceridemia or pure hypertriglyceridemia, is due to high triglycerides. According to the NCEP (National Cholesterol Education Program) definition of high triglycerides, occurrence is about 16% of adult population.

5. Hyperlipoproteinemia Type-V

Hyperlipoproteinemia Type-V is very similar to type I, but have high VLDL in addition to chylomicrons. This disease has glucose intolerance and hyperuricemia.

Classification of antihyperlipidemic agents
(i) HMG-CoA-reductase Inhibitor: e.g. Lovastatin, Simvastatin, Pravastatin
(ii) Fibric acid derivatives: e.g. Clofibrate, Fenofibrate, Ciprofibrate, Bezafibrate, Gemfibrozil
(iii) Bile-acid sequestrants: e.g. Cholestyramine, colestipol
(iv) Inhibition of LDL oxidation: e.g. Probucol
(v) Miscellaneous Agents: e.g. Nicotinic acid, Neomycin, β-Sitosterol, Acipimox, Metformin, Dextrothyroxine (S.L.Brown et al., 1996)

(i) HMG CoA-reductase Inhibitors: A new class of fungal derived compounds are potent inhibitors of the enzyme β-Hydro-β-methyl-glutaryl-CoA reductase (HMG-CoA reductase) and includes compactin and mevinolin. This enzyme is the rate determining step in the endogenous synthesis of cholesterol. This enzymes are often referred to collectively as statins' - a new class of lipid lowering agents.. These drugs bring about specific, reversible and competitive blockage of HMG-CoA reductase eading to decreased hepatic cholesterol synthesis. This induces an increased
rate of hepatic uptake and catabolism of circulating LDL. Thus the levels of total and LDL-
cholesterol are significantly reduced. (G. Davey Smith et al., 1992)

(ii) **Fibric Acid Derivatives:** A series of aryloxy-isobutyric acids was effective in reducing plasma concentrations of triglyceride and cholesterol. Clofibrate, the first compound of this class was clinically effective for the treatment of hypertriglyceridemia. Several chemical analogs, congeners and homologs, collectively referred to as fibric acids have been prepared with lesser toxicity. One of these, Gemfibrozil, has been widely used.

(iii) **Bile-acid sequestrants:** Bile acids are secreted by the liver into intestine where they aid in the dissolution and absorption of lipids. Bile acids are the metabolic end-products of cholesterol which are released into the intestine. Major fraction (about 98%) of bile acids released into the gut is reabsorbed through the enterohepatic circulation and suppresses the microsomal hydroxylase enzyme involved in the conversion of cholesterol to the bile acids. Thus due to enterohepatic reabsorption of the bile acids further of cholesterol is suppressed.