2.1 Introduction to diabetes mellitus

DM is a chronic metabolic disorder characterized by a high blood glucose concentration-hyperglycemia (fasting plasma glucose > 7.0 mmol/l, or plasma glucose > 11.1 mmol/l 2 hours after a meal)-caused by insulin deficiency, often combined with insulin resistance (Rang, Dale, Ritter, & Flower, 2007). Hyperglycaemia occurs because of uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal muscle with reduced glycogen synthesis. When the renal threshold for glucose reabsorption is exceeded, glucose spills over into the urine (glycosuria) and causes an osmotic diuresis (polyuria), which, in turn, results in dehydration, thirst and increased drinking (polydipsia). Hyperglycaemia and diabetes are important causes of mortality and morbidity worldwide, through both direct clinical consequences and increased mortality from cardiovascular and kidney diseases (Nathan et al., 2009).

2.2 There are two main types of DM

Type 1 diabetes (previously known as insulin-dependent diabetes mellitus-IDDM-or juvenile-onset diabetes)

Type 2 diabetes (previously known as non-insulin-dependent diabetes mellitus-NIDDM-or maturity-onset diabetes).

In type 1 diabetes, there is an absolute deficiency of insulin resulting from autoimmune destruction of β cells. Without insulin treatment, such patients will ultimately die with diabetic ketoacidosis.

Type 1 diabetic patients are usually young (children or adolescents) and not obese when they first develop symptoms. There is an inherited predisposition, with a 10-fold increased incidence in first-degree relatives of an index case, and strong associations with particular histocompatibility antigens (HLA types). The patient becomes overtly diabetic only when more than 90% of the β cells have been destroyed. This natural history provides a tantalizing prospect of intervening in the prediabetic stage, and a variety of strategies have been mooted, including immunosuppression, early insulin therapy, antioxidants, nicotinamide and many others, but so far these have disappointed (Hardman & Limbird, 2001).
Type 2 diabetes is accompanied both by insulin resistance (which precedes overt disease) and by impaired insulin secretion, each of which are important in its pathogenesis. Such patients are often obese and usually present in adult life, the incidence rising progressively with age as β-cell function declines. Treatment is initially dietary, although oral hypoglycaemic drugs usually become necessary, and about one-third of patients ultimately require insulin (Derosa & Sibilla, 2007).

### 2.3 Treatment

Diet is the main treatment combined with increased exercise. However patients insulin is mainly used for controlling diabetes mellitus. Patients not responding to insulin as well as dietary control are administered oral hypoglycemic agents, they are used to control symptoms from hyperglycaemia, as well as to limit microvascular complications (Sheehan, 2003).

The main oral hypoglycaemic agents are metformin (a biguanide), sulfonylureas and other drugs that act on the sulfonylurea receptor, and glitazones.

### 2.4 Introduction to sulfonylurea

The sulfonylureas are divided into two groups or generations of agents. The first group of sulfonylureas includes tolbutamide, acetohexamide, tolazamide, and chlorpropamide. A second, more potent generation of hypoglycemic sulfonylureas has emerged, including glyburide (glibenclamide), glipizide, gliclazide, and glimepiride (Rang et al., 2007).

#### 2.4.1 Mechanism of Action

Sulfonylureas cause hypoglycemia by stimulating insulin release from pancreatic β cells. Their effects in the treatment of diabetes, however, are more complex. The acute administration of sulfonylureas to type 2 DM patients increases insulin release from the pancreas. Sulfonylureas also may further increase insulin levels by reducing hepatic clearance of the hormone. In the initial months of sulfonylurea treatment, fasting plasma insulin levels and insulin responses to oral glucose challenges are increased. With chronic administration, circulating insulin levels decline to those that existed before treatment, but despite this reduction in insulin levels, reduced plasma glucose levels are maintained. The explanation for this is not clear, but it may relate to
reduced plasma glucose allowing circulating insulin to have more pronounced effects on its target tissues and to the fact that chronic hyperglycemia per se impairs insulin secretion (Groop, 1992).

Sulfonylureas bind to the SUR1 subunits and block the ATP-sensitive K⁺ channel The drugs thus resemble physiological secretagogues), which also lower the conductance of this channel. Reduced K⁺ conductance causes membrane depolarization and influx of Ca²⁺ through voltage-sensitive Ca²⁺ channels.

2.4.2 Absorption, fate, and excretion.

The sulfonylureas have similar spectra of activities; thus their pharmacokinetic properties are their most distinctive characteristics. Hyperglycemia per se inhibits gastric and intestinal motility and thus can retard the absorption of many drugs. In view of the time required to reach an optimal concentration in plasma, sulfonylureas with short half-lives such as glibenclamide and glimepiride may be more effective when given 30 minutes before eating (Hardman & Limbird, 2001). Sulfonylureas in plasma are largely (90% to 99%) bound to protein, especially albumin; plasma protein binding is least for chlorpropamide and greatest for glyburide (Groop, 1992).

The second-generation agents are approximately 100 times more potent than are those in the first group. Although their half-lives are short (3 to 5 hours), their hypoglycemic effects are evident for 12 to 24 hours, and they often can be administered once daily. The reason for the discrepancies between their half-lives and duration of action is not clear.

2.4.3 Therapeutic uses.

Sulfonylureas are used to control hyperglycemia in type 2 DM patients who cannot achieve appropriate control with changes in diet alone. In all patients, continued dietary restrictions are essential to maximize the efficacy of the sulfonylureas. Contraindications to the use of these drugs include type 1 DM, pregnancy, lactation, and for the older preparations, significant hepatic or renal insufficiency.

Between 50% and 80% of properly selected patients will respond initially to an oral hypoglycemic agent. All the drugs appear to be equally efficacious. Concentrations of glucose often are lowered sufficiently to relieve symptoms of hyperglycemia but may
not reach normal levels. To the extent that complications of diabetes are related to hyperglycemia, the goal of treatment should be normalization of both fasting and postprandial glucose concentrations. About 5% to 10% of patients per year who respond initially to a sulfonylurea become secondary failures, as defined by unacceptable levels of hyperglycemia. This may occur as a result of a change in drug metabolism, progression of b-cell failure, change in dietary compliance, or misdiagnosis of a patient with slow-onset type 1 DM. Additional oral agent(s) can produce a satisfactory response, but most of these patients eventually will require insulin.

2.4.5 Dose and regimen

The initial daily dose of glyburide is 2.5 to 5 mg, and daily doses of more than 20 mg are not recommended. Therapy with glipizide usually is initiated with 5 mg given once daily. The maximal recommended daily dose is 40 mg; daily doses of more than 15 mg should be divided. The starting dose of gliclazide is 40 to 80 mg/day, and the maximal daily dose is 320 mg. Glimepiride therapy can begin with doses as low as 0.5 mg once per day. The maximal effective daily dose of the agent is 8 mg. Treatment with the sulfonylureas must be guided by the patient's response, which must be monitored frequently (Miyahara, 1992)

Combinations of insulin and sulfonylureas have been used in some patients with type 1 and type 2 DM. Studies in type 1 DM patients have provided no evidence that glucose control is improved by combination therapy. The results in type 2 DM patients have shown significant improvements in metabolic control. A prerequisite for a beneficial effect of combination therapy is residual b-cell activity; a short duration of diabetes also may predict a good response (Derosa & Sibilla, 2007).
2.5 Marketed formulations of some drugs from sulfonylurea class

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Drug</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glimicon</td>
<td>Glimipiride</td>
<td>1, 2, 3, 4 mg</td>
</tr>
<tr>
<td>Amaryl</td>
<td>Glimipiride</td>
<td>1, 2, 4 mg</td>
</tr>
<tr>
<td>DiaBeta</td>
<td>Glyburide (micronized)</td>
<td>1.25, 2.5, 5 mg</td>
</tr>
<tr>
<td>Glynase</td>
<td>Glyburide (micronized)</td>
<td>1.5, 3, 6 mg</td>
</tr>
</tbody>
</table>

2.6 Conclusion

During the literature survey on treatment of Type II DM, it was seen that sulfonylurea class of drugs have now been the first line of treatment alone or in combination with other anti diabetic drugs. From the sulfonylurea class two drugs namely glimepiride and glibenclamide are apt candidates for improving the dissolution characteristics, since they are having very low half life (2-3 hrs) and a low dose (2-4 mg). Hence, this two drugs were selected for incorporation in to different drug delivery strategies for improving dissolution characteristics.
1. Introduction

Self-emulsifying drug delivery systems (SEDDS) are relatively newer, lipid-based technological innovations with immense promise in enhancing the oral bioavailability of drugs. These formulations have been shown to reduce the slow and incomplete dissolution of a drug, facilitate the formation of its solubilized phase, increase the extent of its transportation via the intestinal lymphatic system, and bypass the P-glycoprotein efflux, thereby augmenting drug absorption from the gastrointestinal (GI) tract. Self-emulsifying formulations are isotropic mixtures of drug, lipids (natural or synthetic oils), and emulsifiers (solid or liquid), usually with one or more hydrophilic co-solvents/co-emulsifiers (B. Singh, Bandopadhyay, Kapil, Singh, & Katare, 2009).

SEDDS is a broad term encompassing emulsions with a droplet size ranging from a few nanometers to several microns. Depending upon the size of globules, these emulsions are characterized as concentrated microemulsions, nanoemulsions, or pre-concentrates. Self microemulsified drug delivery system (SMEDDS) are formulations forming transparent microemulsions with an oil droplet size ranging between 100 and 250 nm. Self-nanoemulsified drug delivery system (SNEDDS) is relatively a recent term indicating formulations with a globule size less than 100 nm (Nicolas. Anton & Vandamme, 2010).

The SNEDDS formulation forms a clear dispersion instantaneously in the GI tract that remains stable on dilution. A typical SNEDDS formulation basically constitutes apt lipidic and emulsifying excipients having an inherent ability to solubilize the drug. As the release of a drug compound from SNEDDS takes place in the GI tract, the hydrophobic agent should remain solubilized for at least the time period relevant during GI absorption. Therefore, a typical SNEDDS formulation also contains a co-emulsifier in addition to the essential lipid and emulsifier (Sarker, 2005).

The following figure 2.1 illustrates the usual methodology pathways to prepare SNEDDS formulations and the eventual formation of the nanoemulsions following their dilution. These SNEDDS have to be ultimately formulated as an oral solution in
soft gelatin capsules or as solid dosage forms in hard gelatin capsules, depending on the final physical nature of the system as liquid or semisolid/solid, respectively.

Depending upon the relative proportions of lipidic triglycerides, water-soluble or water-insoluble surfactant emulsifiers, and hydrophobic co-emulsifiers or cosolvents, the SNEDDS have been classified as Type I, II, III, III, and IV (P. Li et al., 2009).

*Figure 2.1 Schematic procedure for preparing SNEDDS (adapted from B. Singh et al., 2009))*
Table 2.1 Classification of self nanoemulsifying drug delivery system

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excipients</td>
<td>Oils without surfactants (e.g. tri-, di- and monoglycerides)</td>
<td>Oils and water-insoluble surfactants</td>
<td>Oils, surfactants and cosolvents (both water-insoluble and water-soluble excipients)</td>
<td>Water-soluble surfactants and cosolvents (no oils)</td>
</tr>
<tr>
<td>Properties</td>
<td>Nondispersing, requires digestion</td>
<td>SNEDDS formed without water-soluble components</td>
<td>SNEDDS/SMEDDS formed with water-soluble components</td>
<td>Formulation disperses typically to form a micellar solution</td>
</tr>
<tr>
<td>Pros</td>
<td>GRAS status; simple; excellent capsule compatibility</td>
<td>Unlikely to lose solvent capacity on dispersion</td>
<td>Clear or almost clear dispersion; drug absorption without digestion</td>
<td>Formulation has good solvent capacity for many drugs</td>
</tr>
<tr>
<td>Cons</td>
<td>Formulation has poor solvent capacity unless drug is highly lipophilic</td>
<td>Turbid o/w dispersion (particle size 0.25–2 µm)</td>
<td>Possible loss of solvent capacity on dispersion; less easily digested</td>
<td>Likely loss of solvent capacity on dispersion; might not be digestible</td>
</tr>
</tbody>
</table>
2. Formulation excipients

2.1 Lipids (Chakraborty, Shukla, Mishra, & Singh, 2009)

The lipid is an important component in the formulation of SNEDDS as physicochemical properties of oil (e.g., molecular volume, polarity and viscosity) significantly affect the spontaneity of the nanoemulsification process, droplet size of the nanoemulsion and drug solubility. Not only can lipids solubilize marked amounts of lipophilic drugs and facilitate self-emulsification, but they also have the propensity to augment the fraction of drug transported via intestinal lymphatic system, thereby increasing its absorption from the GI tract. Natural edible oils, comprised of medium-chain triglycerides are not usually used owing to their poor ability to dissolve large amounts of lipophilic drugs. Modified long- and medium-chain triglyceride oils, with varying degrees of saturation or hydrolysis, have widely been used for the design and development of SNEDDS formulations. These oils offer distinct formulative and physiological advantages, as their degradation products resemble that of the natural end-products of intestinal digestion. Both unsaturated and saturated fatty acids have been widely employed in the formulation of lipidic systems. However, the SNEDDS in particular are comprised of saturated fatty acids such as caproic, caprylic, capric, lauric, and myristic acid. (M.-L. Chen, 2008) One can make the appropriate choice of these by examining their composition, potential utilities, physical state, and hydrophilic-lipophilic balance (HLB). Given table provides a comprehensive account of most of such lipidic constituents, along with their characteristics. These amphiphilic excipients are progressively and effectively replacing the conventional (i.e., natural) medium-chain triglyceride oils in SNEDDS systems.

2.2 Surfactant (Bouchemal, Briançon, Perrier, & Fessi, 2004)

Second to the oils, the other most vital component of the SNEDDS is an emulsifier or a surfactant. The selection of surfactant is also critical process for the formulation of SNEDDS. The characteristic of the surfactant, such as HLB (in oil), cloud point, viscosity and affinity for the oily phase, have great influence on the nanoemulsification process, self-nanoemulsification region and the droplet size of nanoemulsion. An
emulsifier, invariably a surfactant, is obligatory to provide the essential emulsifying characteristics. Surfactants, being amphiphilic in nature, can dissolve (or solubilize) relatively high amounts of hydrophobic drug compounds. Emulsifiers from natural sources are regarded as much safer than synthetic ones. However, as the former possess only limited self-emulsification capacities, these are seldom employed for the formulation of SNEDDS. The twin issues that govern the selection of a surfactant are its HLB and safety. The HLB of a surfactant provides important information on its potential utility in the formation of SNEDDS. For imparting high self-emulsifying properties to the SNEDDS formulation, the emulsifier should have a relatively high HLB (i.e., high hydrophilicity) for immediate formation of o/w droplets, and/or rapid spreading of the formulation in the aqueous media. The most widely recommended emulsifiers, which include nonionic surfactants with relatively high HLB values such as solid or liquid ethoxylated polyglycolyzed glycerides, polyoxyethylene (20) sorbitan monooleate (i.e., Tween 80), and poly(ethylene oxide)- poly(propylene oxide), block copolymers such as Pluronic F127. Because at times, high amounts of hydrophobic drugs need to be dissolved, the formulation of an effective SNEDDS usually requires quite high concentrations of an emulsifying surfactant. For forming stable SNEDDS, the surfactant concentration usually should range between 30% and 60% w/w, as higher concentrations may be irritating to the GI mucosa.

2.3 Co-solvents (Biradar, Dhumal, & Paradkar, 2009b)

Co-solvents, such as ethanol, propylene glycol, and PEG, are also commonly required to enable the dissolution of a large quantity of hydrophilic surfactant(s) in SNEDDS. Lipid mixtures with higher surfactant/oil or co-surfactant/oil ratios lead to the formation of SNEDDS. However, co-solvents have a serious limitation of becoming evaporated from the shells of sealed gelatin capsules, leading eventually to the precipitation of drug inside the shell. Newer co-solvents such as Transcutol and Glycofurol have several stellar advantages over traditional ones, including better stability and less volatility.
3. Method of preparation (Nicolas Anton & Vandamme, 2009; Bouchemal et al., 2004; Vyas, Shahiwala, & Amiji, 2008)

The methods for preparation of the nanoemulsions are classified into high-energy emulsification methods or low-energy emulsification methods.

1. High energy emulsification

High Pressure Homogenization
Microfluidization
Ultrasonic emulsification

2. Low energy emulsification

Phase inversion temperature
Solvent displacement method
Self emulsification system.

In high-pressure homogenization, the coarse macroemulsion is passed through a small orifice at an operating pressure in the range of 500 to 5000 psi. The nanoemulsions with desired size range and dispersity can be obtained by varying the operating pressure and the number of passes through interaction chambers like high-pressure homogenization.

Microfluidization is a mixing technique, which makes use of a device called microfluidizer. This device uses a high-pressure positive displacement pump (500 to 20000psi), which forces the product through the interaction chamber, which consists of small channels called ‘microchannels’. The product flows through the microchannels on to an impingement area resulting in very fine particles of sub- micron range.

Ultrasonic emulsification uses a probe that emits ultrasonic waves to disintegrate the macroemulsion by means of cavitation forces. By varying the ultrasonic energy input and time, the nanoemulsions with desired properties can be obtained.
The phase inversion temperature (PIT) method as an alternative to high shear emulsification. In the PIT method, oil, water and nonionic surfactants are mixed together at room temperature and the mixture typically comprises O/W microemulsions coexisting with excess oil, and the surfactant. When this macroemulsion is heated gradually, the surfactant becomes lipophilic and at higher temperatures, the surfactant gets completely solubilized in the oily phase and the initial O/W emulsion undergoes phase inversion to W/O emulsion. (Shafiq et al., 2007)

In solvent displacement method, oily phase is dissolved in water-miscible organic solvents. The organic phase is poured into an aqueous phase containing surfactant to yield spontaneous nanoemulsion by rapid diffusion of organic solvent. The organic solvent is removed from the nanoemulsion by a suitable means, such as vacuum evaporation (Trimaille et al., 2001).

Self emulsification (B. Singh et al., 2009)

The mechanism through which self-emulsification occurs has not yet been thoroughly elucidated. Nevertheless, it has been suggested that self-emulsification takes place when the entropy change favoring dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of a conventional emulsion formulation is a direct function of the energy required to create a new surface between the oil and water phases. The thermodynamic relationship for the net free energy change is described by following equation.

$$\Delta G = \sum N_i 4\pi r_i^2 \sigma \quad \ldots \quad \ldots \quad (1)$$

where $\Delta G$ is the free energy associated with the process, $r_i$ is the radius of the droplets, $N_i$ is the number of droplets, and $\sigma$ is the interfacial energy. The two phases of the emulsion tend to separate with time to reduce the interfacial area and thus minimize the free energy of the system(s). Conventional emulsifying agents stabilize emulsions resulting from aqueous dilution by forming a monolayer around the emulsion droplets, reducing the interfacial energy and forming a barrier to coalescence. On the other hand, emulsification occurs spontaneously with SNEDDS, as the free energy required to form the emulsion is
low, whether positive or negative. For emulsification to take place, it is vital for the interfacial structure to offer negligible or no resistance against surface shearing. The ease of emulsification has been suggested to be related to the ease of water penetration into various liquid crystals or gel phases formed on the surface of the droplet. The interface between the oil and aqueous continuous phases is formed upon addition of a binary mixture (oil/ non-ionic surfactant) to water. This is followed by solubilization within the oil phase as a result of aqueous penetration through the interface. This occurs until the solubilization limit is attained close to the interphase. Further, aqueous penetration will lead to the formation of the dispersed liquid crystal phase. Ultimately, everything that is in close proximity to the interface will be liquid crystal, the actual amount of which depends upon the emulsifier concentration in the binary mixture. Therefore, following gentle agitation of the self-emulsifying system, water rapidly penetrates into the aqueous cores, leading to interface disruption and droplet formation. As a result of the liquid crystal interface formation surrounding the oil droplets, the SNEDDS become quite stable to coalescence. Moreover, the presence of the drug compound may alter the emulsion characteristics, possibly by interacting with the liquid crystal phase. Nevertheless, the correlation between liquid crystal formation and spontaneous emulsification has still not been properly established.

4. Absorption of drug (Pouton, 1997; Sripriya Venkata Ramana Rao, Yajurvedi, & Shao, 2008)

Most of the dietary lipids are triglycerides which are fatty acids ester of glycerol, on ingestion of the triglycerides a coarse emulsion is believed to form in stomach with dietary phospholipids, proteins and polysaccharides are believed to be potent emulsifiers, forming a monolayer around the triglyceride droplets. Around 10 to 40% of normal fat digestion takes place in the stomach, involving hydrolysis to diglycerides and fatty acids. This process is being done by human gastric lipase (HGL). Short chain fatty acids may dissolve into the aqueous phase followed by absorption across the stomach mucosa, while longer chain acids may remain incorporated in the emulsion droplet core. The emulsion passes to the upper section of the large intestine where particle size reduction of the droplets takes place due to the presence of a range of emulsifying agent including bile
salts, monoglycerides, cholesterol, lecithin and lysolecithin, yielding an approximate size range of 0.5 to 1 μm. The mechanism responsible for such efficient emulsification of ingested triglycerides are not yet clear, although in vitro studies have shown that monoolein, oleic acid and monomeric bile salts may at intestinal pH significantly lower the interfacial tension of triolein droplets thereby allowing emulsification to take place under condition of comparatively low shear. Then lypolysis takes place via triacylglycerol acyl hydrolase, typically referred to as pancreatic lipase. This enzyme act specifically at the surface of emulsion droplets and causes hydrolysis of triglyceride at the 1st and 3rd position to produce fatty acids, diglycerides and monoglycerides.

5. **In vitro characterization of self-nanoemulsifying drug delivery systems**

5.1 Equilibrium Phase Behavior (Ehab I. Taha, Al-Saidan, Samy, & Khan, 2004)

Although self-emulsification is a dynamic, non-equilibrium process involving interfacial phenomena, the information about the process can be obtained using equilibrium-phase behavior. There appears to be a correlation between emulsification efficiency and the region of enhanced water solubilization (i.e., a typical characteristic of nonionic surfactant system) and phase inversion region and the formation of lamellar liquid crystalline dispersion phase on further incorporation of water. This method also allows comparison among different surfactants and their synergy with the chosen co-solvent(s) or co-surfactant(s). The boundaries of the monophasic region can be easily demarcated by visual observation of the samples. Phase behavior of the three component system can be represented pictorially by a ternary phase diagram, which can be computed manually or derived using software.

5.2 Spontaneity of self emulsification

Spontaneity or the rate of self-emulsification can be assessed by visual inspection or by monitoring the turbidity change of the dispersion by appropriate instrumental method. The self-emulsifying formulation is added to a known volume of water at room temperature under gentle agitation. The ease of emulsion formation is observed and termed as "good," when the emulsion formation is spontaneous and the formulation spreads into a uniform fine emulsion, or "bad," when poor or no emulsion is formed and
an immediate coalescence of the droplets is observed (A.A. Date & Nagarsenker, 2007). The spontaneity of emulsion formation is also observed by injecting the formulation into a flowing stream of water and measuring the change in turbidity with time (Zidan et al., 2007).

5.3 Droplet size analysis
Droplet size distribution is one of the important physicochemical measurement parameter of a nano-emulsion, and is measured by a diffusion method using a light-scattering particle size analyzer. Many other techniques that have been developed to measure droplet size of nanoemulsions, like laser light scattering (LLS) and energy filtering transmission electron microscopy (EFTEM) (Dabhi, Limbani, & Sheth, 2011). Morphology and structure of the nanoemulsion could be studied using transmission electron microscopy. Combination of bright field imaging at increasing magnification and of diffraction modes was used to reveal the form and size of nanoemulsion droplets. Observations was performed as, a drop of the nanoemulsion was directly deposited on the holey film grid and observed after drying. The average diameters and polydispersity index of nanoemulsion can be measured by photon correlation spectroscopy.

5.4 Viscosity determination (Biradar, Dhumal, & Paradkar, 2009a)
Viscosity is a measure of the resistance of a fluid which is being deformed by either shear or tensile stress. In everyday terms (and for fluids only), viscosity is "thickness" or "internal friction". Viscosity may affect in different way like during the filling in the capsule, converting the SNEDDS in to solid form etc. So, it must be determined for the formulation. Viscosity is measured with various types of viscometers and rheometers. A rheometer is used for those fluids which cannot be defined by a single value of viscosity and therefore require more parameters to be set and measured than is the case for a viscometer. Close temperature control of the fluid is essential to accurate measurements, particularly in materials like lubricants, whose viscosity can double with a change of only 5°C.

5.5 Drug content
Drug from pre-weighed SNEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution drug.

5.6 Zeta potential
The particle charge is of importance in the study of the stability of the nanoemulsion. Zeta potential is used to determine the charge at droplet surface. Particle charge is measured by electrophoresis and expressed as electrophoretic mobility [(μm/S)/(V/cm)] or converted to the zeta potential (mV). Usually the zeta potential of more than ±40mV will be considered to be required for the stabilisation of the dispersions. Minimum ±30mV zeta potential is required for electrostatically stable suspension and in case of combined steric and electrostatic stabilization it should be a minimum of ±20mV of zeta potential is required (Peltonen & Hirvonen, 2010).

5.7 Thermodynamic stability studies
The physical stability of a lipid based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipient matrix. In addition, poor formulation physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well.

• Heating cooling cycle: six cycles between refrigerator temperature (4°C) and 45°C with storage at each temperature of not less than 48 hrs is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.
• Centrifugation: Passed formulations are centrifuged thaw cycles between 21°C and +25°C with storage at each temperature for not less than 48 hrs is done at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.
• Freeze thaw test: Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

5.8 Percentage transmittance
Percentage transmittance of the prepared nanoemulsion formulations are determined to have an insight into the spontaneity of emulsions formation. It could be measured by spectrophotometric technique.

5.9 In vitro drug release
The drug dissolution testing is routinely used to provide critical in vitro drug release information. The dissolution of most commonly dosage form performed by USP dissolution apparatus I/II and drug release is estimated using HPLC-UV visible Spectrophotometry.

6. Application of SNEDDS as different dosage form
The SNEDDS have been formulated as different dosage forms such as Dry Emulsions: (Kohli, Chopra, & Dhar, 2010), Capsules: (Palamakula, Nutan, & Khan, 2004), Tablets, Pellets: (Z. Wang et al., 2010), Nanoparticles, Suppositories, Implants
Introduction

7. Various marketed formulation of SNEDDS

Table 2.2. Marketed formulations of SNEDDS

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Compound</th>
<th>Dosage form</th>
<th>Company</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agenerase®</td>
<td>Amprenavir</td>
<td>Soft gelatin</td>
<td>Glaxo Smithkline</td>
<td>HIV antiviral</td>
</tr>
<tr>
<td>Targretin®</td>
<td>Bexarotene</td>
<td>capsule</td>
<td>Ligand</td>
<td>Antineoplastic</td>
</tr>
<tr>
<td>Rocaltrol®</td>
<td>Calcitriol</td>
<td>capsule</td>
<td>Roche</td>
<td>Calcium regulator</td>
</tr>
<tr>
<td>Neoral®</td>
<td>A/I Cyclosporine</td>
<td>capsule</td>
<td>Novartis</td>
<td>Immune suppressant</td>
</tr>
<tr>
<td>Sandimmune®</td>
<td>A/II Cyclosporine</td>
<td>capsule</td>
<td>Novartis</td>
<td>Immuno Suppressant</td>
</tr>
<tr>
<td>Gengraf®</td>
<td>A/III Capsule</td>
<td>Hard gelatin</td>
<td>Abbott Laboratories</td>
<td>Immuno suppressant</td>
</tr>
<tr>
<td>Lipirex®</td>
<td>Fenofibrate</td>
<td>Capsule</td>
<td>Genus</td>
<td>Antihyperlipoproteinemic</td>
</tr>
<tr>
<td>Norvir®</td>
<td>Ritonavir</td>
<td>capsule</td>
<td>Abbott Laboratories</td>
<td>HIV antiviral</td>
</tr>
<tr>
<td>Fortovase®</td>
<td>Saquinavir</td>
<td>capsule</td>
<td>Hoffmann-La Roche</td>
<td>HIV antiviral</td>
</tr>
<tr>
<td>Convulex®</td>
<td>Valproic acid</td>
<td>capsule</td>
<td>Pharmacia</td>
<td>Antiepileptic</td>
</tr>
</tbody>
</table>

8. Conclusion:

From the literature survey done on the various formulation, development and characterization of self nanoemulsifying systems, it could be concluded that SNEDDS could be employed for improving dissolution characteristics of anti diabetic drugs of sulfonylurea class. Hence it was decided that self nanoemulsifying drug delivery strategy would be employed for improving the dissolution characteristics of selected drugs from sulfonylurea class.
1. Introduction

The basic challenge faced by the researcher for the formulation of poorly soluble drugs is the low oral bioavailability and erratic absorption of the drugs from the gastrointestinal tract due to their low saturation solubility and dissolution velocity. The low saturation solubility results in a low concentration gradient between the gut and blood vessel and leads to a limited transport of drug (Gao, Zhang, & Chen, 2008). For poorly soluble drugs as seen in BCS Class II, the dissolution of the drugs in the gastrointestinal fluid media is the rate limiting step for the absorption of the drugs (Mu’ller, Jacobs, & Kayser, 2001). Hence for efficient absorption of drugs from the gastrointestinal tract for improving their therapeutic efficacy, there is an imminent need for studies in designing novel strategies for their dissolution enhancement.

There are number of formulation approaches viz., salt formation, pH adjustment, cosolvency, complexation, etc (Rabinow, 2004) used for enhancement of dissolution but none of the approach has achieved the merits of being universal. However, there are several disadvantages associated with these approaches. For example, the alteration of chemical structure by forming water-soluble derivatives often requires long processing times at a very expensive cost to derive the new chemical entities (NCEs) (Venkatesh & Lipper, 2000). The use of solubilizing excipients is often limited by their toxicity. For example, the nonionic surfactant polyoxyethylated castor oil (Cremophor EL) has been shown to cause nephrotoxicity, hypersensitivity reactions and lowering of the white blood cell count (neutropenia). Micronization of poorly soluble drugs has been applied for many years to improve dissolution velocity of poorly soluble drugs but reducing the drug to micron size does not increase the saturation solubility of the drug, and at such a low saturation solubility, as generally observed in BCS Class II drug, the increment in the dissolution characteristics does not help to a great extent (Abhijit A. Date & Patravale, 2004; Patravale, Date, & Kulkarni, 2004). Consequently off late nanonisation has been employed for treating the BCS Class II drugs. When the drug is being reduced to nanosized level there is an obvious increase in its saturation solubility assisted by improvement in the dissolution characteristics which could be attributed to the effective
increase in particle surface area according to the Nernst Brunner-Noyes Whitney equation (Shah, Shah, Patel, & Potdar, 2012).

As per FDA a nanoparticulate drug is not considered as “generic” to an approved product and therefore can be patented; and are considered as “newdrug”, because nanoparticulate drug is not bioequivalent to a microcrystalline or solubilized form of the same drug, administered at the same dosage. It also offers a unique advantage to pharmaceutical companies of product line extension for the existing drug formulations (Singare et al., 2010). The nanotechnology is currently gaining attention from researchers and pharmaceutical industry. In the pharmaceutical field, the term “nanoparticle” is generally used to describe submicron sized particles (Brannon-Peppas & Blanchette, 2004; Kawashima, 2001). The drug of interest is dissolved, entrapped or encapsulated within the particles. Nanoparticle technologies have been used as important strategies to deliver drugs, including peptides and proteins, vaccines and more recently nucleotides. In pharmaceutical field nanotechnology covered the area like nanosuspension, nanoemulsion, self nanoemulsifying drug delivery system, solid lipid nanoparticle(SLN) etc. A nanosuspension consists of drug nanocrystals, stabilizing agents, typically surfactants or polymeric stabilizers, and a liquid dispersion medium (Patravale et al., 2004). Drug nanocrystals are pure solid drug particles with a mean particle size below 1 μm, generally between 200 nm and 500 nm (Keck & Müller, 2006). Although the term nanocrystals implicates a crystalline structure, the particles can be crystalline, partially crystalline or completely amorphous. The dispersion medium can be water, mixtures of water with other non-aqueous media or non-aqueous media. Nanosuspension permit delivery of drugs that are poorly soluble in water or unstable in biological fluids.
2. Method of preparation

Nanosuspensions can be prepared using various techniques, which could be classified broadly in two groups based on the principle on which the nanosize is achieved. Top down production, in which the drug macrosuspension is size reduced to nanosuspension and secondly bottom up method in which the drug nanoparticles are assembled from a solution of drug by controlling the rate and growth of nuclei formed.

The bottom up method consists of

- Nanoprecipitation
- Supercritical fluid technology
- Using emulsions and microemulsions as templates.

The top down method consists of

- Media Milling
- Dry Cogrinding
- High Pressure homogenization

The method employed herein are discussed in detail.

**Nanoprecipitation** (Dong, Ng, Shen, Kim, & Tan, 2011; Gao et al., 2008; Kakran, Sahoo, Lia, & Judeh, 2010)

In the precipitation technique the poorly water-soluble drug is dissolved in a suitable solvent and the solution is added into a miscible anti-solvent with stirring and agitation. Stabilizers are used to avoid the spontaneous aggregation of molecules. Types of solvents, the volume ratio of antisolvent to solvent, stirring rate, drug content etc are the factors which affect the final morphology of nanoparticles.

The precipitation process involves nucleation and crystal (particles) growth of drug particles from a supersaturated solution. The supersaturated solution is a solution in
which the concentration of solute exceeds the saturation or equilibrium solute concentration at a given temperature. Thus, a supersaturated solution is not at equilibrium, and crystallization of the solute occurs in order to move the solution towards equilibrium. After initial particle nucleation, both nucleation and crystal growth attempt to bring the supersaturated solution to equilibrium. The time required for crystallization depends on the driving force of supersaturation.

The nucleation rate increases with increasing temperature and degree of supersaturation, but decreases with increasing surface energy. High nucleation rates offer the potential to produce a large number of submicron particles in the final dispersion, as long as the growth can be arrested by stabilizers. Precipitation technologies are used in both the chemical and pharmaceutical industries for the production of nanoparticles. The usual precipitation technologies, including solvent evaporation and salting out, have in common the disadvantages of poor control over particle morphology and particle size and size distribution producing a wide range of particle sizes.

Precipitation has also been coupled with high shear processing. The NANOEDGE process (is a registered trademark of Baxter International Inc. and its subsidiaries) relies on the precipitation of friable materials for subsequent fragmentation under conditions of high shear and/or thermal energy (Zili, Sfar, & Fessi, 2005). This is accomplished by a combination of rapid precipitation and high-pressure homogenization. Rapid addition of a drug solution to an antisolvent leads to sudden supersaturation of the mixed solution, and generation of fine crystalline or amorphous solids. Precipitation of an amorphous material may be favored at high supersaturation when the solubility of the amorphous state is exceeded. The success of drug nanosuspensions prepared by precipitation techniques has been extensively reported (X. Chen, Young, Sarkari, Williams III, & Johnston, 2002; Cho et al., 2010; Kipp, Wong, Doty, & Rebbeck, 2004).

Advantage: It is simple process, low cost equipment, ease of scale up

Disadvantage: Drug has to soluble at least in one solvent and that this solvent needs to be miscible with a non-solvent, growing of drug crystals needs to be limit by surfactant addition.
Media Milling

The pearl milling technique is developed by Liversidge et al. (G. G. Liversidge & Conzentino, 1995) Wet milling is a particle size reduction technology whereby drug crystals are comminuted using high-shear media mills in the presence of surface stabilizer(s) and grinding media (Gao et al., 2008; Niwa, Miura, & Danjo, 2011). In media milling technique the drug is milled with milling media in simple glass vials to specific milling chambers for certain hours to some days and nanosuspensions are produced on a principle of high energy and shear forces generated as a result of the impaction of the milling media with the drug. The media like zirconium oxide beads, highly cross-linked polystyrene resin beads, glass beads are used. A problem associated with the media milling technology is the erosion from the milling material during the milling process. In order to reduce the quantity of impurities caused by an erosion of the milling media, the milling beads are coated with highly cross-linked polystyrene resin. A continuous problem is the adherence of product to the large inner surface area of the milling system. The inner surface area is made up of the surface area of the chamber and of all milling beads together. Even in recirculation systems, this product adherence causes a product loss. Of course, this undesirable drug loss can be an issue in very costly drugs. The level and type of stabilizer are important parameters to achieve nanoparticle size using this technology. The sizes of beads, number of beads, milling time, milling speed, characteristics of drug, temperature are the factors affecting the final product. By using this technique Rapamune was launched by Wyeth as the first product containing Sirolimus NanoCrystals. The coated Rapamune tablets are more convenient and show a 27% increased bioavailability compared to the Rapamune® solution. This is an example to increasing dissolution rate by using nanonization.

Advantage: It includes ease of scale up, little batch to batch variation, high flexibility in handling large quantities of drugs.
Disadvantage includes - Generation of residue of milling media, requires milling process for hours to days, prolonged milling may induce the formation of amorphous lead to instability
3. Theoretical aspects

Increasing saturation solubility and dissolution velocity

Classically saturation solubility in a given solvent is defined as a compound-specific constant depending only on the temperature however the saturation solubility is also a function of the crystalline structure (i.e. lattice energy) and particle size. In general, solubility is best for the polymorphic modification that is characterized by highest energy and lowest melting point. The reason why saturation solubility is also a function of particle size can be explained by the Kelvin and the Ostwald–Freundlich equation as shown in equation (1)

\[
\ln \frac{P_r}{P_\infty} = \frac{2\gamma Mr}{rRT\rho}
\]

(1)

where \(P_r\) is the dissolution pressure of a particle with the radius \(r\), \(P_\infty\) is the dissolution pressure of an infinitely large particle, \(\gamma\) is the surface tension, \(R\) is the gas constant, \(T\) is the absolute temperature, \(r\) is the radius of the particle, \(Mr\) is the molecular weight, and \(\rho\) is the density of the particle. According to the Kelvin equation, the dissolution pressure increases with increasing curvature, which means decreasing particle size. The curvature is enormous when the particle size is in the nanometer range; then a large dissolution pressure can be achieved leading to a shift of the equilibrium toward dissolution. The Ostwald–Freundlich directly describes the relation between the saturation solubility of the drug and the particle size as shown in equation (2)

\[
\log \frac{C_s}{C_\alpha} = \frac{2\sigma V}{2.303RT\rho r}
\]

(2)

where \(C_s\) is the saturation solubility, \(C_\alpha\) is the solubility of the solid consisting of large particles, \(\sigma\) is the interfacial tension of substance, \(V\) is the molar volume of the particle material, \(R\) is the gas constant, \(T\) is the absolute temperature, \(\rho\) is the density of the solid, and \(r\) is the radius. It is obvious that the saturation solubility (\(C_s\)) of the drug increases
with a decrease of particle size (\(r\)). However, this effect is pronounced for materials that have mean particle size of less than 2 \(\mu\)m. The increase of nanocrystals in the dissolution velocity can be explained by the Noyes–Whitney equation. For drug nanocrystals, the increased saturation solubility (CS) and surface area (A) lead to an increase in the dissolution velocity (\(dX/dt\)) as shown in equation (3)

\[
\frac{dX}{dt} = \frac{DA}{hD} X (Cs - Ct)
\]

... ... ... (3)

where \(dX/dt\) is the dissolution velocity, D is the diffusion coefficient, A is the surface area, \(hD\) is the diffusional distance, CS is the saturation solubility, and Ct is the concentration around the particles. Another important factor is the diffusional distance \(hD\), which, as a part of the hydrodynamic boundary layer \(hH\), is also strongly dependent on the particle size, as the Prandtl equation shown in equation (4) (Mosharraf and Nystrom 1995):

\[
hH = k \left( \frac{L^{1/2}}{V^{1/2}} \right)
\]

... ... ... (4)

where \(hH\) is the hydrodynamic boundary layer, \(k\) denotes a constant, L is the length of the particle surface, and \(V\) is the relative velocity of the flowing liquid surrounding the particle.

According to the Prandtl equation, the reduced particle size leads to a decreased diffusional distance \(hD\) and consequently an increased dissolution velocity, as described by the Noyes–Whitney equation. Therefore, to sum up, a reduction in the drug particle size in the nanometer range leads to an increase in solubility as well as the dissolution velocity. Both are very important factors with regard to the aim of improving the bioavailability of poorly soluble drugs.

Another special feature of nanosuspensions is the absence of Ostwald ripening meaning physical long-term stability as an aqueous suspension.
Ostwald ripening has been described for highly dispersed systems, which means a reduction in size of the finest particle fraction and their final disappearance combined with simultaneously growth of the larger particles. Reasons for the Ostwald ripening are the different saturation solubilities in the vicinity of differently sized particles and the concentration gradient existing between them. Molecules from the higher concentrated solution around very small particles diffuse to the vicinity of larger particles where a lower concentration is present. This leads to supersaturation and drug crystallization, which means growth of the larger particles. Simultaneously the vicinity of smaller particles will be below the saturation concentration, thus the new drug will be dissolved and the fine particles are getting smaller. This is a continuous process finally leading to the disappearance of the fine particles. The lack of Ostwald ripening in nanosuspensions is attributed to the uniform particle size created by the homogenization process. The differences in saturation solubility in combination with the a priori low solubility of the poorly soluble drug keeps the concentration differences sufficiently low to avoid the ripening effect.

4. Evaluation parameters

4.1 Shape, size and size distribution

Structural characterization like shape, size, surface morphology, size distribution, etc is a parameter that plays important role in determining various attributes of a nanosystem. The shape of the nanosuspension can be determined using a transmission electron microscope (TEM) and/or a scanning electron microscope (SEM). Size and size distribution are the most important parameter in the evaluation of the suspensions as it is having the direct effects on saturation solubility and dissolution velocity, physical stability of drugs. The mean particle size and the width of particle size distribution i.e. polydispersity index (PI) are determined by Photon Correlation Spectroscopy (PCS). PI governs the physical stability of nanosuspension and should be as low as possible for long-term stability (Should be close to zero). A PI value of 0.1–0.25 indicates a fairly narrow size distribution whereas a PI value greater than 0.5 indicates a very broad distribution. However, due to a narrow measuring range of PCS, approximately from 3
nm to 3 µm, laser diffractometry (LD) is needed to study the content of particles in the micrometer range of approximately 0.05–80 µm up to a maximum of 2000 µm, depending on the type of equipment used.

4.2 Particle charge (zeta Potential)

The particle charge is of importance in the study of the stability of the suspensions. Zeta potential is used to determine the charge at particle surface. Particle charge is measured by electrophoresis and expressed as electrophoretic mobility [(µm/S)/(V/cm)] or converted to the zeta potential (mV). Usually the zeta potential of more than ±40mV will be considered to be required for the stabilization of the dispersions. Minimum ±30mV zeta potential is required for electrostatically stable suspension and in case of combined steric and electrostatic stabilization it should be a minimum of ±20mV of zeta potential is required (Gao et al., 2008).

4.3 Crystalline status

The evaluation of crystalline state is necessary in case of drug exists in different polymorphic forms. When nanosuspensions are prepared drug particles may get converted to amorphous form hence it is essential to measure the extent of amorphous drug generated during the production of nanosuspensions. Differential scanning calorimetry (DSC) and X-ray diffraction can be used to evaluate the crystalline structure of the drug nanosuspension.

4.4 Dissolution velocity and saturation solubility

The main advantage associated with the nanosuspensions is improved saturation solubility as well as dissolution velocity. Measurement of the saturation solubility and dissolution velocity is very important parameter which help to measure the benefits compared to the conventional or microparticle formulation. Dissolution velocity is measured by the method given in pharmacopoeia. Saturation solubility is measured by shaking the drug in different solvent at different temperature up to equilibrium.

4.5 Stability of nanosuspensions
Stability of the suspensions is dependent on the particle size. As the particle size reduces to the nanosize the surface energy of the particles will be increased and they tend to agglomerate. So stabilizers are used which will decrease the chances of Ostwald ripening and improving the stability of the suspension by providing a steric or ionic barrier.

4.6 In vivo evaluation

The in vivo evaluation of the nanosuspensions is specific to drug and route of administration. Most commonly the formulation was given by required route of administration and the plasma drug levels were estimated using HPLC-UV visible Spectrophotometry. Other parameters which are generally evaluated in vivo are surface hydrophilicity/hydrophobicity (determines interaction with cells prior to phagocytosis), adhesion properties, interaction with body proteins etc.

4.7 In vitro drug release

The drug dissolution testing is routinely used to provide critical in vitro drug release information. The dissolution of most commonly dosage form performed by USP dissolution apparatus I/II and drug release is estimated using HPLC-UV visible Spectrophotometry.

5. Application of nanosuspension in different dosage form

Formulating the drug as nanosuspensions increases the saturation solubility, dissolution velocity as well as bioavailability of the drug. From the formulation point of view, nanosuspensions meet almost all the needs of an ideal drug delivery system for the parenteral route. These nanosuspensions are having application in different routes of administrations like oral, parenteral, topical, ophthalmic, mucoadhesive, pulmonary and targeted drug delivery. The administration of nanosuspensions is a drug delivery strategy, not only to improve bioavailability, but also to reduce the amount of those drugs used, to localize the delivery of potent compounds and, therefore, to reduce side effects.

6. Marketed formulations of nanosuspensions

Table 2.3 Marketed formulations of nanosuspensions
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Route</th>
<th>Marketed</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abraxane® (paclitaxel)</td>
<td>Anti-cancer</td>
<td>I.V.</td>
<td>2005</td>
<td>Abraxis Bioscience/Astrazeneca</td>
</tr>
<tr>
<td>Emend® (aprepitant)</td>
<td>Anti-emetic</td>
<td>Oral</td>
<td>2003</td>
<td>Merck/Elan</td>
</tr>
<tr>
<td>Megace ES® (megesterol acetate)</td>
<td>Eating disorders</td>
<td>Oral</td>
<td>2005</td>
<td>Par/Elan</td>
</tr>
<tr>
<td>Rapamune® (sirolimus)</td>
<td>Immuno-suppresant</td>
<td>Oral</td>
<td>2001</td>
<td>Wyeth/Elan</td>
</tr>
<tr>
<td>Tricor® (fenofibrate)</td>
<td>Lipid regulation</td>
<td>Oral</td>
<td>2004</td>
<td>Abbott/Elan</td>
</tr>
<tr>
<td>Triglide® (fenofibrate)</td>
<td>Lipid regulation</td>
<td>Oral</td>
<td>2005</td>
<td>Sciele Pharma/Skyepharma</td>
</tr>
</tbody>
</table>

7. Conclusion

From the literature survey done on the various formulation, development and characterization of nanosuspensions, it could be concluded that nanosuspension approach could be employed for improving dissolution characteristics of anti diabetic drugs of sulfonylurea class. Hence it was decided that nanosuspensions of selected drug from sulfonylurea class would be prepared for improving their dissolution characteristics. Two basic approaches were selected for preparing nanosuspensions viz., media milling and liquid anti solvent precipitation.
2.4 Polymers

2.4.1 Hydroxy propyl methyl cellulose

It is partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity.

Functional Category
Bioadhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film-forming agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; release-modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.

Regulatory Status
GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database

![Figure 2.2 Hydroxy propyl methyl cellulose](image)

Figure 2.2 Hydroxy propyl methyl cellulose

2.4.2 Hydroxy ethyl cellulose

Hydroxyethyl cellulose is a partially substituted poly(hydroxyethyl) ether of cellulose.
It is available in several grades that vary in viscosity and degree of substitution; some grades are modified to improve their dispersion in water. The grades are distinguished by appending a number indicative of the apparent viscosity.

**Functional Category**
Coating agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

**Regulatory Status**
Included in the FDA Inactive Ingredients Database

![Hydroxy ethyl cellulose](image)

**Figure 2.3 Hydroxy ethyl cellulose**

### 2.4.3 Hydroxy propyl cellulose

Hydroxypropyl cellulose is a partially substituted poly(hydroxypropyl) ether of cellulose. It may contain no more than 0.6% of silica or another suitable anticaking agent. Hydroxypropyl cellulose is commercially available in a number of different grades that have various solution viscosities.

**Functional Category**
Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent

**Regulatory Status**
GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database
2.4.4 Poloxamer

The poloxamer polyols are a series of closely related block copolymers of ethylene oxide and propylene oxide conforming to the general formula $\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_a\text{H}$.

Functional Category
Dispersing agent; emulsifying agent; solubilizing agent; tablet lubricant; wetting agent.

Regulatory Status
Included in the FDA Inactive Ingredients Database (IV injections; inhalations, ophthalmic preparations; oral powders, solutions, suspensions, and syrups; topical preparations).
Introduction

2.4.5 Akrysol K 140

Nonproprietary Names Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyethylene castor oil derivatives are complex mixtures of various hydrophobic and hydrophilic components. Members within each range have different degrees of ethoxylation (moles)/PEG units as indicated by their numerical suffix

Functional Category
Emulsifying agent; solubilizing agent; wetting agent.

Regulatory Status
Included in the FDA Inactive Ingredients Database

2.4.6 Labrasol

Mixtures of monoesters, diesters, and triesters of glycerol and monoesters and diesters of polyethylene glycols with mean relative molecular mass between 200 and 400.

Functional Category
Dissolution enhancer; emulsifying agent; nonionic surfactant; penetration agent; solubilizing agent; sustained-release agent.

Regulatory status
Included in the FDA Inactive Ingredients Database (oral route: capsules, tablets, solutions;
topical route: emulsions, creams, lotions; vaginal route: emulsions, creams)

2.4.7 Capmul MCM C8

Synonym: 1,2,3-Propanetriol

Functional Category
Emollient; emulsifying agent; solubilizing agent; stabilizing agent; sustained-release agent; tablet and capsule lubricant.

Regulatory Status
GRAS listed. Included in the FDA Inactive Ingredients Database (oral capsules and tablets; ophthalmic, otic, rectal, topical, transdermal, and vaginal preparations).

2.4.8 Capryol 90

Common name: Propylene glycol monocaprylate

Physical appearance: Oily liquid

HLB Value: 6

Functional category
CapryolTM 90 is an oily liquid used in oral and topical formulations.

It is a solubilizer/bioavailability enhancer for oral formulations.

It can be used in Self Emulsifying Lipidic Formulations (SELF type SMEDDS).

It is a solubilizer/penetration enhancer for topical formulations.

It is a co-surfactant for microemulsions in topical formulations.

Regulatory status
Introduction

Approved by FCC and USFA

2.4.9 Labrafac PG

Common name: Propylene glycol dicaprylocaprate

Physical Form: Oily liquid

HLB Value: 2

Functional category

LabrafacTM PG is a liquid oily vehicle for use in oral and topical formulations:

For oral formulations, it has solubilizing properties for lipophilic drugs.

It can be used in Self Emulsifying Lipidic Formulations (SELF type SEDDS/SMEDDS).

It is an oily phase for microemulsions in topical formulations.

Regulatory status

Approved by USFA

2.4.10 Lauroglycol 90

Common name: Propylene glycol monolaurate

Physical appearance: Liquid

HLB Value: 5

Functional category

Lauroglycol 90 is a liquid used in oral and topical formulations:

It is a solubilizer/bioavailability enhancer for oral formulations.

It can be used as a surfactant in Self Emulsifying Lipidic Formulations (SELF type SMEDDS).
It is a solubilizer/penetration enhancer for topical formulations.

It is a co-surfactant for microemulsions in topical formulations.

Regulatory status
Included in the FDA Inactive Ingredients Database

2.4.11 Transcutol P

Common name: Diethylene glycol monoethyl ether

Physical appearance: Liquid

Functional category

Transcutol P is suitable for oral dosage forms.

It is a high performance solubilizer/solvent for many poorly soluble compounds.

It is soluble in both water and oil.

Regulatory status
Included in the FDA Inactive Ingredients Database

Figure 2.6 Transcutol