3.1 THE BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS)

A classification system that uses solubility and permeability as parameter is the biopharmaceutical classification system (BCS), which is based on estimates of the contribution of solubility, permeability, and dissolution to oral drug absorption from dosage forms. First described in 1995, the BCS and its principles have been used in guidelines issued by the Food and Drug Administration.

According to BCS classification, low-solubility compounds are compounds whose highest dose is not soluble in 250 ml or less of aqueous media from pH 1.2 to 7.5 at 37±0.8°C.

High permeability is defined as human absorption of 90% or more of the administered dose. Based on these definitions, drugs fall into one of four BCS categories that explain the drug’s permeability and absorption properties as well as its dissolution.

Class I: High solubility, high permeability compounds.

In vivo behavior of these drugs, mimics like an oral solution having fast dissolution and rapid bioavailability. Since the dissolution and absorption of class I drugs is very quick, bioavailability and bioequivalence are needless for the products of such drugs. These drugs are good candidates for controlled drug delivery if they qualify pharmacokinetically and pharmacodynamically for the purpose. Gastric emptying is often the rate governing parameter for these drugs.
Class II: *Low-solubility, high-permeability compounds.*

These classes of compounds have dissolution as the rate limitation step. In general i.e., the rate of drug solubilization is much lower than the rate of drug absorption. For these class of compounds, the solubility of the drug was improved by using different solubility enhancing techniques such as cyclodextrin complex, cosolvency, salt formation, crystallization etc.

Class III: *High solubility, low permeability compounds*

Permeation through the intestinal membrane forms the rate-determining step for these drugs. Since absorption is permeation rate limited, bioavailability is independent of drug discharge from the dosage form. These drugs in general display low bioavailability and permeability enhancement is generally necessary. These drugs are problematic for controlled release development.

Class IV: *Low-solubility, low permeability compounds*

These compounds have solubility and permeability limited absorption. The overall bioavailability is governed by several factors such as rate of dissolution, intestinal permeability, gastric emptying, and so on. These types of compounds are difficult to administer and attain the required bioavailability\(^ {38, 39} \).
Oral route is the easiest and most suitable route for non invasive administration. Oral drug delivery system is the most cost effective and leads the worldwide drug delivery market. The oral route is a problematic route for those drug molecules which exhibit poor aqueous solubility.40

3.2. SELF EMULSIFYING DRUG DELIVERY SYSTEMS (SEDDS)

SEDDS are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co solvents/co surfactants, which emulsify spontaneously to produce fine oil-in-water emulsions when initiated into aqueous phase under mild agitation.41

➢ Advantages of SEDDS over Conventional DDS42-46

1. Upon gentle agitation followed by dilution in aqueous media, such as gastrointestinal (GI) fluids, these systems will form fine oil in water (o/w) emulsion or micro/nano emulsion. Fine oil droplets would pass quickly wide distribution of the drug throughout the stomach and promote wide distribution
of the drug throughout the GI tract, in this manner minimizing the irritation frequently encountered during expanded contact between bulk drug substance and the gut wall.

2. SEDDS are physically stable formulations that are easy to manufacture whereas emulsions are sensitive and metastable dispersed forms.

3. As compared with oily solutions, they provide a large interfacial area for loading of the drug.

4. These systems show enhanced oral bioavailability, selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment in the gut.

5. Reduction in inter-subject and intra-subject variability and food effects

➢ Disadvantages of SEDDS\textsuperscript{47, 48}

1. Lack of good predicative \textit{in vitro} models for assessment of the formulations because traditional dissolution methods do not work, as these formulations potentially are dependent on digestion prior to release of the drug.

2. Need of different prototype lipid based formulations to be developed and tested \textit{in vivo} in a suitable animal model.

3.3. COMPOSITION OF SEDDS

3.3.1. Oils

The one of the most significant excipients in the formulation of SEDDS is oil, as it can solubilize significant amounts of the lipophilic drug or ease self emulsification and as it can take up the fraction of lipophilic drug transported via the intestinal lymphatic system, and thus improving absorption from the GI tract depending on the molecular nature of the triglyceride.
In the design of SEDDS, both long and medium chain triglyceride oils with different degrees of saturation are used. Furthermore, edible oils/natural oils are preferred lipid excipient for the development of SEDDS. But they are not repeatedly chosen because of their poor capability to dissolve large amounts of lipophilic drugs.

A long-chain fatty acid in the SEDDS may also develop the oral bioavailability of highly lipophilic drugs by forming chylomicrons (80-1000 nm) within the enterocytes during the digestion and absorption of lipids, ending in the stimulation of transport into Payer’s patches for systemic circulation directly without experiencing first pass metabolism\(^9\).

Modified or hydrolyzed vegetable oils are used since these excipients form good emulsification systems with a large number of permitted surfactants for oral administration and exhibit improved drug solubility properties. They offer formulative and physiological advantages, their degradation products resemble the natural end products of intestinal digestion. Novel semisynthetic medium chain derivatives, which are amphiphilic compounds with surfactant properties, are progressively and productively replacing the regular medium chain triglyceride oils in the SEDDS\(^0\).

Polyglycolyzed glycerides (PGG) with diverging fatty acid and polyethylene glycol (PEG) chain lengths giving them a varied hydrophilic-lipophilic balance (HLB) value. PGG and PEG with vegetable oils have been used to solubilize poorly water-soluble drugs and improve their bioavailability\(^1\).

Recently, the emulsification and solubilisation properties of polyglycolyzed glyceride (PGG) based oils, Labrafil M 1944 CS (oleoyl macrogolglycerides), Labrafil M 2125CS (linoleoyl macrogolglycerides), Labrasol (caprylocaproyl macrogolglycerides) in self emulsifying formulations have been explored using.
Tween 80 and Tween 20 as surfactants. The more hydrophilic oil-surfactant mixtures showed greater emulsification ability and a smaller particle size\textsuperscript{52}.

The droplet size of the emulsion depends on the lipophilicity of the oil and concentration of oily phase in SEDDS. Hence, it may be difficult for a single oily component to contain optimum properties with respect to nano emulsification and drug delivery. In certain cases, mixture of oils can also be used to meet optimum properties of the oily phase\textsuperscript{53}.

Hence, the choice of the oily phase is often depends on its ability to solubilize the drug and its ability to facilitate formation of nanoemulsion with desired characteristics\textsuperscript{54}.

### 3.3.2. Surfactant

Based on the nature of the hydrophilic group within the surfactant molecules, surfactants are classified into four main groups and are defined as follows,

- Anionic surfactants
- Cationic surfactants
- Ampholytic surfactants
- Nonionic surfactants

**Anionic Surfactants**, in which the hydrophilic group carries a negative charge such as carboxyl (RCOO\textsuperscript{−}), sulphonate (RSO\textsuperscript{3−}) or sulphate (ROSO\textsuperscript{3−}).

Examples: Potassium laurate, sodium lauryl sulphate etc.

**Cationic surfactants**, where the hydrophilic group carries a positive charge.

Example: quaternary ammonium halide.
**Ampholytic surfactants** (also called zwitterionic surfactants) contain both negative and positive charge.

Example: sulfobetaines.

**Nonionic surfactants**, where the hydrophilic group carries no charge but obtains its water solubility from highly polar groups such as hydroxyl or polyoxyethylene (OCH₂CH₂O).

Examples: Sorbitan esters (Spans), polysorbates (Tweens) etc.

Nonionic surfactants with high hydrophilic lipophilic balance (HLB) values are used in formulation of SEDDS. Surfactants carrying a high HLB and hydrophilicity facilitate the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. The customary surfactant strength ranges between 30-60% w/w of the formulation in order to form a stable SEDDS.

### 3.3.3. Co-surfactant

Most single chain surfactants do not reduce the oil-water interfacial tension sufficiently to form nanoemulsions. Further under certain condition, a combination of oil, water and surfactant will result in a phase where there are orderly planes of oil and water separated by monomolecular layer of surfactant. This type of phase is known as liquid crystal (lamellar phase). With large augment in viscosity, liquid crystals formation can be detected. Co-surfactant is incorporated to further lower the interfacial tension between the oil and water phase, fluidize the hydrocarbon region of the interfacial-film, and to influence the film curvature (i.e. droplet size). Some studies wrapped up that co surfactant free nanoemulsion in most system cannot be made except at high temperature.
Typical co-surfactants used are short chain alcohols, glycols such as propylene glycol, medium chain alcohols, amines or acids\textsuperscript{56,57,58}.

3.3.4. Co-solvents

Co-solvents like propylene glycol, diethylene glycol monoethyl ether (transcutol), polyethylene glycol, propylene carbonate, polyoxyethylene, tetrahydrofurfuryl alcohol, polyethylene glycol ether (glycofurol) may aid to dissolve large amounts of hydrophilic surfactants or the hydrophobic drugs in the lipid base. These solvents frequently play the role of the co surfactant in the SEDDS. The use of alcohol has drawbacks of leaching of capsule, when self emulsifying formulation is sealed in capsule shells\textsuperscript{59}.

3.4. Mechanism of self emulsification

The mechanism by which self emulsification happens is not clearly understood. There are many theories which explain the self emulsification process. No single theory explains all aspects of emulsion formation. Thermodynamic theory of formation of emulsion explains that self emulsification occurs when the entropy alter favoring dispersion is greater than the energy necessary to increase the surface area of the dispersion.

\[ \Delta G = \sum N \pi r^2 \sigma \]

Where, \( \Delta G \) 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.

The free energy of a conventional emulsion formulation is a direct function of the energy necessary to create a new surface between the oil and water phases. The
two phases of the emulsion tend to separate with time to lessen the interfacial area and thus the free energy of the system. The conventional emulsifying agent stabilizes emulsion consequential from aqueous dilution by forming a monolayer around the emulsion droplets, lessening the interfacial energy and forming a barrier to coalescence.

On the other hand, emulsification occurs impulsively with SEDDS because the free energy required to form the emulsion is either low and positive or negative. It is essential for the interfacial structure to show no resistance against surface shearing in order for emulsification to occur. The ease of emulsification was suggested to be related to the ease of water penetration into the various liquid crystalline (LC) or gel phases formed on the surface of the droplets. The interface between the oil and aqueous continuous phases is formed upon addition of a binary mixture. This is followed by the solubilization of water within the oil phases as a product of aqueous penetration through the interface. This will happen until the solubilization limit is reached close to the interphase. Further aqueous penetration will be loaded to the formation of the dispersed LC phase. In the end, everything that is in close proximity with the interface will be LC, the actual amount of which depends on the surfactant concentration in the binary mixture. Thus, following mild agitation of the self-emulsifying system, water will rapidly penetrate into the aqueous cores and lead to interface disruptions and droplet formation.

As a consequence of the LC interface formation surrounding the oil droplets, SEDDS turn out to be very stable coalescence. Detailed studies have been carried out to decide the involvement of LC phase in the emulsion formation process. Also, particle size analysis and low frequency dielectric spectroscopy (LFDS) were utilized...
to scrutinize the self-emulsifying properties of a series of Imwitor 742 (a mixture of mono- and diglycerides of capric acids)/Tween 80 system. The results suggested that there might be a complex relationship between LC formation and emulsion formation. Moreover, the presence of the drug compound may modify the emulsion characteristics, probably by interacting with the LC phase. Nevertheless, the association between the LC formation and spontaneous emulsification has still not been established\textsuperscript{60,61}.

3.5. BIOPHARMACEUTICAL ASPECTS

The ability of lipids and/or food to enhance the bioavailability of inadequately water soluble drugs is well proposed. Although incompletely understood, the currently accepted view is that lipids may enhance the bioavailability via a number of potential mechanisms, which includes:

a) Alterations (reduction) in gastric transit, thereby slowing delivery to the absorption site and increasing the time available for dissolution.

b) Improvement in effective luminal drug solubility. The lipids presence in the GI tract arouses an increase in the secretion of bile salts (BS) and endogenous biliary lipids together with phospholipids (PL) and cholesterol (CH), results in the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilization capacity of the GI tract. However, intercalation of administered (exogenous) lipids into these BS structures either unswervingly (if sufficiently polar), or secondary to digestion, leads to swelling of the micellar structures and a further increase in solubilization capacity.

c) Stimulation of intestinal lymphatic transport. For highly lipophilic drugs, lipids may enhance the amount of lymphatic transport and increase bioavailability.
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directly or indirectly via a reduction in first-pass metabolism. A hydrophilic drug is less likely to be absorbed through the lymphatic (chylomicon) and instead may diffuse directly into the portal supply. Hence in this case, increased dissolution from the large surface area afforded by emulsion may be a contributing factor to enhanced absorption of drugs.

d) Changes in the biochemical barrier function of the GI tract. It is obvious that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as specified by the p-glycoprotein efflux pump, and thus reduce the extent of enterocyte based metabolism.

e) Changes in the physical barrier function of the GI tract. Different combinations of lipids, lipid digestion products and surfactants have been exposed to have permeability enhancing properties. For the most part, however, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water-soluble, and particularly, lipophilic drugs.$^{62, 63, 64}$

3.6. CONSTRUCTION OF PHASE DIAGRAM$^{65, 66}$

The relationship between the phase behavior of a mixture and its composition can be presented with the help of a phase diagram. Compositional variables can also be studied as a function of temperature and pressure, although majority of systems are studied under conditions of ambient pressure. The phase behavior of simple nanoemulsion systems comprise of oil, water and surfactant that can be studied with the aid of ternary phase diagram in which each corner of the diagram represents 100% of that particular component. In the case of nanoemulsions in pharmaceutical applications, the nanoemulsion will enclose additional components such as a co surfactant and/or drug. The co surfactant is amphiphilic with an affinity for both the
oil and aqueous phases and partitions to a considerable extent into the surfactant interfacial monolayer present at the oil-water interface. The co surfactants need not forcibly to be capable of forming association structures on its own. An extensive variety of molecules can function as surfactants including non-ionic surfactants, alcohols, alkanoic acids, alkanediols and alkyl amines. Surprisingly few studies have examined the effect of drug on phase behavior, this is regardless of the fact that large numbers of drug molecules are themselves surface active and as such would be expected to influence phase behavior.

In the case where four or more components are examined, pseudo-ternary phase diagrams are used where a corner will typically represent a binary mixture of two components such as surfactant / co-surfactant. The number of different phases present for a particular mixture can be visually assessed. A highly schematic (pseudo) ternary phase diagram illustrating these features is depicted in Figure 3.2.

![Phase Diagram](image)

**Figure 3.2: Typical phase diagram**

The surfactants and co surfactant (Smix) was mixed at different ratios. For each phase diagram, oil and Smix at a specific ratio was mixed thoroughly at different mass ratios from 1:9 to 9:1 in different glass vials.
It should be noted that not every sequence of components produce nanoemulsions over the whole range of possible compositions, in some instances the extent of nanoemulsion formation may be very finite.

Constructing phase diagrams is prolonged, particularly when the aim is to accurately delineate a phase boundary, as the time taken for the system to equilibrate can be greatly increased as the phase boundary is approached. However, time limitations impose a physical limit on the length of time system can be left to equilibrate and as a result the elimination of metastable states can be difficult to ensure in practice, although centrifugation can be useful to speed up any separation. Within this region, and indeed other multi phase regions of the ternary phase diagram, nanoemulsions can exist in equilibrium with excess water or oil phases.

It is well accepted that the emulsification is based on two opposite processes: drop breakup resulting in the production of several finer droplets from a larger drop, and droplet-droplet coalescence leading to the formation of a larger drop from two small droplets. Competition between these two processes, generally determines the drop size during emulsification.

At high surfactant concentrations, the contribution of the droplet-droplet coalescence is negligible so that the process of drop breakup determines the evolution of the drop-size distribution in the formed emulsion. After a long enough emulsification time, a “steady-state” is reached, which is characterized by a relatively slow change of the drop-size distribution in the formed emulsions. In the surfactant rich regime, the mean drop size practically does not depend on surfactant concentration and is affected by the type of used surfactant mainly through the equilibrium value. At lower emulsifier concentration, the mean drop size depends strongly on the emulsifier type and concentration.
3.7. SOLID SELF EMULSIFYING DRUG DELIVERY SYSTEM (S-SEDDS)

SEDDS can exist in either liquid or solid states. SEDDS are usually, however, limited to liquid dosage forms, as many excipients used in the formulation of SEDDS are not solids at room temperature. To incorporate the advantages of solid dosage forms, S-SEDDS have been generously explored in recent years, as they often represent more effective alternatives to conventional liquid SEDDS. From the point of view of dosage forms, S-SEDDS mean solid dosage forms with self emulsification properties. S-SEDDS focus on the incorporation of liquid/semisolid SE ingredients into powders/nanoparticles by different solidification techniques.

➢ Capsule filling with liquid and semi-solid lipid-based formulations

The simplest and most common technology to encapsulate liquid or semi-solid lipid-based formulations for the oral route is capsule filling.

• For semi-solid formulations, it is a four step-process:

Heat the semi-solid excipient at least 20°C above its melting point, incorporate the active substances under stirring, and fill the molten mixture in capsules (hard or soft capsules) and cool down to room temperature.

• For liquid formulations, it involves a two step-process:

Fill the formulation into the capsules and then sealed the body and the cap of the capsule either by banding (depositing a gelatin band) or by microspray sealing (LEMS® system).

The compatibility of the excipients with the capsule shell is the significant consideration in capsule filling. Before filling, in the case of semi-solid or solid lipid-based excipients, the bulk fill reservoir should be heated to maintain the formulation
molten and under stirring to avoid phase separation and sedimentation of the drug if dispersed. The temperature of the filling process is one of the key parameters for capsule filling; it should be at least 2°C above the temperature at which the apparent viscosity of the drug-excipient mixture significantly increases during cooling. The maximum filling temperatures are 70°C for hard shell capsules and 40°C for soft gelatin capsules. Another critical parameter is the physical state of the drug in the formulation (suspension or solution). For filling of suspensions in soft capsules, the factors to be considered are size of particle (distribution must be below 250 µm) and the viscosity (should be controlled to ensure a homogeneous suspension and an easy filling). Semi-solid formulations must be permitted to cool for at least 24 h at room temperature after filling to allow complete crystallization of the excipient(s) prior to evaluation of the formulation. Numerous publications have described the use of this technology for enhancing drug solubility and absorption via the gastro-intestinal tract. The advantages of capsule filling are: simplicity of manufacturing, suitability for low dose, highly potent drugs; high drug loading (up to 50% w/w) potential; and possibility for high lipid exposure (up to 99% w/w).

The excipients used in capsule filling may be classified into four categories, according to the classification introduced by Colin Pouton,68 ‘oils’, ‘water-insoluble surfactants’ (HLB<12), ‘water-soluble surfactants’ (HLB>12), and ‘hydrophilic cosolvents’. Only examples of the first three categories are listed below as they are lipid-based or related excipients:

(i) ‘Oils’ or lipophilic excipients i.e. medium chain triglycerides, corn oil, and acetylated monoglycerides
(ii) ‘Water-insoluble surfactants’: propylene glycol monolaurate, glyceryl monolinooleate
(iii) ‘Water-soluble surfactants’: lauroyl polyoxylglycerides, polysorbate, PEG stearate, ethoxylated castor oil; caprylocaproyl polyoxylglycerides or d-alpha-tocopheryl polyethylene glycol 1000 succinate68.

** Adsorption on solid carriers **

Free flowing powders may be obtained from liquid self emulsifying formulations by adsorption on to solid carriers. The process involved in adsorption is simple and just involves addition of the liquid formulation onto carriers by mixing in a blender. The obtained powder may then be filled directly into capsules or, alternatively, mixed with appropriate excipients before compression into tablets. A main benefit of the adsorption technique is good content uniformity.

SEDDS can be adsorbed at high levels (up to 70% w/w) onto suitable carriers. The solid carriers can be micro porous inorganic substances, high surface area colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticle adsorbents, for instance, silica, silicates, magnesium trisilicate, magnesium hydroxide, talc, crospovidone, cross-linked sodium carboxymethyl cellulose and cross linked polymethyl methacrylate69. Crosslinked polymers create a favorable environment to sustain drug dissolution and also help out in slowing down drug reprecipitation70.

Nanoparticle adsorbents encompass porous silicon dioxide (Sylsia 550), carbon nanotubes, carbon nanohorns, fullerene, charcoal and bamboo charcoal24,71.

** Spray drying **

In this technique, formulation involves mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixtures previous to spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The unstable phase (e.g.
the water contained in an emulsion) evaporates as the droplets introduced into a drying chamber, forming dry particles under controlled temperature and airflow conditions.

Critical parameters of spray drying includes inlet temperature, outlet temperature, viscosity, solid content, surface tension, feed temperature, volatility of solvent, nozzle material. According to the drying characteristics of the product and powder specification the atomizer, the temperature, the most fitting airflow pattern and the drying chamber design are selected\textsuperscript{72, 73}.

- **Melt extrusion**

  This formulation technique depends on the property of the plastic mass material which can be with no trouble extruded and spheronised with pressure. Here there is no need for adding up of liquid form of excipient but a steady temperature and pressure need to be maintained\textsuperscript{74}.

- **Melt granulation**

  Melt granulation is a process in which powder agglomeration is obtained by the addition of a binder that melts or softens at relatively low temperatures. As a ‘one-step’ operation, melt granulation offers a number of advantages compared with conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted. Moreover, it is also a good alternative to the use of solvent. The main parameters that control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder. A wide range of solid and semisolid lipids can be applied as meltable binders. There into, Gelucire, a family of vehicles derived from the mixtures of mono-/di-/tri-glycerides and polyethylene
glycols (PEG) esters of fatty acids, is able to further increase the dissolution rate compared with PEG usually used before, probably owing to its SE property. Other lipid-based excipients evaluated for melt granulation to create solid SEDDS include lecithin, glycerides or polysorbates. The melt granulation process was usually used for adsorbing SEDDS (lipids, surfactants, and drugs) onto solid neutral carriers (mainly silica and magnesium aluminometasilicate).\textsuperscript{75}

\begin{itemize}
\item \textbf{Spray cooling}
\end{itemize}

Spray cooling, also referred as spray congealing, is a process whereby the molten formula is sprayed into a cooling chamber. Upon contact with the cooling air, the molten droplets congeal and re-crystallize into spherical solid particles that fall to the bottom of the chamber and then collected as fine powder. The fine powder may subsequently be used for development of solid dosage forms, tablets or direct filling into hard shell capsules. Many types of equipment are accessible to atomize the liquid mixture and to generate droplets: rotary, pressure, two-fluid or ultrasonic atomizers.\textsuperscript{76}

Recently most of the research conducted on spray cooling with lipid-based excipients was done with ultrasonic atomizers. The main parameters for spray cooling are the melting point of the excipient that should range between 50 to 80°C, the viscosity of the formulation during atomization, and the cooling air temperature inside the atomizer to allow a quick and entire crystallization of droplets.

The spray cooling technique can be used for bioavailability enhancement and or sustained release formulations - depending on the choice of lipid matrix, and the drug behavior in that matrix (solution or dispersion). The drug loading capacity is limited by formulation viscosity as dispersions generally have a tendency to be more
viscous than solutions. A maximum of 30% drug loading capacity has been reported in the literature\textsuperscript{77}.

\textbf{Supercritical fluid based method}

Lipids may be used in supercritical fluid based methods either for coating of drug particles, or for producing solid dispersions. For environmental reasons, the preferred supercritical fluid of choice is supercritical carbon dioxide. Examples consist of controlled release applications using glyceryltrimyristate (Dynasan\textsuperscript{TM} 114) and stearoylpolyoxylglycerides (Gelucire® 50/02)\textsuperscript{78}.

\section*{3.8. ADVANCES IN DOSAGE FORMS OF SOLID SEDDS}

\textbf{Dry emulsions}

Dry emulsions are powders from which emulsion spontaneously occurs \textit{in vivo} or when exposed to an aqueous solution. Dry emulsions can be useful for further preparation of tablets and capsules. Dry emulsion formulations are typically prepared from oil/ water (O/W) emulsions containing a solid carrier (lactose, maltodextrin etc) in the aqueous phase by rotary evaporation, freeze-drying or spray drying. Myers and Shively\textsuperscript{79} obtained solid state glass emulsions in the form of dry ‘foam’ by rotary evaporation, with heavy mineral oil and sucrose. Such emulsifiable glasses have the advantage of not requiring surfactant. Cryoprotectants have the best stabilizing effects, while heat treatment earlier than thawing decreases the stabilizing effects. The technique of spray drying is more often used in preparation of dry emulsions. The O/W emulsion was formulated and then spray-dried to eliminate the aqueous phase. The most exciting finding in this field ought to be the newly developed enteric-coated dry emulsion formulation, which is potentially applicable for the oral delivery of
peptide and protein drugs. This formulation consisted of surfactant; a vegetable oil, and a pH-responsive polymer, with lyophilisation used. Recently prepared dry emulsions by spreading liquid O/W emulsions on a flat glass then dried and triturated to powders.

**Self emulsifying solid dispersion**

Liquid self-emulsifying formulations rely on micelle or solvent/co solvent systems to fully solubilize the drug dose, which helps to ensure optimal absorption. However the worth of these formulations can be limited by their incapability to solubilize the entire drug dose in the volume of a single oral capsule. In these instances, solid dispersion formulations, which may not fully solubilize the drug in the excipient matrix, can provide a viable, although not necessary as effective, alternative oral formulation. These formulations consist of a dispersion of the drug in an inert excipient matrix, where the drug could exist in either the finely divided crystalline, solubilized or amorphous states or a mixture thereof. This can increase the dissolution rate of the drug and subsequent absorption from, the GI tract relative to the steady crystalline drug substance\textsuperscript{12}. These excipient have the potential to further increase the absorption of poorly water-soluble drugs relative to previously used PEG solid dispersions and may also be filled directly into hard gelatin capsules in the molten state, thus obviating the former requirement for milling and blending prior to filling\textsuperscript{80}.

**Self emulsifying sustained/controlled release tablets**

Lipids and surfactants combination have present great potential of preparing SE tablets that have been extensively researched. Nazzal and Khan\textsuperscript{81} evaluated the effect of some processing parameters (colloidal silicates-X1, magnesium stearate
mixing time- X2, and compression force-X3) on hardness and coenzyme Q10 (CoQ10) dissolution from tablets of eutectic-based SMEDDS. The optimized conditions (X1 = 1.06%, X2 = 2 min, X3 = 1670 kg) were achieved by a face-centered cubic design. In order to reduce significantly the amount of solidifying excipients needed for transformation of SEDDS into solid dosage forms, a gelled SEDDS has been developed by Patil et al.\textsuperscript{82} In their study, colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems, which served the dual purpose of reducing the amount of required solidifying excipients and aid in slowing down of the drug release. SE tablets are of great utility in obviating adverse effect, as disclosed by Schwarz in a patent\textsuperscript{83}. Inclusion of indomethacin (or other hydrophobic NSAID), for example, into SE tablets may increase its penetration efficacy through the GI mucosal membranes, potentially reducing GI bleeding. In these studies, the SES was composed of glycerol monolaurate and Tyloxapol TM (a copolymer of alkyl phenol and formaldehyde).

➢ Self emulsifying sustained/controlled release pellets

Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage forms, such as flexibility of manufacture, reducing intrasubject and intersubject inconsistency of plasma profiles and minimizing GI irritation without lowering drug bioavailability. Thus, it is very appealing to combine the advantages of pellets with those of SEDDS by SE pellets. Serratoni et al\textsuperscript{84} prepared SE controlled-release pellets by incorporating drugs into SES that improved their rate of release, and then by coating pellets with a water-insoluble polymer that reduced the rate of drug release. Pellets were prepared by extrusion/ spheronization and contained two water-insoluble model drugs (methyl and propyl parabens); SES contained mono-diglycerides and Polysorbate 80. This research demonstrated that
combinations of coating and SES could control in vitro drug release by providing a range of release rates; and the presence of the SEDDS did not influence the ability of the polymer film to control drug dissolution. There is another report that SE sustained-release matrix pellets could be fruitfully formulated with glycercylpalmitostearate (Gelucire 54/02) and glycerylbhenate (Gelucire 70/02)\textsuperscript{85}.

- **Gelled self emulsifying system for extended release**

  Gelled self-emulsifying drug delivery system containing ketoprofen as an intermediate in the growth of sustained release solid dosage form was developed by Patil et al\textsuperscript{86}. Silicon dioxide was used as a gelling agent to aid in solidification and retardation of drug release. The authors studied effect of concentrations of cosurfactant and gelling agent on emulsification process and in vitro drug diffusion. Results showed that liquid crystal phase viscosity augmented significantly with increasing amount of silicon dioxide, which in turn caused an increase in average droplet size of resultant emulsion and slower drug diffusion.

  Another gelled self-emulsifying system of felodipine was developed by same authors using Aerosil 200 as gelling agent. The gelled self-emulsifying system was further covered within the hydrophobic Gelucire® 43/01 coat to extend the release of felodipine\textsuperscript{87}.

- **Self emulsifying suppositories**

  Some investigators proved that S-SEDDS could amplify not only GI adsorption but also rectal/vaginal adsorption. Glycyrhrizin, which, by the oral route, barely achieves therapeutic plasma concentrations, can gain satisfactory therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE suppositories. The
formulation included glycyrrhizin and a mixture of a C6–C18 fatty acid glycerol ester and a C6-C18 fatty acid macrogol ester.88

➢ Self emulsifying implants

Research into SE implants has greatly enhanced the utility and application of S-SEDDS. As an example, 1, 3-bis (2-chloroethyl)-1-nitrosourea (carmustine, BCNU) is a chemotherapeutic agent used to treat malignant brain tumors. However, its effectiveness was hindered by its short half-life. Loomis invented copolymers having a bio-resorbable region, a hydrophilic region and at least two cross-linkable functional groups per polymer chain. Such copolymers show SE property without the requirement of an emulsifying agent. These copolymers can be used as good sealants for implantable prostheses.89

➢ Supersaturatable self emulsifying drug delivery systems

Hydroxypropyl methylcellulose (HPMC) propels self-emulsifying drug delivery systems (SEDDS) to achieve the supersaturated state in gastrointestinal tract, which possesses important significance to enhance oral absorption for poorly water-soluble drugs. This study investigated capacities and mechanisms of HPMC with different viscosities (K4M, K15M and K100M) to inhibit drug precipitation of SEDDS in the simulated gastrointestinal tract environment in vitro.

The results showed that HPMC inhibited drug precipitation during the dispersion of SEDDS under gastric conditions by inhibiting the formation of crystal nucleus and the growth of crystals. HPMC had evident effects on the rate of SEDDS lipolysis and benefited the distribution of drug molecules across into the aqueous phase and the decrease of drug sediment. The mechanisms were linked to the
formed network of HPMC and its viscosities and molecular weight. These results offered a reference for selecting appropriate type of HPMC as the precipitation inhibitor of supersaturatable SEDDS.

Table 3.1: List of marketed products based on self-emulsifying drug delivery systems

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>Dosage Form</th>
<th>Lipidic components</th>
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</thead>
<tbody>
<tr>
<td>Amprenavir</td>
<td>Agenerase/ GlaxoSmithkline</td>
<td>SG capsule</td>
<td>D-alpha TPGS</td>
</tr>
<tr>
<td>Bexarotene</td>
<td>Targretin/Ligand</td>
<td>SG capsule</td>
<td>Polysorbate 80</td>
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<tr>
<td>Calcitriol</td>
<td>Rocaltrol/Roche</td>
<td>SG capsule, solution</td>
<td>Fractionated medium chain TG of coconut oil and palm seed oil</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>CoregCR/ GlaxoSmithkline</td>
<td>CR HG capsule</td>
<td>Hydrogenated castor oil, Hydrogenated vegetable oil</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>CoregCR/ GlaxoSmithkline</td>
<td>CR HG capsule</td>
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<tr>
<td>Ciprofloxacin</td>
<td>Cipro/Bayer</td>
<td>Microcapsules for suspension</td>
<td>Medium-chain TG</td>
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<tr>
<td>Cyclosporin A</td>
<td>Neoral/Novartis</td>
<td>SG capsules, Oral suspensions</td>
<td>dl-alpha tocopherol, corn oil-mono dl-TG, CremophorRH 40</td>
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<tr>
<td>Dronabiol</td>
<td>Marino/roxane and Unimed</td>
<td>SG capsule</td>
<td>Sesame oil</td>
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<tr>
<td>Dutasteride</td>
<td>Avodart/GSK</td>
<td>SG capsule</td>
<td>Mixture of mono-and diglycerides of caprylic/capric acid</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Lipofen/Kowa pharmaceuticals America, Inc</td>
<td>HG capsule</td>
<td>Gelucire 44/14</td>
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<tr>
<td>Drug</td>
<td>Manufacturer</td>
<td>Formulation</td>
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</tr>
<tr>
<td>Ibuprofen</td>
<td>Solufen/</td>
<td>HG capsule</td>
<td>Hydrogenated vegetable oils</td>
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<td>Sanofi-Aventis</td>
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<tr>
<td>Isotretinoin</td>
<td>Accutane/Roche</td>
<td>SG capsule</td>
<td>Bees wax, Hydrogenated oil flaxes, Hydrogenated vegetable oils, soyabean oil</td>
</tr>
<tr>
<td>Lopinavir and Ritonavir</td>
<td>Kaletra/Abbott</td>
<td>Tablet, SG capsule</td>
<td>Span 20</td>
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<tr>
<td>Mesalamine</td>
<td>Pentasa/ShireUS inc.</td>
<td>CR capsules</td>
<td>Acetylated monoglyceride, castor oil</td>
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<td>Omega-3-acid esters</td>
<td>Lovaza/GSK</td>
<td>HG capsule</td>
<td>Alpha-tocopherol</td>
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<tr>
<td>Paricalcitol</td>
<td>Zemplar/Abbott</td>
<td>SG capsule</td>
<td>Fractionated medium chain TG of coconut oil or palm Kernel oil</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Fortovase/Roche</td>
<td>SG capsule</td>
<td>Medium-chain mono- and diglycerides, dl-alpha tocopherol</td>
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<tr>
<td>Sirolimus</td>
<td>Rapamune/Wyeth-Ayerst</td>
<td>Oral solution</td>
<td>Phosal 50, PG, Polysorbate 80</td>
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<tr>
<td>Tipranavir</td>
<td>Aptivus/boehringer/Ingelheim</td>
<td>SG capsule</td>
<td>Cremophor EL, Medium-chain mono-and diglycerides</td>
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<tr>
<td>Tolterodine tartrate</td>
<td>DetroILA/Pharmacia</td>
<td>ER HG capsule</td>
<td>Medium-chain triglycerides, oleic acid</td>
</tr>
<tr>
<td>Tretinon</td>
<td>Vesanioid/Roche</td>
<td>SG capsule</td>
<td>Bees wax</td>
</tr>
</tbody>
</table>
DRUG PROFILE

**EFAVIRENZ** \(^{93, 32, 33}\)

![Chemical Structure of Efavirenz](image)

**Molecular formula:** \(\text{C}_{14}\text{H}_9\text{ClF}_3\text{NO}_2\)

**Average Mol. Wt:** 315.7

**IUPAC name:** \((4S) - 6 - \text{chloro} - 4 - (\text{cyclopropylethynyl})-1, 4\text{-dihydro}-4-(\text{trifluoromethyl}) - 2\text{H}-3,1\text{-benzoxazin}-2\text{-one}.

**Description:** White to slightly pink powder.

**Solubility:** Practically insoluble in water, freely soluble in methanol.

**Log P:** 4.6

**Half life:** 40-55 hours

**Bioavailability:** 40-45%

**Melting point:** 139-141°C

**Log P:** 4.6

**Pharmacodynamics:** Efavirenz (dideoxyinosine, ddI) is an oral nucleoside reverse transcriptase inhibitor (NRTI). It is a synthetic purine derivative and, similar to zidovudine, zalcitabine, and stavudine. Efavirenz was originally approved specifically
for the treatment of HIV infections in patients who failed therapy with zidovudine. Currently, the CDC recommends that Efavirenz be given as part of a three-drug regimen that includes another nucleoside reverse transcriptase inhibitor (e.g., lamivudine, stavudine, zidovudine) and a protease inhibitor or efavirenz when treating HIV infection.

**Mechanism of action:** Similar to zidovudine, efavirenz inhibits the activity of viral RNA-directed DNA polymerase (i.e., reverse transcriptase). Antiviral activity of efavirenz is dependent on intracellular conversion to the active triphosphorylated form. The rate of efavirenz phosphorylation varies, depending on cell type. It is believed that inhibition of reverse transcriptase interferes with the generation of DNA copies of viral RNA, which, in turn, are necessary for synthesis of new virions. Intracellular enzymes subsequently eliminate the HIV particle that previously had been uncoated, and left unprotected, during entry into the host cell. Thus, reverse transcriptase inhibitors are virustatic and do not eliminate HIV from the body. Even though human DNA polymerase is less susceptible to the pharmacologic effects of triphosphorylated efavirenz, this action may nevertheless account for some of the drug's toxicity.

**Metabolism:** Efavirenz is principally metabolized by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1.

**Category:**
- Anti-HIV Agents
- Nonnucleoside Reverse Transcriptase Inhibitors
- Reverse Transcriptase Inhibitors
**ATORVASTATIN CALCIUM**\textsuperscript{93,34,35}

![Molecular structure of Atorvastatin Calcium]

**Molecular formula:** C\textsubscript{33}H\textsubscript{35}FN\textsubscript{2}O\textsubscript{5}

**Average Mol. Wt:** 558.64

**IUPAC name:** (3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid calcium salt (2:1) trihydrate.

**Solubility:** Very slightly soluble in distilled water, pH 7.4, phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol

**Melting point:** 159.2-160.7°C

**Log P:** 5.7

**Bioavailability:** Approximately 14%

**Half-life:** 14 h

**Pharmacodynamics:** Atorvastatin calcium, a selective, competitive HMG-CoA reductase inhibitor, is used to lower serum total and LDL cholesterol, apolipoprotein B and triglyceride levels while increasing HDL cholesterol. By decreasing LDL-C and TG and increasing HDL-C, atorvastatin reduces the risk of cardiovascular morbidity and mortality. Atorvastatin has a unique structure, long half-life, and...
hepatic selectivity, explaining its greater LDL-lowering potency compared to other HMG-CoA reductase inhibitors.

**Mechanism of action:** Atorvastatin calcium selectively and competitively inhibits the hepatic enzyme HMG-CoA reductase. As HMG-CoA reductase is responsible for converting HMG-CoA to mevalonate in the cholesterol biosynthesis pathway, these results in a subsequent decrease in hepatic cholesterol levels. Decreased hepatic cholesterol levels stimulate upregulation of hepatic LDL-C receptors which increases hepatic uptake of LDL-C and reduces serum LDL-C concentrations.

**Metabolism:** Atorvastatin calcium is extensively metabolized to ortho and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. CYP3A4 is also involved in the metabolism of atorvastatin.

**Toxicity:** Generally well-tolerated. Side effects may include myalgia, constipation, asthenia, abdominal pain, and nausea. Other possible side effects include myotoxicity (myopathy, myositis, rhabdomyolysis) and hepatotoxicity. To avoid toxicity in Asian patients, lower doses should be considered.

**Categories:**

- Anticholesteremic Agents,
- HMG-CoA Reductase Inhibitors
ROSUVASTATIN CALCIUM\textsuperscript{93,36,37}

\[\text{Molecular formula: } 2(\text{C}_{22}\text{H}_{27}\text{FN}_{3}\text{O}_{6}\text{S})\text{ Ca}\]

\[\text{Average Mol. Wt: } 481.538\]

\[\text{IUPAC name: } (3R,5S,6E)-7-[4-(4-fluorophenyl)-2-(N-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid calcium salt\]

\[\text{Solubility: Sparingly soluble in water and methanol, and slightly soluble in ethanol.}\]

\[\text{Bioavailability: Approximately } 20\%\]

\[\text{Log P: } 5.7\]

\[\text{Melting point: } 122^\circ\text{C}\]

\[\text{Half-life: } 19\text{ hours}\]

\[\text{Pharmacodynamics: } \text{Rosuvastatin calcium is a synthetic, enantiomerically pure antilipemic agent. It is used to lower total cholesterol, low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apoB), non-high density lipoprotein-cholesterol (non-HDL-C), and triglyceride (TG) plasma concentrations while increasing HDL-C concentrations. High LDL-C, low HDL-C and high TG concentrations in the plasma are associated with increased risk of atherosclerosis and cardiovascular disease. The total cholesterol to HDL-C ratio is a strong predictor of coronary artery disease and high ratios are associated with higher risk of disease. Increased levels of}\]
HDL-C are associated with lower cardiovascular risk. By decreasing LDL-C and TG and increasing HDL-C, rosuvastatin reduces the risk of cardiovascular morbidity and mortality.

**Mechanism of action:** Rosuvastatin calcium is a competitive inhibitor of HMG-CoA reductase. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, an early rate-limiting step in cholesterol biosynthesis. Rosuvastatin acts primarily in the liver. Decreased hepatic cholesterol concentrations stimulate the upregulation of hepatic low density lipoprotein (LDL) receptors which increases hepatic uptake of LDL. Rosuvastatin also inhibits hepatic synthesis of very low density lipoprotein (VLDL). The overall effect is a decrease in plasma LDL and VLDL. *In vitro* and *in vivo* animal studies also demonstrate that rosuvastatin exerts vasculoprotective effects independent of its lipid-lowering properties.

**Metabolism:** Not extensively metabolized. Only ~10% is excreted as metabolite. Cytochrome P450 (CYP) 2C9 is primarily responsible for the formation of rosuvastatin's major metabolite, N-desmethylrosuvastatin. N-desmethylrosuvastatin has approximately 50% of the pharmacological activity of its parent compound in vitro. Rosuvastatin accounts for greater than 87% of the pharmacologic action. Inhibitors of CYP2C9 increase the AUC by less than 2-fold. This interaction does not appear to be clinically significant.

**Toxicity:** Generally well-tolerated. Side effects may include myalgia, constipation, asthenia, abdominal pain, and nausea. Other possible side effects include myotoxicity (myopathy, myositis, rhabdomyolysis) and hepatotoxicity. To avoid toxicity in Asian patients, lower doses should be considered. Pharmacokinetic studies show an approximately two fold increase in peak plasma concentration and AUC in Asian
patients (Philippino, Chinese, Japanese, Korean, Vietnamese, or Asian-Indian descent) compared to Caucasians patients.

Categories:

- Anticholesteremic Agents,
- HMG-CoA Reductase Inhibitors,
EXCIPIENTS

TWEEN 20

W + X + Y + Z = 20 (Polysorbates 20, 40, 60, 65, 80, and 85)

Molecular formula: C_{58}H_{114}O_{26}

Molecular weight: 1128

Nonproprietary Names: BP: Polysorbate 20

Chemical name: Polyoxyethylene 20 sorbitan monolaurate

Description: Polysorbates have a characteristic odor and a warm, somewhat bitter taste. They are Yellow oily liquid at 25°C, although it should be noted that the absolute color intensity of the products may vary from batch to batch and from manufacturer to manufacturer.

HLB value: 16.7

Functional Category: Dispersing agent; emulsifying agent; nonionic surfactant; solubilizing agent; suspending agent; wetting agent.

Safety:

Polysorbates are widely used in cosmetics, food products, and oral, parenteral and topical pharmaceutical formulations, and are generally regarded as nontoxic and
nonirritant materials. There have, however, been occasional reports of
hypersensitivity to polysorbates following their topical and intramuscular use.

Polysorbate 20 Moderate toxicity by IP and IV routes. Moderately toxic by ingestion.

Human skin irritant.

LD50 (hamster, oral): 18 g/kg (8)

LD50 (mouse, IV): 1.42 g/kg

LD50 (rat, oral): 37 g/kg

**Regulatory Status**

Polysorbates 20, 40, 60, 65, and 80 are accepted as food additives in Europe.

Polysorbates 20, 40, 60, and 80 are included in the FDA Inactive Ingredients Database (IM, IV, oral, rectal, topical, and vaginal preparations). Polysorbates are included in parenteral and nonparenteral medicines licensed in the UK. Polysorbates 20, 21, 40, 60, 61, 65, 80, 81, 85, and 120 are included in the Canadian List of Acceptable Non-medicinal Ingredients.
TWEEN 80  

\[ W + X + Y + Z = 20 \] (Polysorbates 20, 40, 60, 65, 80, and 85)

**Nonproprietary Names:** Polysorbate 80

**Molecular formula:** \( \text{C}_{64}\text{H}_{124}\text{O}_{26} \)

**Molecular weight:** 1310

**Chemical name:** Polyoxyethylene 20 sorbitan monooleate

**HLB value:** 15.0

**Specific gravity at 25°C:** 1.08

**Viscosity:** 425 mPas

**Functional Category:** Dispersing agent; emulsifying agent; nonionic surfactant; solubilizing agent; suspending agent; wetting agent.

**Incompatibilities:** Discoloration and/or precipitation occur with various substances, especially phenols, tannins, tars, and tarlike materials. The antimicrobial activity of paraben preservatives is reduced in the presence of polysorbates.
LABRAFAC™ PG

Propylene glycol dicaprylocaprate EP
Propylene glycol dicaprylate/dicaprate NF

Key Features

Oral

Oily vehicle for use in self-emulsifying lipid formulations to obtain a coarse dispersion ie. emulsion (SEDDS) or a fine dispersion ie. microemulsion (SMEDDS).

Topical

Oily phase for emulsion or ointment with emollient properties.

Good solvent for lipophilic active pharmaceutical ingredients.

Safety of use is supported by substantial toxicological data and precedence of use in approved pharmaceutical products.

Physical Form: liquid

Hydrophilic-Lipophilic Balance (HLB): 2

Field of use

Human pharmaceutical products, veterinary products including food producing animals

Administration Route

Oral, Topical

Formulation techniques and dosage forms

Suitable for hard gelatin and soft gelatin capsules.
Suitable for adsorption onto neutral carrier powders for use in tablets, capsule filling and sachets.

Use in topical ointments, microemulsions and emulsions

**CAPMUL MCM**

**Product description:** Mono diglycerides

**Chemical Name:** Glyceryl Mono-Dicaprylate

**Physical state:** Liquid

**Odour:** Mild, fatty or grease smell

**Appearance:** Off white liquid

**Colour:** Off white

**Solubility:** Partially soluble in water

**Stability:** Stable under normal conditions

**Characteristics:** They are lipophilic, partially soluble in water and soluble in oils at elevated temperatures. They are used to produce stable emulsions and to modify viscosity. Caprylic and capric mono-diglyceride esters function as very effective carriers and solubilizers of active compounds. Mono-diglyceride medium chain esters are particularly recommended for the dissolution of difficult compounds such as sterols and have also exhibited bacteriostatic activity.

**Application:** It is recommended for creams, lotions, ointments and lipsticks. Capmul® MCM has pharmaceutical and nutritional applications of a carrier (vehicle), solubilizer, emulsifier/co-emulsifier, bioavailability enhancer, and penetration enhancer (dermatological applications).

**Toxicity:** None expected acute toxicity or chronic toxicity.
PEG 200

Structural Formula

![Structural Formula](image_url)

**Synonyms:** Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; macrogola; PEG; Pluriol E; polyoxyethylene glycol.

**Chemical Name:** $\alpha$-Hydro-\(\omega\)-hydroxypoly(oxy-1,2-ethanediyl).

**Empirical Formula:** \(\text{HOCH}_2\text{(CH}_2\text{OCH}_2)\text{mCH}_2\text{OH}\)

where \(m\) represents the average number of oxyethylene groups (\(m = 4.2\))

**Molecular weight:** 190–210

**Description:** Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste.

**Density:** 1.11–1.14 g/cm\(^3\) at 25°C

**Viscosity at 25°C:** 39.9 [mm\(^2\)/s (cSt)]

**Solubility:** All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher molecular weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and...
methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

**Functional Category:** Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

**Safety**

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials. Adverse reactions to polyethylene glycols have been reported, the greatest toxicity being with glycols of low molecular weight. However, the toxicity of glycols is relatively low.

**Regulatory Status**

Included in the FDA Inactive Ingredients Database (dental preparations; IM and IV injections; opthalmic preparations; oral capsules, solutions, syrups, and tablets; rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

**Stability and Storage Conditions**

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid.
PROPYLENE GLYCOL

Synonyms: 1,2-Dihydroxypropane; E1520; 2-hydroxypropanol; methyl ethylene glycol; methyl glycol; propane-1,2-diol; propylenglycolum.

Chemical Name: 1,2-Propanediol.

Empirical Formula: C₇H₆O₂

Molecular Weight: 76.09

Solubility: Miscible with acetone, chloroform, ethanol (95%), glycerin, and water; soluble at 1 in 6 parts of ether; not miscible with light mineral oil or fixed oils, but will dissolve some essential oils.

Functional Category: Antimicrobial preservative; disinfectant; humectant; plasticizer; solvent; stabilizing agent; water-miscible cosolvent.

Description: Propylene glycol is a clear, colorless, viscous, practically odorless liquid, with a sweet, slightly acrid taste resembling that of glycerin.

Boiling point: 188°C

Density: 1.038 g/cm³ at 20°C
Review of Literature

Solubility: Miscible with acetone, chloroform, ethanol (95%), glycerin, and water; soluble at 1 in 6 parts of ether; not miscible with light mineral oil or fixed oils, but will dissolve some essential oils.

Viscosity (dynamic): 58.1 mPas at 20°C.

Stability and Storage Conditions

At cool temperatures, propylene glycol is stable in a well-closed container, but at high temperatures, in the open, it tends to oxidize, giving rise to products such as propionaldehyde, lactic acid, pyruvic acid, and acetic acid. Propylene glycol is chemically stable when mixed with ethanol (95%), glycerin, or water; aqueous solutions may be sterilized by autoclaving.

Safety

Propylene glycol is used in a wide variety of pharmaceutical formulations and is generally regarded as a relatively nontoxic material. It is also used extensively in foods and cosmetics. Probably as a consequence of its metabolism and excretion, propylene glycol is less toxic than other glycols.

Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (dental preparations; IM and IV injections; inhalations; ophthalmic, oral, otic, percutaneous, rectal, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.
COLLOIDAL SILICON DIOXIDE

Synonyms

Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica; fumed silicon dioxide; hochdisperses silicum dioxid; SAS; silica colloidalis anhydrica; silica sol; silicic anhydride; silicon dioxide colloidal; silicon dioxide fumed; synthetic amorphous silica;

Chemical Name: Silica

Empirical Formula and: SiO₂

Molecular Weight: 60.08

Functional Category: Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

Description

Colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.

Solubility

Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.

Safety

Colloidal silicon dioxide is widely used in oral and topical pharmaceutical products and is generally regarded as an essentially nontoxic and nonirritant excipient.
However, intraperitoneal and subcutaneous injection may produce local tissue reactions and/or granulomas. Colloidal silicon dioxide should therefore not be administered parenterally.

LD50 (rat, IV): 0.015 g/kg(16)

LD50 (rat, oral): 3.16 g/kg

**Regulatory Acceptance**

GRAS listed. Included in the FDA Inactive Ingredients Database (oral capsules, suspensions, and tablets; transdermal, rectal, and vaginal preparations). Also approved by the FDA as a food additive and for food contact. Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Nonmedicinal Ingredients.
ACCUREL® MP 1000 (Low density polypropylene foam powder)

Structure:

\[
\begin{array}{c}
\text{CH}_3 \\
\text{CH}_3
\end{array}
\]

**Synonym:** Microporous polypropylene homopolymer powder

**Appearance:** White to off-white powder

**Application:** Microporous carrier for the production of additive concentrate at temperature up to 80°C via physical absorption of the additive. This product is most effective for the incorporation of thermally sensitive additive and for those which cannot be processed by conventional extrusion compounding techniques.

**Solubility:** Practically insoluble in water

**Particle size:** < 1.5 mm

**Melting point:** 156 °C

**Void content:** 73 ± 2%

**Bulk density:** 125 ± 20 kg/m³

**Toxicological information:** LD₅₀: Oral > 2000 mg/kg, Dermal > 2000 mg/kg.
**TULSION® ADS-600**

It is a robust, polymeric adsorbent synthesized from cross-linked polystyrene having no ionic functional group. It is used to adsorb hydrophilic solutes from hydrophobic solvents and hydrophobic solutes from hydrophilic solvents.

**Typical Characteristics**

**Matrix structure:** Polystyrene copolymer

**Functional Group:** None

**Physical Form:** Moist spherical beads

**Screen Size US mesh (wet):** 16 to 50

**Particle size (95% min):** 0.30 to 1.0 mm

**Moisture:** 57 ± 3 %

**Specific gravity of beads:** 1.02 to 1.05 g/ml

**Porosity of dry beads:** 0.4 ml/ml of bead

**Surface area of dry beads min:** 550 m$^2$/g (BET)

**Bulk Density:** 700 - 750 (43 - 47 lbs/cft)

**Maximum operating temperature:** 300° F/150° C

**Suitable pH range:** 0 to 14

**Solubility:** Insoluble in all common solvents
3.9. REVIEW OF RESEARCH PAPERS

- **Schwendi MVS et al.,** evaluated the pharmacokinetics of tacrolimus (Tac) in a novel self-microemulsifying drug delivery system (SMEDDS) for improved oral administration. SMEDDS Tac consisted of ethyl oleate as the oily phase, Solutol HS 15 as the surfactant and glycofurol as the co-surfactant and contained 0.5 mg/mL tacrolimus. Maximum concentrations of the drug were three times higher ($P < 0.05$) in the SMEDDS Tac group accompanied by a 3-fold earlier peak time. Elimination half-life was significantly lower in the SMEDDS Tac group. Application of SMEDDS Tac increased tissue accumulation. However, the Tac concentration in the kidney was significantly lower in the SMEDDS Tac group. Formulation of SMEDDS did not affect blood-brain barrier function. The study suggests SMEDDS is a potentially useful method for a local delivery of Tac to target organs.

- **Tran PHL et al.,** prepared Self-emulsifying solid dispersions (SESD) of isradipine (IDP) using surfactant and fatty acid in poloxamer 407 as a carrier and were manufactured by the melting method. Controlled release HPMC matrix tablet containing SESD were prepared via direct compression. The dissolution rate of IDP from SESD was markedly enhanced because of increased solubility and wetting effect. HPMC matrix tablets containing SESD, released drug in a controlled manner and were stable during storage over 3 months at 40°C/75% RH. Furthermore, the tablet containing 5 mg IDP SESD showed significantly increased oral bioavailability and extended plasma concentration compared with the marketed 5 mg Dynacirc® capsule. A combined method of solid dispersion and
controlled release technology could provide versatile dosage formulations containing IDP with poor water solubility and short half-life.

- **Saifee M et al.,** developed solid self micro emulsifying drug delivery system (S-SEDDS) with Aerosil 200 for enhancement of dissolution rate of model drug Glibenclamide (GBM). SEDDS was prepared using Capmul MCM C8\textsuperscript{TM}, Cremophor RH 40, and Transcutol Prm as oil, surfactant and cosurfactant respectively. Results showed that prepared liquid SEDDS passed all evaluation tests. Globule size was 142.8 nm with polydispersity index 0.396. S-SEDDS showed good flow property and drug content. From the experiment, it is clear that even after conversion of the liquid SEDDS into the solid one there was no significant alteration in the properties of solid SEDDS. *in-vitro* dissolution studies showed that there was enhancement of dissolution rate of GBM as compared with that of plain drug and marketed formulation. From the results it is concluded that, Aerosil 200 can be used to develop S-SEDDS by adsorption technique to enhance dissolution rate of poorly water soluble model drug GBM.

- **Mekjaruskul C et al.,** developed self-microemulsifying drug delivery system (SMEDDS) and cyclodextrin (CD) complex to improve the oral absorption of methoxyflavones. Polyoxyethylene castor oil (53.3%), propylene glycol (26.7%), and triglyceride of coconut oil (20%) were combined to form KP(Kaempferia parviflora) SMEDDS. A complex of 2-hydroxypropyl-\(\beta\)-cyclodextrin (2-HP-\(\beta\)-CD) and KP was prepared by lyophilization. The developed formulations were evaluated for their physicochemical properties, *in vitro* dissolution tests, permeability through Caco-2 cells, and *in vivo* oral absorption in rats. The results showed that KP-SMEDDS and KP-2-HP-\(\beta\)-CD complex improved the
dissolution rate of methoxyflavones in both 0.1 N HCl and 0.2 M PBS pH 6.8 compared to KP dissolved in a solution of propylene glycol, PEG 400, ethanol, and water. KP-SMEDDS and KP-2-HP- β -CD formulations showed about 10 and 3.5 fold greater Papp values of methoxyflavones in Caco-2 cells. The oral bioavailability values of KP SMEDDS and KP-2-HP- β -CD formulations were higher than those of KP. Therefore, these two novel formulations, KP-SMEDDS and KP-2-HP- β -CD, were successfully developed to improve the dissolution rate, drug permeability through Caco-2 cells and oral bioavailability of methoxyflavones in KP.

- Dixit RP et al.,99 formulated self-nanoemulsifying granules with the objective of enhancing the bioavailability of the ezetimibe. The self-nanoemulsifying systems were formulated into free flowing self-nanoemulsifying granules using varying proportions of hydrophilic colloidal silicon dioxide as an adsorbing agent. Self-nanoemulsifying granules were characterized by X-ray diffraction pattern, differential scanning calorimetry, dissolution profile and for in vivo performance in rats. X-ray diffraction studies indicated loss of crystallinity and/or solubilisation of ezetimibe in the self-nanoemulsifying granules. It was supported by SEM studies, which did not show evidence of precipitation of the drug on the surface of the carrier. Dissolution studies revealed remarkable increase in dissolution of the drug as compared to plain drug. In vivo evaluation in rats showed significant decrease in the total cholesterol levels as compared to positive control. The SNGs filled into hard gelatin capsules showed two to threefold increase in the dissolution rate as compared to plain drug filled capsules signifying its potential in improved delivery of lipophilic drugs.
Setthacheewakul S et al.,\textsuperscript{100} developed self-microemulsifying drug delivery systems (SMEDDS) in liquid and pellet forms that result in improved solubility, dissolution, and \textit{in vivo} oral absorption curcumin. The optimized SMEDDS used for curcumin formulations in liquid and pellet forms contained 70% mixtures of two surfactants: Cremophor EL and Labrasol (1:1), and 30% mixtures of oil: Labrafac PG and Capryol 90 (1:1). The curcumin SMEDDS in liquid and pellet formulations rapidly formed fine oil in water microemulsions, with particle size ranges of 25.8-28.8 nm and 29.6-32.8 nm, respectively. The \textit{in vitro} rate and extent of release of curcumin from liquid SMEDDS and SMEDDS pellets was about 16-fold higher than that of unformulated curcumin. Plasma concentration time profiles from pharmacokinetic studies in rats dosed with liquid and pelleted SMEDDS showed 14 and 10 fold increased absorption of curcumin, respectively, compared to the aqueous suspensions of curcumin. Curcumin SMEDDS liquid and curcumin SMEDDS pellets were found to be stable for 6 months under intermediate and accelerated conditions.

Kallakunta VR et al.,\textsuperscript{101} improved the solubility of poorly soluble lercanidipine hydrochloride (LCH) as self emulsifying powder (SEP). Liquid SEDDS of LCH was formulated with Capmul MCM L8 as oil, Tween (R) 80 as surfactant and PEG 400 as co surfactant after screening various vehicles. The optimized system possessed a mean globule size of 169±06 nm and cloud point of 76°C. The self emulsifying powder was prepared by adsorbing the liquid SEDDS on to neusilin as carrier. The SEP formulated was free flowing with similar emulsification characteristics as that of liquid SEDDS. The X-ray diffraction, differential scanning calorimetric studies of SEP revealed transformation of crystalline structure of LCH because of its molecularly dissolved state in the liquid SEDDS.
This was further confirmed by scanning electron microscopy. High dissolution efficiency value of SEP compared with pure drug indicated the increase in dissolution characteristics of LCH in SEP.

- **Beg S et al.,**\(^{102}\) prepared the solid self-nanoemulsifying granules (SSNEGs) of ondansetron hydrochloride (ONH) to enhance its oral bioavailability using Capmul MCM as lipid, Labrasol as surfactant, and Tween 20 as cosurfactant. The TEM study confirmed the formation of nanoemulsion following dilution of liquid SNEDDS. The optimized liquid SNEDDS were transformed into free flowing granules by adsorption on the porous carriers like Sylysia (350, 550, and 730) and NeusilinTM US2. *In vitro* drug release studies indicated faster solubilization of the drug by optimized SSNEGs (over 80% within 30 min) vis-à-vis the pure drug (only 35% within 30 min). *In vivo* pharmacokinetic studies in wistar rats showed significant increase in Cmax (3.01-fold) and AUC (5.34-fold) using SSNEGs compared to pure drug.

- **Agarwal V et al.,**\(^{103}\) studied the dynamics of powder flow upon addition of griseofulvin-self-emulsified drug delivery system (SEDDS) to silica and silicates and the effect of these adsorbents on drug release. SEDDS was adsorbed at SEDDS/adsorbent ratios from 0.25:1 to 3:1 on magnesium aluminum silicate, calcium silicate, and silicon dioxide. Powder rheometer profiles indicated that effect of SEDDS on the flow behavior of the adsorbents could be correlated to stepwise or continuous growing behavior as observed in wet granulation process. Dissolution of drug from adsorbed-SEDDS was found to be dependent on pore length and nucleation at the lipid/adsorbent interface. Increase in dissolution rate was observed with an increase in surface area and was independent of the chemical nature of the adsorbents.
Hu X et al.,\textsuperscript{28} prepared self microemulsifying pellets of sirolimus (SRL). The selected liquid SRL SMEDDDS formulations were prepared into pellets by extrusion spherization method and the optimal formulation of 1 mg SRL-SMEDDDS pellets capsule (1.0, 22.4, 38.4, 19.2, 121.6, 30.4 and 8.0 mg of SRL, Labrafil M1944CS, Cremophor EL, Transcutol P, MCC, Lactose and CMS-Na, respectively) was finally determined by the feasibility of the process and redispersibility. Pharmacokinetic study in beagle dogs showed the oral relative bioavailability of SRL SMEDDDS pellets to the commercial SRL tablets Rapamune® was about 136.9%.

Villar AMS et al.,\textsuperscript{104} prepared Self-nanoemulsifying drug delivery systems of gemfibrozil under Quality by Design (QBD) approach for improvement of dissolution and oral absorption. Preliminary screening was performed to select proper components combination. Box-Behnken experimental design was employed as statistical tool to optimize the formulation variables, X1 (Cremophor® EL), X2 (Capmul® MCM-C8), and X3 (lemon essential oil). Following optimization, the values of formulation components (X1, X2, and X3) were 32.43%, 29.73% and 21.62%, respectively (16.22% of gemfibrozil). Transmission electron microscopy demonstrated spherical droplet morphology. SNEDDS release study was compared to commercial tablets. Optimized SNEDDS formulation of gemfibrozil showed a significant increase in dissolution rate compared to conventional tablets. Both formulations followed Weibull mathematical model release with a significant difference in the parameter in favor of the SNEDDS. Equally the calculated dissolution efficiency significantly was higher for SNEDDS, confirming that the developed SNEDDS formulation was superior to commercial formulation with respect to \textit{in vitro} dissolution profile.
Gupta S et al., developed self-nanoemulsifying drug delivery systems (SNEDDS) of Adefovir dipivoxil (ADV) with the objective of increasing its bioavailability by enhancing its intestinal permeability and minimizing the effect of pH. The nanoemulsion system selected from the phase diagram was transformed into solid-SNEDDS (S-SNEDDS) by lyophilization using D-mannitol as cryoprotectant. The liquid SNEDDS (L-SNEDDS) showed mean globule size of 110±10 nm while mean globule size of 150±16 nm was obtained with S-SNEDDS. The formulations were robust to dilution and showed cloud point at 80-85°C. TEM and SEM studies of nanoemulsion reconstituted from S-SNEDDS demonstrated the spherical shape and size of the globules. Results of DSC and XRD studies confirmed that the drug was incorporated in the S-SNEDDS. No significant difference was observed in the globule size within physiological variations of pH and temperature. The in vitro and ex vivo drug release from ADV SNEDDS was found to be significantly higher in comparison to that from plain drug suspension, irrespective of pH.

Bhagwat DA et al., developed S-SMEDDS of poorly water soluble drug Telmisartan (TEL) using Aerosil 200 as solid carrier. Liquid SMEDDS was prepared using Acrysol EL 135, Tween 80 and PEG 400 as oil, surfactant and co-surfactant and was converted to S-SMEDDS by adsorbing it on Aerosil 200. Results showed that prepared S-SMEDDS have good flow property with 99.45 ± 0.02% drug content. Dilution study by visual observation showed that there was spontaneous micro emulsification and no sign of phase separation. Droplet size was found to be 0.34 µm with polydispersity index of 0.25. DSC thermogram showed that crystallization of TEL was inhibited. SEM photograph showed smooth surface of S-SMEDDS with less aggregation. Drug releases from S-
SMEDDS were found to be significantly higher as compared with that of plain TEL. *Ex-vivo* intestinal permeability study revealed that diffusion of drug was significantly higher from S-SMEDDS than that of suspension of plain TEL.

- Shanmugam *et al.*, 106 prepared solid self-nanoemulsifying drug delivery system (S-SNEDDS) containing phosphatidylcholine (PC), an endogenous phospholipid with excellent in vivo solubilization capacity, as oil phase for the delivery of bioactive carotenoid lutein, by spray drying the SNEDDS (liquid system) containing PC using colloidal silica (Aerosil 200 VV Pharma) as the inert solid carrier, and to evaluate the enhanced bioavailability (BA) of lutein from S-SNEDDS. The droplet size analyses revealed droplet size of less than 100 nm. The solid state characterization of S-SNEDDS by SEM, DSC, and powder XRD revealed the absence of crystalline lutein in the S-SNEDDS. The bioavailability study performed in rabbits resulted in enhanced values of Cmax and AUC for S-SNEDDS. The enhancement of Cmax for S-SNEDDS was about 21-folds and 8 folds compared with lutein powder (LP) and commercial product (CP), respectively. The relative bioavailability of S-SNEDDS compared with CP or LP was 2.74 folds and 11.79 folds respectively. These results demonstrated excellent ability of S SNEDDS containing PC as oil phase to enhance the bioavailability of lutein in rabbits.