2.1 ORAL DELIVERY

Oral route is the most common and preferred route for drug administration. This choice is mainly related with its non-invasiveness and ease of administration, which increases patient's compliance and therapeutic success. Oral administration is limited by problems related to physicochemical properties of the drug, including poor solubility, low permeability, instability, and rapid metabolism, all of which decrease oral bioavailability (BA). However, the hydrophilic environment of the gastrointestinal tract (GIT) can limit the bioavailability of lipophilic and/or other poorly water-soluble compounds (Figure 2.1). The trend in drug discovery toward lipophilic molecules has increased the need to develop alternative oral delivery systems for poorly soluble compounds (1). Hepatic first-pass metabolism is the major cause of poor BA upon peroral administration. Poor solubility of the drugs not only influence oral BA but also hinders the development of suitable delivery system. Nevertheless, oral formulations are being developed keeping in consideration the basic biological and pharmaceutical approaches of drug delivery via the oral route.

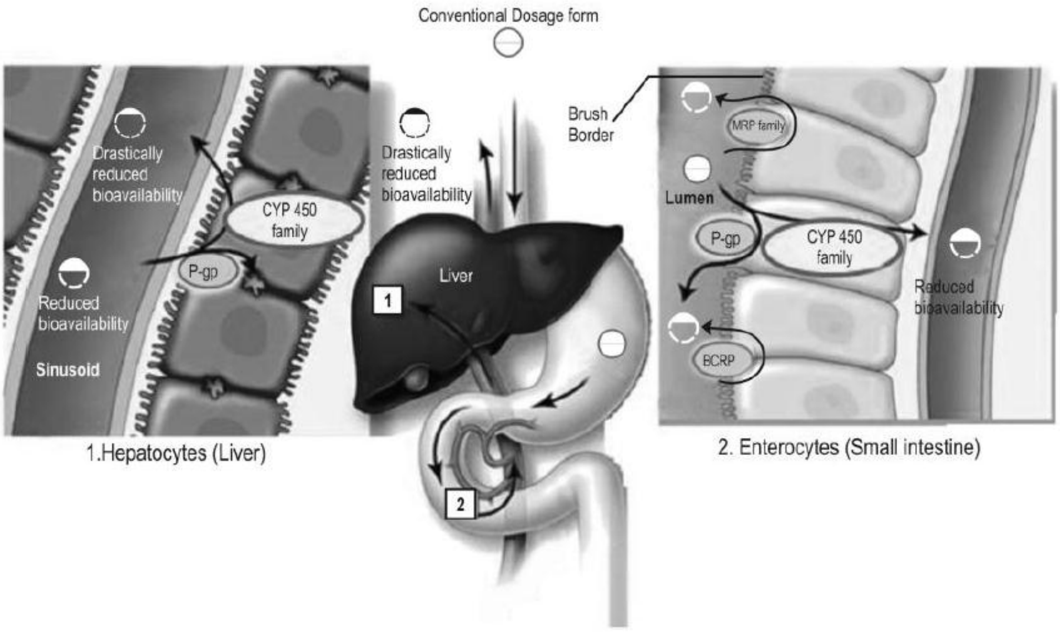

Figure 2.1: Physiological constraints leading to reduction in bioavailability through oral delivery

With the advent of drug design, various molecules have been created that have a potential for therapeutic action. But most of the newly discovered chemical entities are of high molecular weight and belong to biopharmaceutical classification system (BCS) – II, with poor aqueous solubility and high membrane permeability. Hence these two characteristics limit the bioavailability of orally administered drugs. These drugs have low solubility which leads to low dissolution and limits absorption. This poor solubility not only gives low oral bioavailability but also leads to high inter- and intra-subject variability and lack of dose proportionality. So, the solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs (2). The chemical, physical and biological interactions of the drug with the physiological components of the GI tract determine whether or not and to which extent the therapeutic can reach intact the blood circulation and elicit a systemic effect.

2.1.1 Challenges to oral drug delivery

More than 60% of conventional small molecule drug products available in the market are administered via the oral route. The physiological and anatomical barriers to bioactive absorption via the GI tract are primarily chemical, enzymatic and permeability related (e.g. mucus layer, intestinal epithelium). Poor hydrophilicity and intrinsic dissolution rate are the major factors that affect oral delivery of many existing drugs.

2.2 NANOTECHNOLOGY

Recent years have witnessed unprecedented growth of research and applications in the area of nanoscience and nanotechnology. It is anticipated that application of nanotechnology to field of medicine will bring advances in the diagnosis and treatment of any disease (3). The overall goal of nanotechnology is: to diagnose disease as early as possible and to treat it as effectively as possible without any side effects.

Nanocarriers have higher surface area to volume ratio which can aid in improving pharmacokinetics and biodistribution of therapeutic agent and thus minimize its toxicity by delivering it at the target site (4). Furthermore, they increase the stability of a variety of therapeutic agents, like peptides, oligonucleotides, and so forth. They can be used to deliver the drug to the central nervous system owing to their smaller size and higher barrier permeability. Use of biodegradable materials minimizes the possibilities of hypersensitivity reactions and affords good tissue compatibility (5). Ideally, a nanocarrier should be capable of providing extended blood circulation, delivering the active moiety at the targeted site and bypassing the endosome-lysosome processing (6). Nanotechnology presents some promotional benefits to the drug delivery field in general and oral drug delivery in particular. It permits (i) delivery of poorly water-soluble drugs, (ii) targeting of drugs to precise parts of the GI tract, (iii) transcytosis of drugs across the GI tract barrier and (iv) intracellular and transcellular delivery of large macromolecules. Nanoconstruct-based oral delivery can improve efficacy, specificity, tolerability and therapeutic index of corresponding drugs (7). The role of nanocarrier in oral drug delivery is shown in figure 2.2.

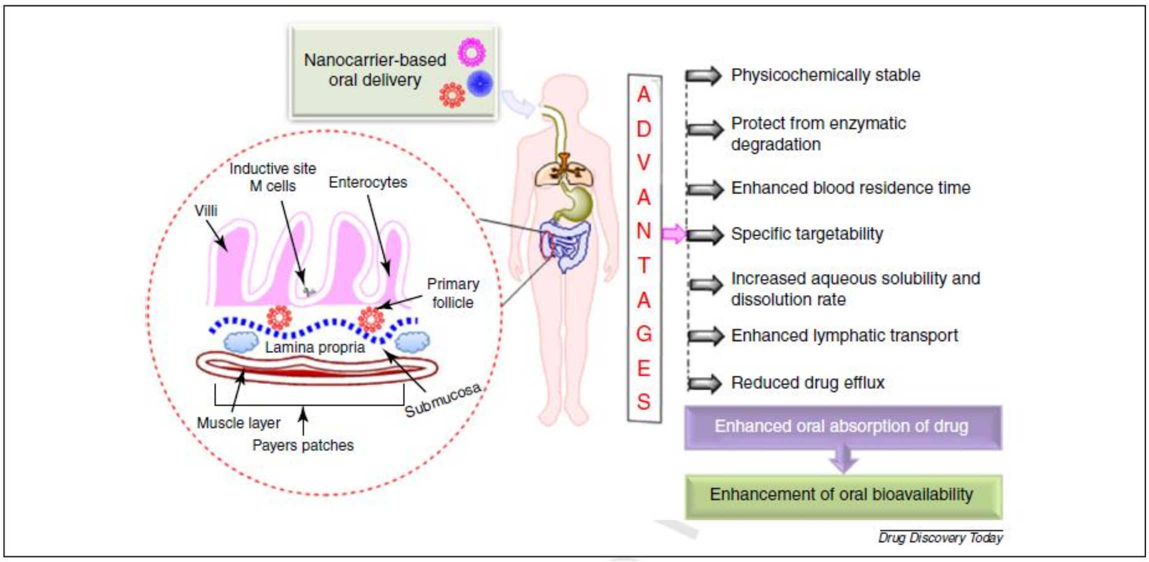

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Figure 2.2: Role of nanocarrier based formulations in oral drug delivery

2.3 LIPID BASED DRUG DELIVERY SYSTEMS (LBDDS)

In the present scenario, oral drug delivery is continuously looking into newer avenues due to realization of the factors like poor drug solubility and/or absorption, rapid metabolism, high fluctuation in the drug plasma level and variability due to food effect which are playing major role in disappointing in vivo results leading to failure of the conventional delivery system. Since the last decade, the oral drug delivery has taken a new dimension with the increasing application of lipid as a carrier for the delivery of poorly water soluble, lipophilic drugs.

Lipid-based drug delivery systems (LBDDS) are experiencing a resurgence of interest lately (8,9) since their introduction in 1974 by Attwood et al (10). This growing interest is partly due to the fact that anywhere from 40% to 70% of new chemical entities entering drug development pipelines have been found to possess inadequate aqueous solubility and limited absorption in the GI tract, which reduces the therapeutic concentrations attainable at a given dose.

Interest in LBDD is relatively recent and relates to the developments in the past 10 to 15 years, largely driven by the growing need for novel drug delivery systems to deal with the vast majority of the new chemical entities (NCE) that have poor solubility or permeability, to improve the delivery of existing drugs, and for line extensions. The primary application for lipid-based excipients is in bioavailability enhancement where the aim may be increased solubility, targeting lymphatic transport, and or modulation of enterocytes-based drug transport and disposition. Other applications include drug coating for either taste masking or protection of the active, and in sustained release dosage forms (11,12). LBDDS have been exhibited to be useful in enhancing the bioavailability of poorly soluble drugs because they can keep the drug in the dissolved state in the lipid phase until it is absorbed and hence, can overcome barrier of poor dissolution. The main advantage of LBDDS is that it can keep drug molecule in pre-dissolved state in the lipid component which aids in avoiding rate limiting dissolution step in GIT, thereby can achieve increased and consistent bioavailability.

The absorption of drug from lipid based formulation depends on numerous factors, including particle size, degree of emulsification, rate of dispersion and precipitation of drug upon dispersion. The mechanism of intestinal drug transport from lipid-based formulations is shown in the figure 2.3. Lipid-based formulations may include microemulsion, nanoemulsion, oil solution or suspensions, emulsions, self-micro or self-nano emulsifying drug delivery systems, solid lipid nanoparticle etc. Some of the drugs that are successfully marketed as lipid based formulations include efavirenz (Sustivas), clofazamine (Lamprenes) etc. An appropriate selection of lipid component, formulation strategies and rational delivery system design can lead to the success of lipid based drug delivery systems (13).

Partially digested lipids from the stomach are solubilised in the GI fluids in the presence of both bile and pancreatic juice, fine emulsions are further converted to bile salt micelles and lamellar vesicles. These particles deliver digested lipids and drug molecules to enterocytes, and both the lipid and drug molecules are subsequently absorbed. The dispersion of lipids in the GI fluids affects the kinetics of lipid digestion and absorption, as well as solubility and absorption of drugs from lipid-based formulations (14).

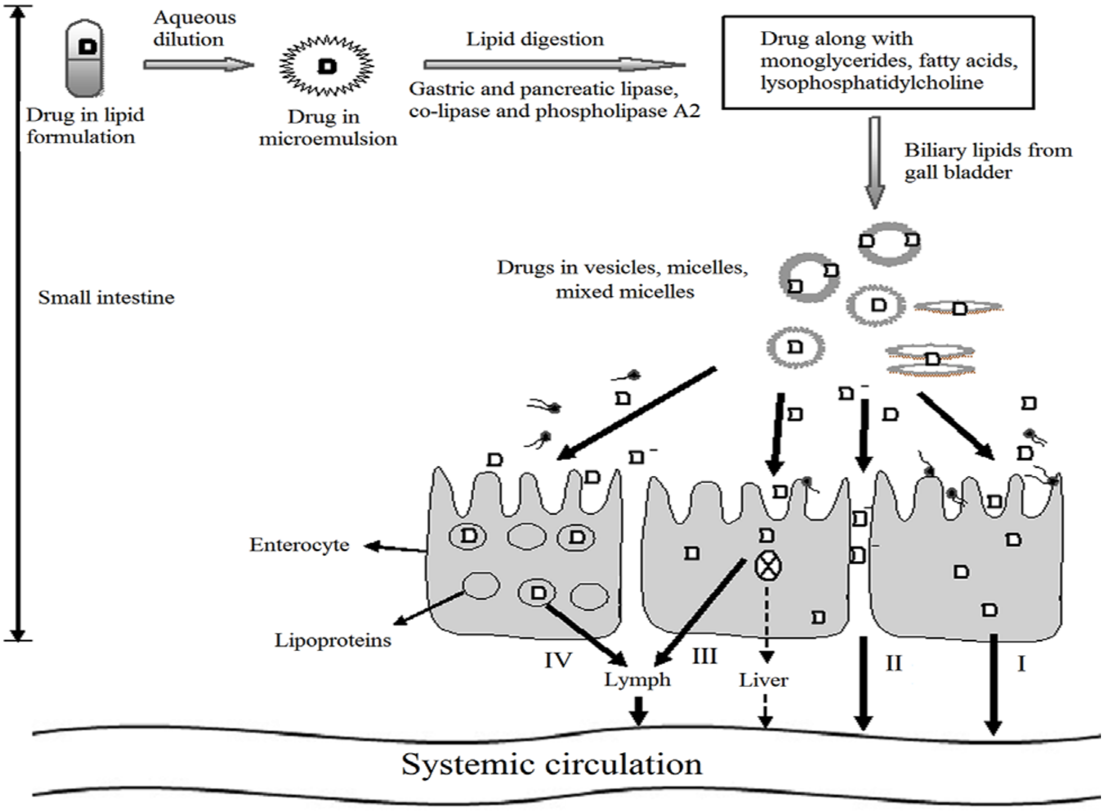


Figure 2.3: Schematic diagram of mechanisms of intestinal drug transport from lipid-based formulations

Successful drug design with lipids depends largely on understanding the physicochemical and physiological factors that promote or inhibit bioavailability. It requires a grasp of not only the drug candidate issues but also the role of the drug delivery system or the potential for drug-excipient interplay in vitro as well as in vivo conditions (12).

2.3.1 Interaction of lipophilic drugs with the lipid digestion/absorption cascade

The inherent physicochemical similarities between many lipophilic drugs and dietary and/or formulation-derived lipids in terms of high partition co-efficient and low water solubility suggests that the processes that control lipid digestion, absorption, and distribution may similarly affect the disposition of lipophilic drugs. Therefore, the co-administration of lipids might be expected to have an impact on the disposition of lipophilic drugs in the following ways (15):

1. By stimulating the release of biliary and pancreatic secretions, thereby providing an intestinal micellar phase into which a poorly water-soluble drug may become solubilized—increasing its effective solubility, dissolution rate, lumen-to-enterocyte concentration gradient and, consequently, extent of absorption. Increasing evidence

suggests that co-administered lipids also have significant effects on drug absorption and metabolism at a cellular level through attenuation of enterocyte based metabolic and anti-transport processes.

2. By enhancing the formation and turnover of lymph lipoproteins through the enterocyte and provoking, or improving, the targeting of orally administered lipophilic drugs to the intestinal lymphatics.

3. By altering the relative proportions and constituents of plasma lipoproteins and changing the degree of binding of lipophilic drugs to discreet lipoprotein (LP) subclasses. The presence of specific receptors for lipoprotein subclasses such as the low-density lipoprotein receptor suggests that alteration of LP-binding profiles may have a significant impact on both pharmacokinetic issues such as drug clearance and volume of distribution and on pharmacodynamic end points such as toxicity and activity. Lipids may also have effects on gastric transit (in terms of delaying gastric emptying) and intestinal permeability (enhancing the absorption of poorly permeable compounds).

2.3.2 Role of lipids in bioavailability enhancement

The effect of lipids on the oral bioavailability of poorly water-soluble drugs may be classified as ‘‘physicochemically’’ mediated (solubility, dissolution, surface area) and ‘‘biochemically’’ mediated effects (metabolism, transport related events), and stimulation of intestinal lymphatic transport.

2.3.2.1 Bioavailability enhancement by means of physicochemical mechanisms

Simple suspensions and solutions of drugs in lipids have been shown to enhance the oral bioavailability of a number of poorly water-soluble compounds, including phenytoin, progesterone and cinnarazine (16–21). In these examples, bioavailability enhancement appears to have been mediated by way of improved drug dissolution from lipid solutions (compared with aqueous suspensions) and enhanced drug solubility in the lipid bile salt-rich GI contents. Optimal bioavailability enhancement was generally provided by lipids in which the drug was most soluble, although factors including the solubility of the lipid in the GI fluids (short chain lipids typically dissolve in the intestinal lumen leading to drug precipitation) and the ability of long-chain lipids to stimulate lymphatic transport complicate choice of the optimal lipid.

As a consequence of the intestinal processing that lipids undergo before absorption, there has been significant interest in assessing the ‘‘digestibility’’ of formulation lipids as a potential indicator of in vivo bioavailability enhancement.

In this regard, digestible lipids such as dietary fats (triglycerides, diglycerides, fatty acids, phospholipids, cholesterol, etc) are generally more effective in terms of bioavailability enhancement than indigestible oils such as mineral oil (22–24). However, more complex correlations of lipid chain length (medium chain versus long chain lipids) or lipid class (triglycerides versus diglycerides or monoglycerides) with digestibility and bioavailability enhancement have met with little success.

The degree of dispersion of a lipid-based delivery system appears to have the most marked effect on the bioavailability of a co-administered drug, and this has stimulated many of the most recent articles in the literature. Clearly, by decreasing the particle size of a dispersed formulation, the surface area available for lipid digestion and drug release or transfer is enhanced. In this regard, the bioavailability of griseofulvin (25,26), danazol (27), REV 5901 (28), and more recently, ontazolast (29) has been shown to be enhanced after administration in an emulsion formulation compared with a tablet, aqueous solution, or suspension formulation. It is not clear in these cases how much more efficient the emulsion formulation would have been compared with a simple lipid solution.

In many cases the relatively complex nature of lipid-based formulations in terms of lipid class, chain length, degree of dispersion, and choice of surfactant makes explanation of the mechanistic information difficult. For example, the bioavailability of vitamin E after administration of vitamin E acetate is greater after administration in a medium-chain triglyceride (MCT)-based emulsion compared with a long-chain triglyceride (LCT)-based lipid solution (30).

2.3.2.2 Bioavailability Enhancement by Means of Biochemical/Metabolic Mechanisms

Formulation components may enhance the extent of oral drug bioavailability by altering the extent of absorption (by means of improvements in drug dissolution, GI solubility, GI stability, and intestinal permeability) or by reducing drug metabolism. Historically, the role of liver in drug metabolism was considered paramount, and alterations in the extent of hepatic presystemic metabolism—the first pass effect—the most likely mechanism to improve drug bioavailability.

Recently, however, interest has increased in the potential role of prehepatic metabolic processes as a major limitation to the oral bioavailability of some drugs. It is now accepted that enterocyte-based processes play a central role in the metabolism of many drugs such as ketaconazole, midazolam, cyclosporin , tacrolimus etc. (15) and in most cases this has been attributed to metabolism by cytochrome P450 enzymes and more specifically the CYP3A subfamily of enzymes (15). Over a similar time frame interest has also increased in the role of intestinal efflux pumps that limit drug transfer through the enterocyte by pumping xenobiotics from inside the cell back into the lumen of the intestine (i.e., a counter transport function). Recent data have implicated P-glycoprotein (P-gp) (the MDR 1 gene product) located in the enterocyte brush border membrane in the limitation of the oral bioavailability of cyclosporin (31), vinblastine (32) and othes. P-gp and CYP3A are co-localized within the apex of absorptive enterocytes, they have similar substrate specificities, and they are co-inducible in response to some xenobiotics. These observations have led to the proposition that P-gp and CYP3A may be functionally linked and act in concert to limit the exposure of xenobiotics/drugs to the small intestine and portal circulation (33).

Because of the relatively recent and growing realization of the importance of enterocyte-based CYP3A and P-gp in the limitation of drug bioavailability, few published studies have addressed the potential impact of formulation components such as lipids on these processes (15). However, a recent patent has described in some detail the potential for many lipids to inhibit both CYP3A-based metabolic processes and P-gp–mediated antitransport processes (34). The patent covers the use of essential oils to improve bioavailability and presents data detailing the inhibitory capacity of essential oils using in vitro drug metabolism screens. Surfactants found in many dispersed lipid formulations have also been shown to inhibit the extent of P-gp –mediated efflux of a model peptide (35). However, research in this area is in its infancy and the factors controlling the intracellular fate of lipophilic drugs via metabolism by CYP3A or binding to the P-gp efflux pump are not well known.

2.3.2.3 Bioavailability Enhancement via Lymphatic Targeting

The lymphatic system plays a significant role in enhancing oral bioavailability. The intestinal lymphatic system is a pathway through which fat-soluble vitamins, food-derived lipids, and water-insoluble peptide-like molecules can be transported into systemic circulation. Drugs transported via the intestinal lymphatic system can bypass the liver and thus avoid hepatic first-pass metabolism; they have potential to target specific disease states known to spread via lymphatics, e.g., certain lymphomas, Human Immunodeficiency Virus (HIV), etc. Lipid vehicles may enhance lymphatic transport of lipophilic compounds by stimulating the production of chylomicrons. Lipophilic drugs enter the lymphatic system in association with the triglyceride core of the chylomicrons. Strong correlation, therefore, has been established between the degree of lymphatic transport and the triglyceride content of the lymph (36,37).

Drug delivery to the intestinal lymphatics confers two primary advantages over conventional absorption by means of the portal blood. First, transport through the intestinal lymph avoids presystemic hepatic metabolism and therefore enhances the concentration of orally administered drugs reaching the systemic circulation. Second, from a site specific delivery or targeting perspective, the lymphatics (i) contain relatively high concentrations of lymphocytes and therefore provide attractive targets for cytokines such as interferon and immunomodulators in general, (ii) serve as the primary conduit for the dissemination of many tumor metastases and therefore show promise as a target for cytotoxics, and (iii) may provide an efficient route of delivery to HIV-infected T-cells, because recent findings have suggested that a significant proportion of the HIV viral burden resides in the lymphoid tissue (16,38).

2.4 FACTORS AFFECTING LYMPHATIC TRANSPORT OF NANOPARTICLES

The uptake and distribution of the lipid-based nanocarriers through the gastrointestinal epithelium to the peripheral lymphatic duct have been explored. Some groups have reported that uptake of lipid-based nanoparticles by the lymphatic system and their distribution in the lymphatic circulation is dependent on route of administration. Moreover, other factors such as size, surface charge, molecular weight, hydrophobicity, types of lipid, and concentration of the emulsifier used have also been observed to influence the uptake and distribution of lipid based nanoparticles in the lymphatic circulation (38).

2.4.1 Size of nanoparticles

The size and composition of nanoparticles play an important role in lymphatic uptake and particle retention in lymph nodes. Carriers such as colloidal and lipid particles show more efficiency in lymphatic uptake. Several drug molecules, including anticancer and monoclonal antibodies, have been incorporated into dendrimers and lipid-based nanoparticles, such as liposomes, SLNs, and Nano structured Lipid carriers (NLCs), on the basis of their size and the nature of the preparations for lymphatic targeting (39). Oussoren et al reported that a particle size of 10–100 nm is optimal for lymphatic uptake via subcutaneous administration (40). A particle size smaller than 10 nm is absorbed via the systemic circulation, whereas a particle larger than 100 nm shows preferential uptake via the lymphatic system but at a slower rate. However, particles larger than 100 nm have not been clearly defined (38).

2.4.2 Surface charge on nanoparticles

The charge on a drug carrier is also an important factor in lymphatic uptake. Some negatively charged carriers, such as dendrimers, proteins, polylactic-co-glycolic acid nanospheres, and lipid-based nanoparticles (eg, liposomes) have been reported to show higher lymphatic uptake than neutral or positively charged surfaces, which could be due to the fact that the interstitial matrix contains a net negative charge (41-45). Therefore, in the interstitium, anionic carrier particles encounter electrostatic repulsion and move more quickly. Highly negatively charged particles have been reported to be retained for a longer period of time in the lymph nodes (38,45). Conversely, positively charged particles in the interstitium encounter more resistance to move towards the negatively charged interstitium matrix because of the increased electrostatic attraction force. The zeta potential provides information regarding the ionic nature of carrier particles. A zeta potential ±30 mV indicates a strongly anionic nature, values between +10 and -10 mV indicate neutral behavior, and values +30 mV indicate a cationic nature (46).

2.4.3 Molecular weight of drugs

Lymphatic drug delivery via the subcutaneous route shows a linear relationship between molecular weight and extent of absorption of macromolecules. Increasing the molecular weight causes a decrease in uptake of molecules by the capillaries and increased uptake into the lymphatic system at the injection site. Molecules weighing less than 1000 Da are easily absorbed by the capillaries before they are taken into the lymphatic circulation. In contrast, molecules weighing more than 16,000 Da tend to be absorbed by the lymphatic system rather than by the capillaries (47).

2.4.4 Hydrophobicity of nanoparticles

Hawley et al showed that hydrophobicity plays an important role in facilitating lymphatic uptake of lipid-based nanoformulations from the administration site (47).

The hydrophobicity of the particles can be correlated with their surface properties, and is mainly responsible for phagocytosis and lymphatic uptake. Dahlback et al demonstrated that decreasing the hydrophobicity of bacteria would decrease phagocytosis (48). The increased opsonization could be because opsonins attach more easily to hydrophobic surfaces than to hydrophilic surfaces. Because of this phenomenon, phagocytosis would increase, thus increasing lymphatic uptake (49).

2.4.5 Lipid solubility and partition coefficient of drugs

Lipid solubility and the partition coefficient are essential physicochemical properties of drugs, and have a major role in lymphatic drug transport. For example, Charman and Stella reported that triglyceride solubility and the log P value of a drug should be 50 mg/mL and 5 respectively, for effective lymphatic transport (50). They compared the lymphatic transport of dichlorodiphenyltrichloroethane and hexachlorobenzene, which have log P values of 6.19 and 6.53, respectively. Although the log P values of both drugs were similar, the drugs were dissimilar in their triglyceride solubility, with dichlorodiphenyltrichloroethane having a 13-fold higher triglyceride solubility than hexachlorobenzene. Their transport results showed that dichlorodiphenyltrichloroethane had higher lymphatic uptake (33.5%) than hexachlorobenzene (2.3%). These authors concluded that the difference in lymphatic transport could be due to the difference in triglyceride solubility between the two drugs. However, Myers and Stella observed in their study that higher log P values and increased lipid solubility did not always result in significant lymphatic uptake. Penclomedine has poor lymphatic transport (only about 3% of the dose administered is transported) despite its log P value of 5.48 and lipid solubility of 175 mg/mL. Reduced lymphatic transport of penclomedine could be due to the stronger affinity of this drug for red blood cells and plasma proteins than for chylomicrons. Thus, higher concentrations of penclomedine have been detected in the blood circulation than in the lymphatic circulation (51).

2.4.6 Types of lipids used in nanoparticles

Lipid-based nanoformulations are essentially composed of triglycerides which arrange themselves in such a way that the polar head is exposed to the aqueous phase. This arrangement is similar to that of chylomicrons. The composition of lipids in lipid-based nanoformulations may influence their absorption through the transcellular route via polar intestinal epithelial cells.

2.4.7 Concentration of emulsifiers in nanoparticles

The concentration of the emulsifier directly influences partitioning of a drug in a lipid-based formulation. Thus, it can indirectly affect delivery of the drug in the lipid-based formulation to the target site. Sanjula et al prepared carvedilol SLNs containing 5%–15% Poloxamer 188 as an emulsifier. They have reported that higher concentrations of Poloxamer 188 would reduce the hydrophobicity of the SLNs and decrease lymphatic uptake of carvedilol, which would result in lower oral bioavailability of the drug (52).

2.5 TRANSPORT MECHANISMS ACROSS INTESTINAL EPITHELIUM

There are four distinct mechanisms for molecules to cross the cell membrane: via paracellular, transcellular, carrier-mediated, and receptor-mediated transport (Figure 2.4). Absorption through each pathway is dependent on different physical characteristics, such as molecular weight, hydrophobicity, ionization constants, and pH stability of absorbing molecules as well as biological barriers that restrict protein absorption from the GI tract. Thus, an understanding of biomolecules and these distinct mechanisms are important in designing delivery systems for oral delivery of drugs (53).

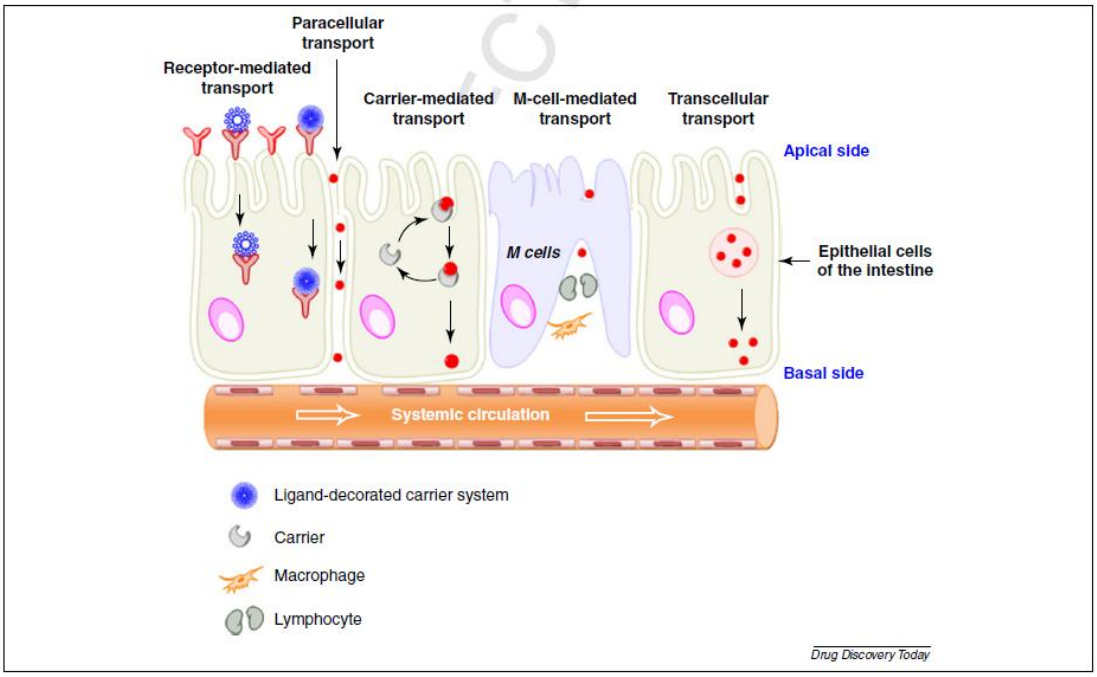


Figure 2.4: Transport mechanism across intestinal epithelium

2.5.1 Paracellular transport

Paracellular transport is defined as “the pathway of substances across an epithelium by passing through the intercellular spaces in between epithelial cells”. Paracellular transport results from passive diffusion and under the control of tight junctions. A tight junction constitutes a rate limiting barrier towards the paracellular transport for permeation of ions and larger substances (54). The dimension of the paracellular space is on the order of 10 Å. In the human intestine, average aqueous pores size created by epithelial tight junctions is approximately 7–9 Å, 3–4 Å and 8–9 Å for the jejunum, ileum, colon respectively (55). This data suggests that solutes with a molecular radius exceeding 15 Å (approximately 3.5 kDa) cannot be transported via this route. Furthermore, tight junctions comprise only about 0.01% of the total absorption surface area of the intestine (56). Consequently, one would conclude that protein delivery across mucosal epithelia using paracellular transport is severely restricted.

Paracellular transport varies among epithelia in terms of electrical resistance and shows differences in ionic selectivity. The paracellular transport complements the transcellular mechanism by defining the degree and selectivity for ions and solutes, making tissue-specific contribution to transport (53). The tight junction provides biophysical properties with ion channels, including its size and charge selectivity, ion concentration dependent permeability, competition between permeant molecules, anomalous mole-fraction effects, and sensitivity to pH (57). The paracellular pathway is not largely determined by the hydrogen bonding capacity and lipophilicity.

2.5.2 Transcellular transport

Transcellular transport occurs through the intestinal epithelial cells by transcytosis, a particular process by which particles are taken up by cells. A typical example is the movement of glucose from the intestinal lumen to extracellular fluid by epithelial cells. This starts with an endocytic process that takes place at the cell apical membrane. Then, particles are transported through the cells and released at the basolateral pole (58). The basolateral membrane is thinner and more permeable than the apical membrane because the protein-to lipid ratio is very low in the basolateral membrane. Transport of particles by the transcellular transport depends on several factors: (i) various physicochemical properties of particles, such as size, lipophilicity, hydrogen bond potential, charge, surface hydrophobicity or the presence of a ligand at the particle surface; (ii) the physiology of the GI tract; and (iii) the animal model used to study the uptake (59, 60).

Enterocytes and M cells are the primary intestinal cells for transport. Enterocytes represent the majority of cells lining the gastrointestinal tract and M cells are mainly located within the epithelium of Peyer's patches and represent a very small proportion of the intestinal epithelium (5% of the human follicle-associated epithelium (FAE), i.e., about 1% of the total intestinal surface) (61). M cells in the FAE of Peyer's patches are specialized for an antigen. M cells deliver proteins and peptides from the lumen to the underlying lymphoid tissues for the induction of immune responses. However, M cells are also exploited by a range of pathogens as a route for host invasion (62). Furthermore, M cells represent a potential portal for oral delivery of proteins and peptides due to their high endocytosis ability. M cells possess a high transcytotic capacity and transport a wide variety of materials, including nanoparticles (63,64).

M cells take up macromolecules, particles and microorganisms by adsorptive endocytosis via clathrin-coated pits and vesicles, fluid phase endocytosis and phagocytosis (65). Although there has been some controversy in the literature on the extent of particle absorption, there is evidence that particle translocation can occur across enterocytes in the villipart of the intestine. However, less number of particles are translocated through this route because of low endocytic activity of the enterocytes. It has been generally observed that the bulk of particle translocation mainly occurs in FAE. Many researchers have studied transport through the Peyer's patches and M cells which have adapted to absorb a large range of materials. This route is limited to the transport of low molecular weight lipophilic drugs. Furthermore, studies in humans have demonstrated that absorption by the transcellular route decreases significantly in the colon, whereas no such gradient exists for the paracellular route (53).

2.5.3 Carrier-mediated transport

Drugs are transferred across the cell membrane or entire cell and then released from the basal surface of the enterocyte into circulation (66). The process is suitable and utilized by small hydrophilic molecules. Active absorption requires energy-dependent uptake of specific molecules by carriers. The carriers recognize target molecules through membrane receptors and transport them across the membranes into the GI epithelium, even against the concentration gradient and in trace quantities. For example, small di/tripeptides (including β-lactam antibiotics and angiotensin-converting enzyme (ACE) inhibitors), monosaccharides, and amino acids are transported transcellularly by a carrier-mediated transport process (66).

2.5.4 Receptor-mediated transport

In receptor-mediated transport, protein drugs act either as a receptor specific ligand for surface-attached receptors or as a receptor for surface-attached ligands (67). Receptor mediated transport has also been exploited to increase the oral bioavailability of protein drugs by modification such as receptor specific ligands with peptide and protein drugs. This transportation entails cell invagination, which leads to formation of a vesicle. This transportation, in general, is known as endocytosis and comprises phagocytosis, pinocytosis, receptor-mediated endocytosis (clathrin-mediated), and potocytosis (nonclathrin-mediated) (68). The first step in this process includes binding of the ligand to a specific cell-surface receptor, receptor clustering and internalization through coated vesicles into endosomal acidic compartments. The subsequent pathway is strongly dependent on the type of the receptor/ligand pair; the low endosomal pH may or may not trigger dissociation of the receptor and ligand, and sorting processes may lead to degradative lysosomal compartments. After protein drugs are transported to the GI tract, they take access to the systemic circulation via two separate and functionally distinct absorption pathways: portal blood and the intestinal lymphatics.

The physicochemical and metabolic features of the proteins and the characteristics of the formulation majorly control the protein absorption via these two pathways. Portal blood represents the major pathway for absorption of orally administered protein drugs. During this process, hydrophilic ligands are carried to the liver via the hepatic portal vein, and then reach to systemic circulation via hepatic artery and then subsequent delivery to their site of action. On the other hand, highly lipophilic ligands (log $P > 5$) that cross the same epithelial barrier are transported to the intestinal lymphatics, which directly deliver them to the vena cava, thereby bypassing the hepatic first-pass metabolism (69).

2.6 SCHIZOPHRENIA

Schizophrenia is a complex neuropsychiatric disorder that produces severe symptoms and significant lifelong disability, causing massive personal and societal burden. About 1% of the world’s population is affected by schizophrenia. Despite the strong genetic component, showing increasing risks for those related to schizophrenic patients, and the known role of environment as a trigger, schizophrenia signs and symptoms have unknown etiology. Currently, the disease diagnosis is essentially clinically defined by observed signs of psychosis, which often include paranoid delusions and auditory hallucinations, with onset during late adolescence and/or early adulthood (70).

Despite more than a hundred years of research, the etiology of schizophrenia remains elusive. Neurodegeneration, neurodevelopmental alterations and the interplay between genetic and environmental factors have been used to provide a pathophysiological theory of schizophrenia. Apart from the dopamine hypothesis of schizophrenia, which is one of the best-established theories in psychiatry, alterations in many other neurotransmitter systems have been reported. In particular, dysfunctions in glutamatergic, gamma-aminobutyric-acid (GABA) ergic and cholinergic neurotransmission seem to be associated with the disease's pathophysiology. Alterations to all of these various neurotransmitters can be linked to disturbed micro- and macro-circuitry, connectivity and plasticity in schizophrenia patients (disconnection hypothesis). The involvement of a hypofunction of glutamatergic N Methyl-aspartate-receptors (NMDAR) in schizophrenia has been discussed based on the findings that NMDAR anatgonists such as ketamine and phencyclidine (PCP) cause positive and negative symptoms and cognitive impairments in healthy subjects related to those seen in schizophrenia (glutamate hypothesis). One recent study conducted on healthy subjects displayed that acute administration of ketamine impaired synaptic plasticity during the mismatch negativity encoding of prediction errors but not neuronal adaptation and that this effect was related to the psychopathology (71). Negative symptoms and cognitive deficits in schizophrenia are thought to be caused by low mesocortical dopamine levels (72).

There are mainly two types of antipsychotics used in the treatment of schizophrenia: Typical and Atypical antipsychotics. The primary distinction between classical and second-generation antipsychotics has been made on clinical basis. “Typical” antipsychotics are characterized by undesirable side effects such as extrapyramidal symptoms (EPS), hyperprolactinaemia, tardive dyskinesia and possible neuroleptic malignant syndrome. These symptoms are specific to the group as a whole and generally associated with high doses but in some cases also at clinically effective dosages. The second-generation or “atypical” antipsychotic drugs can be differentiated from traditional antipsychotics by their low or negligible levels of these unwanted side effects, by effectiveness and in general supposed increased safety. Over the past decade, atypical (or second-generation) antipsychotics have been increasingly used in the treatment of schizophrenia in preference to typical antipsychotics (73-76).

2.7 NANOPARTICLES AS A DRUG DELIVERY SYSTEM IN BRAIN DELIVERY

Two main reasons for the failure of drug delivery to the brain are:

1) Poor penetration of the drug molecule across the BBB.
2) Back transport (efflux) of drugs from the brain to the blood.

Various colloidal delivery systems have been tried upon by different researchers to overcome, especially the first aspect. These systems include liposomes, microspheres, lipid microspheres, niosomes, nanoparticles, and solid lipid nanoparticles (SLNs) etc.

Chen et al. have discussed polymeric nanoparticles for brain delivery (77). They have described mechanisms of nanoparticle mediated drug uptake by the brain. These include:

1. Enhanced retention of drug molecules in the brain–blood capillaries, with an adsorption on to the capillary walls which lead to high concentration gradient across the BBB.
2. Opening of tight junctions due to the presence of nanoparticles.
3. Transcytosis of nanoparticles through the endothelium.

They (77) also reported that Polysorbate can improve the brain bioavailability:

1. Solubilization of endothelial cell membrane lipids and membrane fluidization, due to surfactant effects of polysorbates.
2. Endocytosis of polymeric nanoparticles due to facilitated interaction with BBB endothelial cells.
3. Inhibition of efflux system, especially P-gp.

2.8 SOLID LIPID NANOPARTICLES (SLNs)

SLNs are aqueous colloidal dispersions, the matrix of which comprises of solid biodegradable lipids, in the size range of 10-500 nm. SLNs with combinational advantages from different carrier systems have emerged as propitious carriers in the armory of oral drug delivery systems. Nanopellets, lipospheres and SLNs are the analogous systems made of solid lipids introduced by different co-workers having a range of properties. The main reasons for development of SLNs are combinational advantages from different carrier systems such as liposomes and polymeric NPs. Similar to nanoemulsions and liposomes, they are composed of physiologically accepted biocompatible excipients (fatty acids and lipids) (78). These vehicles are composed of naturally occurring physiological lipids such as phospholipids, cholesterol, cholesterol esters and triglycerides. Owing to the natural and biological origin of the carrier material, it results in much lower toxicological risk than that of the polymeric particles (79). Identical to polymeric NPs, their solid matrix can effectively protect the incorporated active ingredients against chemical degradation under harsh biological milieu and provide the highest flexibilities in the modulation of the drug release profiles. Further, they can be produced at large industrial scale by high-pressure homogenization. All these constructive attributes make SLNs excellent carriers for oral drug delivery.

SLNs are safely taken up by brain and exhibit least toxicity due to the biodegradable nature of the carrier lipid. Smaller size (around 10 to 200 nm) and narrow size range (100 to 200 nm) allows them to cross tight endothelial cells of the Blood Brain Barrier (BBB), escape from the reticuloendothelial system (RES), and bypass liver. They have relatively higher drug entrapment efficiency, make the drug molecule more stable in the lipid matrix, and provide a controlled drug release lasting up to several weeks. The production of SLNs can be scaled up with excellent reproducibility (80,81). The advantages of SLN over other nanoparticulate systems are as follows (80):

1. The SLNs particularly those in the range of 120–200 nm, are not taken up readily by RES (Reticulo Endothelial System) and thus can bypass liver and spleen filtration.
2. They provide controlled drug release property upto several weeks. Furthermore, coating or attaching ligands to SLNs, there is an increased scope of drug targeting.
3. SLN formulations stable for even three years have been developed. This is of prime importance with respect to the other colloidal carrier systems.
4. They provide high drug payload.
5. They have excellent reproducibility with a cost effective high pressure homogenization (HPH) method as the preparation procedure.
6. The feasibility of incorporating both hydrophilic and hydrophobic drugs.
7. The carrier lipids are biodegradable and hence safe.
8. Avoidance of organic solvents.
9. Feasible large-scale production and sterilization.

2.8.1 PREPARATION OF SOLID LIPID NANOPARTICLES

2.8.1.1 High Pressure Homogenization (HPH)

HPH is a reliable technique for the preparation of SLNs. HPH is widely used for the preparation of SLNs, Nanostructured Lipid Carriers (NLCs) and can be performed at elevated temperature (hot HPH technique) or at below room temperature (cold HPH technique). R.H. Muller was the first to report and patent this HPH method. Skye Pharma, London, currently holds the worldwide patent rights of HPH technology (82).

2.8.1.1.1 Hot homogenization

In the hot HPH technique, the lipids are melted at 5 -10 ºC above their melting points and the drug is dispersed. The drug loaded lipids are dispersed in hot aqueous surfactant solution maintained at the same temperature. A hot pre-emulsion is formed by high speed stirring using high shear mixing device (Ultra - Turrax). The hot pre-emulsion is then passed through HPH, at a temperature above the melting point of the lipid. The obtained nanoemulsion recrystallizes upon cooling down to room temperature, forming SLN (79).

2.8.1.1.2 Cold homogenization

The cold HPH technique is used for temperature labile or hydrophilic drugs. The drug is then dispersed in this melted lipid followed by rapid cooling using liquid nitrogen or dry ice. This is then milled in a ball mill/mortar to generate microparticles. A pre-suspension is formed by high speed mixing of the particles in a cold aqueous surfactant solution. It is then homogenized at or below room temperature to form SLN. Thus, cold homogenization can be used to overcome the problems of temperature induced drug degradation (79).

2.8.1.2 Microemulsion Technique

Microemulsions are clear, thermodynamically stable systems, composed of lipophilic phase (oil), a surfactant, co-surfactant and water. Gasco & coworkers have developed and patented (79) a suitable method for the preparation of SLN via microemulsions which has been adapted and/or modified by different labs. In this method, the lipid is melted and the drug is dispersed in the molten lipid. A mixture of surfactant, co-surfactant and water is heated at the same temperature that of the lipid. Then aqueous surfactant solution is added to the lipid melt under stirring to obtain transparent microemulsion. This microemulsion is then dispersed in water at 2 - 10ºC under mild mechanical stirring. Typical ratio of hot microemulsion to cold water is in the range of

1:25 to 1:50. The excess water is then removed by ultra-filtration or lyophilization in order to increase the particle concentration. The drawback of this technique is that high concentrations of surfactants and co-surfactants are necessary for formulation purposes, which is not desirable with respect to regulatory purposes and applications (79).

2.8.1.3 Solvent Evaporation Method

In this method, lipid is dissolved in a water-immiscible organic solvent (e.g. cyclohexane, chloroform). Then it is emulsified in aqueous phase containing surfactant. Solvent is evaporated under continuous stirring which results in precipitation of the lipid. As this method avoids use of heat, this method is highly suitable for thermolabile drugs. However, these dispersions are quite dilute and need to be concentrated using ultra-filtration or evaporation (83).

2.8.1.4 Solvent diffusion method

In this method, partially water miscible solvents (e.g. benzyl alcohol, ethyl formate) are saturated with water to ensure initial thermodynamic equilibrium of both liquids. Then a transient o/w emulsion is passed into water and continuously stirred which leads to solidification of dispersed phase due to diffusion of the organic solvent as lipid nanoparticles. The dispersion produced by this method is fairly dilute and needs to be concentrated by means of ultra-filtration or lyophilization. Average particle sizes around 100 nm and very narrow particle size distributions can be achieved by both solvent evaporation based methods (83,84).

2.8.1.5 Solvent Injection Method

The principle of the solvent diffusion method has been extended for the formation of SLNs by solvent injection method. In this method, the lipids are dissolved in a water miscible solvent or water miscible solvent mixture (acetone, isopropanol and methanol) and rapidly injected through an injection needle into an aqueous phase containing surfactants. Schubert and Muller-Goymann prepared SLNs by this method wherein the effect of various process and formulation parameters such as volume of solvent injected, emulsifier concentration, lipid concentration, viscosity of the aqueous phase and ethyl acetate concentration in the organic phase on particle size was evaluated. Particle size was found to be in the range of 80-300 nm, depending on the process parameters used. About 96.5% of the used lipid was transformed into SLNs and the formation of SLNs seemed to be controlled via diffusion mechanism (87,88).

This method offers clear advantages over the existing methods such as easy handling and a fast production process without need of sophisticated equipment like HPH. A disadvantage of this method is the use of organic solvents. Although some of the solvents are pharmaceutically acceptable, they cannot be used for certain routes like parenteral, ocular etc. as any residual solvent may harm the patient (85).

2.8.1.6 W/O/W Double Emulsion Method

This method has been introduced as a novel method based on solvent emulsification – evaporation for the preparation of SLNs loaded with hydrophilic drugs (79). The hydrophilic drug along with a stabilizer is encapsulated in the inner water phase of a w/o/w double emulsion. The stabilizer is claimed to prevent drug partitioning to the external water phase during the solvent evaporation. This technique has been used for the preparation of sodium cromoglicate containing SLNs. However, the average size was found in the range of micrometer so the term ‘‘lipospheres’ should be used for these ‘SLNs’.

2.8.1.7 High Shear Homogenization or Ultrasonication Technique

This method is based on the mechanism of cavitation. Here, the drug is added in the melted solid lipid. Then, the heated aqueous phase at the same temperature that of lipid phase is added to the melted lipid and emulsified using probe sonication or using high-speed stirrer or aqueous phase is added dropwise to lipid phase under mild magnetic stirring. This obtained pre-emulsion is then ultrasonicated using probe sonicator. The production temperature is kept at least 5ºC above the lipid melting point to prevent recrystallization during the process. Finally, the obtained dispersion is filtered through a 0.45µm membrane in order to remove impurities carried in during ultrasonication (86).

2.8.1.8 Phase inversion temperature (PIT) method

In this method, two main components are used: an oil phase containing solid lipids and non-ionic surfactants and an aqueous phase containing NaCl. Both phases are separately heated at ~90° C (above the PIT); then the aqueous phase is added dropwise to the oil phase at constant temperature and under continuous stirring in order to obtain a W/O emulsion. The mixture is then cooled under slow and continuous stirring at room temperature. When PIT is reached, the turbid mixture becomes clear and below the PIT, an O/W nanoemulsion is formed, which forms SLNs below the melting point of lipid (85).

2.8.1.9 Supercritical fluid (SCF) technology

SCF is a relatively new technique for SLN production and has the advantage of solvent free processing. This is a platform technology for powder and nanoparticle preparation. SLN can be prepared by the rapid expansion of supercritical carbon dioxide solutions (RESS) method. In this method, carbon dioxide (99.99%) is the good choice as a solvent (89).

2.8.1.10 Spray drying method

This is an alternative procedure to lyophilization in order to transform an aqueous SLN dispersion into final product. It is cheaper than lyophilization. Because of high temperature, high shear forces, this method cause particle aggregation (86).

2.8.2 TYPES OF SOLID LIPID NANOPARTICLES

The types of SLNs depends on the solubility of the actives in the lipid, chemical nature of the active ingredients and lipids, nature and concentration of surfactant, type of method used production of SLNs and finally the production temperature. This lead to generation of mainly three drug incorporation SLN models (82,83).

2.8.2.1 SLN Type 1, Homogenous matrix model

The SLN type 1, is produced from a solid solution of active ingredient in the lipid. A solid solution can be obtained when SLN are produced by cold homogenization method and using no surfactant. A lipid blend obtained contains a active ingredient in the molecularly dispersed form. After the solidification of this blend, it is ground in its solid state to avoid the enrichment of active ingradient in different parts of lipid nanoparticles.

2.8.2.2 SLN, type 2 Drug-enriched shell model

This type of SLNs are obtained when hot homogenization technique is employed and the active ingredient concentration in melted lipid is low during the cooling process of the hot oil in water nanoemulsion. The lipid will precipitate first which lead to a steadily increasing concentration of active ingredient in the remaining melt and an outer shell will solidify containing both active and lipid. The enrichment of the outer area of the particle causes burst release of active moiety.

2.8.2.3 SLN, type 3 Drug-enriched core model

SLN, type 3 is produced when the concentration of active ingredient is relatively high or close to its saturation solubility. In most cases, cooling down the hot oil droplet will reduce the solubility of the active in the lipid melt. When the saturation solubility exceeds active molecule precipitates and lead to formation of drug enriched core model (82,83).

2.8.3 ABSORPTION OF DRUG-LOADED SLNs

Absorption is a vital process which takes place right from the mouth to the stomach, small intestine and finally colon. Like micro/ macromolecules, drugs get absorbed through GIT membrane by one or more transport mechanism. Absorption of nanoparticulate systems may be possible by one or more of the aforementioned mechanisms.

Solid lipid nanoparticles are colloidal drug carriers that hold significant promise for oral administration. Generally non-engineered nanoparticles of 50-1000 nm and microspheres < 10 μm have shown the adequate uptake into lymphatics. However, microparticles showed only 2 - 3% of absorption through Peyer’s patches and were retained in the gut of rats and mice for protracted time periods (87-88). The routes for particle uptake after oral application are transcellular (via the M cells in the Peyer’s patches or enterocytes) or paracellular (diffusion between the cells). However, the uptake via M cells is the major pathway, resulting in the transport of the particles to the lymph (88). Additionally, in case of lipid based systems containing self-emulsifying excipients, apart from M cell and paracellular uptake, absorption through lipase mediated chylomicron formation into lymphatic system (similar to absorption of long chain fatty acids via facilitated chylomicron formation) further increases the absorption. Through M cell uptake, drugs can be effectively transported to the systemic circulation through intestinal lymphatics via thoracic lymph duct. At the capillary level, the intercellular junctions between endothelial cells of lymphatic capillaries are more open as compared to blood capillaries that results in molecular sieving of NPs of large size directly into lymphatics, avoiding direction to blood capillaries.

The M cell uptake of SLNs was found to be size-dependent (i.e., smaller the size, higher the uptake), but independent of the animal model (78). Thus, nanoparticulate systems can effectively improve BA and mean residence time (MRT) with concomitant enhancement of therapeutic efficacy. Improvement of oral BA after oral administration of SLNs has secured many advantages. Lymphatic delivery is helpful not only for absorption of poorly soluble drugs but also for targeting drug carriers to the lymphatics. Moreover, lymphatic delivery of SLNs evades the hepatic first-pass effect, and increases plasma concentration of drug (89).

2.8.4 Examples of Solid Lipid Nanoparticles (SLNs) for Bioavailability Enhancement

Cho et al (90) prepared solid lipid nanoparticles (SLNs) of docetaxel by surface-modification using Tween 80 or D-alpha-tocopheryl poly (ethylene glycol 1000) succinate (TPGS 1000) using solvent diffusion method. An in vitro release study of docetaxel SLN showed a sustained-release profile as compared with an intravenous docetaxel formulation (Taxotere®). The particle size and entrapment efficiency was found in the range of 189 nm to 215 nm and 80.7% to 83.1%, respectively. Tween 80-emulsified SLNs showed enhanced intestinal absorption, lymphatic uptake, and relative oral bioavailability of docetaxel compared with Taxotere in rats. This may be attributable to the absorption-enhancing effects of the tristearin nanoparticle. Moreover, compared with Tween 80-emulsified SLNs, the intestinal absorption and relative oral bioavailability of docetaxel in rats were further improved in TPGS 1000-emulsified SLNs, probably due to better inhibition of drug efflux by TPGS 1000, along with intestinal lymphatic uptake. Hence, it can be concluded that surface-modified SLNs may serve as efficient oral delivery systems for docetaxel.

Ravi et al (91) prepared Lipid nanoparticles (SLN) of raloxifene (RLX) with glyceryl tribehenate to enhance its oral bioavailability. Optimized batch of RLX-SLNs showed particle size and entrapment efficiency of 167 ± 3 nm and >92%. Respectively. The oral bioavailability of RLX in female Wistar rats was improved by 3.24 folds by SLNs compared to free RLX. Both clathrin and caveolae mediated endocytosis pathways were involved in the uptake of RLX-SLN across Caco-2 cell line. A lymphatic transport inhibitor, cycloheximide had significantly reduced oral bioavailability of RLX-SLNs.

Negi et al (92) prepared Solid lipid nanoparticles (SLNs) of poor orally bioavailable drug lopinavir using hot self nano-emulsification (SNE) technique. Self nano-emulsification ability of stearic acid, poloxamer and polyethylene glycol mixture was assessed by ternary phase diagram study. Optimized SLNs were having particle size of 180.6±2.32 nm (Polydispersity Index (PDI) = 0.133±0.001), 91. ±1.3% entrapment efficiency and zeta potential of -13.4±0.56 mV. SLNs were evaluated by transmission electron microscopy (TEM) and atomic force microscopy (AFM), Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) study. Higher oral bioavailability was found for lopinavir loaded SLNs in comparison to bulk lopinavir due to higher lymphatic drug transport ($p< 0.05$).

Bhandari et al (93) prepared SLNs of Isoniazide to achieve improved bioavailability and prolonged effect. Developed SLNs showed high entrapment efficiency (69%) and small size (d_{90} 48.4 nm). Single dose oral pharmacokinetic studies in rats showed a significant improvement ($p < 0.001$) in relative bioavailability in plasma (6 times) and brain (4 times) after administration of isoniazid-SLNs with respect to the free drug solution at the same dose. Insignificant changes in liver concentration coupled with bypass of first pass metabolism and slow release of isoniazid (60%, in 24 h) indicated low incidence of hepatotoxicity. Isoniazid-SLNs showed 3 times higher LD50.

Burra et al (94) investigated the utility of triglyceride (trimyristin, tripalmitin and tristearin) based solid lipid nanoparticles (SLNs) for improved oral delivery of raloxifene hydrochloride (RXH). The SLN formulations prepared were evaluated for particle size, zeta potential, DSC, % entrapment and the optimized formulation was lyophilized. In situ perfusion studies carried out in rat intestine revealed the potential of SLN for enhanced permeation of raloxifene HCl across gastrointestinal barrier. In vivo pharmacokinetic study showed two fold increase in bioavailability with SLN formulations confirming their potential for improved oral delivery of RXH.

Zhang et al (95) prepared Candesartan cilexetil -loaded solid lipid nanoparticles (CLNs) and evaluated them for physicochemical properties, and the pharmacokinetic behavior. CLNs exhibited nanometer-sized spherical particles with high entrapment efficiency (91.33%). The absorption of CLNs in the stomach was only 2.8% of that in intestine. Moreover, CLNs could be internalized into the enterocytes and then transported into the systemic circulation via the portal circulation and intestinal lymphatic pathway. The pharmacokinetic results in rats showed that the oral bioavailability of candesartan was improved over 12-fold after incorporation into SLNs.

Luo et al (96) developed and evaluated Puerarin loaded SLNs to enhance its oral absorption. The C_{max} value of puerarin after the administration of Pue-SLNs was significantly higher than that obtained with puerarin suspension (0.33±0.05 μg/mL vs. 0.16±0.06 μg/mL). The T_{max} of the Pue-SLNs (40±0 min) was significantly shorter than that of puerarin suspension (110±15.49 min, $P < 0.01$). The $AUC_{0\rightarrow t}$ values of puerarin of puerarin suspension and Pue-SLNs were 0.80±0.23 mg h/L, and 2.48±0.30 mg h/L respectively after oral adsministration. Tissue distribution of puerarin is also increased, especially in the target organs such as the heart and brain after incorporation into SLNs. Hence, the oral bioavailability of puerarin was enhanced.

Zhang et al (97) prepared Simvastatin (SV) loaded lipid nanoparticles (SLNs) with different components to enhance its oral bioavailability. The experimental results showed that SLNs were spherical nano-sized particles with high encapsulation efficiency (>95%). The in situ intestinal absorption indicated that the absorption of SLNs was greatly improved compared with that of free SV, and the absorption was changed with the site of the intestinal segments. SLNs could be uptaken through both clathrin and caveolae mediated endocytosis pathways into enterocytes. The oral bioavailability of SV was improved by 3.37-fold for SLNs I and 2.55-fold for SLNs II as compared to free SV in rats. The bioavailability of the SVA was significantly enhanced using SLNs.

Li et al (98) developed and characterized quercetin-loaded solid lipid nanoparticles (QT-SLNs), clarify the absorption mechanism of QT-SLNs and to evaluate the potential of using solid lipid nanoparticles (SLNs) as an oral delivery carrier for poorly water-soluble drugs. QT-SLNs were prepared by an emulsification and low-temperature solidification method. The QT-SLNs presented as spherically shaped under transmission electron microscopy, with an average diameter of 155.3 nm. The average drug entrapment efficiency, drug loading and zeta potential were 91.1%, 13.2% and −32.2 mV, respectively. Drug release from QT-SLNs was fitted to a double phase kinetics model and the equation was as follows: $100-Q=98.87e^{-0.1042t}+42.45e^{-0.0258t}$. The absorption of QT-SLNs in the gastrointestinal (GI) tract was studied using an in situ perfusion method in rats. It was found that the absorption percent in the stomach for 2 h was only 6.20%, the absorption process of intestine was first-process with passive diffusion mechanism, and the main absorptive segments were ileum and colon. A pharmacokinetic study was conducted in rats after oral administration of quercetin at 50 mg/kg in the form of either QT-SLNs or suspension. The plasma concentration-time curves were both fitted to a one-compartment model. The relative bioavailability of QT-SLNs to quercetin suspension was 571.4%. The T_{max} and MRT for quercetin in plasma were both delayed. The studies provide evidence that SLNs are valuable as an oral delivery carrier to enhance the absorption of a poorly water-soluble drug, quercetin.

Zhang et al (99) prepared SLNs delivery systems of oridonin using stearic acid, soybean lecithin and pluronic F68 using solvent evaporation method to overcome its very low oral bioavailability due to its poor solubility. The prepared SLNs were characterized for particle size, zeta potential transmission electron microscopy (TEM), Differential scanning calorimetry (DSC), powder x-ray diffraction (PXRD) and in vitro release study. The tissue distribution in mice and the pharmacokinetics in rabbits were studied to evaluate the tissue targeted property of SLNs. Stable SLN formulations of oridonin having a mean size range of 15–35 nm and mean zeta potential −45.07 mV was developed. More than 40% oridonin was entrapped in SLNs. DSC and PXRD analysis showed that oridonin is dispersed in SLNs in an amorphous state. The release pattern of the drug was analyzed and found to follow the Higuchi equations. In vivo studies demonstrated that oridonin-loaded SLNs obviously increased the concentration of oridonin in liver, lung and spleen, while its distribution in heart and kidney decreased.

Venkateswarlu et al (100) prepared SLNs delivery systems of clozapine have been developed using various lipids, soylecithin 95%, poloxamer 188 and charge modifier stearylamine. Hot homogenization followed by ultrasonication at temperature above the melting point of lipid was used to prepare SLN. Prepared SLNs were characterized for particle size, zeta potential, Differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and in vitro release study. Stable SLN formulations of clozapine having mean size range of 60–380 nm and zeta potential range of -23 to + 33 mV were developed. More than 90% clozapine was entrapped in SLN. DSC and PXRD analysis showed that clozapine was dispersed in SLN in an amorphous state. The release pattern of drug is analyzed and found to follow Weibull and Higuchi equations.

2.9 SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS)

2.9.1 INTRODUCTION

SMEDDS are defined as “isotropic mixture of natural or synthetic oils, surfactants and/or one or more hydrophilic co-solvents (101). It can form o/w microemulsion upon dilution and mild agitation provided by GIT. SMEDDS formulations spread easily in the GI tract, and motility of the stomach and the intestine provide the gentle agitation required for self-emulsification of formulation. Self-Emulsifying Drug Delivery System (SEDDS) produces emulsions having droplet size in the range of 100 to 300 nm whereas SMEDDS produces transparent microemulsion having droplet size less than 50 nm. When compared with emulsions, SEDDS are physically stable formulations that are easy to manufacture as compared to emulsion which is metastable. Thus, lipophilic drugs which exhibit dissolution rate limited absorption, SMEDDS offers advantages for improvement in its absorption.

The SMEDDS are thought to improve drug absorption is by keeping drug in dissolved state in GIT and hence, can eliminate need of dissolution in the GIT. The other mechanisms may include protection from chemical and enzymatic degradation localized in the aqueous environment of the GIT and promotion of lymphatic drug transport, which circumvents hepatic first-pass metabolism.

The physicochemical properties of active ingradients, excipients used in the formulation and dispersibility of the formulation in vivo will determine both the uptake of the drug in the GIT.

2.9.2 ADVANTAGES OF SMEDDS

- Oral bioavailability improvement: It can keep the drug in solubilized form in the GIT and produces formulation having globule size between 1 and 100 nm. This lead to subsequent increase in surface area which aids in efficient drug transport through the intestinal aqueous boundary layer and through the absorptive brush border membrane of intestine, leading to improved bioavailability.
- Ease of manufacture and scale-up: This makes these lipid formulations unique and easy to scale up as compared to other bioavailability enhancement techniques like solid dispersions, liposomes, and nanoparticles.
- Reduction in inter-subject and intra-subject variability: Most of the drugs show large inter-subject and intra-subject variation in their absorption, leading to decreased performance of drug and patient noncompliance.
- Prevention of enzymatic hydrolysis in GIT: SEDDS can protect drugs against enzymatic hydrolysis in the GI tract and can reduce presystemic clearance in the GI mucosa and hepatic first-pass metabolism. SEDDS are superior compared to other drug delivery systems in terms of its ability to deliver macromolecules like peptides, hormones, enzyme substrates, and inhibitors and its ability to protect them from enzymatic hydrolysis.
- Increased drug loading capacity: SMEDDS can increase drug loading capacity of drugs by dissolving in oil phase as compared to conventional lipid solutions. The solubility of lipophilic drugs having partition coefficient ($2<\log P<4$) are low in natural lipids and high in amphiphilic surfactant and/or cosolvents (36).

2.9.3 FORMULATION CONSIDERATION

To formulate and characterize the performance of lipid-based formulations, much work has been done to classify them according to composition. A lipid formulation classifying system has been published to provide a basis for evaluating the characteristics and performance of different types of formulations.

2.9.3.1 Lipid Formulation Classification System (LFCS)

LFCS was introduced as in 2000 by Colin Pouton, and one extra ‘type’ of formulation was added in 2006. The purpose of this LFCS is to allow in vivo studies to be interpreted more easily and, subsequently, to help the identification of the most appropriate formulations for specific drugs according to its physicochemical properties (89). Table 2.1 indicates the fundamental differences between types I, II, III and IV formulations.

Table 2.1: The Lipid Formulation Classification System: characteristic features, pros and cons of the four essential types of 'lipid' formulations

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

2.9.3.2 Composition of SMEDDS

2.9.3.2.1 Lipids (Oils)

Oils are the main component of SMEDDS because solubilization and access of the drug to the lymphatic transport of lipophilic drugs depend on the type and concentration of oil used in the formulation. Various digestive lipids such as triglycerides, diglycerides, phospholipids, fatty acids, cholesterol etc. based on synthetic origin are widely used. Oils from Synthetic origin offer improvement in bioavailability of the drug in contrast to the non-digestible lipids with which reduced bioavailability may occur due to impairment in absorption caused by retention of the fraction of administered drug in the formulation itself.

Although edible oils based on natural origin are favored, they are not useful as they do not have sufficient capacity to solubilize large amount of lipophilic drug and self-emulsification is also problematic with them as they possess a large molecular volume. Instead, modified or hydrolyzed oils of vegetable origin are beneficial due to their superior emulsification properties and compatibility with oral administration as their end products of degradation bear a resemblance to the end products produced by digestion process in the intestine. Polyglycolized glycerides of varying Hydrophilic lipophilic balance (HLB) attributed to difference in fatty acid chain length and PEG chain length are used along with vegetable oils for the improvement in the bioavailability of drug and are used for the reason of better tolerability by the human body (102-104). Triglycerides with long and medium chain length containing different degrees of saturation are commonly used in the preparation of SMEDDS. Medium chain triglycerides have the capacity to get digested efficiently compared to the long chain triglycerides and also exhibit greater fluidity, improved solubility properties, and good ability to self-emulsify along with the reduced tendency towards oxidation due to which they contribute to the increase of drug absorption and in turn have positive effects on bioavailability. These attractive properties made them more commonly used compared to Long chain triglycerides (LCTs) (36).

2.9.3.2.2 Surfactants

Surfactant is necessary to adopt self-emulsification property by SMEDDS which is prime process to form microemulsion. It is also helpful to solubilize the hydrophobic drug which in turn can improve the dissolution rate (30). Permeability barrier that is intestinal cell membrane comprised of lipids can be disrupted by surfactant partition; thereby permeability will be enhanced. The opening of tight junctions by the surfactants also contributes to the improvement in permeability with surfactant labrasol due to opening of tight junctions. The inhibitory effect of surfactants on p-glycoprotein aids in the improvement of bioavailability of many drugs which are substrates of p-glycoprotein transporter (36).

Most of the surfactants have impact on lipid digestion that is catalyzed by lipase in various ways like the formation of complexes with the enzyme at interface, by preventing the adsorption of enzyme at interface or by the interaction with the lipase itself. Inhibition of lipid digestion may also occur as the surfactant has the tendency to interact with other components like bile salts and phospholipids. When different surfactants are compared in this aspect, non ionic surfactants have little impact on lipid digestion, promoting effects on lipid digestion with the use of cationic surfactants and inhibitory effect is observed with anionic surfactants (102-104).

SMEDDS composed of surfactants in the range of 30–60%. Minimum surfactant concentration should be used because the use of high concentration of surfactants has disadvantages like GI irritation, decrease in self-emulsification efficiency, and dehydrating effect on soft and hard gelatin capsules (caused by some nonionic surfactants like polysorbates and polyoxyls) with consequent brittleness. High surfactant concentration lead to GI irritation due to tissue damage and decrease in the self-emulsification efficiency because of formation of liquid crystalline phase at the interface which in turn is due to viscous nature (36).

Inverse relationship between the droplet size and the concentration of the surfactant has been usually reported. This phenomenon could be attributed to the stabilization of the oil droplets as a consequence of the localization of the surfactant molecules at the oil-water interface. However, in some cases, the droplet size tends to increase after attaining a critical concentration. This is amenable to the interfacial disruption caused by enhanced water penetration into the oil droplets, mediated by the increased surfactant concentration, thus leading ultimately to the ejection of oil droplets into the aqueous phase.

2.9.3.2.3 Cosurfactants

Cosurfactants facilitate the dissolution of surfactant and hydrophobic drug in oil phase because of their ability to access the entry of water into the formulation. Some of the commonly used cosurfactants are short chain alcohols like Transcutol HP, ethanol, n-butanol, propylene glycol, and polyethylene glycol etc (3, 30). The addition of cosurfactants imparts flexibility to the interface which is helpful for the free movement of the hydrophobic tails of surfactant at interface which in turn imparts dynamic behavior to microemulsions. Alcoholic, low molecular weight cosurfactants may cause precipitation of the drug when the formulation is filled in gelatin capsules since they are absorbed onto the capsule shells. Along with the nature, the concentration of cosurfactant also has an impact on drug precipitation.

Due to their high polarity, they tend to migrate towards aqueous phase upon dispersion into aqueous media leading to drug precipitation. Hence it is advisable to formulate SMEDDS in minimum concentration. The surfactant and cosurfactant should be selected by considering the efficacy, irritancy, change in efficacy caused by repeated administration of formulation, their interaction with the proteins and lipids of the mucosa, and metabolic pathway followed by them (102-104).

2.9.4 MECHANISM OF SELF EMULSIFICATION

It was reported by Reiss (105) that self-emulsification process occurs when entropy of the dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phases (106) and can be described by the following equation:

$$\Delta G = \sum (N_i 4\pi \, r_i^2 \sigma) \dots\dots\dots\dots\dots\dots\dots . Equation \; 2.1$$

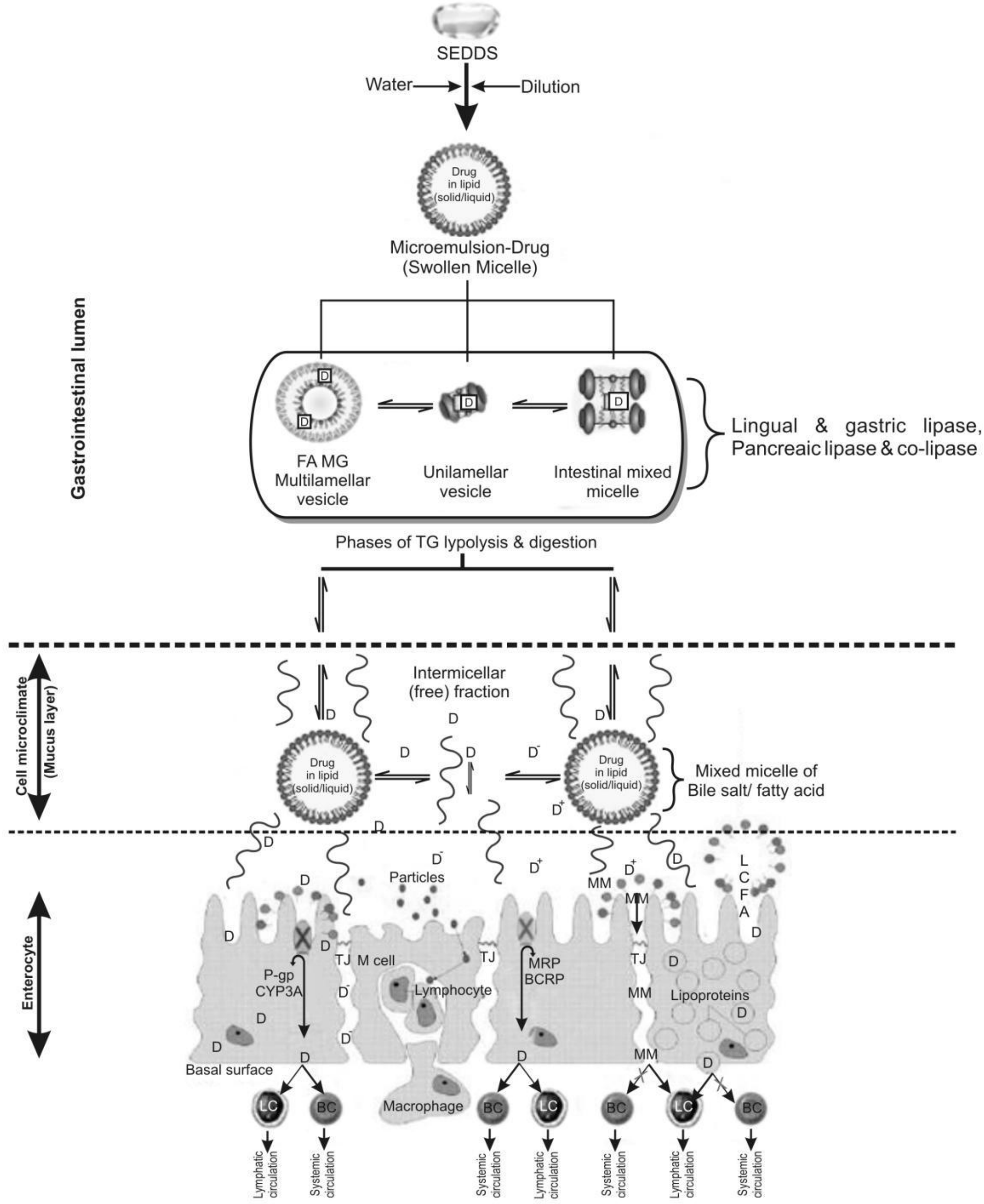
where ΔG is the free energy associated with the process, N is the number of droplets of radius r and σ is the interfacial energy. Formed phases tend to separate over time to reduce the interfacial energy and, hence, reduce the free energy of the system. Generally, two phases of emulsion tend to separate with time to reduce the interfacial area. Hence, the emulsion is stabilized by using emulsifying agent, which forms a monolayer around emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence.

The ease of emulsification of SMEDDS is related to the ease of water penetration into the various liquid crystal (LC) or gel phases formed on the surface of the droplet. The interface between the oil and aqueous continuous phase is formed upon addition of a oil/nonionic surfactant micture to water. This is followed by the solubilization of water within the oil phase as a result of aqueous phase penetration through the interface. This will occur until the solubilization limit is reached close to the interphase. Further, aqueous phase penetration will lead to the formation of the dispersed LC phase.

Eventually, everything that is in close proximity to the interface will be LC; the actual amount depends on the surfactant concentration in the binary mixture. Thus, following gentle agitation of the self-emulsifying system, water rapidly penetrates into the aqueous cores, leading to interface disruption and droplet formation. As a consequence of the LC interface formation surrounding the oil droplets, self-emulsifying formulations become stable to coalescence (36).

2.9.5 MECHANISM OF DRUG TRANSPORT FROM SMEDDS

The pathway of lipidic transport from the GI lumen to the systemic circulation is of utmost significance for interpretation of the biopharmaceutical properties of oral lipid-based formulations and successful product development. After oral administration, the SMEDDS formulation undergoes three phases: digestive, absorptive and circulatory phases. Figure 2.6 presents a comprehensive pictorial view of such pathways through which the drug molecules form self-emulsifying systems tend to get absorbed into the circulatory system. Understanding the effect of lipid type and lipid digestion, in addition to drug load potential and the ease of dispersion of the SEDDS formulation, is necessary to precisely predict and explain its in vivo bio-performance. The intra-luminal processing of lipids prior to absorption (Figure 2.5) dictates the GI solubilization and bioavailability of the drug (107).



FA MG: Fatty acid monoglyceride, TG: Triglyceride, LCFA: Long chain fatty acid, D: Drug, D⁻& D⁺: Ionized drug, TJ: Tight junction, MM: Macromolecules, LC: Lymphatic cells, BC: Blood cells, MRP: Multiple resistance proteins, BCRP: Breast cancer resistance protein, P-gp: P-glycoprotein

Figure 2.5: Diagrammatic representation depicting the probable mechanistic pathways for transportation of drugs across the GI lumen using SEDDS

The combined effect of antral contraction, retropulsion and gastric emptying, during digestive phase, disperses the lipidic formulation into a coarse emulsion. This emulsion undergoes enzymatic hydrolysis at the oil/water interface converting the digestion products into an absorbable form. These dispersed lipid digestion products, along with the undigested lipids, then empty into the duodenum causing the release of secretin from the duodenal mucosa. This, in turn, maximizes the activity of pancreatic lipase and co-lipase through the secretion of bicarbonate. Digestion is completed by the action of these interfacial enzymes that act on the surface of the emulsified triglyceride droplets to quantitatively produce the corresponding 2-monoglyceride and two fatty acids. The digestion phase terminates with the interaction of fatty acids and monoglycerides with bile salts resulting in the formation of mixed micelles, while a part of the triglycerides and fatty acids may form vesicles after digestion in this pre-absorptive phase. It is at this phase that the drug released from the SEDDS due to either precipitation or dissolution into the gastric media is resolubilized as micelles or mixed micelles by emulsification (104,107-109).

The colloidal species produced as a result of lipid digestion during the absorptive phase are taken up either by passive diffusion, facilitated diffusion or active transport through the enterocyte membrane. In the cytosol, a fatty acid-binding protein transports these micelles through the apical membrane by a carrier-mediated transport process (108). Alternatively, the absorbed free drug may be merged with the chylomicrons (i.e., intestinal lipoproteins) within the enterocyte. These chylomicrons are relatively large colloidal systems capable of selective intestinal lymphatic transport of the lipophilic compounds. The endothelial architecture of the lymphatic vessels facilitates the size-selective transport of chylomicrons for which simplistic access across the blood capillary endothelium is restricted. Chylomicrons travel through the lacteals to join lymphatic vessels from other parts of the body, and enter the systemic circulation via the thoracic duct into the subclavian vein, thus protecting the drug from hepatic first-pass metabolism. During the circulatory phase, the blood-borne chylomicrons rapidly disassemble releasing the encapsulated drug. The residual constituent lipids of SEDDS are utilized throughout the body (104, 107-109).

Possible mechanisms of drug transport through intestinal barriers using the SEDDS. These mechanisms include, an increase in membrane fluidity facilitating transcellular absorption, opening of the tight junction to allow paracellular transport, mainly relevant for ionized drugs or hydrophilic macromolecules, inhibition of P-gp and/or CYP450 to increase intracellular concentration and residence time, and stimulation of lipoprotein/chylomicron production as described in figure 2.5. The latter two mechanisms are likely the most promising for intestinal lymphatic transport of drugs using lipid-based vehicles (109).

2.9.6 APPLICATIONS OF SMEDDS IN ORAL DELIVERY

After oral administration SMEDDS gets spontaneously emulsified upon contact with gastric components and further emulsified by the bile salt resulting into formation of small oil droplets of approximately 0.5 μm size. It is important to study in vivo behavior of constituent components to understand drug absorption from emulsion (102-106). Various modes of enhanced drug absorption from SMEDDS can be hypothesized as follows:

Stimulation of body secretions that help in digestion of lipids: Administration of lipid can stimulate the biliary and pancreatic secretions which are helpful for the digestion of lipids. The enzymes present in the secretions are water soluble and act at water/lipid interface. Fatty acids liberated from the lipid digestion process interact with the bile salts and result in the formation of mixed micelles and micelles in which the drug gets solubilized.

Prolongation of GI residence time: Administration of lipid along with the drug allows the drug to be present for prolonged duration of period in the GIT which facilitates the absorption of the drug.

Stimulation of lymphatic transport: The highly lipophilic drug ($\log P > 5$) which has high solubility in triglycerides (>50mg/mL) can undergo lymphatic transport when co-administered with esters of unsaturated long chain fatty acids; thereby bioavailability can be improved. This restricted lymphatic transport is mainly due to low lymph-to-blood flow ratio. This enhanced lymph delivery of the drug can bypass the first pass extraction whereby the bioavailability of drugs that undergo extensive first pass effect can be improved (36).

Increased intestinal wall permeability: Opening of tight junctions in the intestine caused by lipids contributes to the increased permeability of poorly permeable drugs. Although this mechanism not essential in case of BCS Class II drugs, it leads to marked improvement in absorption of Class IV drugs which have both dissolution and permeability rate limited absorption.

Reduced efflux of the drug in the GIT: Lipids such as anionic phospholipids (cardiolipin and phosphatidylserine) may inhibit permeability glycoprotein (P-gp) by interaction with membrane lipids. So, the drugs which have propensity to be effluxed from the GIT can be formulated as lipid based delivery systems for the improvement of bioavailability. The inhibitory effect is due to competition for binding with the transporter and due to membrane perturbation caused by the excipients, mainly surfactants. The residence time of the drug can be prolonged by this inhibition of efflux.

2.9.7 EXAMPLES OF SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS) FOR BIOAVAILABILITY ENHANCEMENT

Li et al (110) prepared Curcumin (CUR) and piperine (PIP) SMEDDS to improve the stability and water-solubility of CUR and enhance its anticolitis activity. The formulation was characterized by assessing appearance, morphology, particle size, zeta potential and drug encapsulation efficiency. The vitro stability investigation of in colon tissue suggested that CUR was more stable in SMEDDS than drug solution. The anti-inflammatory activity SMEDDS was evaluated on Dextran Sulfate Sodium induced colitis model showed that CUR–PIP-SMEDDS exhibited definite anti-colitis activity by directing CUR–PIP-SMEDDS to inflammatory colon tissue through retention enema administration.

Qureshi et al (111) formulated and evaluated a solid SMEDDS of lovastatin. SMEDDS was prepared using Peceol, Cremophor RH 40 and Transcutol-P and subjected to droplet size, zeta potential measurement, dispersibility studies and release studies. The in vitro release study showed that the drug release from lovastatin loaded SMEDDS was significantly higher than that of plain lovastatin powder. Pharmacodynamic study showed that Neusilin® was found to be a suitable carrier for SMEDDS and was too effective in reducing the elevated lipid profile in healthy diet induced hyperlipidemic rabbits.

Nipun et al (112) developed and evaluated SEDDS of a poorly soluble drug, gliclazide. In-vitro drug release from optimized batch showed higher drug release (99% within 20 min) than other formulations. In-vivo performance of SEDDS showed significant reduction in plasma glucose level, after oral administration n albino mice by taking plasma glucose level as a pharmacodynamic marker parameter.

Baek et al (113) developed and evaluated SMEDDS for improving the oral absorption of a poorly water-soluble drug, pranlukast hemihydrate (PLH). The formulations were characterized by assessing self-emulsification performance, droplet size analysis, in vitro drug release characteristics and formulation stability studies. The SMEDDS readily released the lipid phase to form a fine oil-in-water microemulsion with a narrow distribution size. Saturated solubility of PLH from SMEDDS in water, pH 4.0 and 6.8, were over 150 times greater than that of plain PLH. The in vitro release profile showed 100% release of PLH from SMEDDS which was considerably higher compared to only 1.12% in simulated intestinal fluid (pH 6.8) from plain PLH after 2 hours. The absorption of PLH from SMEDDS resulted in about a threefold increase in bioavailability in rats compared with plain PLH aqueous suspension.

Negi et al (114) formulated SMEDDS by using P-gp modulator excipients to evaluate systemic availability of Irinotecan. A much deeper penetration to the intestine was observed with SMEDDS by using confocal laser scanning microscopy (CLSM). Flow-cytometric studies also revealed the greater uptake of fluorescent probe in Caco-2 cell-lines with the use of SMEDDS. The $AUC_{0 \rightarrow t}$ of Irinotecan from the optimized SMEDDS formulation was found to be 4 times greater than that of Irinotecan suspension after oral administration. The optimized formulation was found to be effective in maintaining the sustained plasma drug level of Irinotecan with better bioavailability.

Sha et al (115) designed a SMEDDS to improve the bioavailability of probucol. SMEDDS was composed of probucol, olive oil, Lauroglycol FCC, Cremophor EL, Tween-80, and PEG-400. Pharmacokinetics and bioavailability of probucol suspension, oil solution, and SMEDDS in rats showed that relative bioavailability of SMEDDS was dramatically enhanced as compared to that of oil solution and suspension.

Zhang et al (116) developed a SMEDDS to enhance the oral bioavailability of the poorly water-soluble drug, oridonin. The influence of the oil, surfactant and co-surfactant types on the drug solubility and their ratios on forming efficient and stable SMEDDS were investigated in detail. The optimum formulation consisted of 30% mixture of Maisine 35-1 and Labrafac CC (1:1), 46.7% Cremopher EL, and 23.3% Transcutol P. In vitro release test showed a complete release of oridonin from SMEDDS in an approximately 12 h. The relative bioavailability of oridonin from SMEDDS was increased 2.2-fold as compared to that of the suspension.

Wu et al (117) prepared SMEDDS containing curcumin to overcome its low solubility, stability in aqueous solution, and low bioavailability. Pseudoternary phase diagrams and solubility test were used to formulate SMEDDS composed of 20% ethanol, 60% Cremophor RH40®, and 20% isopropyl myristate. Curcumin was released completely from SMEDDS at 10 minutes. The developed SMEDDS formulation improved the oral bioavailability of curcumin significantly, and the relative oral bioavailability of SMEDDS compared with curcumin suspension was 1213%.

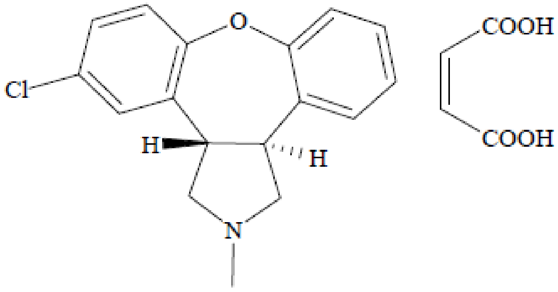
Dixit et al (118) developed a SMEDDS to enhance diffusion rate and oral bioavailability of valsartan. The particle size distribution, zeta potential, and polydispersity index were determined and were found to be 12.3 nm, −0.746, and 0.138, respectively. Valsartan SMEDDS showed maximum drug release when compared to pure drug solution and marketed formulation. The area under curve and time showed significant improvement for SMEDDS in comparison to market formulation suggesting significant increase ($p<0.01$) in oral bioavailability of valsartan SMEDDS upon oral administration in rabbits.

Singh et al (119) prepared the SMEDDS of exemestane to improve the solubility and bioavailability. The droplet size and zeta potential was found ranging from 22 nm to 66 nm and -5.7 mV to -10.9 mV. The percentage release of exemestane SMEDDS was significantly higher ($p< 0.05$) than that from the conventional marketed formulation. The absorption of exemestane from SMEDDS resulted about 2.9-fold increase in bioavailability as compared to the suspension.

2.10 DRUG PROFILES

2.10.1 ASENAPINE MALEATE

Table 2.2 Properties of Asenapine maleate (120,121)

Name	Asenapine maleate
CAS No	65576-45-6
Non-Proprietary Name	(3a*RS*,12b*RS*)-5-Chloro-2-methyl-2,3,3a,12b-tetrahydro-1*H*dibenzo[2,3:6,7]oxepino[4,5-*c*]pyrrole (2*Z*)-2-butenedioate (1:1)
Chemical Structure	
Formula	$C_{17}H_{16}ClNO.C_4H_4O_4$
Mol. Mass	401.84
Description	White to off-white powder having melting point 140-145 ˚C
Category	Antimanic Agents, Antipsychotic Agents
Solubility	Slightly soluble in water
Log P	4.9
PHARMACOLOGY	
Indication	It is used in the treatment of psychosis, schizophrenia and schizoaffective disorders, manic disorders, and bipolar disorders as a monotherapy or in combination.
Pharmacodynamics	Asenapine is a serotonin, dopamine, noradrenaline, and histamine antagonist. Asenapine possess more potent activity with serotonin receptors than dopamine. Sedation in patients is observed with asenapine's antagonist activity at histamine receptors. It lowers the incidence of extrapyramidal side (EPS) effects associated with the upregulation of D1 receptors. This upregulation occurs due to asenapine's dose-dependent effects on glutamate transmission in the brain.It does not have any

	significant activity with muscarinic, cholinergic receptors. Therefore, symptoms associated with anticholinergic drug activity like dry mouth or constipation are not expected to be observed. Asenapine has a higher affinity for all aforementioned receptors compared to first-generation and second-generation antipsychotics except for 5-HT1A and 5-HT1B receptors.
Mechanism of action	Asenapine maleate is an atypical antipsychotic multireceptor neuroleptic drug which shows strong $5HT_2A$ (serotonin) and D_2 (dopamine) receptor antagonism, which has been shown to enhance dopamine (DA) and acetylcholine (Ach) efflux in rat brains. Asenapine may improve cognitive function and negative symptoms in patients with schizophrenia.
Absorption	Bioavailability, sublingual administration = 35%; Bioavailability, oral administration (swallowed) = <2%; Time to steady state, 5 mg = 3 days; Peak plasma concentration occurs within 0.5 to 1.5 hours. Doubling dose of asenapine results in 1.7-fold increase in maximum concentration and exposure. Drinking water within 2-5 minutes post administration of asenapine results in a decrease in exposure.
Volume of distribution	20-25 L/kg
Protein binding	95% protein bound
Metabolism	Asenapine is oxidized via cytochrome P450 isoenzymes (CYP1A2) and undergoes direct glucuronidation via UGT1A4. Oxidation via CYP1A2 is asenapine's primary mode of metabolism.
Route of elimination	Urine (50%) and faeces (50%)
Half life	24 hours (range of 13.4 - 39.2 hours)
Available Preparations	Sublingual tablet, 5 mg, 10 mg

2.10.1.1 Analytical methods

1. A simple, accurate, precise and sensitive UV spectrophotometric method was developed for the determination of Asenapine maleate in methanol at 270 nm (122).
2. A simple, accurate, precise and sensitive UV spectrophotometric method was developed for the determination of Asenapine maleate in 0.1 N HCl at 269 nm (123).
3. A novel isocratic reverse-phase high performance liquid-chromatography method for determination of asenapine maleate was developed using acetonitrile: 0.1M phosphate buffer (pH 3.2) 65:35%v/v as mobile phase and 1 ml/min flow rate at 272 nm. The retention time was found to be 5 min (124).
4. A reverse phase liquid chromatography method for determination of Asenapine Maleate was developed using mobile phase containing 0.05 M potassium dihydrogen phosphate:acetonitrile [60:40, v/v, pH 2.7 adjusted with 1% o-phosphoric acid]. The flow rate was 1.0 ml/min and effluents were monitored at 270 nm. The retention time of asenapine was found to be 4.2min (125).

2.10.1.2 Research work done

1. Singh SK et al (126) prepared asenapine (ASM) loaded nanostructured lipid carriers (ANLC) for the delivery of drugs in the brain by an intranasal route to enhance therapeutic efficacy. The observed particle size, entrapment efficiency and zeta potential of ANLC was found to be 167.30 ± 7.52 nm, 83.50 ± 2.48% and −4.33 ± 1.27 mV, respectively. A brain pharmacokinetic study indicated a significantly higher ($p < 0.05$) peak drug concentration, area under the drug concentration–time curve and mean residence time of ANLC compared to ASM in the brain via an intranasal route. The results of behaviour studies of ANLC showed a significant decrease in extra-pyramidal side effects with increasing antipsychotic effect after 1–2 week(s) of treatment.

2. Kulkarni et al (127) prepared thermo-responsive in situ nasal gel containing asenapine using maleate-hydroxyl propyl β cyclodextrin inclusion complex (AM-HPβCD). Locomotor activity was improved with nasal gel containing AM-HPβCD as compared to AM and AM-HPβCD oral solution in rats. Cmax for nasal gel was found to be more (9 ng/ml) as compared to AM-

HPβCD (5.5 ng/mL) and oral standard solution (2 ng/ml) and thus bioavailability in rats by nasal route was increased by 2.5 fold.

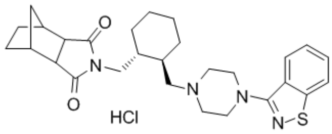
3. Avachat et al (128) prepared biodegradable injectable in-situ forming implants (ISFI) of asenapine maleate (ASM) using PLGA which would release drug uniformly for 21 days. PLGA 50:50 with different drug: polymer ratios were tried. *N*-methyl-2-pyrrolidone and dimethyl sulphoxide were used as organic solvents. In-vitro dissolution studies indicated that drug: polymer ratio of 1:2 and *N*-methyl-2-pyrrolidone (0.3 ml) gave desired release profile, total cumulative drug released being 97.66% at the end of 21 days. Ex-vivo studies confirmed the formation of implant in extensor digitorum muscle with desired drug release profile. In-vivo study was performed in Sprague– Dawley rats. Compared to marketed sublingual formulation area under curve of ASM implant was found to increase 2.215 fold. The *C*max was found to be 11 ng/ml. Thus, long acting ISFI of ASM was successfully formulated showing improved therapeutic results for the treatment of schizophrenia and bipolar disorders which could be a potential substitute to marketed sublingual tablets.

2.10.1.3 Patents on Asenapine Maleate

Inventors	**Title**	**Description**
Werenfridus Adrianus Faassen, Gerardus Johannes Huissen Kemperman, Johannes Antonius Hendrikus van Laarhoven (129)	Injectable formulations containing asenapine and method of treatment using same	The present invention provides a formulation comprising asenapine hemipamoate suspended particles, which can be administered as Depot provided by an IM injection of the formulation. The present invention provides also methods of treatment using the same.
Gianpiero Ventimiglia, Guiseppe Barreca, Domenico Magrone (130)	Polymorphic forms of AM and processes for their preparation	They disclosed new crystalline forms of asenapine maleate, useful in the production of pharmaceutical formulations for the treatment of diseases of the central nervous system, in particular schizophrenia;
Gerhardus Johannes Heeres (131)	Crystal form of asenapine maleate	This invention relates to an orthorhombic crystal form of compound trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz [2,3:6,7] oxepino [4,5-c] pyrrole (Z)-2-butenedioate, methods for the preparation of this crystal form and to pharmaceutical compositions comprising an orthorhombic crystal form.
Max Born, Diana Fischer, Ina Otto, Yvonne Fischer, Carsten Brauer (132)	Compressed oral dosage form for asenapine maleate	This invention is related to a compressed pharmaceutical dosage form intended for sublingual or buccal administration which is capable of being rapidly disintegrated and the compressed pharmaceutical dosage form containing asenapine maleate in a microcrystalline monoclinic form. It also relates to a method of preparing the same and to a container comprising the dosage form.

2.10.2 LURASIDONE HCl

Table 2.3: Properties of Lurasidone HCl (133)

Name	Lurasidone hydrochloride
CAS No	367514-87-2
IUPAC Name	(1R,2S,6R,7S)-4-{[(1R,2R)-2-{[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]methyl}cyclohexyl]methyl}-4-azatricyclo[5.2.1.$0^{2,6}$]decane-3,5-dione
Chemical Structure	
Formula	C_{28}-H_{37}-Cl-N_4-O_2-S
Mol. Mass	529.14
Description	White to off-white powder having melting point >250 ˚C
Solubility	Very slightly soluble in water
PHARMACOLOGY	
Indication	In the treatment of schizophrenia and bipolar disorder**.**
Pharmacodynamics	Lurasidone is a benzothiazol derivative that is an antagonist and binds with high affinity to Dopamine-2 (D2), 5-HT2A receptors, and 5-HT7 receptors. It also binds with moderate affinity to alpha-2C adrenergic receptors and is a partial agonist at 5-HT1A receptors. Its actions on histaminergic and muscarinic receptors are negligible.
Mechanism of action	Lurasidone is an atypical antipsychotic that is a D2 and 5-HT2A (mixed serotonin and dopamine activity) to improve cognition. It is thought that antagonism of serotonin receptors can improve negative symptoms of psychoses and reduce the extrapyramidal side effects that are often associated with typical antipsychotics.
Absorption	Lurasidone is readily absorbed and quickly reaches maximal concentrations (Cmax) within 1-4 hours. When taken with food,

	there is a two-fold increase in exposure and time to maximal concentration is increased by 0.5-1.5 hours. This occurs regardless of fat or caloric content. Bioavailability = 9-19%. Tmax is about 1.5 and 3 hours after single and multiple dose administration, respectively. Lurasidone exposure (AUC and Cmax) is proportional to dose in the range of 20 to 160 mg. **FOOD:** Mean peak serum concentrations and AUCs of lurasidone increased by about threefold and twofold, respectively, when administered with food compared with values obtained under fasting conditions. But there was no significant difference in exposure based on the caloric/fat content of the meal.
Metabolism	Lurasidone is metabolized by CYP3A4 in which its major active metabolite is referred to as ID-14283 (25% of parent exposure). Its two minor metabolites are referred to as ID14326 and ID11614 which make up 3% and 1% of parent exposure respectively. Its two non-active metabolites are referred to as ID-20219 and ID-20220.
Excretion	Urine (~9%) and faeces (~80%)
Half life	40 mg dose= 18 hours ,120 mg - 160 mg dose = 29-37 hours
Available Preparations	Tablet, oral, 20 mg, 40 mg, 80 mg, 120 mg.

2.10.2.1 Analytical methods

1. Three new, simple and cost-effective UV-Spectrophotometric methods were developed for the estimation of Lurasidone hydrochloride in methanol at 227 nm (134).
2. A convenient, simple, specific, accurate, precise, rapid, inexpensive isocratic Reversed Phase-High Performance Liquid Chromatography (RP-HPLC) method was developed using c18 column. The mobile phase composed of 10mM Phosphate buffer (pH-3.0, adjusted with triethylamine): acetonitrile (50:50 v/v). The flow rate was set to 1.0 ml/min with the responses measured at 235nm. The retention time of Lurasidone HCl was found to be 4.33 min (135).

2.10.2.2 Research work Done

1. Madan et al (136) prepared fast dissolving tablet of lurasidone HCl using concept of mixed hydrotrophy. The optimized batch tablets showed 88% cumulative drug release within 14 min and in vitro dispersion time was 32 min. it was concluded that mixed hydrotropic solid dispersion enhanced bioavailability of lurasidone HCl.
2. Shah et al (137) developed, optimized, and evaluated nanocrystals of lurasidone hydrochloride for improving its solubility and dissolution characteristics. Nanocrystals were prepared by media milling technique using zirconium oxide beads. The particle size of optimized batch was found to be 228 nm and released t all the drug within first 5 min. Since the crystallinity of the drug is maintained, improvement in saturation solubility and dissolution efficiency could be attributed to decrease in mean particle size of the drug.
3. Quian et al (138) prepared coamorphous form of lurasidone hydrochloride (LH) with saccharin (SAC) in a 1:1 molar ratio. In comparison to crystalline LH, amorphous LH showed similar solubility and temporary improvement in the intrinsic dissolution rate and supersaturated dissolution, while coamorphous LH-SAC exhibited greatly improved solubility with pH-independent solubility behavior in pH range of 2 to 5.5, as well as persistent enhanced intrinsic dissolution rate and supersaturated dissolution. In addition, coamorphous LH-SAC showed superior physical stability than amorphous LH under long-term storage condition.

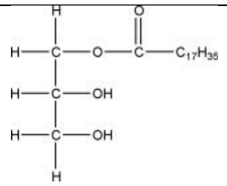
2.10.2.3 Patents on Lurasidone Hydrochloride

Inventors	**Title**	**Description**
Reddy Bandi Parthasaradhi, Reddy Kura Rathnakar, Reddy Dasari Muralidhara, Reddy Itiyala Srinivas, Chander Reddy Kesireddy Subash, Krishna Bandi Vamsi (139)	Lurasidone hydrochloride solid dispersion	The present invention relates to a novel amorphous solid dispersion of lurasidone hydrochloride using pharmaceutically acceptable carrier, process for its preparation and pharmaceutical compositions comprising it.
Reddy Bandi Parthasaradhi, Reddy Kura Rathnakar, Reddy Dasari Muralidhara, Reddy Itiyala Srinivas, Krishna Bandi Vamsi (140)	Novel polymorph of lurasidone hydrochloride	The present invention provides a novel amorphous form of lurasidone hydrochloride, process for its preparation and pharmaceutical compositions comprising it. In one aspect, the invention provides an amorphous form of lurasidone hydrochloride. In another aspect, it provides a process for the preparation of lurasidone hydrochloride amorphous form, which contains: a) dissolving lurasidone hydrochloride in a mixture of alcoholic solvent and water; and b) then subjecting the resulting solution to lyophilization to obtain lurasidone hydrochloride amorphous form.

2.11 EXCIPIENTS PROFILE

2.11.1 Glyceryl Monostearate (GMS)

Table 2.4: Properties of GMS (141)

Nonproprietary Names	BP: Glyceryl monostearate JP: Glyceryl monostearate PhEur: Glyceroli monostearas USPNF: Glyceryl monostearate
Synonyms	Capmul GMS-50, Imwitor 191, glycerine monostearate, glycerol monostearate; glycerol stearate.
Chemical Name and CAS Registry Number	Octadecanoic acid, monoester with 1,2,3-propanetriol [31566-31-1]
Empirical Formula and Molecular Weight	$C_{21}H_{42}O_4$ and 358.6
Structural Formula	
Functional Category	Emollient, emulsifying agent, solubilizing agent, stabilizing agent, sustained-release Ingredient, tablet and capsule lubricant.
HLB value	3.8
Flash point	~240 °C
Melting point	55-60 °C
Polymorphs	The α-form is converted to the ß-form at 50°C.
Solubility	soluble in hot ethanol, ether, chloroform, hot acetone, mineral oil, and fixed oils. Practically insoluble in water, but may be dispersed in water with the aid of a small amount of soap or surfactant.
Specific gravity	0.92

2.11.1.1 Description

While the names glyceryl monostearate and mono- and di-glycerides are used for a variety of esters of long-chain fatty acids, the esters fall into two distinct grades:

- 40–55 percent monoglycerides: The European Pharmacopoeia (PhEur) 2005 describes glyceryl monostearate 40–55 as a mixture of monoacylglycerols, mostly monostearoylglycerol, together with quantities of di- and triacylglycerols. It contains 40–55% of monoacylglycerols, 30–45% of diacylglycerols, and 5–15% of triacylglycerols. This PhEur grade corresponds to mono- and di-glycerides USPNF, which has similar specifications (not less than 40% monoglycerides).
- 90 percent monoglycerides: The USPNF 23 (Suppl. 1) describes glyceryl monostearate (GMS) as consisting of not less than 90% of monoglycerides, chiefly glyceryl monostearate ($C21H42O4$) and glyceryl monopalmitate ($C19H38O4$). The commercial products are mixtures of variable proportions of glyceryl monostearate and glyceryl monopalmitate.
- GMS is a white to cream-colored, waxlike solid in the form of beads, flakes, or powder. It is waxy to the touch and has a slight fatty odor and taste.

2.11.1.2 Stability and Storage Conditions

If stored at warm temperatures, glyceryl monostearate increases in acid value upon aging owing to the saponification of the ester with trace amounts of water. Effective antioxidants may be added, such as butylated hydroxytoluene and propyl gallate. Glyceryl monostearate should be stored in a tightly closed container in a cool, dry place, and protected from light.

2.11.1.3 Applications in Pharmaceutical Formulation or Technology

The many varieties of glyceryl monostearate are used as nonionic emulsifiers, stabilizers, emollients, and plasticizers in a variety of food, pharmaceutical, and cosmetic applications. It acts as a stabilizer, that is, as a mutual solvent for polar and nonpolar compounds that may form water-in-oil or oil-in-water emulsions. These properties also make it useful as a dispersing agent for pigments in oils or solids in fats, or as a solvent for phospholipids, such as lecithin.

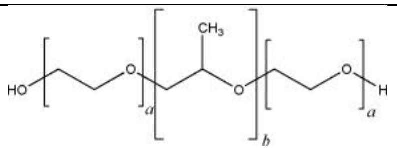
- GMS has also been used in a novel fluidized hot-melt granulation technique for the production of granules and tablets.
- It is used as a lubricant for tablet manufacturing and may be used to form sustained-release matrices for solid dosage forms. Sustained-release

applications include the formulation of pellets for tablets or suppositories and the preparation of a veterinary bolus. It is also used as a matrix ingredient for a biodegradable, implantable, controlled-release dosage form.

- When using GMS in a formulation, the possibility of polymorph formation should be considered. The denser, more stable, ß-form is suitable for wax matrices. This application has been used to mask the flavor of clarithromycin in a pediatric formulation.
- Glyceryl Monostearate (GMS) is used as solid lipid in formulation of solid lipid nanoparticles for encapsulation of drugs.

2.11.2 Pluronic F-68

Table 2.5: Properties of Pluronic F-68 (141)

Nonproprietary Names	Poloxamer 188
Synonyms	Lutrol, Monolan
Chemical Name and CAS Registry Number	Octadecanoic acid, monoester with 1,2,3-propanetriol [31566-31-1]
Empirical Formula and Molecular Weight	HO(C2H4O)*80*(C3H6O)*27*(C2H4O)*7*H and
Structural Formula	
Functional Category	Dispersing agent, emulsifying and co-emulsifying agent, solubilizing agent, tablet lubricant, wetting agent.
HLB value	29
Flash point	260 °C
Melting point	52–57°C
Flowability	Solid poloxamers are free flowing
Solubility	Soluble in water and ethanol
Density	1.06 g/cm^3 at 25°C
Cloud point	>100°C for a 1% w/v aqueous solution, and a 10% w/v aqueous solution of poloxamer 188

2.11.2.1 Description

Poloxamers generally occur as white, waxy, free-flowing pilled granules, or as cas solids. They are practically odorless and tasteless.

2.11.2.2 Stability and Storage Conditions

Poloxamers are stable materials. Aqueous solutions are stable in the presence of acids, alkalis, and metal ions. However, aqueous solutions support mold growth. The bulk material should be stored in a well-closed container in a cool, dry place.

2.11.2.3 Incompatibilities

Depending on the relative concentrations, poloxamer 188 is incompatible with phenols and parabens.

2.11.2.4 Method of Manufacture

Poloxamer polymers are prepared by reacting propylene oxide with propylene glycol to form polyoxypropylene glycol. Ethylene oxide is then added to form the block copolymer.

2.11.2.5 Safety

- They are used in a variety of oral, parenteral, and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials. Poloxamers are not metabolized in the body.
- Animal toxicity studies, with dogs and rabbits, have shown poloxamers to be non-irritating and non-sensitizing when applied in 5% w/v and 10% w/v concentration to the eyes, gums, and skin.
- In a 14-day study of intravenous administration at concentrations up to 0.5 g/kg/day to rabbits, no adverse effects were noted. A similar study with dogs also showed no adverse effects at dosage levels up to 0.5 g/kg/day. In a longer-term study, rats fed 3% w/w or 5% w/w of poloxamer in food for up to 2 years did not exhibit any significant symptoms of toxicity. No hemolysis of human blood cells was observed over 18 hours at 25°C, with 0.001–10% w/v poloxamer solutions. Acute animal toxicity data for poloxamer 188:
  LD50 (mouse, IV): 1 g/kg
  LD50 (mouse, oral): 15 g/kg
  LD50 (rat, IV): 7.5 g/kg
  LD50 (rat, oral): 9.4 g/kg

2.11.2.6 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

2.11.2.7 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IV injections; inhalations, ophthalmic preparations; oral powders, solutions, suspensions, and syrups; topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

2.11.2.8 Applications in Pharmaceutical Formulation or Technology

- Poloxamers are nonionic polyoxyethylene (hydrophilic part)–polyoxypropylene (hydrophobic) copolymers used primarily in pharmaceutical formulations as emulsifying or solubilizing agents. All poloxamers are similar in composition, differing only in the relative amounts of propylene and ethylene oxides added during manufacturing process.
- Poloxamers can also be used as emulsifying agents in intravenous fat emulsions, and as solubilizing and stabilizing agents to maintain the clarity of elixirs and syrups. They are also used as wetting agents; in ointments, suppository bases, and gels; and as tablet binders and coatings.
- Poloxamer 188 can be used as emulsifying agent in the formulation of solid lipid nanoparticles and stabilize the nanodroplets.
- Poloxamer 188 is also administered orally as a wetting agent and stool lubricant in the treatment of constipation; it is usually used in combination with a laxative such as danthron. Poloxamers are also used as wetting agent in eye-drop formulations, in the treatment of kidney stones, and as skin-wound cleansers.

Table 2.6: Uses of Poloxamer

Use	Concentration (%)
Fat emulsifier	0.3
Flavor solubilizer	0.3
Fluorocarbon emulsifier	2.5
Gelling agent	15–50
Spreading agent	1
Stabilizing agent	1–5
Suppository base	4–6 or 90
Tablet coating	10
Tablet excipient	5–10
Wetting agent	0.01–5

2.11.3 Capmul MCM C-8 EP

Table 2.7: Properties of Capmul MCM C8 (142)

Nonproprietary Names	Glyceryl Caprylate
Synonyms	Glycerol monocaprylate (type I), Medium chain mono- & diglycerides, Glyceroli monocaprylas
Functional Category	Caprylic and capric mono-diglyceride esters function as very effective carriers and solubilizers of active compounds. Mono-diglyceride medium chain esters are recommended for the dissolution of some difficult compounds such as sterols and have also showed bacteriostatic activity.
Physical state	Soft solid or liquid
Appearance	Slightly brown
HLB	5
Boiling point	> 227 °C
Solubility in water	Slightly soluble

2.11.3.1 Description

It is a mono-, diglyceride of medium chain fatty acids (mainly caprylic acid). It is a mixture of monoacylglycerols, mainly mono-O-octanoylglycerol, containing variable quantities of di- and triacylglycerols, obtained by direct esterification of glycerol with caprylic (octanoic) acid. It meets the requirements of the European Pharmacopoeia Monograph for “Glycerol Monocaprylate” Type I.

2.11.3.2 Toxicological Information

Eyes: Not known
Dermal LD50: Not known
Skin absorption: Not known
Oral LD50: > 5 g/kg (rat)
Inhalation LD50: 20 mg/l (rats)
Eye effects: Non-irritant (rabbits)
Skin effects: Non-irritant (rabbits)

2.11.3.3 Handling and Storage:

General procedure: Contents of package must be heated slightly with agitation to ensure uniformity before use.

Handling: Materials may be hot. Take precautions against thermal burns.

Storage:

Keep away from heat and flame. Keep container closed when not in use. Store in a dry area. Stainless steel storage tanks are recommended. Lined or unlined mild steel drums are suitable.

Storage temperature: (68°F) minimum to (77°F) Maximum

Storage pressure: Not determined

Shelf life: Retest and requalify one year from date of manufacture.

2.11.3.4 Regulatory Status:

Meets the requirements of the European Pharmacopoeia Monograph for “Glycerol Monocaprylate” Type I, Mono- and diglycerides prepared from edible fats and oils or fat-forming acids are generally recognized as safe (GRAS) according to 21 CFR 184.150, Drug Master File (DMF) 3700.

2.11.3.5 Application in Pharmaceutical formulation

Capmul MCM C8 is used as oil phase in the formulation of Self microemulsifying drug delivery system, microemulsion, nanoemulsion etc.

2.11.4 POLYOXYL 35 CASTOR OIL

Table 2.8: Properties of Polyoxyl 35 castor oil (141)

Nonproprietary Names	Polyoxyl 35 castor oil
Synonyms	Cremophor EL, Cremophor ELP, PEG-35 castor oil, polyoxyethylene 35 castor oil.
Chemical Name and CAS Registry Number	Polyethoxylated castor oil [61791-12-6]
Empirical Formula and Molecular Weight	$C_{47}H_{51}NO_{14}$ and 853.91
Functional Category	Emulsifying agent; solubilizing agent; wetting agent.
HLB value	12-14
Acid value	2
Hydroxyl value	65-78
Iodine number	25-35
Saponification value	65-70
Melting point	19-20°C
Solubility	soluble in ethanol, chloroform, water.
Density	1.05- 1.06 g/cm^3 at 25°C
Cloud point	72.5°C for a 1% w/v aqueous solution

2.11.4.1 Stability and Storage Conditions

Polyoxyl 35 castor oil (Cremophor EL and Cremophor ELP) forms stable solutions in many organic solvents such as chloroform, ethanol, and propan-2-ol; it also forms clear, stable, aqueous solutions. Polyoxyl 35 castor oil (Cremophor EL and Cremophor ELP) is miscible with other polyoxyethylene castor oil derivatives and on heating with fatty acids, fatty alcohols, some animal and vegetable oils.

On heating of an aqueous solution, the solubility of polyoxyl 35 castor oil (Cremophor EL and Cremophor ELP) is reduced and the solution becomes turbid. Aqueous solutions of polyoxyl 35 castor oil (Cremophor EL and Cremophor ELP) are stable in the presence of low concentrations of electrolytes such as acids or salts, with the exception of mercuric chloride.

Aqueous solutions of polyoxyl 35 castor oil (Cremophor EL and Cremophor ELP) can be sterilized by autoclaving for 20 minutes at 121°C. In this process, a product may acquire a deeper color but this has no significance for product stability.

2.11.4.2 Incompatibilities

In strongly acidic or alkaline solutions, the ester components of polyoxyethylene hydrogenated castor oil are liable to saponify.

In aqueous solution, polyoxyl 35 castor oil (Cremophor EL and Cremophor ELP) is stable toward most electrolytes in the concentrations normally employed. However, it is incompatible with mercuric chloride since precipitation occurs.

Some organic substances may cause precipitation at certain concentrations, especially compounds containing phenolic hydroxyl groups, e.g. phenol, resorcinol, and tannins.

2.11.4.3 Method of Manufacture

Polyoxyethylene castor oil derivatives are prepared by reacting varying amounts of ethylene oxide with either castor oil or hydrogenated castor oil under controlled conditions. Polyoxyl 35 castor oil is produced in this way by reacting 1 mole of castor oil with 35–40 moles of ethylene oxide.

2.11.4.4 Safety

They are used for oral, topical, and parenteral administration. Acute and chronic toxicity tests in animals have shown polyoxyethylene castor oil derivatives are nontoxic and nonirritant materials.

Table 2.9: LD_{50} value of cremophor EL

Animal and route	LD50 (g/kg body-weight)
Cat (oral)	>10
Dog (IV)	0.64
Mouse (IV)	2.5
Rabbit (oral)	>10
Rat (oral)	>64

However, there are reports of cardiovascular changes and nephrotoxicity in various species of animals. Several serious anaphylactic reactions, cardiotoxicity, nephrotoxicity, neurotoxicity, and pulmonary toxicity have also been observed in humans and animals following parenteral administration of formulations containing polyoxyethylene castor oil derivatives.

2.11.4.5 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

2.11.4.6 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IV injections and ophthalmic solutions). Included in parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

2.11.4.7 Application in Pharmaceutical formulation

Polyoxyl 35 castor oil is used as emulsifying agent and permeation enhancer in the formulation of Self microemulsifying drug delivery system, microemulsion, nanoemulsion etc.

2.11.5 PROPYLENE GLYCOL MONOCAPRYLATE (TYPE II) NF

Table 2.10: Properties of Propylene glycol monocaprylate (143)

Nonproprietary Names	Propylene glycol monocaprylate
Synonyms	Capryol 90
Chemical Name and CAS Registry Number	Propylene glycol monocaprylate and 85883-73-4
Functional Category	A water insoluble surfactant for use in self emulsifying systems to obtain a coarse dispersion i.e. emulsion (SEDDS) or a fine dispersion i.e. microemulsion (SMEDDS) in oral delivery. A water-in-oil surfactant / solubilizer in topical delivery.
HLB value	5
Color	Light yellow
Odour	Light
Boiling point	>120°C
Flash point	>120°C
Self igniting	Product is not self igniting.
Solubility	Insolublt in water, soluble in organic solvent
Density	1.05- 1.06 g/cm^3 at 25°C
Cloud point	72.5°C for a 1% w/v aqueous solution
Additional toxicological information	The product is not subject to classification according to the calculation method of General EU Classification Guidelines for Preparations as issued in the latest version.

2.11.5.1 Applications in Pharmaceutical Formulation or Technology

It is suitable for hard gelatin and soft gelatin capsules. Also, suitable for adsorption onto neutral carrier powders for use in tablets, capsule filling and sachets. Use in topical ointments, microemulsions and emulsions.

It can be used as solubilizer and emulsifier in the formulation of SMEDDS, nanoemulsion etc.

2.11.6 HIGHLY PURIFIED DIETHYLENE GLYCOL MONOETHYL ETHER EP/NF

Table 2.11: Properties of diethylene glycol monoethyl ether (144)

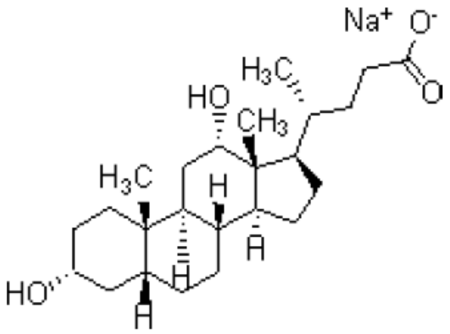
Nonproprietary Names	Diethylene glycol monoethyl ether
Synonyms	Transcutol CG, Transcutol P, Transcutol V, Transcutol HP
Chemical Name and CAS Registry Number	Diethylene glycol monoethyl ether and 111-90-0
Color	Colorless
Odour	Light
Boiling point	>198°C
Flash point	>94°C
Self igniting	250°C
Solubility	Water soluble
Density	0.985- 0.991 g/cm^3 at 25°C
Additional toxicological information: Acute toxicity	Oral, LD50: > 5001 mg/kg (rat) Oral, LD50: 6031 mg/kg (mouse) Dermal, LD50: 6000 mg/kg (rat) Dermal, LD50: 9143 mg/kg (rabbit) Dermal, LD50: 5900 mg/kg (guinea Pig) Oral, LD50(2): 6300 mg/kg (rat) Inhalative, LC0: (8H) 0.025 mg/l (rat) Oral, SubChronicTox: (13W) 1000 mg/kg (Dog) Dermal, SubChronicTox: (28D) > 1000 mg/kg (rabbit)

2.11.6.1 Applications in Pharmaceutical Formulation or Technology

A highly purified powerful solvent for poorly water soluble active pharmaceutical ingredients. Hydrophilic cosolvent for use in oral self-emulsifying lipid formulations to obtain a coarse dispersion ie. emulsion (SEDDS) or a fine dispersions ie. microemulsion (SMEDDS). Highest purity grade of DEGEE available (99,9%) advised for oral, mucosal and parenteral medicines.

2.11.7 SODIUM DEOXYCHOLATE

Table 2.12: Properties of Sodium deoxycholate (145)

Nonproprietary Names	Sodium deoxycholate
Chemical Name and CAS Registry Number, mol wt	C24H39NaO4 and 302-95-4, 414.55 g/mol
Chemical structure	
Color	White to Off-White
Appearance	Powder
HLB	16
CMC	2-6 mM (20-25°C)
Solubility	Water soluble 50 mg/ml.

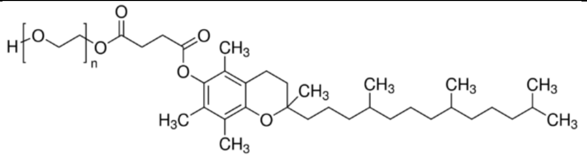
2.11.7.1 Applications in Pharmaceutical Formulation or Technology

It is used as an anionic detergent; Also, useful for extraction of membrane receptors and plasma membrane proteins and for nuclei isolation.

It solubilizes fats for absorption in the intestine.

2.11.8 D-A-TOCOPHEROL POLYETHYLENE GLYCOL 1000 SUCCINATE (TPGS)

Table 2.13: Properties of TPGS (146)

Non-proprietary Names	D-α-Tocopherol polyethylene glycol 1000 succinate
Synonyms	D-α-Tocopherol polyethylene glycol succinate, TPGS, Vitamin E polyethylene glycol succinate, Vitamin E-TPGS
IUPAC	α-[4-[[(2R)-3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-2H-1-benzopyran-6-yl]oxy]-1,4- dioxobutyl]-ω-hydroxy-poly(oxy-1,2-ethanediyl)
Chemical Name, CAS Registry Number, Molecular Weight	$C_{33}O_5H_{54}(CH_2CH_2O)n$ and 9002-96-4, 1513
Chemical structure	
Functional Category	As solubilizer of poorly soluble drugs, absorption enhancer, emulsifier, vehicle for lipid-based drug formulation and antioxidant
Color	White to light tan
Melting point	>36 °C
HLB	13
CMC	0.02 weight % at 37°C
Solubility	Water soluble
Toxicology data (LD-50)	Oral, Higher than 7,000 mg/kg in rat Skin, Higher than 2,000 mg/kg in rat

2.11.8.1 Applications in Pharmaceutical Formulation or Technology

Enhancement of Bioavailability by increasing solubility of poorly water-soluble APIs and by formulation of Self Emulsifying Drug Delivery System (SEEDS).

Thermal stability for hot melt extrusion as a versatile plasticizer with solubilizer properties and as Antioxidant for sensitive excipients

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