2.0 FACTORS INFLUENCING DRUG RELEASE

2.1 Drug Release

Oral route has been the most popular and successfully used for controlled delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design (possible cause of versatility of GI anatomy and physiology) and ease of production and low cost of such a system. The drug release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. Depending upon the manner of drug release, these systems are classified as follows:

The polymers have unique properties that are not offered by polymers intended for general applications. In general, the desirable polymer properties in pharmaceutical applications are film forming (coating), thickening (rheology modifier), gelling (controlled release), adhesion (binding), pH-dependent solubility (controlled release), solubility in organic solvents (taste masking), and barrier properties (protection and packaging).

There are several types of sustained release systems that are designed and categorised according to the mechanism they employ. These include diffusion controlled, dissolution controlled, erosion controlled, ion exchange controlled and transport control also known as osmotic pump systems (Aulton, 2008).

2.1.1 Diffusion controlled drug delivery systems

Diffusion controlled systems also known as matrix systems are very popular for sustained release formulations (Colombo et al., 2000). The can be divided into different types of mechanisms by which they prolong drug release, these include reservoir matrix
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systems, monolithic matrix systems and osmotic pump systems. In such systems, the diffusion of dissolved drug through a polymeric barrier is a rate limiting step. The drug release rate is never zero-order, since the diffusional path length increases with time as the insoluble matrix is gradually depleted of drug. Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems. Similar to the dissolution-controlled systems, the diffusion controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix. Unlike the dissolution controlled systems, the drug is made available as a result of partitioning through the polymer. In the case of a reservoir type diffusion controlled device, the rate of drug released (dm/dt) can be calculated using the following equation,

\[
\frac{dm}{dt} = ADK \frac{\Delta C}{l}
\]

Where,

- \( A \) = Area,
- \( D \) = Diffusion coefficient,
- \( K \) = Partition coefficient of the drug between the drug core and the membrane,
- \( l \) = Diffusion path length and
- \( C \) = Concentration difference across the membrane.

2.1.1A Reservoir matrix systems

This system involves a membrane which controls the release of drugs from the matrix system. The drug will eventually diffuse through the membrane and its release is kept constant by the diffusion distance that the drug particles have to cover as shown in the Figure 2.1.

Figure 2.1 : Schematic representation of Reservoir matrix systems
2.1.1B Monolithic matrix systems
These systems involve drug to be encapsulated or dispersed in a matrix (Kim, 2000). These systems can be employed by forming hydrophobic matrices (Varshosaz et al., 2006) and/or hydrophilic matrices to allow for control of drug release (Colombo, 1993; Nerurkar et al., 2005 and Thawatchai, 2008). They can be either into soluble/hydrophilic matrix systems which swell on hydration and dissolve to release the drug or insoluble/hydrophobic matrix systems which release the drug after being dissolved by a solvent (Figure 2.2).

Figure 2.2: Schematic representation of drug release from different types of matrix tablets.

Hydrophobic matrix systems are formulated by waxes mainly and can be suitable for drugs which have a high solubility (Tiwari et al., 2003). Investigations on wax based matrices have revealed that increasing the amount of drug or wax concentration, or incorporating hydrophilic polymers could be used for modulating drug release (Sudha et al., 2010).

Hydrophilic matrix systems tend to be more popular in tablet manufacture for controlled release drug delivery systems due to their low manufacturing cost (Tiwari et
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...al., 2003). On contact with water a hydrophilic matrix increases in size due to the entry of the solvent. This then allows the polymer to swell up forming a barrier to drug release. The drug particles then move through this gel layer via diffusion or erosion of the gel, eventually allowing the drug to be released (Maderuelo et al., 2011). There has been a lot of research into the mechanisms of drug release from hydrophilic matrices and the critical factors that influence the release rate (Colombo et al., 2000; Maggi et al., 2002; Siahi, 2005; Conti et al., 2007; Thawatchai, 2008; Maderuelo et al., 2011 and Siahi-Shadbad et al., 2011). These swellable matrices have more than one ‘front’ as a part of its release mechanism (Colombo et al., 2000) as depicted in Figure 2.3.

![Figure 2.3: Different front within a matrix tablet containing colouring agent to distinguish different swelling fronts.](image)

2.1.2 Dissolution controlled release systems

These types of systems are easiest to design. The drug present in such system may be one whose dissolution rate is inherently slow. Drugs having high aqueous solubility and dissolution rate pose a great challenge in controlling their dissolution rate. Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of such drugs is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer. The rate of dissolution...
(dm/dt) can be approximated by equation,

\[
dm/dt = ADS/h,\]

Where,

\[
S = \text{Aqueous solubility of the drug, } A = \text{Surface area of the dissolving particle or tablet.} \\
D = \text{Diffusivity of the drug, } h = \text{Thickness of the boundary layer.}
\]

### 2.1.3 Pulsatile drug delivery systems

Pulsatile drug delivery systems (PDDS) are gaining importance as these systems deliver the drug at specific time according to the pathophysiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. Diseases wherein PDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, attention deficit syndrome in children and hypercholesterolemia. PDDS can be classified into time controlled systems wherein the drug release is controlled primarily by the delivery system; stimuli induced PDDS in which release is controlled by the stimuli, like the pH or enzymes present in the intestinal tract or enzymes present in the drug delivery system and externally regulated system where release is programmed by stimuli like magnetism, ultrasound, electrical effect and irradiation (Survase and Kumar, 2007; Dusane et al., 2011) as shown in figure 2.4.

![A typical pulsatile drug delivery system](image_url)

**Figure 2.4**: A typical pulsatile drug delivery system
2.1.4 Floating drug delivery systems

Floating drug delivery systems (FDDS) or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased gastro retentive time and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres (Gopalkrishnan et al., 2011). Table 2.1 shows lists of approved products marketed worldwide as floating tablets.

Table 2.1: Lists of marketed floating (gastroretentive) tablets available worldwide.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Active Ingredient</th>
<th>Product</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Levodopa and benserzide</td>
<td>Madopar®</td>
<td>Roche, USA</td>
</tr>
<tr>
<td>2</td>
<td>Diazepam</td>
<td>Valrelease</td>
<td>Roche, USA</td>
</tr>
<tr>
<td>6</td>
<td>Ciprofloxacin</td>
<td>Cifran OD</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>6</td>
<td>Misoprostol</td>
<td>Cytotec®</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>6</td>
<td>Ferrous sulphate</td>
<td>Conviron®</td>
<td>Pharmacia, USA</td>
</tr>
</tbody>
</table>

2.1.5 Polymers In Pharmaceutical And Biomedical Applications

2.1.5A Water-Soluble Synthetic Polymers

- Poly (acrylic acid) Cosmetic, pharmaceuticals, immobilization of cationic drugs, base for Carbopol polymers
- Poly (ethylene oxide) Coagulant, flocculent, very high molecular-weight up to a few millions, swelling agent
- Poly (ethylene glycol) $M_w <10,000$; liquid ($M_w <1000$) and wax ($M_w >1000$), plasticizer, base for suppositories
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- Poly (vinyl pyrrolidone) Used to make betadine (iodine complex of PVP) with less toxicity than iodine, plasma replacement, tablet granulation
- Poly (vinyl alcohol) Water-soluble packaging, tablet binder, tablet coating
- Polyacrylamide Gel electrophoresis to separate proteins based on their molecular weights, coagulant, absorbent
- Poly (isopropyl acrylamide) and poly (cyclopropyl methacrylamide)
- Thermogelling acrylamide derivatives, its balance of hydrogen bonding, and hydrophobic association changes with temperature (Reja et al., 2003; Verhoeven et al., 1988)

2.1.5B Cellulose-Based Polymers
- Ethyl cellulose Insoluble but dispersible in water, aqueous coating system for sustained release applications
- Carboxymethyl cellulose Super disintegrant, emulsion stabilizer
- Hydroxyethyl and hydroxypropyl celluloses
- Soluble in water and in alcohol, tablet coating
- Hydroxypropyl methyl cellulose Binder for tablet matrix and tablet coating, gelatin alternative as capsule material
- Cellulose acetate phthalate Enteric coating

2.1.5C Hydrocolloids
- Alginic acid Oral and topical pharmaceutical products; thickening and suspending agent in a variety of pastes, creams, and gels, as well as a stabilizing agent for oil-in-water emulsions; binder and disintegrant
- Carrageenan Modified release, viscosifier
- Chitosan Cosmetics and controlled drug delivery applications, mucoadhesive dosage forms, rapid release dosage forms
- Hyaluronic acid Reduction of scar tissue, cosmetics
- Pectinic acid Drug delivery

2.1.5D Water-Insoluble Biodegradable Polymers
- (Lactide-co-glycolide) polymers Microparticle–nanoparticle for protein delivery
2.1.5E Starch-Based Polymers

- Starch Glidant, a diluent in tablets and capsules, a disintegrant in tablets and capsules, a tablet binder (Reja et al., 2003; Verhoeven, 1988)
- Sodium starch glycolate Super disintegrant for tablets and capsules in oral delivery

When the drug is delivered to the site of action by using polymer based drug delivery approaches the safety and bio compatibility is questionable. The characterization of biocompatible polymers is more focused in the field of formulation development and drug delivery approaches etc. the biodegradable polymers have properties of degrading in biological fluids with progressive release of dissolved or dispersed drug. There is various novel drug delivery approaches are developed in the pipeline of polymer based drug delivery approaches. The bio-safety and biocompatibility are the important characteristics needed for the use of polymers in the field of pharmaceutical formulation and in novel drug delivery approaches.

Biodegradable polymers find widespread use in drug delivery as they can be degraded to nontoxic monomers inside the body. Novel supra molecular structures based on polyethylene oxide copolymers and dendrimers are being intensively researched for delivery of genes and macromolecules. Hydrogels that can respond to a variety of physical, chemical and biological stimuli hold enormous potential for design of closed-loop drug-delivery systems (Gilding and Reed, 1979)

2.2 DRUG RELEASE MECHANISM

The release behaviour of drugs from hydrophilic matrices can be mathematically expressed by the following equation which is known as Higuchi equation:

\[ M = k \cdot t^{0.5} \]

Where \( k \) is a constant and \( M \) is the amount of drug released at time \( t \).

Higuchi’s equation initially was valid only for planar matrix systems, and later it was modified to consider different geometrical shapes and matrix characteristics including porous structures (Lapidus and Lordi, 1968; Higuchi, 1963 and Desai et al., 1965). It should be kept in mind that the classical equation was derived under pseudo-steady state assumptions and cannot be applied to real controlled release systems.
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(Peppas, 1984). The final equation shows that if a system is predominantly diffusion-controlled, then it is expected that a plot of the drug release against square root of time will result in a straight line.

The mechanism of drug release from hydrophilic matrix tablets after ingestion is complex but it is based on diffusion of the drug through, and erosion of, the outer hydrated polymer on the surface of the matrix. In the case of a highly soluble drug, this phenomenon may lead to an initial burst release due to the presence of the drug on the surface of the matrix tablet. The gel layer (rubbery state) grows with time as more water permeates into the core of the matrix, thereby increasing the thickness of the gel layer and providing a diffusion barrier to drug release (Rajabi-Siahboomi et al., 1996). The gel layer thickness behaviour is crucial in describing the release kinetics of swellable matrices. Simultaneously, as the outer layer becomes fully hydrated, the polymer chains become completely relaxed and can no longer maintain the integrity of the gel layer, thereby leading to disentanglement and erosion (dissolution) of the surface of the matrix. Water continues to penetrate towards the core of the tablet, through the gel layer, until it has been completely eroded (Lee and Peppas, 1987; Narasimhan and Peppas, 1997). At the point of disentanglement an abrupt change occurs in the rheological properties of the gel layer (Caramella et al., 1989). This indicates that the interactions between polymer-polymer and polymer-solvent are important in controlling the gel network structure and erosion. In addition, the strength of gel can play a major role in controlling the drug release from this type of matrices.

A large number of mathematical models have been developed to describe drug release profiles from matrices (Siepmann et al., 1999; Siepmann and Peppas, 2000; Siepmann and Peppas, 2001a; Siepmann and Peppas, 2001b; Siepmann et al., 2002; Siepmann and Siepmann, 2008). The simple and more widely used model is the one derived by Korsmeyer et al. (Siepmann et al. 1999) and is as follows:

\[ \frac{M_t}{M_\alpha} = k t^n \]

where \( \frac{M_t}{M_\alpha} \) is the fraction of drug release, \( k \) is the diffusion rate constant, \( t \) is the release time and \( n \) is the release exponent indicative of the mechanism of drug release.
It is clear from equations 6 and 7 that when the exponent $n$ takes a value of 1.0, the drug release rate is independent of time. This case corresponds to zero-order release kinetics (also termed as case II transport). Here, the polymer relaxation and erosion (Bajwa et al., 2006) are the rate-controlling steps. When $n = 0.5$, Fickian diffusion is the rate-controlling step (case I transport). Values of $n$ between 0.5 and 1 indicate the contribution of both the diffusion process as well as polymer relaxation in controlling the release kinetics (non-Fickian, anomalous or first-order release). It should be noted that the two extreme values of $n = 0.5$ and 1 are only valid for slab geometry. For cylindrical tablets, these values range from $0.45 < n < 0.89$ for Fickian, anomalous or case II transport respectively (Siepmann and Peppas, 2001b).

2.3 CHALLENGES OFFERED BY GASTROINTESTINAL TRACT (GIT) IN DRUG ABSORPTION

2.3.1 Gastro-intestine anatomy and physiology

In humans, the GIT consists mainly of the stomach, small intestine (the duodenum, jejunum, and ileum) and large intestine (cecum, colon and rectum). The total length of the human GIT is 8.35 m and the relative size of the human small intestine, which is considered the primary site of drug absorption, to the total length of the GI tract is 81%. As for the large intestine, its relative size in humans is 19%. It may also be pointed out that the cecum, which is the major site of microbial digestion, forms only 5% of the length of the human large intestine (DeSesso and Jacobson, 2001). The surface area is attributed to the fact that the human small intestine has three anatomical modifications that significantly increase the surface area of the human small intestine (Shargel and Yu, 1999). The human small intestine has grossly observable folds of mucosa (plicae circularis or folds of kerckring) that increase the surface area threefold. From the plicae circularis, microscopic finger-like pieces of tissue called villi project, which increase the surface area by 10-fold for humans. Each villus is covered in microvilli, which increase the surface area by 20-fold. Unlike the small intestine, the large intestine surface area does not have villi and is divided into geographical areas by transverse furrows. In addition, the large intestine enterocytes differ slightly from that of the small intestine and its microvilli are less packed (Kararli, 1995). Overall, this significantly
contributes to the smaller surface area of the large intestine in humans and is consistent with the fact that small intestine is the major site of drug absorption in humans.

### 2.3.2 Gastrointestinal transit times

The absorption rate of a drug molecule is generally a function of drug absorption through the GIT, which is determined by the residence time and absorption in each GIT segment (Kimura and Higaki, 2002). In general, gastric transit time impacts the systemic exposure of rapidly dissolved and well absorbed drugs. However, intestinal transit time influences the absorption of drugs with limited mucosal permeability, carrier mediated uptake, drugs subject to intestinal degradation, or products whose dissolution is the rate limiting step for systemic absorption (Martinez and Amidon, 2002). In contrast to gastric transit time, intestinal transit time is independent of the feeding conditions and the physical composition of the intestinal contents (Garanero et al., 2005). The human intestinal transit time is ~3 – 4 h (DeSesso and Jacobson, 2001; Kimura and Higaki, 2002). Several studies suggested that in human small intestine, there is a gradient of velocity where the small intestinal transit in the proximal intestine was faster compared with the distal intestine. The transit time in human large intestine can vary in the range of 8 – 72 h (DeSesso and Jacobson, 2001).

### 2.3.3 The GIT pH

The extent of ionization plays a pivotal role in determining the drug dissolution rate and passive permeability across the GIT. Therefore, it becomes clear that the pH at the absorption site is a critical factor in facilitating or inhibiting the dissolution and absorption of various ionizable drug molecules (DeSesso and Jacobson, 2001). It should be stressed that the pH of the luminal content (chyme) is altered by the luminal secretions. The pH of chyme is acidic and can be as low as 2.3. When the chyme arrives in the duodenum, it is quickly neutralized by the secretion of the pancreatic bicarbonate and bile. The pH values of chime become progressively more alkaline in the distal portion of the small intestine in humans. However, the pH of chyme in the large intestine is generally more acidic than the pH observed in the small intestine in humans, possibly due to the fermentation mediated by the microbial flora (Kararli, 1995).
2.3.4 Bile fluid
Bile is produced by hepatocytes and drained through the many bile ducts that penetrate the liver (DeSesso and Jacobson, 2001). During this process, the epithelial cells add a watery solution that is rich in bicarbonates which increases the alkalinity of the solution. In humans, the bile is stored and concentrated up to five times its original potency in the gall bladder. It is to be noted that the human gall bladder secretes bile at a rate of 2 – 22 ml/kg/day. In humans, bile acts as a detergent to emulsify fats by increasing the surface area to help enzyme action, and thus aid in their absorption in the small intestine. In addition to bicarbonate solution, bile is composed of bile salts, such as the salts of taurocholic acid and deoxycholic acid, which are combined with phospholipids to break down fat globules in the process of emulsification by associating their hydrophobic side with lipids and the hydrophilic side with water. Emulsified droplets are then organized into many micelles which increases their absorption. Because bile increases the absorption of fats, it also plays a pivotal role in the absorption of the fat-soluble vitamins and steroids (Hanano, 1993; Kirilenko and Gregoriadis, 1993).

2.3.5 Bacterial microflora
In humans, bacterial microflora exists in most of the GIT and become an important component of the luminal content. However, there is no bacterial microflora in the stomach and upper intestine. This is mainly attributed to the low pH of the human gastric content. However, a large number of bacterial microflora populates the human’s distal small and large intestines (Cummings and Macfarlane, 1997). These bacterial microflora play a role in the metabolism of various chemicals and xenobiotics through hydrolysis, dehydroxylation, deamidation, decarboxylation and reduction of azide groups (Lichtenstein, 1990; Cummings and Macfarlane, 1997; Blaut et al., 2003). Among these reactions, hydrolysis of the glucuronide conjugates is the most important metabolic reaction that is mediated by the glucuronidase enzyme and produced by the bacterial microflora found in the GIT of humans.
2.3.6 Lymphatic absorption
The intestinal lymphatic route plays a key role in the absorption of drugs that are highly lipophilic. It has many advantages, such as increase in the oral bioavailability of highly lipophilic drugs by avoiding hepatic first pass effect, direct targeting of lymphoid tissue, indirect targeting of specific sites associated with low-density lipoprotein receptors, and alteration in the rate of oral drug input to the systemic circulation thereby providing opportunity for controlled release drug formulation (Cheema et al., 1987; Trevaskis et al., 2005; Trevaskis et al., 2006; Trevaskis et al., 2006).

2.3.7 Intestinal drug transporters
P-glycoprotein (P-gp)
P-gp, an ATP-dependent transmembrane efflux pump belonging to ATP binding cassette (ABC) superfamily, shows affinity to a wide variety of structurally unrelated compounds (Juliano and Ling, 1976). It is expressed as a 1280 amino acid long (MW ~170 kDa) single chain glycoprotein with two homologous portions of equal length, each containing six transmembrane (TM) domains and two ATP binding regions separated by a flexible linker polypeptide region (Schinkel et al., 1993 and Ambudkar et al., 1999). Immunohistochemical analysis using monoclonal antibody provided evidence for localization of P-gp in a wide range of tissues, particularly in columnar epithelial cells of the lower GIT, capillary endothelial cells of brain and testis, canalicular surface of hepatocytes and apical surface of proximal tubule in kidney. Due to selective distribution at the port of drug entry and exit, P-gp has been speculated to play a major physiological role in the absorption, distribution and excretion of xenobiotics and endogenous substrates. Overall, P-gp functions as a biochemical barrier for entry of drugs across intestine and brain, as well as a vacuum cleaner to expel drugs from the intestine, liver, kidney, etc. A number of clinically important drugs are P-gp substrates, which are as diverse as anthracyclines (doxorubicin, daunorubicin), alkaloids (reserpine, vincristine, vinblastine), specific peptides (valinomycin, cyclosporine), steroid hormones (aldosterone, hydrocortisone) and local anesthetics (dibucaine) (Polli et al., 2001; Mahar Doan et al., 2002; Varma et al., 2003 and Takano et al. 2006). P-gp substrates, digoxin and talinolol, show pharmacokinetic changes in
human upon coadministration with P-gp inhibitors (Gramatte et al., 1996 and Fenner et al., 2009). Greiner et al., studied the effect of rifampicin pretreatment on the oral pharmacokinetics of digoxin and suggested that rifampicin induced duodenal P-gp expression and thus significantly reduced AUC of digoxin (Greiner et al., 1999). Similarly, rifampicin decreased talinolol oral exposure, which is consistent with ~4 fold increase in duodenal P-gp expression (Westphal et al., 2000). P-gp affinity screening using various in vitro culture models is now an integral part of drug discovery due to wide substrate specificity and clinical relevance in drug disposition and associated drug-drug interactions (Varma et al., 2004a). Tailoring of molecules to reduce substrate specificity to P-gp may help in improving the oral bioavailability of drugs. Seelig and coworkers suggested that the partitioning into the lipid membrane is the rate limiting step for the interaction of a substrate with P-gp and that dissociation of the P-gp substrate complex is determined by the number and strength of the hydrogen bonds formed between the substrate and the transporter (Seelig and Landwojtowicz, 2000). Several studies have related the binding affinity ($K_m$) of P-gp for substrates and modulators to their lipid-water partition coefficient ($\log P$). Evidence suggests that a drug with high $\log P$ will accumulate to a high concentration within the cytoplasmic membrane and favors binding to P-gp with low $K_m$ value, while a drug with low partitioning will have a lower membrane concentration and a high $K_m$ value.

2.3.8 Gastric Emptying Time

Gastric emptying time refers to the time needed for the stomach to empty the total initial stomach contents. During digestion, gastric emptying depends on the tone of proximal stomach and pylorus, which is under reflex and hormonal control. Generally, anything that slows down gastric emptying is likely to slow down the rate (not extent) of drug absorption, and thus affect onset of the therapeutic response. A lot of factors promote gastric emptying, such as hunger, lying on right side, noncaloric liquid intake, drugs (metoclopramide, prokinetic drugs), and some excipients. On the other hand, factors, such as meals (especially with fatty, bulky, and viscous food), lying on left side, and other drugs (tricyclic antidepressants, anticholinergics, and alcohol) retard gastric emptying. Gastric emptying of solution-type dosage forms and suspensions of
fine drug particles is generally much faster and less variable than that of solid, nondisintegrating dosage forms and aggregated particles. For drugs with high solubility and high membrane permeability, gastric emptying rate will control the absorption rate and onset of the drugs. There will be a direct relation between gastric-emptying rate and maximal plasma concentration, and an inverse relation between gastric-emptying rate and the time required to achieve maximal plasma concentrations (Fleisher, 1990).

2.3.9 Surface Area
Surface area of different regions of GI influences drug absorption. Small intestine has largest effective surface area for drug absorption due to the presence of folds of mucosa, villi, and microvilli. For carrier-mediated drug absorption, small intestine is also the most important region for most drug transporters that are also expressed in this area. In contrast, stomach and large intestine have no villi, microvilli, or less transporter expression (Fleisher, 1990).

2.3.10 Intestinal Motility
Intestinal motility is another factor that influences oral drug absorption. Intestinal movement includes propulsion and mixing. Propulsive movement determines the intestinal transit time and is important for slow release dosage forms, enteric coated drug that is only released in intestine, slowly dissolving drugs, and carrier mediated absorption. Mixing movement increases dissolution rate where the drug molecule contacts with endothelial surface area for absorption (Fleisher, 1990).

2.3.11 Components, Volume, and Properties of Gastrointestinal Fluids
Components, volume, and properties of gastrointestinal fluids especially GI pH will change the drug’s ionization, solubility, dissolution rate, and therefore affect drug absorption. The rate of dissolution from a dosage form, particularly tablets and capsules, is dependent on pH. Acidic drugs dissolve most readily in alkaline media and will have a greater dissolution in the intestinal fluids than in gastric fluids. Basic drugs will dissolve most readily in acidic solution, and thus the dissolution will be greater in gastric fluids than in intestinal fluids. GI pH depends on general health of the individual, disease conditions, age, type of food, and drug therapy. Anticholinergic
drugs and H2-blockers increase gastric pH and significantly decrease bioavailability of some weakly basic drugs with pH-dependent solubility (Fleisher, 1990).

2.3.12 Blood Flow

Blood flow in the GI tract also plays an important role in drug absorption. GI tract is highly vascularized and receives 28% of the cardiac output. The higher blood flow promotes the higher drug absorption, especially for those active-absorption mediated and highly permeable drugs (Fleisher, 1990).

2.4 SUSTAINED DRUG DELIVERY AND ITS NEED:

Conventional IR dosage forms have to be administered several times as to maintain a therapeutically effective plasma level of the drug, which is a major drawback in terms of patient compliance. Fluctuating plasma concentrations may result in alternating periods of toxicity and ineffectiveness, despite a proper choice of the dosing regimen plasma. In order to improve the therapeutic efficacy of oral administration, and to overcome many drawbacks of conventional dosage forms, researchers are focusing on the development of oral controlled release technologies and newer controlled releasing technique. Figure 2.5 represents plasma concentrations of a conventional immediate release (IR) dosage form, a sustained release (SR) dosage form and an idealized zero order controlled release dosage form (in combination with a start up dose).

Figure 2.5: Characteristic representation of plasma concentrations of a conventional immediate release dosage (IR) form, a sustained release dosage form (SR) and an idealized zero order controlled release (ZOCR) dosage form
Historically, oral drug administration is known to be the most popular route of drug administration due to the fact the gastrointestinal physiology offers more flexibility in dosage form design than most other routes (Gupta and Robinson, 1992; Tongwen and Binglin, 1998; Chen et al., 2010; Maderuelo et al., 2011,). A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time (Chen et al., 2010, Nair et al., 2010, Rajput et al., 2010). The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels (Lordi, 1986; Grundy and Foster, 1996; Chen et al., 2010). Drug release is dependent on polymer properties, thus proper selection of these polymers can produce well characterised and reproducible dosage forms (Levina and Rajabi-Siahboomi, 2004). Controlled release systems can be influenced by physiological conditions such as motility, ions, pH and enzymes (Singh et al., 1968 and Abrahamsson et al., 2004).

Hydrophillic matrix systems are among the most commonly used means for oral controlled drug delivery as they can produce a desirable drug profile and are cost effective (Prajapati and Patel, 2010). The primary mechanism of drug release from hydrophilic matrices is polymer swelling on contact with the aqueous medium to form a gel layer on the surface of the system. The drug is then released by dissolution, diffusion and/or erosion (Colombo, 1993; Siepmann and Peppas, 2001a; Siepmann and Peppas, 2001b; Tiwari and Rajabi-Siahboomi, 2008).

- **Advantages of oral controlled release formulations**

This type of drug delivery has been at the centre of research due to its many benefits over conventional dosage forms, some of which are as follows:

1. The frequency of dosing is reduced due to drug being released over a longer period of time unlike conventional tablets (Kojima et al., 2008). This is extremely valuable for patients with chronic illnesses which require the plasma concentrations of a drug to be within its therapeutic range to avoid breakthrough symptoms, for example, overnight management of pain in terminally ill patients (Aulton, 2008).
2. The reduction or avoidance of side effects due to high plasma drug concentrations or ‘dose dumping’ (Maderuelo et al., 2011).
3. Improvement in patient compliance due to reduced dosing (Maderuelo et al., 2011).
4. Better control of therapeutic drug concentration;
5. Cost effective manufacturing (Maderuelo et al., 2011) as the amount of tablets needed per patient would be reduced compared to its conventional form.

➢ **Disadvantages of oral controlled release formulations**

Oral controlled release formulations like other formulations have few disadvantages (DiMatteo and DiNicola, 1982; Sansom, 1999; Kayser et al., 2005 and Jayanthi et al., 2011) including:

1. Development costs: Expensive specialized equipment and inert ingredients may be required for some controlled release formulations.
2. Release rate: Alteration of drug release rate due to food and gastric transit time.
3. Failure of the dosage form may suddenly produce high drug concentration.

2.4.1 **The effect of drug properties in developing oral controlled release** Sustained release dosage forms pose many challenges for pharmaceutical technologists (Khan, 1996). In order for drug release to be manipulated and for the resulting product to possess the above mentioned characteristics there are many factors that need to be taken into consideration while designing such formulations. Some of these are as follows:

1. Different drug solubilities need to be considered (Sudha et al., 2010) as highly soluble drugs dissolve immediately after administration (Siahi et al., 2005). Reduced drug solubility increases the tendency of the tablet to erode due to particle displacement (Bettini et al., 2001).
2. The drug should have a short half-life (Aulton, 2008). If a drug has a long half-life then there is a risk of accumulated pharmacological response (Kim, 2000).
3. A drug tested *in-vitro* is needed to provide similar release characteristics once administered (Khan, 1996 and Diakidoua et al., 2009). A direct correlation of *in-vitro* data with *in-vivo* release is not possible without thorough and careful analysis. For example, there is a difference in the availability of water in different parts of the gastrointestinal tract and such factors need to be considered when designing tablets for extended release (Khan, 1996 and Kojima et al., 2008).
4. The dissolution characteristics should allow for drug to be released in a controlled manner, highlighting the importance for the correct selection of polymers according to their physical, mechanical and pharmacokinetic properties (Kim, 2000).

2.4.2 Types of sustained release systems

There are several types of sustained release systems that are designed and categorised according to the mechanism they employ. These include diffusion controlled, dissolution controlled, erosion controlled, ion exchange controlled and transport control also known as osmotic pump systems (Aulton, 2008).

2.4.3 Osmotic drug delivery systems

In a typical therapeutic regimen the drug dose and dosing interval are optimized to maintain drug concentration within the therapeutic window, thus ensuring efficacy while minimizing toxic effects. Survey indicated that dosing more than one or twice daily, greatly reduces patient compliance. So in recent year considerable attention has been focused on the development of novel drug delivery system and the main reason for this paradigm shift is relatively low development cost and time required for introducing a novel drug delivery system as compared to a new chemical entity. In the form of novel drug delivery system, an existing drug molecule can get a new life thereby increasing its market value competitiveness and patent life among the various novel drug delivery system available in the market, per oral controlled release system hold the major market share because of their obvious advantages of ease of administration and better patient compliance. These products provide significant benefits over immediate release formulation, including greater effectiveness in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to simplified dosing schedule (Verma et al., 2000).

A number of design options are available to control or modulate the drug release from a dosage form. Majority of per oral dosage form fall in the category of matrix, reservoir or osmotic system. In matrix system, the drug is embedded in polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the release medium. In contrast, reservoir systems have a drug core surrounded/coated by the rate controlling membrane. However factor like pH, presence of food and other
physiological factor may affect drug release from conventional controlled release systems. Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system (Theeuwes et al., 1985).

The oral osmotic pumps have certainly came a long way and the available products on this technology and number of patent granted in the last few years makes their presence felt in the market. They are also known as gastro intestinal therapeutic system. Alza corporation was first to develop an oral osmotic pump and today also they are the leaders in this field with a technology named OROS. Osmotic drug delivery has come long way since Australian pharmacologist Rose and Nelson developed an implantable osmotic pump in 1955. Next quantum leap in osmotic dosage form came in 1972 when Theeuwes et al. (1985) invented elementary osmotic pump (Verma et al., 2000).

- **Advantages**
Osmotic drug delivery system for oral and parenteral use offer distinct and practical advantage over other means of delivery. The following advantages contributed to the popularity of osmotic drug delivery system (Kumar et al., 2006).

- Decrease frequency of dosing.
- Reduce the rate of rise of drug concentration in the body.
- Delivery may be pulsed or desired if required.
- Delivery ratio is independent of pH of the environment.
- Delivery is independent of hydrodynamic condition, this suggest that drug delivery is independent of G.I. motility.
- Sustained and consistence blood level of drug within the therapeutic window.
- Improve patient compliance.
- High degree of in vitro- in vivo correlation is obtained in osmotic system.
- Reduce side effect.
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- Delivery rate is also independent of delivery orifice size within the limit.
- Customised delivery profiles and reduced side effects [Theeuwees et al., 1985].

**Disadvantages**

- Expensive
- Slow onset of delivery
- If the coating process is not well controlled, chances of dose dumping
- Pore size is critical
- Quality control is much more extensive that required for conventional counterparts. These systems have an edge over other oral sustained release dosage forms because:
  - Zero order Release is obtainable
  - Drug release is independent of the system’s environment
  - Reformulation is not required for different drugs.

### 2.4.3A Developments in Oral osmotic Drug Delivery Devices

They fall in two categories:

**a. Implantable**

I. The Rose and Nelson Pump
II. Higuchi Leeper Pump
III. Higuchi Theuwes pump
IV. Implantable Miniosmotic pump

**b. Oral osmotic Pump**

I. Single chamber osmotic pump
   - Elementary osmotic pump
II. Multi chamber osmotic pump
   - Push pull osmotic pump
2.4.3B Techniques used in various types of oral osmotic drug delivery Devices:

I. Elementary Osmotic Pump

The elementary osmotic pump is a new delivery system for drugs. It delivers the agent by an osmotic process at a controlled rate. Control resides in the:

1. Water permeation characteristics of a semi-permeable membrane surrounding the formulating agent
2. Osmotic properties of the formulation

The was introduced in 1970s to deliver drug at zero order rates for prolonged periods, and is minimally affected by environmental factors such as pH or motility. The tablet consists of an osmotic core containing the drug surrounded by a semipermeable membrane laser drilled with delivery orifice. Following ingestion, water in absorbed into system dissolving the drug, and the resulting drug solution is delivered at the same rate as the water entering the tablet. The disadvantages of the elementary pump are that it is only suitable for the delivery of water soluble drugs (Theeuwes, 1975 and Theeuwes et al., 1983)

Fig. 2.5a shows schematic diagram of elementary osmotic pump (EOP), which in its simplest design, consists of an osmotic core (containing drug with or without an osmogen) coated with a semipermeable membrane (SPM). The dosage form, after coming in contact with the aqueous fluids, imbibes water at a rate determined by the fluid permeability of the membrane and osmotic pressure of core formulation. This osmotic imbibition of water results in formation of a saturated solution of drug within the core, which is dispensed at a controlled rate from the delivery orifice in the membrane. Though 60–80% of drug is released at a constant rate from EOP, a lag time of 30–60 min is observed in most of the cases as the system hydrates before zero-order delivery from the system begins. These systems are suitable for delivery of drugs having moderate water solubility (Theeuwes, 1975 and Theeuwes et al., 1983).

II. Push Pull Osmotic Pump

Push pull osmotic pump is a modified EOP through, which it is possible to deliver both poorly water-soluble and highly water soluble drugs at a constant rate. This system resembles a standard bilayer coated tablet. One layer (depict as the upper layer)
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contains drug in a formulation of polymeric, osmotic agent and other tablet excipients. This polymeric osmotic agent has the ability to form a suspension of drug in situ. When this tablet later imbibes water, the other layer contains osmotic and coloring agents, polymer and tablet excipients. These layers are formed and bonded together by tablet compression to form a single bilayer core. The tablet core is then coated with semipermeable membrane. After the coating has been applied, a small hole is drilled through the membrane by a laser or mechanical drill on the drug layer side of the tablet. When the system is placed in aqueous environment, water permeates into the tablet due to the presence of an osmotic agent in both the layers. The osmotic action in the drug layer pulls water into the compartment to form in situ a suspension of drug. The osmotic agent in the non-drug layer simultaneously attract water into that compartment, causing it to expand volumetrically and the expansion of non drug layer pushes the drug suspension out of the delivery orifice (Parmar et al., 2001). Figure 2.6a shows drug release from elementary osmotic pump and push-pull type osmotic pump by two different mechanisms (Figure 2.6b).

![Schematic diagram of an elementary osmotic pump (a) and a push–pull osmotic pump (b).](image)

Figure 2.6: Schematic diagram of an elementary osmotic pump (a) and a push–pull osmotic pump (b).
III. Osmotic Pump with Non Expanding Second Chamber

The second category of multi-chamber devices comprises system containing a non-expanding second chamber. This group can be divided into two sub groups, depending on the function of second chamber.

In one category of these devices, the second chamber is used to dilute the drug solution leaving the devices. This is useful because in some cases if the drug leaves the oral osmotic devices a saturated solution, irritation of GI tract is a risk.

Example: - Before the drug can escape from the device, it must pass through a second chamber. Water is also drawn osmotically into this chamber either because of osmotic pressure of drug solution or because the second chamber contain, water soluble diluents such as NaCl. This type of devices consist of two rigid chamber, the first chamber contains a biologically inert osmotic agent, such as sugar or a simple salt like sodium chloride, the second chamber contains the drug. In use water is drawn into both the chamber through the surrounding semi permeable membrane. The solution of osmotic agent formed in the first chamber then passes through the connecting hole to the drug chamber where it mixes with the drug solution before exiting through the micro porous membrane that form a part of wall surrounding the chamber. The device could be used to deliver relatively insoluble drugs (Srenivasa et al., 2001).

IV. Osmotic Bursting Osmotic Pump

This system is similar to an EOP expect delivery orifice is absent and size may be smaller. When it is placed in an aqueous environment, water is imbibed and hydraulic pressure is built up inside until the wall rupture and the content are released to the environment (Parmar et al., 2001). Varying the thickness as well as the area the semi permeable membrane can control release of drug. This system is useful to provide pulsated release.

V. Liquid Oral Osmotic System

To overcome the drug solubility issue Alza developed the L-OROS system where the liquid soft gelatin product containing the drug in a dissolved state is initially manufactured and then
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cated with a barrier membrane, then the osmotic push layer and then semi permeable membrane containing a drilled orifice (Garg et al., 2002). Liquid OROS are designed to deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability (Dong et al, 2000). They are of three types:

1. L-OROS hard cap,
2. L-OROS soft cap
3. Delayed liquid bolus delivery system

Liquid OROS controlled release systems are designed to deliver drugs as liquid formulations and combine the benefits of extended-release with high bioavailability (Dong et al., 2000). Figure 2.7 shows the cross-sectional diagram for L-OROS SOFTCAP delivery system before and during operation. These systems are suitable for controlled delivery of liquid drug formulations including lipophilic self-emulsifying formulations (SEF). The liquid drug formulation is present in a soft gelatin capsule, which is surrounded with the barrier layer, the osmotic layer, and the release rate controlling membrane. A delivery orifice is formed through these three layers. When the system is in contact with the aqueous environment, water permeates across the rate controlling membrane and activates the osmotic layer. The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to break through the hydrated gelatin capsule shell at the delivery orifice. The liquid drug formulation is pumped through the delivery orifice. L-OROS hardcap is similar to L-OROS softcap and consists of a liquid drug layer, a barrier layer, and an osmotic engine, all encased in a hard gelatin capsule and coated with a SPM (Dong et al., 2001). A delivery orifice, drilled in the membrane at the end of the drug layer, provides an outlet for the drug suspension. After coming in contact with the aqueous environment, water is imbibed across the SPM, expanding the osmotic engine. The osmotic engine pushes against the barrier, releasing drug through the delivery orifice. In majority of cases, osmotic systems have a pre-formed passageway in the membrane from where the drug release takes place. Controlled porosity osmotic pumps (CPOP), contain water-soluble additives in the coating membrane, which after coming in contact with water, dissolve resulting in an in situ
formation of a microporous membrane (Figure 2.7). The resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from these systems was found to be primarily osmotic, with simple diffusion playing a minor role (Dong et al., 2000 and Verma et al., 2002).

**Figure 2.7: Cross-sectional diagram of L-OROS delivery system before and during operation.**

**VI. Delayed Delivery Osmotic Device**

Because of their semi permeable walls, an osmotic device inherently show lag time before drug delivery begins. Although this characteristic is usually cited as a disadvantage, it can be used advantageously. The delayed release of certain drug (drugs for early morning asthma or arthritis) may be beneficial. The following text describe other means to further delay drug release (Theeuwes et al., 1993; Kaushal and Garg, 2003).
VII. Telescopic Capsule for Delayed Release

This device consists of two chambers, the first contains the drug and an exit port, and the second contains an osmotic engine. A layer of wax like material separates the two sections. To assemble the delivery device, the desired active agent is placed into one of the sections by manual or automated fill mechanism. The bilayer tablet with the osmotic engine is placed into a completed cap part of the capsule with the convex osmotic layer pointed into the closed end of the cap and the barrier into the closed end of the cap and the barrier layer exposed towards the cap opening. The open end of the filled vessel is fitted inside the open end of the cap, and the two pieces are compressed together until the cap, osmotic bilayer tablet and vessel fit together tightly. As fluid is imbibed the housing of the dispensing device, the osmotic engine expand and exerts pressure on the slidable connected first and second wall sections. During the delay period the volume of reservoir containing the active agent is kept constant, therefore a negligible pressure gradient exists between the environment of use and interior of the reservoir. As a result, the net flow of environmental fluid driven by the pressure enter the reservoir is minimal and consequently no agent is delivered for the period (Chein et al., 1982).

VIII. OROS-CT

OROS-CT is used as a once or twice a day formulation for targeted delivery of drugs to the colon. The OROS-CT can be a single osmotic agent or it can be comprise of as many as five to six push pull osmotic unit filled in a hard gelatin capsule. After coming in contact with the gastric fluids, gelatin capsule dissolved and the enteric coating prevents entry of fluids from stomach to the system as the system enters into the small intestine the enteric coating dissolves and water is imbibed into the core thereby causing the push compartment to swell (Theeuwes et al., 1993). At the same time flowable gel is formed in the drug compartment, which is pushed out of the orifice at a rate, which is precisely controlled, by the rate of water transport across the semi permeable membrane (Figure 2.8).
IX. Sandwiched Osmotic Tablets (SOTS)

It is composed of polymeric push layer sandwiched between two drug layers with two delivery orifices. When placed in the aqueous environment the middle push layer containing the swelling agents swells and the drug is released from the two orifices situated on opposite sides of the tablet and thus SOTS can be suitable for drugs prone to cause local irritation of the gastric mucosa (Liu et al., 2000)
In sandwiched osmotic tablet (SOTS), a tablet core consisting of a middle push layer and two attached drug layers is coated with a SPM (Liu et al., 2000). As seen in Figure 2.9, both the drug layers are connected to the outside environment via two delivery orifices (one on each side). After coming in contact with the aqueous environment, the middle push layer containing swelling agents swells and the drug is released from the delivery orifices. The advantage with this type of system is that the drug is released from the two orifices situated on two opposite sides of the tablet and thus can be advantageous in case of drugs which are prone to cause local irritation of gastric mucosa. Figure 2.9 shows the cross-sectional diagram of sandwiched oral osmotic drug delivery system.

X. Monolithic Osmotic System

It constitutes a simple dispersion of water-soluble agent in polymer matrix. When the system comes in contact with the aqueous environment water imbibation takes place by rupturing the polymer matrix capsule surrounding the drug (Figure 2.10), thus liberating it to the outside environment. Initially this process occurs at the outer environment of the polymeric matrix, but gradually proceeds towards the interior of the matrix in a serial fashion. However, this system fails if more then 20 –30 volume per
liter of the active agents is incorporated into the device as above this level, significant contribution from the simple leaching of the substance takes place (Zenter et al., 1985).

![Matrix ("Monolithic") DDS](image)

**Figure 2.10:** Cross-sectional diagram of Matrix (Monolithic) drug delivery system.

### XI. Osmat

It is a novel osmotically driven matrix system, which utilizes the hydrophilic polymers to swell and gel in aqueous medium forming a semipermeable membrane in-situ. Drug released from such a matrix system containing an osmogen could, therefore be modulated by the osmotic phenomenon. Osmat, thus, judiciously combines both matrix osmotic characteristics resulting a quantum improvement in drug delivery from swellable matrix system. Osmat produces controlled drug release with adequate delivery rates which is dependent upon agitational intensity *in vitro*. Thus osmat represents simple, versatile, and easy to fabricate osmotically driven controlled drug delivery system based upon low cost technology (Zenter et al., 1991).

### XII. Controlled Porosity Osmotic Pump

The pump can be made with single or multicompartiment dosage form, in either form, the delivery system comprises a core with the drug surrounded by a membrane which has an asymmetric structure, i.e. comprises a thin dense skin layer supported by a porous substructure. The membrane is formed by phase inversion process controlled by the evaporation of a mixed solvent system (Cardinal et al., 1997). Membrane is
permeable to water but impermeable to solute and insensitive pore forming additive dispersed through out the wall as shown in Figure 2.11. Some of the approved tablets based on OROS technologies are internationally available for human use are enlisted in Table 2.2.

When exposed to water, low levels of water-soluble additive are leached from polymer materials that are permeable to water yet remain insoluble. Then resulting sponge like structure are formed which control porosity of the walls and allow permeation of both water and dissolved drug agents. Rate of drug delivery depends upon the factors are water permeability of the semi permeable membrane and the osmotic pressure of the core formulation, thickness and total surface area of coating. All of these variables are under the control of the designer and do not vary under physiological condition, leading to the robust performance allued to above. The rate of flow dv/dt of water into the device can be represented as

\[
\frac{dv}{dt} = \frac{Ak}{h} (Dp-DR), \quad \text{Where} \quad k = \text{Membrane permeability}, \quad A = \text{Area of the membrane}
\]

\[
Dp = \text{Osmotic pressure difference}, \quad DR = \text{Hydrostatic pressure difference}
\]

**Figure 2.11:** Schematic diagram of controlled porosity osmotic pump before and during operation.
Table 2.2: Commercially available brands of osmotic delivery systems for different drugs intended for human use

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Chemical Name</th>
<th>Type of delivery</th>
<th>Developer / Marketer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acutrim</td>
<td>Phenylpropalamine</td>
<td>Elementary Osmotic Pump</td>
<td>Alza / Heritage</td>
</tr>
<tr>
<td>Alpress LP</td>
<td>Prazosin</td>
<td>Push – Pull</td>
<td>Alza / Pfizer</td>
</tr>
<tr>
<td>Cardura XL</td>
<td>Doxazosin</td>
<td>Push – Pull</td>
<td>Alza / Pfizer</td>
</tr>
<tr>
<td>Concerta</td>
<td>Methylphenidate</td>
<td>Push – Pull (Trilayer)</td>
<td>Alza</td>
</tr>
<tr>
<td>Ditropan XL</td>
<td>Oxybutynin HCl</td>
<td>Push – Pull</td>
<td>Alza / UCB Pharma</td>
</tr>
<tr>
<td>DynaciroCR</td>
<td>Isradipine</td>
<td>Push – Pull</td>
<td>Alza / Novartis</td>
</tr>
<tr>
<td>Efidac 24</td>
<td>Chlorpheniramine maleate</td>
<td>Elementary Osmotic Pump</td>
<td>Alza / Novartis</td>
</tr>
<tr>
<td>Glucotrol XL</td>
<td>Glipizide</td>
<td>Push – Pull</td>
<td>Alza / Pfizer</td>
</tr>
<tr>
<td>Procardia XL</td>
<td>Nifedipine</td>
<td>Push – Pull</td>
<td>Alza / Pfizer</td>
</tr>
<tr>
<td>Sudafed 24 Hours</td>
<td>Pseudoephedrine</td>
<td>Push – Pull</td>
<td>Alza / Warner Lambert</td>
</tr>
<tr>
<td>Teczam</td>
<td>Enalapril and Diltiazem</td>
<td>Elementary Osmotic Pump</td>
<td>Merck / Aventis</td>
</tr>
<tr>
<td>Tiamate</td>
<td>Diltiazem</td>
<td>Push – Pull</td>
<td>Merck / Aventis</td>
</tr>
<tr>
<td>Volmax</td>
<td>Albuterol</td>
<td>Push – Pull</td>
<td>Alza / Muro Pharmaceuticals</td>
</tr>
</tbody>
</table>

2.4.3C Formulation variables in Oral Osmotic Drug Delivery systems:
I. Solubility

The kinetics of osmotic drug release is directly related to the solubility of the drug within the core. Assuming a tablet core of pure drug, the fraction of core released with zero-order kinetics is given by the following equation (Zentner et al., 1991 and McClelland et al. 1991):

\[
F(z) = 1 - \frac{S}{\rho} \quad \text{Eqn (1)}
\]

where \(F(z)\) is the fraction released by zero-order kinetics, \(S\) is the drug’s solubility.
(g/cm\(^3\)), and \(r\) is the density (g/cm\(^3\)) of the core tablet. Drugs with a solubility of \#0.05 g/cm\(^3\) would be released with 95% zero-order kinetics according to Eq. (1). However, the zero-order release rate would be slow due to the small osmotic pressure gradient. Conversely, highly water-soluble drugs would demonstrate a high release rate that would be zero-order for a small percentage of the initial drug load. Thus, the intrinsic water solubility of many drugs might preclude them from incorporation into an osmotic pump. However, it is possible to modulate the solubility of drugs within the core, and thus, extend this technology for delivery of drugs that might otherwise have been poor candidates for osmotic delivery. Some of the approaches that have been used to deliver drugs having extremes of solubility are:

a) Use of encapsulated excipients

Thombre and coworkers (Thombre, 1997 and Thombre et al., 1999) described a capsule device coated with asymmetric membranes to deliver drugs having poor water-solubility (Figure 2.12). In the examples, solubility of a poorly water-soluble drug, glipizide, was improved by incorporation of encapsulated excipients (pH-controlling excipients) within the capsule device. The solubility modifier (meglumine), in the form of mini-tablets, was coated with a rate controlling membrane to prolong its availability within the core. Thus, the solubility of glipizide was improved leading to its prolonged release from the device.

Figure 2.12: Schematic view of delivery system having encapsulated excipients.
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b) Use of swellable polymers

Swellable polymers can be utilized for osmotic delivery of drugs having poor aqueous solubility. Examples using this approach are reported in US patent no. 4,992,278 (Khanna, 1991) for carbamazepine, theophylline, acetylsalicylic acid, and nifedipine. The formulation mainly consists of a compartment, containing the drug, swelling agents, and osmogens, coated with a rate controlling membrane. Vinylpyrrolidone / vinyl acetate copolymer (Kollidon® VA 64, BASF) and polyethylene oxide (MW: 53 x 10^6, Polyox®,-coagulant, Union Carbide) were used as swelling agents. Uniform rate of swelling of these polymers ensures that the drug is released at a relatively constant rate. Also, the pressure produced during swelling does not lead to rupture of the system.

In addition, push-pull osmotic pump (PPOP) can also be utilized for delivery of drugs having either high, e.g. oxybutynin chloride (Guittard et al., 1998), or low water solubility, e.g. glipizide (Kuczynski et al., 1991; Kuczynski et al., 1992; Kuczynski et al., 1996 and Kuczynski et al., 1997). Drug is released from the delivery orifice in the form of a very fine dispersion ready for dissolution and absorption.

Sandwiched osmotic tablets (SOTS) have also been utilized for osmotic delivery of water insoluble drugs, such as nifedipine (Liu et al., 2000). The release profile from the tablets was found to be comparable with the commercially available push–pull osmotic system of the drug.

c) Use of effervescent mixtures

Use of effervescent mixture, can be another approach to deliver poorly water-soluble drugs from osmotic dosage forms. After administration, the effervescent mixture containing drug is delivered under pressure through the delivery orifice in the membrane. This method of enhancing release of poorly water-soluble drug is reported in US patent no. 4,036,228 (Theeuwes, 1977). In one of the examples, citric acid and sodium bicarbonate were used as the effervescent couple for the delivery of acetyl salicylic acid. The formulation imbibes aqueous fluids across the membrane causing the couple to generate an effervescent solution that dispenses the drug in a suspension form.
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d) Use of cyclodextrin derivatives

Incorporation of the cyclodextrin–drug complex has also been used as an approach for delivery of poorly water-soluble drugs from the osmotic systems. A controlled porosity osmotic pump (CPOP) has been described for testosterone (having a solubility of 0.039 mg / ml at 37 °C), solubility of which was improved to 76.5 mg / ml through complexation with sulfobutyl ether-b-cyclodextrin sodium salt, (SBE)-7m-b-CD (Okimoto et al., 1999). In a comparative study with hydroxypropyl-b-cyclodextrin (HP-b-CD) and a sugar mixture, it was found that testosterone release from the device in the presence of (SBE)- 7m -b-CD was mainly due to osmotic pumping while for HP-b-CD, the major contribution was due to diffusion. In case of the sugar mixture, the drug was poorly released due to the absence of solubilizer. Similar results were obtained with prednisolone (Okimoto et al., 1998) and chlorpromazine (Okimoto et al., 1999). It was reported that (SBE)- 7m -b-CD could serve both as a solubilizer and osmotic agent.

e) Resin modulation approach

Release of a highly water-soluble drug, diltiazem hydrochloride from a CPOP was modulated effectively using positively charged anion-exchange resin, poly (4-vinyl pyridine) (Zentner et al., 1991). Pentaerythritol was used as osmotic agent and citric and adipic acids were added to maintain a low core pH to assure that both the drug and resin carry a positive charge. The solubility of diltiazem hydrochloride was reduced for an extended period and pH-independent zero-order release was obtained.

f) Use of alternative salt form

For an ionic drug, an alternative salt form can also be used as reported for metoprolol and oxprenolol (Theeuwes et al., 1985). Hydrochloride salt used in commercial formulations of oxprenolol was found to have high water solubility (70% w / v) making it difficult to achieve extended zero-order delivery from osmotic systems. The authors replaced it by the less soluble succinate salt. In case of metoprolol, they used fumarate salt form as drug and osmotic driving agent, instead of tartrate salt. These salt forms were found to have optimum solubility and provided extended release up to 24 h.

g) Use of crystal habit modifiers

If the drug exists in more than one crystal form, each having different aqueous
solubility, it is beneficial to include a crystal modifying agent. One such example is reported in US patent no. 5,284,662 (Koparkar and Shah, 1994), wherein a slightly soluble drug, carbamazepine, along with crystal modifying agents (combination of hydroxymethyl cellulose and hydroxyethyl cellulose) and other excipients was formulated in the form of osmotic pumps that were able to provide approximately zero-order release for the desired period of time.

\( h) \) Use of lyotropic crystals

Use of lyotropic liquid crystals, to assist osmotic delivery of poorly water-soluble drugs, is also reported in the literature (Curatolo, 1989 and Curatolo, 1992). The lyotropic liquid crystals are non-polymeric compounds, generally in the molecular weight range of 200–1500. Also known as amphipathic compounds, these form mesophases and swell in presence of water. Compounds that can be used as lyotropic liquid crystals include natural phosphatides such as phosphatidylcholine (lecithin), phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerol, and the like. Few examples using this approach are mentioned in US patent no. 5,108,756 and 5,030,452. In these examples, Alcolec lecithin (American Lecithin Co., Atlanta, GA) and mixture of soybean phospholipids was utilized for osmotic delivery of two insoluble drugs, namely, glipizide and prazosin. The inventors claimed that the extended drug release up to 24 h was achieved.

\( i) \) Use of wicking agents

Inclusion of wicking agents in the osmotic formulations has also been reported as an approach for poorly water-soluble drugs (Rudnic et al., 2000). A wicking agent is dispersed throughout the composition that enhances the contact surface area of drug with the incoming aqueous fluids. Thus, the drug is released predominantly in a soluble form through the delivery orifice in the membrane. The authors delivered nifedipine using this approach and some of the reported wicking agents are colloidal silicon dioxide, PVP, sodium lauryl sulfate, etc.

\[ \text{II. Osmotic pressure} \]

Osmotic pressure, like vapor pressure and boiling point, is a colligative property of a solution in which a nonvolatile solute is dissolved in a volatile solvent. Osmotic pressure of a solution is dependent on the number of discrete entities of solute present
in the solution. The release rate of a drug from an osmotic system is directly proportional to the osmotic pressure of the core formulation. For controlling the drug release from these systems, it is important to optimize the osmotic pressure gradient between inside compartment and the external environment. It is possible to achieve and maintain a constant osmotic pressure by maintaining a saturated solution of osmotic agent in the compartment (Jerzewski and Chien, 1992). If a drug does not possess sufficient osmotic pressure, an osmagent can be added in the formulation. Some of the compounds that can be used as osmogens are listed in Table 2.3. Polymeric osmogens are mainly used in the fabrication of PPOPs and other modified devices for controlled release of drugs with poor water solubility. These are swellable, hydrophilic polymers that interact with the aqueous fluids and swell or expand to an equilibrium state. These polymers have a capacity to retain a significant portion of the imbibed water within the polymer structure (Cortese and Theeuwes, 1992).

It is possible to confirm the contribution of osmotic pressure in drug release from osmotic systems by conducting the release studies in media of different osmotic pressure. The release rates obtained can be plotted against the osmotic pressure difference across the device wall. Using this approach, release of potassium chloride from controlled porosity osmotic pump (CPOP) was studied in aqueous media of different osmotic pressure and as seen from figure 2.14, an inverse relationship was found as pressure difference across the device walls (Zentner et al., 1985 and Zentner et al., 1985). A linear relationship was obtained confirming osmotic release from the system.

Table 2.3: Compounds used as osmogens

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water-soluble salts of inorganic acids</td>
<td>Magnesium chloride or sulfate; lithium, sodium, or potassium chloride; lithium, sodium, or potassium sulfate; sodium or potassium hydrogen phosphate, etc.</td>
</tr>
<tr>
<td>Water-soluble salts of organic acids</td>
<td>Sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate, etc.</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>Arabinose, ribose, xylose, glucose, fructose, galactose, mannose, sucrose, maltose, lactose, raffinose, etc.</td>
</tr>
<tr>
<td>Water-soluble amino acids</td>
<td>Glycine, leucine, alanine, methionine, etc.</td>
</tr>
<tr>
<td>Organic polymeric osmogens</td>
<td>Sodium carboxy methylcellulose, HPMC, hydroxyethyl methylcellulose, cross-linked PVP, polyethylene oxide, carbopol, polyacrylamides, etc.</td>
</tr>
</tbody>
</table>
III. Delivery orifice

Osmotic delivery systems contain at least one delivery orifice in the membrane for drug release. The size of delivery orifice must be optimized in order to control the drug release from osmotic systems. If the size of delivery orifice is too small, zero-order delivery will be affected because of development of hydrostatic pressure within the core. This hydrostatic pressure may not be relieved because of the small orifice size and may lead to deformation of delivery system, thereby resulting in unpredictable drug delivery. On the other hand, size of delivery orifice should not also be too large otherwise; solute diffusion from the orifice may take place. There are mathematical calculations that can be used to calculate the optimum size of the delivery orifice (Theeuwes, 1975). Drug release from osmotic systems is not affected by the size of the delivery orifice within certain limits as reported. Drug release from osmotic pumps of nifedipine was studied as a function of orifice diameter and no significant differences were found in the release profiles for orifice diameter ranging from 0.25 to 1.41 mm (Liu et al., 2000). Drug release was somewhat rapid with an orifice diameter of 2.0 mm possibly because of significant diffusion. On the other hand, a longer lag time and unpredictable and slower release rates were obtained from the systems without any orifice.

In a study by Theeuwes (Theeuwes, 1975), a complete membrane controlled delivery of potassium chloride was obtained with orifice diameter in the range of 0.075–0.274 mm. At orifice size of 0.368 mm and above, control over the delivery rate was lost because of significant contribution from diffusion and possibly convection. However, no systematic trends were observed within the orifice diameter between 0.075 and 0.274 mm. Delivery orifices in the osmotic systems can be created with the help of a mechanical drill (Theeuwes et al., 1983; Ozdemir and Sahin, 1997; Sastry, 1997; Sastry, 1997; Sastry, 1998; Sastry and Khan, 1998; Verma and Mishra, 1999; Mohammadi-Samani et al., 2000) but for commercial production scale, tablets need to be produced using a continuous process. Some of the reported processes to create delivery orifices in the osmotic systems are:
a) Laser drilling

Laser drilling is one of the most commonly used techniques to create delivery orifice in the osmotic tablets. In simple words, the tablets in which holes are to be formed are charged in the hopper. The tablets drop by gravity into the slots of the rotating feed wheel and are carried at a predetermined velocity to the passageway forming station. At the passageway forming station, each tablet is tracked by an optical tracking system. If the speed of the moving tablets increases, the hole may become elliptical because of movement of tablets during the laser firing time. To avoid this problem, tracking velocity is synchronized with the velocity at which the tablets are moving. The tracking is accomplished by the rotational oscillation of the mount and tracking mirror of the optical tracking system. During tracking, laser beam is fired in a pulse mode fashion and the beam is transmitted by the optical tracking mechanism onto the surface of the moving tablets and moves with the moving tablets as the mirror oscillates clockwise. The walls of the tablet absorb the energy of the beam and gets heated ultimately causing piercing of the wall and, thus forming passageway. After completion, the tracking mirror oscillates counterclockwise back to its starting position to track the next tablet. It is possible to control the size of the passageway by varying the laser power, firing duration (pulse time), thickness of the wall, and the dimensions of the beam at the wall (Theeuwes et al., 1978; Theeuwes and Ayer, 1978)).

b) Use of pore formers

CPOP are extension of elementary osmotic pump (EOP) and are essentially similar, except that there is no need to create a delivery orifice. Drug release from these types of system takes place through controlled porosity pores formed in situ. Incorporation of water-soluble additives in the membrane wall is the most widely reported method for the formation of pores in CPOP (Haslam and Rork, 1989; Zentner et al., 1990). These water-soluble additives dissolve on coming in contact with water, leaving behind pores in the membrane through which drug release takes place. Drug release from these types of system is independent of pH and has been shown to follow zero-order kinetics (Zentner et al., 1985 and Zentner et al., 1985). Water-soluble additives that can be used for this purpose include dimethyl sulfone, nicotinamide,
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saccharides, amino acids, sorbitol, pentaerythritol, mannitol, organic aliphatic and aromatic acids, including diols and polyols, and other water-soluble polymeric materials (Zentner, 1985). Erodible materials, such as poly(glycolic), poly(lactic) acid, or their combinations can also be used for the purpose of formation of pores in the membrane. These erodible or leachable materials produce one or more passageways with different geometrical shapes. The pores may also be formed in the wall prior to the operation of the system by gas formation within curing polymer solutions, resulting in voids and pores in the final form of the membrane. The pores may also be formed in the walls by the volatilization of components in the polymer solution or by chemical reactions in the polymer solution leading to evolution of gases resulting in the creation of the polymer foams serving as the porous wall from where the drug release can take place (Zentner, 1990).

Zentner and coworkers (Zentner, 1985 and Zentner, 1985) studied drug release from CPOP as a function of water-soluble additive (sorbitol) in the coating membrane and reported that the release rates increased as the sorbitol content in the wall increased from 10 to 50% w/w of cellulose acetate (CA). In a similar study by Appel and Zentner (Haslam and Rork, 1989), potassium chloride release from CPOP was found to increase with increasing pore-former (urea) concentration in the membrane. There was also a critical point (50% urea) above which there was a near linear dependence of release rate on urea content. In devices with less than 50% urea, swelling of the devices was observed whereas devices with more than 50% urea retained their characteristic tablet shape. It was suggested that at lower urea concentration, the pores were not continuous and at higher concentrations greater fraction of the pores were continuous.

In another study (Kelbert and Bechard, 1992), propranolol HCl tablets were coated with CA plasticized with either triethyl citrate (TEC) or triacetin (TA). Membrane permeability to the drug was increased by the addition of HPMC or sucrose. In case of TA plasticized films (at 150% w/w level), tablets with 15% w/w of HPMC had a tendency to swell and the film to rupture, showing insufficient porosity and / or film strength. Sucrose containing films showed a decrease in lag time with an increase in sucrose content. However, higher levels of sucrose (20% w/w and higher) caused
rupturing of CA films. In case of TEC plasticized films (at 120% w/w level), higher levels of sucrose (50% w/w and higher) caused rupturing of CA films in the dissolution medium. In this study, the authors concluded that the film plasticized with TEC and containing 40% sucrose and 10% PEG 8000 were found to provide the best release characteristics in terms of small lag time and extended drug release profile for over 12 h. When sucrose was added to TA and TEC plasticized films, a macroporous membrane was created during exposure to the dissolution fluid because of release of sucrose from the film. The mechanism of drug release was mainly a combination of molecular diffusion and osmosis.

IV. Membrane types and characteristics

The choice of a rate-controlling membrane is an important aspect in the formulation development of oral osmotic systems. The importance of rate-controlling membrane in the drug release can be easily recognized. Drug release from osmotic systems is independent of the pH and agitational intensity of the GI tract to a large extent. This is because of selectively water permeable membrane and effective isolation of dissolution process from the gut environment (Theeuwes et al., 1985; Jerzewski and Chien, 1992). To ensure that the coating is able to resist the pressure within the device, thickness of membrane is usually kept between 200 and 300 mm (Santus and Baker, 1995). However, this may be problematic in cases where the drug is having low osmotic pressure that may contribute to incomplete / slow drug release. Selecting membranes that are having high water permeabilities can be a solution to this problem. One approach that can be utilized is by using composite walls (Theeuwes and Ayer, 1978). The tablet cores are coated with a membrane that has a passageway through the wall for releasing the agent. The wall is formed of a multiplicity of materials comprising a material permeable to an external fluid and substantially impermeable to agent (like CA) and at least one additional material selected from a group of materials that imparts stability to the wall and enhances the permeability of the wall to fluids (like HPMC or hydroxybutyl methylcellulose). Another approach that can be explored is to use a multilayer composite coating around the tablet (Theeuwes and Ayer, 1977). The first layer is a thick microporous film that provides the strength required to withstand the internal pressure, while the second layer is a relatively thin SPM that produces the
osmotic flux. Hence, high delivery rates can be obtained even for drugs with poor water solubility.

Some of the membrane variables that are important in the design of oral osmotic systems are;

a) **Type and nature of polymer**

   Since the membrane in osmotic systems is semipermeable in nature, any polymer that is permeable to water but impermeable to solute can be selected. Some of the polymers that can be used for above purpose include cellulose esters such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, etc. (Guittard *et al.*, 1987); cellulose ethers like ethyl cellulose (Seminoff and Zentner, 1992); and eudragits (Jensen *et al.*, 1995).

   Cellulose acetate (CA) has been widely used to form rate-controlling membranes for osmotic systems. CA films are insoluble, yet semipermeable to allow water to pass through the tablet coating. The water permeability of CA membrane is relatively high and can be easily adjusted by varying the degree of acetylation. As the acetyl content in the CA increases, the CA film permeability decreases, and solvent resistance increases. The permeabilities of these films can be further increased by the addition of hydrophilic flux enhancers. Incorporation of plasticizer in CA coating formulation generally lowers the glass transition temperature, increases the polymer-chain mobility, enhances the flexibility, and affects the permeability of the film (Yuan and Wu, 2000).

   Ethyl cellulose is also widely used in the formation of membranes for oral osmotic systems. However, the water permeability of pure ethyl cellulose membrane is very low that may result in slow release of drugs (Lindstedt, 1989). Nevertheless, drug release from osmotic systems coated with ethyl cellulose membrane can be enhanced by incorporation of water-soluble additives. Addition of HPMC in the coating composition improves the permeability of ethyl cellulose membranes. Tablet cores of potassium chloride coated with a mixture of ethyl cellulose and up to 24% of HPMC, were shown to release the contents mainly through osmotic mechanism (Lindstedt, 1989 and Lindstedt, 1991). In another study (Appel and Zentner, 1991), urea was added to commercially available ethyl cellulose aqueous dispersion (Aquacoat) in an attempt
to increase the release rates of potassium chloride and diltiazem chloride from osmotic tablets. It was found that the drug release from these systems is affected by coating thickness, plasticizer type and concentration, and pore-former level.

The use of eudragit acrylic latexes as membrane formers for osmotic systems has also been reported in the literature (Jensen et al., 1995). Potassium chloride tablets were coated with mixtures of eudragit RS30D and RL30D containing triethyl citrate or acetyl tributyl citrate as plasticizers and urea as a pore-forming agent. The release rate was most affected by the ratio of RS30D to RL30D and the level of urea was found to have effect on lag time and burst strength. The type of plasticizer and amount of pore former were also found to be critical for the desired release rates. The mechanism of release from the formulations containing acetyl tributyl citrate as plasticizer and 100% urea level (of total polymer solids) was found to be primarily osmotic and these formulations exhibited similar release rates in water and phosphate buffer saline pH 7.4.

b) Membrane thickness

Thickness of the membrane has a profound effect on the drug release from osmotic systems. The release rate from osmotic systems is inversely proportional to membrane thickness. Pellets of phenylpropanolamine coated with an aqueous ethyl cellulose based films were found to release the drug mainly through the mechanisms of osmotic pumping and diffusion (Ozturk, 1990). On studying the release as a function of coating thickness, it was found that as the coating thickness increased from 9 to 50 mm, the drug release decreased in an inversely proportional manner. In case of monolithic osmotic tablets of nifedipine, release rates were found to decrease with increase in membrane thickness from 85 to 340 mm (Liu et al., 2000). An increased resistance of the membrane to water diffusion resulted in this effect.

On the other hand, thickness of the membrane in case of asymmetric coating was found to have insignificant effect on drug release. In a study by Herbig et al. (Herbig et al., 1995), release rates were found to be virtually unaffected by the overall membrane thickness in the range of 95–150 mm. The possible reason for this may be the unique structure of the asymmetric membrane coatings in which the porous substrate consists of open pores (void volume between 60 and 90%). Since most of
resistance to the transport is the skin structure rather than the porous substrate of the asymmetric membranes, the thickness of the porous substrate had only a slight effect on the release kinetics.

c) Type and amount of plasticizer

In pharmaceutical coatings, plasticizers or low molecular weight diluents are added to modify the physical properties and improve film-forming characteristics of polymers. Plasticizers can change viscoelastic behavior of polymers significantly. In particular, plasticizers can turn a hard and brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress. These changes also affect the permeability of polymer films. The effect of different types of plasticizers (Triacetin and polyethylene glycols) on the water permeation and mechanical properties of CA was reported by Guo (Guo, 1993). The water permeability of CA films was found to decrease with increasing plasticizer concentration to a minimum and then increases with higher concentration of plasticizer. Low plasticizer concentrations were found to decrease water permeability by their antiplasticization effect. This antiplasticization effect could be because of interaction between the polymer and the plasticizer molecules that decreased the molecular mobility of the polymer. In a similar study (Guo, 1994), Guo investigated the effect of PEG-6000 on the sucrose permeability, void volume, and morphology of CA films. The sucrose permeability was found to decrease with increasing PEG-600 concentration and increase dramatically when they were plasticized by over 30% (w / w). The decrease in sucrose permeability at lower plasticizer concentration was attributed to the antiplasticization effect. The increase in sucrose permeability at higher plasticizer concentration was because of formation of plasticizer channels, results of which were confirmed by the void volume and scanning electron microscopic studies.

Liu et al. (Liu, 1999) studied the influence of nature and amount of plasticizers on the properties of CA membrane including drug release profile, thermal properties, microporosity, and mechanical properties. Hydrophilic plasticizer (PEG-200) was found to increase the drug release, whereas hydrophobic plasticizer triacetin (TA) was found to decrease the drug release from osmotic pumps of nifedipine. Films plasticized
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with PEG developed completely porous structure after 24 h leaching, whereas films plasticized with TA retained their dense structure and porosity was observed only on the surface. At low plasticizer levels (0–5% w/w), it was found that both the ultimate tensile strength and elastic modulus (E) of dry membranes increased as the plasticizer level increased and there was no significant difference because of the nature of plasticizer. However, at higher plasticizer levels (5–40% w/w), both su and E of membranes decreased as plasticizer levels increased.

Drug release from potassium chloride tablets coated with microporous membrane was found to decrease with increasing plasticizer concentrations from 24 to 48% w/w (Appel and Zentner, 1991). Higher release rates were observed with triethyl citrate (TEC) as compared to dibutyl sebacate (DBS) at equal concentrations. These results can be attributed to differences in aqueous solubilities of plasticizers. Since DBS is more hydrophobic than TEC, it decreases the water permeability of the membrane and hence the drug release.

In another study by Okimoto et al. (Okimoto et al., 1999), chlorpromazine (CLP) release from controlled porosity osmotic tablets was found to increase with decreasing amounts of TEC. Drug release was also found to be much faster in formulations containing PEG-400 as a plasticizer than with TEC and was similar to that obtained without a plasticizer. It was concluded that PEG-400 is not a very effective plasticizer. Bindshaedler et al. (Bindschaedler et al., 1987) have described mechanically strong films produced from CA latexes. By proper choice of type of plasticizer and its content in the coating composition, membranes comparable with those obtained from organic solutions can be produced from CA latexes. Water-soluble plasticizers possessing some degree of volatility resulted in films that had high ultimate tensile strength and elasticity modulus. In the series of films prepared with cellulose latexes containing different types and amount of plasticizers, it was found that the films plasticized with volatile additives (ethylene glycol monoacetate and ethylene glycol diacetate) were nearly as strong as those resulting from evaporation of solution in acetone. The majority of volatile plasticizer evaporates during the processing of the film at 60.8°C. On the other hand, more permanent plasticizers (triethyl phosphate and
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diethyl tartarate) are retained in the film and yield membranes that are weak and less resistant. Thus, by proper selection of these volatile plasticizers, it is possible to balance two contradictory requirements, i.e. high mechanical strength of films and initial high amounts of plasticizer. In a similar study by the same group of workers (Bindschaedler et al., 1987), very volatile plasticizers, such as ethylene glycol monoacetate and ethylene glycol diacetate, were used to produce films with low permeability. More permanent plasticizers, such as diethyl tartrate or diacetin, resulted in films that were much more permeable.

2.5 HOT MELT GRANULATION:
Extrusion is broadly elaborated as a technique to “press out”, a process of forming a new material (the extrudate) by forcing it through an orifice or die under controlled conditions, such as temperature, mixing, feed-rate and pressure (Andrews, 2009). Extrusion technology using traditional processing techniques such as aqueous or organic solvent extrusion and spheronization has been in use since quite a long time in the pharmaceutical applications. The major advantage of the Hot-Melt Extrusion (HME) process as compared to traditional process is that drying step is not involved (McGinity et al., 2000). The process involves transfer of a powder blend of active substance, polymer and excipients by a rotating screw through the heated barrel of an extruder. Polymers and excipients such as poly-methacrylate co-polymers, substituted celluloses, polyvinyl pyrrolidone (PVP), poly vinyl acetate (PVA), polyethylene glycol (PEG), polyethylene oxide (PEO) can be used (Williams et al., 2010). All the required inputs may be fed individually or as pre-blended material into the extruder. The process involves intense mixing and agitation resulting in a more uniform dispersion of fine particles and a good content uniformity of the extruded product. Entire procedure is simple, continuous and efficient with fewer mixing steps. The selection of polymer and all the ingredients should be such that they can be processed at a relatively low temperature because of the thermal sensitivity of most drugs. When compared to the traditional processes of aqueous and organic solvent extrusion, HME offers advantages as well as certain disadvantages, but all the limitations with the HME process can be overcome once the process and the desired parameters are finalised. Young et al.
investigated the particle size distribution, morphology and dissolution properties of spherical pellets produced by hot-melt extrusion and spheronization and compared the properties of hot-melt extruded pellets with beads manufactured by a traditional wet-mass extrusion and spheronization method (Young et al., 2007]. Unlike wet-mass extruded pellets, pellets prepared from hot-melt extrusion displayed both a narrow particle size distribution and controlled drug release in dissolution media less than pH 7.4 and theophylline release from the hot-melt extruded pellets was described using the Higuchi diffusion model. Indian patent application 960/MUM/2004 of Sakarkar et al. mentions a novel pelletization process in which an active ingredient and appropriate excipients are blended and formed into spherical particles without the need for water or organic solvents and provides particles that fall within a narrow particle size range (Sakarkar et al., 2004).

**ADVANTAGES**

- Increased solubility and bioavailability of water insoluble compounds
- Solvent free non ambient process
- Economical process with reduced production time, fewer processing steps, and a continuous operation
- Capabilities of sustained, modified and targeted release, (e) better content uniformity in extrudates,
- No requirements on the compressibility of active ingredients,
- Uniform dispersion of fine particles,
- Good stability at changing pH and moisture levels and safe application in humans,
- Reduced number of unit operations and production of a wide range of performance dosage forms, and
- A range of screw geometries (Grunhagen and Muller, 1995; McGnity and KOleng, 2004; Jones, 2008 and Singhal et al., 2011).

**DISADVANTAGES**

- Thermal process (drug/polymer stability), limited polymers, high flow properties of
- Polymers and excipients required and not suitable for relatively high heat sensitive
- Molecules such as microbial species, proteins etc (Grunhagen and Muller, 1995; Singhal, 2011).
2.5.1 Hot-melt extrusion (HME): Process technology

Joseph Brama first invented the extrusion process for the manufacturing of lead pipes at the end of the eighteenth century (James, 2004). Since then, it has been used in the plastic, rubber and food manufacturing industries to produce items ranging from pipes to sheets and bags. With the advent of high throughput screening, currently more than half of all plastic products including bags, sheets, and pipes are manufactured by HME and therefore various polymers have been used to melt and form different shapes for a variety of industrial and domestic applications. The technology (HME) has proven to be a robust method of producing numerous drug delivery systems and therefore it has been found to be useful in the pharmaceutical industry as well (Andrews GP and Jones DS, 2010). Extrusion is the process of pumping raw materials at elevated controlled temperature and pressure through a heated barrel into a product of uniform shape and density (Breitenbach, 2002). Breitenbach first introduced the development of melt extrusion process in pharmaceutical manufacturing operations (Andrews et al., 2009), however, Follonier and his co-workers first examined the hot melt technology to manufacture sustained release polymer based pellets of various freely soluble drugs (Follonier, 1994). HME involves the compaction and conversion of blends from a powder or a granular mix into a product of uniform shape (Breitenbach, 2002). During this process, polymers are melted and formed into products of different shapes and sizes such as plastic bags, sheets, and pipes by forcing polymeric components and active substances including any additives or plasticisers through an orifice or die under controlled temperature, pressure, feeding rate and screw speed (Breitenbach, 2002 and Gryczke, 2006).

2.5.2 Hot-melt extrusion, equipment and process

The HME equipment comprises of an extruder that consists of a feeding hopper, barrel, screw, die, screwdriving unit and a heating/cooling device. Downstream auxiliary equipment and other monitoring tools such as temperature gauges, screw-speed controller, an extrusion torque monitor and pressure gauges used for evaluation of performance and product quality are also an integral part of the HME equipment (Kruder and Kroschwitz, 1985; McGinity and KOleng, 2004 and Andrews et al., 2009).
The downstream equipment is used for collection and shaping of extrudates (films, tablets and pellets). All the materials are resistant to abrasion, corrosion and adhesion. The entire product touching parts (processing unit) are made of stainless steel. During the HME process, a blend of the thermoplastic polymers and other processing aids is fed into the barrel of the extruder through the hopper and conveyed inside the heated barrel by a rotating screw that in turn mixes, compresses and melts the polymeric materials and pumps the molten mass through the die attached to the end of the barrel. The extrudates are subject to further processing by auxiliary downstream devices. An extruder comprises of three parts, feeding section, melting section and metering section (McGinity et al., 2000). Previously, single screw extruders were used and later in the late 1930s, twin screw extruders were introduced. Twin screw extruders may either be co-rotating (rotating in the same direction) or counter-rotating (rotating in opposite direction). Twin screw extruders possess many advantages over single screw extruders such as convenient material feed, better mixing, reduced tendency to overheat the materials and a shorter residence time. The feeding section transfers the feed stock into the barrel of machine and the purpose of the compression/ melting section is to melt the polymer material. Different types of downstream processing equipment are required for the HME process. For extruded film preparations, chill rolls are used to cool down and control the film temperature before it is taken up by the roller (McGinity et al., 2000). Extruder may be of different types (Thoma and Ziegler, 1998) such as screw extruders, radial screen extruders, roll extruders, gear extruders, koller presses, planetary spindle extruder and ram extruder. Screw extruders involve high densification and high drug loading in a low volume of pellets but there is a risk of undesired heat generation due to which chilling of extrusion head is necessary in many cases. These may be axial or radial screw extruders. Axial screw extruders may be single or twin screw extruders as discussed earlier. Co-rotating screws have an advantage of self-cleaning and intermeshing over the counter-rotating screws (Brietenbach, 2002). Twin screw extruder is more suitable than the single screw extruder and is the first choice. Radial low pressure extruders can be used for extrusion of moist, granulated masses. The extrusion die is formed like a screen or a basket and pressure build up is there only
within the extrusion screen. Generally chilling of extrusion head is not required since there is no heat generation. Roll extruders may be used for extrusion of granulated masses. Various combinations of extrusion rolls and pressure rolls or gear rolls may be used. There is a gravity induced forced transport of granules into the gap between rolls. The pressure build up is only inside the extrusion zone and there is almost no heat generation. Figure 2.13 showed unit operations involved in a hot melt extrusion process.

![Figure 2.13: Unit operations involved in a HME process](image)

2.5.2A Equipment: Single screw and twin screw extruder

A single screw extruder consists of one rotating screw positioned inside a stationary barrel at the most fundamental level. In the more advanced twin-screw systems, extrusion of materials is performed by either a co-rotating or counter-rotating screw configuration (Maniruzzaman et al., 2012). Irrespective of type and complexity of the function and process, the extruder must be capable of rotating the screw at a selected predetermined speed while compensating for the torque and shear generated from both the material being extruded and the screws being used. However, regardless of the size
and type of the screw inside the stationary barrel a typical extrusion set up consists of- a motor which acts as a drive unit, an extrusion barrel, a rotating screw and an extrusion die (Chokshi and Zia, 2004). A central electronic control unit is connected to the extrusion unit in order to control the process parameters such as screw speed, temperature and therefore pressure (Whelan and Dunning, 1998). This electronic control unit acts as a monitoring device as well. The typical length diameter ratios (L/D) of screws positioned inside the stationary barrel are another important characteristic to consider whether the extrusion equipment is a single screw or twin screw extruder. The L/D of the screw either in a single screw extruder or a twin screw extruder typically ranges from 20 to 40:1(mm). In case of the application of pilot plant extruders the diameters of the screws significantly ranges from 18-30 mm. In pharmaceutical scale up, the production machines are much larger with diameters typically exceeding 50-60mm (Andrews et al., 2008). In addition, the dimensions of a screw change over the length of the barrel. In the most advanced processing equipment for extrusion, the screws could be separated by clamps or be extended in proportion to the length of the barrel itself. A basic single screw extruder consists of three discrete zones: feed zone, compression and a metering zone (Figure 2.16). Under the compression zone which is basically know as processing zone could be accompanied by few other steps such as mixing, kneading, venting etc (Chokshi and Zia, 2004; Andrews et al., 2008). Figure 2.14 shows schematic diagram of a single screw extruder. Figure 2.15 shows schematic diagram of a twin screw extruder.
The depth along with the pitch of the screw flights (both perpendicular and axial) differ within each zone, generating dissimilar pressures along the screw length. Normally the pressure within the feed zone is very low in order to allow for consistent feeding from the hopper and gentle mixing of API, polymers and other excipients and therefore the screw flight depth and pitch are kept larger than that of other zones. At this stage of the process the pressure within the extruder is very low which subsequently gets increased in the compression zone. This results in a gradual increase in pressure along the length of the compression zone which effectively imparts a high degree of mixing and compression to the material by decreasing the screw pitch and/or
the flight depth (Brietenbach, 2002; Andrews et al., 2008). Moreover the major aim of the compression zone is not only to homogenize but also compress the extrudate to ensure the molten material reaches the final section of the barrel (metering zone) in a form appropriate for processing. Finally the final section which is known as the metering zone stabilizes the effervescent flow of the matrix and ensures the extruded product has a uniform thickness, shape and size. A constant and steady uniform screw flight depth and pitch helps maintain continuous high pressure ensuring a uniform delivery rate of extrudates through the extrusion die and hence a uniform extruded product. The extruder generally consists of one or two rotating screws (either co-rotating or counter rotating) inside a stationary cylindrical barrel. The barrel is often manufactured in sections in order to shorten the residence time of molten materials. The sectioned parts of the barrel are then bolted or clamped together (Figure 2.16). An end-plate die is connected to the end of the barrel which is determined according to the shape of the extruded materials.

![Screw geometry (extrusion).](image_url)

The single screw extrusion system is simple and offers lots of advantages but still does not acquire the mixing capability of a twin-screw machine and therefore is not the preferred approach for the production of most pharmaceutical formulations.
Moreover, a twin-screw extruder offers much greater versatility (process manipulation and optimisation) in accommodating a wider range of pharmaceutical formulations making this set-up much more constructive. The rotation of the screws inside the extruder barrel may either be co-rotating (same direction) or counter-rotating (opposite direction), both directions being equivalent from a processing perspective. A greater degree of conveying and much shorter residence times are achievable with an intermeshing set-up. Furthermore, the use of reverse-conveying and forward-conveying elements, kneading blocks and other intricate designs as a means of improving or controlling the level of mixing required can help the configuration of the screws themselves to be varied (White, 1991). Figure 2.17 shows internal geometry (alignment) of a twin screw extruder.

![Diagram of twin screw extruder](image)

**Figure 2.17: The alignment of a twin screw extruder.**

### 2.6 EVALUATION OF OSMOTIC TABLETS:
#### 2.6.1 Evaluation of Powder

*A. Bulk density:* The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void
volume. Hence, the bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed. The bulk density is expressed in grams per mL (g/mL) although the international unit is kilograms per cubic meter (1 g/mL = 1000 kg/m$^3$) because the measurements are made using cylinders (USP, 2009). It may also be expressed in grams per cubic centimeter (g/cm$^3$).

B. Tapped density: The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. Tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel containing a powder sample. After observing the initial powder volume or weight, the measuring cylinder or vessel is mechanically tapped, and volume or weight readings are taken until little further volume or weight change is observed. The mechanical tapping is achieved by raising the cylinder or vessel and allowing it to drop under its own weight a specified distance by either of three methods as described below. Devices that rotate the cylinder or vessel during tapping may be preferred to minimize any possible separation of the mass during tapping down (USP, 2009).

C. Hausner ratio and Compressibility Index:

The Compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed as described above. As such, they are measures of the powder’s ability to settle, and they permit an assessment of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio (USP, 2009).

Compressibility Index—Calculate by the formula:

$$100\left(\frac{V_0 - V_F}{V_0}\right)$$

$V_0$ = unsettled apparent volume
$V_F$ = final tapped volume
$V_0/V_F$ = Hausner Ratio
2.6.2 Evaluation of Osmotic tablet

A. In vitro Dissolution methodologies:

The in vitro dissolutions were performed using standard USP dissolution methodology (Apparatus 2, rotating paddles, 50 rpm, 37°C, and 900 or 1000 ml of medium). In all cases the samples were assayed by either by a direct UV or an HPLC/UV method obtained active agent studied (Thombre et al., 1999).

The core and coated tablets were evaluated for weight variation. Thickness and diameter of the core and coated tablets was measured using a thickness gauge (Digimatic, Mitutoyo, Japan). Hardness of the randomly selected tablets was tested using hardness tester (TBH-20, Erweka, Germany). Friability of the core tablets was carried out on a friabilator (EF-2, Electrolab, India) for which 20 accurately weighed tablets were used. The developed formulations of glipizide ðn ¼ 6Þ were subjected to release studies using USP-I dissolution apparatus (Electrolab, India) at 100 rev./min. Dissolution medium used was simulated intestinal fluid (SIF, pH 6.8, 1000 ml) maintained at 37 ^ 0.5 8C, which was found to provide sink conditions (solubility of glipizide in SIF was determined to be 0.078 mg/ml). The samples were withdrawn (10 ml) at different time intervals and replaced with an equivalent amount of fresh medium. The dissolution samples, after filtration through 0.45-mm nylon membrane filters, were analyzed using a validated UV spectroscopic method at 276 nm (Verma et al., 2002). However, as the excipients present in Glucotrol XL interfered with the UV method, it was ruled out for analysis. HPLC method was developed and used for the analysis of dissolution samples of Glucotrol XL (Verma and Garg, 2004).

Dissolution study was conducted in 900 ml pH 6.8 phosphate buffer maintained at 37° C using USP 27 apparatus II (paddle) at 75 rpm (VK 7000, Vankel, Cary, NC). Additionally, dissolution of the selected HPMC formulation was evaluated in pH 6.8 phosphate buffer at 100 rpm and in pH 2 HCl/KCl buffer and pH 4.4 acetate buffer at 75 rpm. In cases of tablet sticking to the bottom of the dissolution vessel a single ring-mesh device was placed within the vessel in order to provide unconstrained hydration and swelling in all directions (Durig and Fassihi, 2000). Samples were taken automatically and passed through a 35 _m filter. UV absorbance was determined at 276
nm (Cary-50 UV–vis spectrophotometer), compared against the calibration curve, and % dissolved versus time profiles were constructed (Jamzad and Fassihi, 2006).

A Distek_ dissolution system (model 2100B, North Brunswick, NJ, USA) and an Erweka_ dissolution system (model DT6, Erweka GmbH, Heusenstamm, Germany) were used. In all cases, the volume of the release medium was 500 ml. After confirming that rotational speed of the paddle did not affect the release rates in SGF (for speeds between 50 and 150 rpm), experiments in FaSSIF and SCoF were performed with the paddle rotating at 100 rpm. Three-milliliter samples were withdrawn (with replacement) and immediately filtered through a 0.45 lm Teflon filter (Titan_ filter 0.45 lm (Scientific Resources Inc., NJ, USA). Absence of drug adsorption onto the filters was confirmed in preliminary experiments. An appropriate volume of the filtrate was analyzed with HPLC (Fotaki et al., 2009)

a) Dissolution method by Office of generic drugs (OGD), USFDA:
Dissolution was conducted through 16 h at pH 7.5 in simulated intestinal fluid (SIF) without pancreatin (USP31-NF26, 2013).

b) In vivo evaluation of osmotic tablets:
The newer second-generation sulfonylureas (eg, glipizide) are preferred by more physicians in the management of type II diabetes mellitus because they exhibit greater potency, rapid metabolism with no significant active metabolites, rapid excretion, and noncompetitive binding to serum proteins.2*3,21 In this study, the pharmacokinetic properties of two different glipizide formulations, Sucrazide and Minidiab, were assessed. After oral administration of the single dose (5mg tablet) the mean values for $C_{\text{max}}$, $T_{\text{max}}$, AUC, half-life, and elimination constants were similar for both brands with no statistical differences between Sucrazide and Minidiab. Glipizide was rapidly and completely absorbed from the gastrointestinal tract and extensively bound to plasma proteins. The individual distribution of the peak values covered the period of 1.5 to 3.5 hours for Sucrazide and 1.5 to 4 hours for Minidiab. The values of plasma levels for some subjects showed secondary peaks for both brands that may have been due to the reabsorption process. Comparison between the formulations is based on the overall $C_{\text{max}}$, $T_{\text{max}}$, and AUC. Therefore, the presence or absence of a double peak is not
expected to affect the accuracy of the measurements. Comparable glipizide pharmacokinetic data have been previously reported by many investigators. As is the case with all bioavailability and pharmacokinetic studies, minor differences may be attributed to individual variation in response to different formulations (Zmeili et al., 1995).

Draft guidance by USFDA (August 2010) recommends bioequivalence studies to be carried out in single-dose, two-way crossover design for glipizide extended release tablets in healthy males and nonpregnant females of general population. To avoid hypoglycemic episodes in healthy volunteers, each dose in the study should be administered with 240 mL of a 20% glucose solution in water, followed by 60 mL of the 20% glucose solution administered every 15 minutes for up to 4 hours after dosing.

A rise in immunoreactive insulin and decrease in blood glucose concentration level occur within 30 min of ingestion of glipizide on a weight basis. Glipizide is approximately 100 times more potent than tolbutamide. Gastrointestinal absorption of glipizide is uniform, rapid and essentially complete, providing peak plasma level concentrations about 1–3 h after a single oral dose. Normal subjects demonstrate an elimination half-life ranging from about 2 to 4 h after both intravenous and oral administration. In addition, glipizide does not accumulate in the plasma following repeated oral dosing (Kadhe G and Arasan RE, 2002).

2.7 GLIPIZIDE

Glipizide is an oral blood-glucose-lowering drug of the sulfonylurea class. The chemical Abstracts name of glipizide is 1-cyclohexyl-3-[[p-[2-(5-methylpyrazinecarboxamido)ethyl] phenyl]sulfonyl]urea. The molecular formula is C21H27N5O4S; the molecular weight is 445.55; the structural formula is shown below (Figure 2.18):
Figure 2.18: Chemical structure of Glipizide.

The various physiochemical properties of glipizide are listed in Table 2.4.

Table 2.4: Physiochemical parameters of glipizide

<table>
<thead>
<tr>
<th>Chemical IUPAC Name</th>
<th>1-cyclohexyl-3-[[p-[2-(5-methylpyrazinecarboxamido)ethyl]phenyl]sulfonyl]urea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Formula</td>
<td>C21H27N5O4S</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>445.55 g/mol</td>
</tr>
<tr>
<td>Melting Point</td>
<td>208-209°C</td>
</tr>
<tr>
<td>Solubility</td>
<td>It is insoluble in water and alcohols, but soluble in 0.1 NaOH; it is freely soluble in dimethylformamide.</td>
</tr>
<tr>
<td>State</td>
<td>Solid</td>
</tr>
<tr>
<td>Drug Category</td>
<td>Oral blood-glucose-lowering drug of the sulfonylurea class</td>
</tr>
<tr>
<td>Half Life(T$_{1/2}$)</td>
<td>2 to 5 hours</td>
</tr>
<tr>
<td>Protein binding</td>
<td>98 – 99%</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>00% (regular formulation)</td>
</tr>
<tr>
<td></td>
<td>90% (extended release)</td>
</tr>
</tbody>
</table>

### 2.7.1 Pharmacological Properties

Glipizide is an oral blood glucose lowering drug of the sulphonylurea class. The primary mode of action of glipizide is the stimulation of insulin secretion from the beta-
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cells of pancreatic islet tissue. Stimulation of insulin secretion by glipizide in response to a meal is of major importance. Fasting insulin levels are not elevated even on long-term glipizide administration, but the post-prandial insulin response continues to be enhanced after at least 6 months of treatment. The insulinotropic response to a meal occurs within 30 minutes after oral dose of glipizide in diabetic patients, but elevated insulin levels do not persist beyond the time of the meal challenge. There is also increasing evidence that extrapancreatic effects involving potentiation of insulin action form a significant component of the activity of glipizide.

Blood sugar control persists for up to 24 hours after a single dose of glipizide, even though plasma levels have declined to a small fraction of peak levels by that time (Medicines.org.uk, 2013).

2.7.2 Effects on Blood Glucose

The effectiveness of Glucotrol XL (glipizide extended release) Extended Release Tablets in type 2 diabetes at doses from 5–60 mg once daily has been evaluated in 4 therapeutic clinical trials each with long-term open extensions involving a total of 598 patients. Once daily administration of 5, 10 and 20 mg produced statistically significant reductions from placebo in hemoglobin A\(_1\)C, fasting plasma glucose and postprandial glucose in patients with mild to severe type 2 diabetes. In a pooled analysis of the patients treated with 5 mg and 20 mg, the relationship between dose and Glucotrol XL (glipizide extended release)’s effect of reducing hemoglobin A\(_1\)C was not established. However, in the case of fasting plasma glucose patients treated with 20 mg had a statistically significant reduction of fasting plasma glucose compared to the 5 mg-treated group (Rxlist.com, 2013).

2.7.3 Pharmacokinetic Properties

Gastrointestinal absorption of glipizide in man is uniform, rapid and essentially complete. Peak plasma concentrations occur 1-3 hours after a single oral dose. The half-life of elimination ranges from 2-4 hours in normal subjects, whether given intravenously or orally. The metabolic and excretory patterns are similar with the two routes of administration, indicating that first-pass metabolism is not significant.
Glipizide does not accumulate in plasma on repeated oral administration. Total absorption and disposition of an oral dose was unaffected by food in normal volunteers, but absorption was delayed by about 40 minutes. Thus, glipizide was more effective when administered about 30 minutes before, rather than with, a test meal in diabetic patients. Protein binding was studied in serum from volunteers who received either oral or intravenous glipizide and found to be 98-99% one hour after either route of administration. The apparent volume of distribution of glipizide after intravenous administration was 11 litres, indicative of localisation within the extracellular fluid compartment. In mice, no glipizide or metabolites were detectable autoradiographically in the brain or spinal cord of males or females, nor in the foetuses of pregnant females. In another study, however, very small amounts of radioactivity were detected in the foetuses of rats given labelled drug.

The metabolism of glipizide is extensive and occurs mainly in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Less than 10% unchanged glipizide is found in urine (Medicines.org.uk, 2013).