CHAPTER 1

Introduction
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1.1 Introduction to OCDDS

Novel drug delivery systems (NDDS) are the key area of pharmaceutical research and development. The reason is relatively low development cost and time required for introducing a NDDS ($20-50 million and 3-4 years, respectively) as compared to new chemical entity (approximately $500 million and 10-12 years, respectively). The focus in NDDS includes design of NDDS for new drugs on one hand and on the other NDDS for established drugs to enhance commercial viability. (Verma and Garg 1-14)

During the past three decades significant advances have been made in the area of NDDS. Among the various NDDS available in market, controlled drug delivery system has taken major role in the pharmaceutical development. This is due to improved patient convenience and compliance, reduction in fluctuation in steady state plasma level so decrease intensity of local or systematic side effects and increase safety margin of high potency drugs. In control release (CR) systems, there is maximum utilization of drug enabling reduction in total amount of dose administered and possibility of delivering drugs having short biological half-life. (Prescott and Nimmo 1-11)

Various designs are available to control or modulate the drug release from a dosage forms. Majority of oral CR dosage forms fall in the category of matrix, reservoir or osmotic systems. Conventional matrix or reservoir type formulations exhibits problem of bioavailability fluctuations due to gastric pH variations. Moreover, the release of drugs from these systems is affected by the hydrodynamic conditions of the body.

Osmotically controlled drug delivery systems (OCDDS) is one of the most promising drug delivery technology that use osmotic pressure as a driving force for controlled delivery of active agents. (Verma, Mishra and Garg 695-708) Drug release from OCDDS is independent of pH and hydrodynamic conditions of the body because of the semipermeable nature of the rate-controlling membrane and the design of deliver orifice used in osmotic systems, so a high degree of In vitro/In vivo correlation is achieved. It is also possible to obtain higher release rates through these systems than through other diffusion-based systems. (Wright et al. 1-10; Baker and Baker) There are over 240 patented osmotic drug delivery systems. They are also known as GITS (gastro-intestinal therapeutic system) and today, different types of osmotic pumps, of various drugs, are available in the market to fulfil patient’s need and requirement. (Verma, Krishna and Garg 7-27) This chapter mainly focuses on the theoretical
aspects, basic components of OCDDS, factors affecting OCDDS, different technologies, marketed products and future aspects of OCDDS.

1.1.1 Key Milestones in OCDDS development

1.1.1.1 Rose-Nelson Pump

About 75 years after discovery of the osmosis principle, it was first used in the design of drug delivery systems. (Rose and Nelson 415) Rose and Nelson, the Australian scientists, were initiators of osmotic drug delivery. In 1955, they developed an implantable pump, which consisted of three chambers: a drug chamber, a salt chamber contains excess solid salt, and a water chamber. The drug and water chambers are separated by rigid semipermeable membrane. The difference in osmotic pressure across the membrane moves water from the water chamber into the salt chamber. The volume of the salt chamber increases because of this water flow, which distends the latex diaphragm separating the salt and drug chambers, thereby pumping drug out of the device. The design and mechanism of this pump is comparable to modern push-pull osmotic pump. The major disadvantage of this pump was the water chamber, which must be charged before use of the pump. The pumping rate of this push-pull pump is given by the equation.

\[ \frac{dM}{dt} = \frac{dV}{dt} \times c \]

Where, \( \frac{dM}{dt} \) is the drug release rate, \( \frac{dV}{dt} \) is the volume of water into the salt chamber, and \( c \) is the concentration of drug in the drug chamber.

In general, this equation, with or without some modifications, applies to all other type of osmotic systems.

1.1.1.2 Higuchi-Leeper Pump

Several simplifications in Rose-Nelson pump were made by Alza Corporation in early 1970s. The Higuchi-Leeper pump is modified version of Rose-Nelson pump. It has no water chamber, and the device is activated by water imbibed from the surrounding environment. The pump is activated when it is swallowed or implanted in the body. This pump consists of a rigid housing, and the semi permeable membrane is supported on a perforated frame. It has a salt chamber containing a fluid solution with excess solid salt. Recent modification in Higuchi-Leeper pump accommodated pulsatile drug delivery. The pulsatile release was achieved by the production of a critical pressure at which the delivery orifice opens and releases the drug. (Higuchi and Leeper; Higuchi and Leeper)
1.1.1.3 Higuchi-Theeuwes Pump

In the early 1970s, Higuchi and Theeuwes developed another, even simpler variant of the Rose-Nelson pump. As with the Higuchi-Leeper pump, water to activate the osmotic action of the pump is obtained from the surrounding environment. In the Higuchi-Theeuwes device, however, the rigid housing is dispensed with and the membrane acts as the outer casing of the pump. This membrane is quite sturdy and is strong enough to withstand the pumping pressure developed inside the device. The device is loaded with the desired drug prior to use. When the device is placed in an aqueous environment, release of the drug follows a time course set by the salt used in the salt chamber and the permeability of the outer membrane casing. Most of the Higuchi-Theeuwes pumps use a dispersion of solid salt in a suitable carrier for the salt chamber of the device. (Malaterre et al. 311-23)

Figure 1.1: Higuchi-Leeper Pump and Higuchi-Theeuwes Pump (Malaterre et al. 311-23)
1.1.2 Advantages of Osmotic Drug Delivery System (Verma, Arora and Garg)

Apart from the general advantages of controlled drug delivery systems, osmotic pumps have certain unique advantages, as follows:

1. Delivery of drug from osmotic pumps can be designed to follow true zero-order kinetics.
2. Delivery may be delayed or pulsed, if desired.
3. Drug release from osmotic pumps is independent of the gastric pH and hydrodynamic conditions of the body.
4. Higher release rates are possible from osmotic systems than with conventional diffusion based drug delivery systems.
5. The delivery rate of drug(s) from these systems is highly predictable and programmable by modulating the release control parameters.
6. A high degree of In vitro/In vivo correlation can be obtained from osmotic pumps.
7. Drug release from the osmotic systems is minimally affected by the presence of food.

1.1.3 Basic Concepts

1.1.3.1 Principle of Osmosis

Osmosis can be defined as the spontaneous movement of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal semipermeable membrane, which is permeable only to the solvent but impermeable to the solute. The pressure applied to the higher-concentration side to inhibit solvent flow is called the osmotic pressure.

In 1748, Abbe Nollet first reported the osmotic process. In 1877, Pfeffer separated a sugar solution from water using a sugar-impermeable membrane and quantified the water transport.

In 1886, Van’t Hoff identified an underlying proportionality between osmotic pressure, concentration, and temperature in Pfeffer’s experiment.

According to Van’t Hoff’s equation, the osmotic pressure of a dilute solution will be equal to the pressure that the solute would exert if it was a gas, occupying the same volume.

\[ \pi V = nRT \]  

(1)
where, $\pi$ stands for osmotic pressure in atm, $V$ stands for volume of solution in liters, $n$ stands for the number of moles of solute, $R$ stands for gas constant (0.082 liter atm/mole deg), and $T$ stands for absolute temperature. (Li and Jasti 203-29)

### 1.1.3.2 Delivery Rate

The OCDDS consists of an osmotic core containing drug and an osmogen surrounded by a semipermeable membrane with an aperture. A system with constant internal volume delivers a volume of saturated solution equal to the volume of solvent uptake in any given time interval. Excess solids present inside a system ensure a constant delivery rate of solute. The rate of delivery generally follows zero-order kinetics and declines after the solute concentration falls below saturation. (Martin, Swarbrick and Cammarata 143-60) The solute delivery rate from the system is controlled by solvent influx through the semipermeable membrane.

The osmotic flow of the liquid depends on the osmotic and hydrostatic pressure differences across the semipermeable membrane of the system. This phenomenon is the basic feature of nonequilibrium thermodynamics, which describes the volume flux across the semipermeable membrane. (Lakshminarayanaiah 247–48)

### 1.1.4 Formulation Considerations of OCDDS

Generally OCDDS consists of two parts: One of this is core and another is semipermeable membrane (coating). Core of OCDDS consists of drugs, osmotic agents, hydrophilic and hydrophobic polymers, flux regulating agents, wicking agents, while coating includes polymer, coating solvent, plasticizers and poreforming agents.

#### 1.1.4.1 Drugs

Drugs which have short biological half-life (2-6hr) and which are used for prolonged treatment are ideal candidate for osmotic systems. Various drug candidates such as Diltiazem hydrochloride (McClelland et al. 88-92), Carbamazepine, Metoprolol (Bauer, Kaik and Kaik 339-46), Oxprenolol, Nifedipin (Swanson et al. 3-9), Glipizide (Thombre, DeNoto and Gibbes 333-41), etc are formulated as osmotic delivery.

#### 1.1.4.2 Osmotic Agents

Osmotic agents maintain a concentration gradient across the membrane. They also generate a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation. Osmotic components usually are ionic compounds consisting of either inorganic
salts or hydrophilic polymers. (Gohel M.C ) Different type of osmogens can be used for such systems are categorized in Table 1.1.

1.1.4.3 Hydrophilic and Hydrophobic Polymers

These polymers are used in the formulation development of osmotic systems for making drug containing matrix core. The selection is based on the solubility of the drug as well as the amount and rate of drug to be released from the pump.

The polymers are of either swellable or non-swellable nature. Mostly, swellable polymers are used for the pumps containing moderately water-soluble drugs, since they increase the hydrostatic pressure inside the pump due to their swelling nature. The non-swellable polymers are used in case of highly water-soluble drugs.

Ionic hydrogels such as sodium carboxymethyl cellulose are preferably used because of their osmogenic nature. (Patel et al. 88-94)

1.1.4.4 Flux Regulating agents

Delivery systems can be formulated to regulate the permeability of the fluid by incorporating flux-regulating agents in the layer. Hydrophilic substances improve the flux, whereas hydrophobic materials tend to decrease the flux. Insoluble salts or insoluble oxides, which are substantially water-impermeable materials, also can be used for this purpose. (Patel et al. 88-94)

1.1.4.5 Wicking agent

A wicking agent is defined as a material with the ability to draw water into the porous network of a delivery device. A wicking agent is of either swellable or non-swellable nature. The function of wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of increased surface area. (Patel et al. 88-94)

1.1.4.6 Semipermeable Membrane

An important part of the osmotic drug delivery system is the semipermeable membrane housing. Therefore, the polymeric membrane selection is important to the osmotic delivery formulation. The membrane should possess certain characteristics, such as

- Sufficient wet strength and water permeability
- Should be biocompatible
- Rigid and non-swelling
Should be sufficient thick to withstand the pressure within the device.

Any polymer that is permeable to water but impermeable to solute can be used as a coating material in osmotic devices. Some of the polymers that can be used for above purpose are included in Table 1.1. (Gohel M.C; Jensen et al. 530-33; Guittard et al.; Seminoff and Zentner)

1.1.4.7 Coating solvent

Solvents suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents that do not adversely harm the core, wall and other materials. The typical solvents used are listed in Table 1.1. The mixtures of solvents such as acetone-methanol (80:20), acetone-ethanol (80:20), acetone-water (90:10), methylene chloride-methanol (79:21), methylene chloride-methanol-water (75:22:3) etc. can be used. (Vyas and Khar 477-501)

1.1.4.8 Plasticizers

Plasticizers lower the temperature of the second order phase transition of the wall or the elastic modules of the wall and also increase the workability, flexibility and permeability of the fluids.

Generally from 0.001 to 50 parts of a plasticizer or a mixture of plasticizers are incorporated in to 100 parts of wall forming materials.

Suitable polymers should have a high degree of solvent power for the materials, compatible with the materials over both the processing and the temperature range, exhibit permanence as seen by their strong tendency to remain in the plasticized wall, impart flexibility to the materials and should be non-toxic. Examples of plasticizers are included in Table 1.1.

1.1.4.9 Pore forming agents

These agents are particularly used in the pumps developed for poorly water-soluble drug and in the development of controlled porosity or multiparticulate osmotic pumps. These pore forming agents cause the formation of microporous membrane. The microporous may be formed in situ by a pore former by its leaching during the operation of the system. The pore-formers can be inorganic or organic and solid or liquid in nature (Table 1.1).

Pores may also be formed in the wall by the volatilization of components in a polymer solution or by chemical reactions in a polymer solution which evolves gases prior to
application or during application of solution to the core mass resulting in the creation of polymer foams serving as the porous wall.

The pore-formers should be non-toxic, and on their removal, channels should be formed. The channels become a transport path for fluid. (Vyas and Khar 477-501)

Table 1.1: Basic components of OCDDS

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<th>Components</th>
<th>Examples</th>
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<tr>
<td><strong>Osmotic Agents</strong></td>
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<tr>
<td>Water-soluble salts of inorganic acids</td>
<td>Magnesium chloride or sulfate; lithium, sodium, or potassium chloride; sodium or potassium hydrogen phosphate</td>
</tr>
<tr>
<td>Water-soluble salts of organic acids</td>
<td>Sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>Mannose, sucrose, maltose, lactose</td>
</tr>
<tr>
<td>Water-soluble amino acids and organic polymeric osmogents</td>
<td>Sodium carboxymethyl cellulose, Hydroxypropylmethyl cellulose, Hydroxyethylmethylcellulose, Methylcellulose, Polyethylene oxide, Polyvinyl pyrrolidone etc.</td>
</tr>
<tr>
<td><strong>Hydrophilic and Hydrophobic Polymers</strong></td>
<td>Hydrophilic polymers</td>
</tr>
<tr>
<td>Hydroxyl ethylcellulose, carboxy methylcellulose, hydroxyl propyl methylcellulose, high molecular weight poly(vinyl pyrrolidone)</td>
<td>Hydrophilic substances Polyethyleneglycols (300 to 6000 Da), polyhydric alcohols, polyalkylene glycols</td>
</tr>
<tr>
<td><strong>Flux Regulating agents</strong></td>
<td></td>
</tr>
<tr>
<td>Ethyl cellulose and wax materials</td>
<td>Hydrophobic materials Phthalates substituted with an alkyl or alkoxy (e.g., diethyl phthalate or dimethoxy ethylphthalate)</td>
</tr>
<tr>
<td><strong>Wicking agent</strong></td>
<td></td>
</tr>
<tr>
<td>Colloidal silicon dioxide, kaolin, titanium dioxide, alumina, niacinamide, sodium lauryl sulphate (SLS), poly (vinyl pyrrolidone), m-pyrol, bentonite, magnesium aluminium silicate, polyester and polyethylene</td>
<td>Cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, ethyl cellulose and eudragits</td>
</tr>
</tbody>
</table>
### Coating solvent
Methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, water

### Plasticizers
Dialkyl phthalates and other phthalates, trioctyl phosphates and other phosphates, alkyl adipates, triethyl citrate and other citrates, acetates, propionates, glycolates, glycerolates, myristates, benzoates, sulphonamides and halogenated phenyls

### Pore forming agents
- **Alkaline metal salts** such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium sulphate, potassium phosphate etc.,
- **Alkaline earth metals** such as calcium chloride, and calcium nitrate,
- **Carbohydrates** such as sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol and diols
- Polyols such as polyhydric alcohols and polyvinyl pyrrolidone

### 1.1.5 Factors Influencing the Design of Osmotic Controlled Drug Delivery Systems

#### 1.1.5.1 Drug Solubility

For the osmotic system, solubility of drug is one of the most important parameters affecting drug release kinetics from osmotic pumps. The kinetics of osmotic drug release is directly related to the drug solubility within the drug core. Assuming a tablet core of pure drug, the fraction of core released with zero-order kinetics is given by equation (Theeuwes 1987-91)

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

Where, \(F(z)\) is the fraction released by zero-order kinetics, \(S\) is the drug’s solubility (g/cm³), and \(\rho\) is the density (g/cm³) of the core tablet. Drugs with a density of unity and the solubility of \(\leq 0.05\) g/cm³ would be released with \(\geq 95\%\) zero-order kinetics, according to Eq. (1).

At the same time, 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 prohibit them from incorporation into an osmotic pump (Verma, Krishna and Garg 7-27)

Candidate drugs for osmotic delivery have water solubility in the range 50–300 mg/ml. Some of the approaches that have been used to modulate drug solubility within the core include (1) co-compression of the drug with excipients, which modulate the drug’s solubility within the
core (McClelland et al. 88-92; Zentner, McClelland and Sutton 237-43; Herbig et al. 127-36; Verma and Mishra 74-75; Verma and Garg 513-25); (2) use of effervescent mixtures to speed up the release of poorly soluble drug from the orifice; (3) use of various cyclodextrin derivatives to solubilize poorly water soluble drug (Okimoto et al. 1562-68; Okimoto et al. 549-54; Okimoto, Rajewski and Stella 29-38); (4) use of alternative salt form that has optimum water solubility (Theeuwes F 69S-76S); (5) use of encapsulated excipients (Thombre, DeNoto and Gibbes 333-41); (6) use of lyotropic crystals (Curatolo); (7) use of wicking agents (Rudnic EM).

1.1.5.2 Delivery orifice

Majority of osmotic delivery systems contain at least one delivery orifice (preformed or formed in situ) in the membrane for drug release.

Size of delivery orifice must be optimized to control the drug release from osmotic system. The size of the delivery orifice must be smaller than a maximum size $S_{\text{max}}$ to minimize drug delivery by diffusion through the orifice. Furthermore, the area must be sufficiently large, above a minimum size $S_{\text{min}}$, to minimize hydrostatic pressure buildup in the system. Otherwise, the hydrostatic pressure can destroy the membrane and affect the zero-order delivery rate. Therefore, the cross-sectional area of the orifice should be maintained between the minimum and maximum values (Good WR 1-39; Theeuwes F)

Methods to create a delivery orifice in the osmotic tablet coating are:

A. Laser drill

This technology is well established for producing sub-millimeter size hole in tablets. Normally, CO$_2$ laser beam (with output wavelength of 10.6$\mu$) is used for drilling purpose. It offers excellent reliability characteristics at low costs (Gaebler 1-7)

Figure 1.2: Laser Drilling Process (Gaebler 1-7)
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.

**B. Indentation that is not covered during the coating process (Liu and Wang 298-302)**

Indentation is made in core tablets by using modified punches having needle on upper punch. This indentation is not covered during coating process which acts as a path for drug release in osmotic system.

**C. Use of leachable substances in the semipermeable coating**

Incorporation of water-soluble additives in the membrane wall is the most widely reported method for the formation of pores in CPOP take place. These water-soluble additives dissolve on coming in contact with water, leaving behind pores in the membrane through which drug release takes place(Zentner, Rork and Himmelstein 217-29).

**D. Systems with passageway formed in situ**

The system consists of a tablet core of the drug along with water-swellable polymer and osmotic agents, which is surrounded by a rate-controlling membrane. In contact with the aqueous environment, water is imbibed osmotically at a controlled rate and water swellable polymer expands as the osmotic agents dissolves and increases the osmotic pressure inside the tablet. This results in a rate-controlled slight expansion of the partially hydrated core. The expansion of core causes a small opening to form at the edge of the tablet (weakest point in the membrane) from where the formulation is released.(Chen, Lee and Xie)

**1.1.5.3 Osmotic pressure**

The next release-controlling factor that must be optimized is the osmotic pressure gradient between inside the compartment and the external environment.

The release rate of a drug from an osmotic system is directly proportional to the osmotic pressure of the core. The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment. If a saturated solution of the drug does not possess sufficient osmotic pressure, an additional osmotic agent must be added to the core formulation. The addition of carbonate or bicarbonate salt to the drug chamber offers an advantage since the effervescent action prevents the precipitated drug from blocking the delivery orifice in the tablet.(Jerzewski RL 225-53)
Polymeric osmogents 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.

Table 1.2: Osmotic pressures of saturated solution of commonly used osmogents

<table>
<thead>
<tr>
<th>Compound or Mixture</th>
<th>Osmotic Pressure (atm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose-Fructose</td>
<td>500</td>
</tr>
<tr>
<td>Dextrose-Fructose</td>
<td>450</td>
</tr>
<tr>
<td>Sucrose- Fructose</td>
<td>430</td>
</tr>
<tr>
<td>Mannitol- Fructose</td>
<td>415</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>356</td>
</tr>
<tr>
<td>Fructose</td>
<td>335</td>
</tr>
<tr>
<td>Lactose-Sucrose</td>
<td>250</td>
</tr>
<tr>
<td>Potassium Chloride</td>
<td>245</td>
</tr>
<tr>
<td>Lactose-Dextrose</td>
<td>225</td>
</tr>
<tr>
<td>Mannitol-Dextrose</td>
<td>225</td>
</tr>
<tr>
<td>Dextrose-Sucrose</td>
<td>190</td>
</tr>
<tr>
<td>Mannitol-Sucrose</td>
<td>170</td>
</tr>
<tr>
<td>Sucrose</td>
<td>150</td>
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<tr>
<td>Mannitol-Lactose</td>
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<tr>
<td>Dextrose</td>
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<tr>
<td>Potassium Sulfate</td>
<td>39</td>
</tr>
<tr>
<td>Mannitol</td>
<td>38</td>
</tr>
<tr>
<td>Sodium Phosphate Tribasic.12H$_2$O</td>
<td>36</td>
</tr>
<tr>
<td>Sodium Phosphate Dibasic.7H$_2$O</td>
<td>31</td>
</tr>
<tr>
<td>Sodium Phosphate Dibasic.12H$_2$O</td>
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</tr>
<tr>
<td>Sodium Phosphate Dibasic Anhydrous</td>
<td>29</td>
</tr>
<tr>
<td>Sodium Phosphate Monobasic.H$_2$O</td>
<td>28</td>
</tr>
</tbody>
</table>
1.1.5.4 Semi permeable membrane(Theeuwes 1987-91)

Some of the membrane variables that are important in the design of oral osmotic system are:

**A. Type and nature of polymer**

Any polymer permeable to water but impermeable to solute can be selected. Some of the polymers that can be used for above purpose included in Table 1.1.

**B. Membrane thickness**

Thickness of the membrane has a marked effect on the drug release from osmotic system, which is inversely proportional to each other.

**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.

### 1.1.6 Osmotic Pumps in Drug Delivery

Oral osmotic drug delivery systems are principally classified as follows (Table 1.3).

**Table 1.3: Classification of Osmotic Drug Delivery Systems**

<table>
<thead>
<tr>
<th>Single Chamber Osmotic Pumps</th>
<th>Elementary osmotic pump</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple Chamber Osmotic Pumps</strong></td>
<td>Osmotic pump with Non-expanding second chamber</td>
</tr>
<tr>
<td></td>
<td>Push Pull Osmotic pump (PPOP)</td>
</tr>
<tr>
<td>Modified OCDDS</td>
<td>Controlled Porosity Osmotic Pump (CPOP)</td>
</tr>
<tr>
<td></td>
<td>Osmotic Pump for insoluble drugs</td>
</tr>
<tr>
<td></td>
<td>Multiparticulate delayed release systems</td>
</tr>
<tr>
<td></td>
<td>Monolithic osmotic pumps</td>
</tr>
<tr>
<td></td>
<td>Colon targeted Oral osmotic system (OROS-CT)</td>
</tr>
<tr>
<td></td>
<td>Sandwiched Osmotic tablets (SOTS)</td>
</tr>
<tr>
<td></td>
<td>Liquid oral osmotic system (L-OROS)</td>
</tr>
<tr>
<td></td>
<td>Osmotic bursting osmotic pump</td>
</tr>
<tr>
<td></td>
<td>OROS Push-Stick Technology</td>
</tr>
<tr>
<td></td>
<td>Asymmetric membrane osmotic system</td>
</tr>
<tr>
<td></td>
<td>Telescopic capsule for delayed release</td>
</tr>
</tbody>
</table>
1.1.6.1 Single Chamber Osmotic Pumps

A. Elementary Osmotic Pump (EOP)

In 1975, Theeuwes further simplified the Rose-Nelson pump and developed a system known as the elementary osmotic pump (EOP), which is shown schematically in Figure 1.3.

![Elementary Osmotic Pump](image)

**Figure 1.3: Elementary Osmotic Pump**

Elementary osmotic pump consists of an osmotic core (containing drug with or without an osmagent) coated with a semipermeable membrane (SPM) and a small orifice is created in the membrane. (Theeuwes 1987-91; Thakor et al. 771-75)

**Mechanism of drug release**

The dosage form, after coming in contact with the aqueous fluids, imbibes water through the SPM because of the osmotic pressure gradient and forms a saturated solution inside the device. This increases the hydrostatic pressure inside the tablet and forces the saturated drug solution through the orifice present in the membrane. The drug delivery process continues at a constant rate until the entire osmotically active solid agent inside the tablet has been dissolved and only a solution filled coating membrane is left. This residual dissolved agent continues to be delivered at a declining rate, until the osmotic pressure inside and outside the tablet is equal.

**Advantage**

These systems are suitable for delivery of drugs having moderate water solubility. The delivery rate can be modulated by adjusting membrane area, thickness, and its permeability to water. In certain cases, it is required to eliminate the initial time lag by over-coating the membrane with a drug/polymer film, which delivers an initial loading dose.
1.1.6.2 Multiple Chambers Osmotic Pumps

A. Osmotic Pump with Non-Expanding Second Chamber

These multi-chamber devices comprise of systems containing a non-expanding second chamber. The purpose of second chamber is either dilution of drug solution leaving the device (particularly useful in handling drugs with high incidence of GI irritation) or simultaneous delivery of two drugs. Relatively insoluble drugs can also be delivered by formulating them in this type of device. (Verma, Mishra and Garg 695-708)

B. Push-Pull Osmotic Pump (PPOP)

Push–pull osmotic pump (PPOP) is a bilayer tablet coated with a SPM. It consists of two compartments separated by an elastic diaphragm (optional). The upper compartment (drug compartment) contains the drug along with osmotically active agents, while the lower compartment (push compartment) contains the polymeric osmotic agents (Figure 1.4). The drug layer accounts for 60–80% of the tablet weight, while the osmotic polymer layer accounts for 20–40%. (Cortese and Theeuwes; Swanson et al. 3-9)

![Figure 1.4: Push-Pull Osmotic Pump](image)

Mechanism of drug release

When the dosage form comes in contact with the aqueous environment, both compartments imbibe water simultaneously. Because the lower compartment is devoid of any orifice, it expands and pushes the diaphragm into the upper drug chamber, thereby delivering the drug via the delivery orifice. Hydrogel push layer imbibes a fixed amount of water, irrespective of pH, a constant amount of drug is released in the form of finely divided dispersion. Thus, a perfect zero-order delivery, independent of pH, can be achieved for drugs having extremes of water solubility.
Advantage

It can be used to deliver both highly water-soluble (oxybutynin hydrochloride) and practically water-insoluble (nifedipine, glipizide) drugs.

Disadvantage

PPOP is much more complicated than the EOP and CPOP in terms of its design.

Modifications

A number of modifications are available for this type of system such as delayed push–pull system (as used in Covera HS, extended release formulation for verapamil), multi-layer push–pull system (for pulsatile or delayed drug delivery), and push–stick system (for delivery of insoluble drugs requiring high loading, with an optional delayed, patterned, or pulsatile release profile).

1.1.6.3 Modified OCDDS

A. Controlled Porosity Osmotic Pumps (CPOP)

CPOP's are similar to EOP, the only difference being that the delivery orifice from which the drug release takes place is formed by incorporation of a water-soluble additive in the coating.

Mechanism of drug release

After coming in contact with water, water soluble additives present in the coating dissolves and it results in an in situ formation of a microporous membrane as shown in Figure 1.5. The release of drug takes place through these microporous channels.(Edavalath et al. 80; Zentner, Rork and Himmelstein 269-82; Zentner, Rork and Himmelstein 217-29)

![Figure 1.5: Controlled Porosity Osmotic Pump](image)
**Introduction**

**Advantages**

Although this simple design eliminates the need for a separate manufacturing step (creating an orifice using a laser drilling machine), the resultant microporous membrane is substantially permeable to both water and dissolved solutes and may allow some of the contents to be released by simple diffusion, depending upon the level of water-soluble additive in the coating.

CPOP and EOP are suitable for delivery of drugs having intermediate water solubility. Nevertheless, the solubility of the agents to be delivered can be modulated, and these systems can be designed to deliver drugs having extremes of water solubility. The modification required depends mainly upon the dose, intrinsic water solubility and osmotic pressure, and desired release rate of the drug. (Schultz and Kleinebudde 181-89; Liu et al. 145-56)

**B. Osmotic Pump for Insoluble Drugs**

It comprises of coating the particles of osmotic agent (osmogens) with an elastic semi permeable film. These particles are mixed with the insoluble drug and compressed in the form of a tablet, which is subsequently coated with a semipermeable membrane, and an orifice is created in the membrane. Following its contact with the aqueous environment, water is drawn through the two membranes into the osmotic agent particles, which then swell and push the insoluble drug hydrostatically via the delivery orifice.

**C. Multiparticulate Delayed-Release System**

In this system, pellets containing drug with or without osmotic agent are coated with an SPM.

**Mechanism of drug release**

On contact with an aqueous environment, water penetrates into the core and forms a saturated solution of soluble components. The osmotic pressure gradient induces a water influx, resulting in a rapid expansion of the membrane, leading to the formation of pores. The osmotic ingredient and the drug are released through these pores according to zero order kinetics.

Lag time and dissolution rates were found to be dependent on the coating level and osmotic properties of the dissolution medium. Furthermore, dissolution characteristics were found to be influenced by such membrane components as incorporation of plasticizer and its concentration and lipophilicity. (Verma, Krishna and Garg 7-27; Schultz, Tho and Kleinebudde 191-99)
D. Monolithic Osmotic Tablet Systems (MOTS)

In the monolithic osmotic system, a simple dispersion of a water-soluble agent is made in a polymer matrix. (Chen, Jiang and Ding 131-37; Liu and Wang 298-302)

**Mechanism of drug release**

When the system comes in contact with the aqueous environment, water imbibitions by the active agent takes place that ruptures the polymer matrix capsule surrounding the agent, thus liberating it to the outside environment.

Initially, this process occurs at the outer environment of the polymer matrix, but it gradually proceeds toward the interior of the matrix in a serial fashion. A monolithic osmotic tablet system (MOTS) for a water-insoluble drug was developed using gum arabic as the osmotic, suspending, and expanding agent.

**Disadvantage**

This system fails if more than 20 to 30 vol% of the active agent is incorporated into the device because, above this level, significant contribution from the simple leaching of the substance takes place.

**E. OROS-CT**

The system can be a single osmotic unit or it may contain as many as 5–6 push–pull units enclosed within a hard gelatin capsule (Figure 1.6).

![Figure 1.6: OROS-CT](image)
**Mechanism of drug release**

Immediately after ingestion, the hard gelatin capsule shell dissolves. However, the push-pull unit is prevented from absorbing water in the acidic environment of the stomach by the enteric coating. The osmotic pumping action results when the coating dissolves in the higher pH environment (pH > 7) of the small intestine, and the drug is delivered out of the orifice at a rate controlled by the rate of water transport across the membrane. (Edavalath et al. 438-46; Zentner, Rork and Himmelstein 269-82)

**Advantages**

OROS-CT is used as a once- or twice-a-day formulation for targeted delivery of drugs to the colon.

**F. Sandwiched Osmotic Tablet (SOTS)**

In SOTS, a tablet core consisting of a middle push layer and two attached drug layers is coated with a SPM. As seen in Figure 1.7, both the drug layers are connected to the outside environment via two delivery orifices (one on each side). (Liu et al. 145-56)

![Figure 1.7: Sandwiched Osmotic Tablet](image)

**Mechanism of drug release**

After coming in contact with the aqueous environment, the middle push layer containing swelling agent swells and the drug is released from the delivery orifices.

**Advantage**

It may decrease the potential local irritation of the drug because the system delivers drug from two opposite orifices, rather from the single orifice of the PPOP.
G. Liquid OROS Controlled Release System (L-OROS)

A class of osmotic pumps is also designed to deliver liquid formulations. They are of two types: *L-OROS Soft cap* and *L-OROS hard cap*.

In the L-OROS SOFTCAP™, 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 as shown in Figure 1.8.(Dong, Espinal and Wong; Dong et al.)

**Mechanism of drug release from L-OROS Soft cap**

When the system is in contact with the aqueous environment, water permeates across the membrane and activates the osmotic layer, the expansion of which results in the development of hydrostatic pressure inside the system. The pressure generated forces the liquid formulation to break through the hydrated gelatin capsule shell at the delivery orifice, from which the drug release takes place.

![Diagram of L-OROS SOFTCAP and HARDCAP](image)

Figure 1.8: L-OROS SOFTCAP and HARDCAP
The L-OROS HARDCAP™ is similar to the L-OROS SOFTCAP™, comprising a drug suspension in a self-emulsifying formulation (SEF) to enhance the oral bioavailability of hydrophobic drugs. It consists of a liquid drug layer and an osmotic engine, all encased in a hard gelatin capsule and coated with SPM. A delivery orifice drilled in the membrane at the end of the drug layer provides an outlet for the drug suspension. Figure 1.8 shows the cross-sectional view of L-OROS HARDCAP™.

**Mechanism of drug release from L-OROS Hard cap**

After coming in contact with the aqueous environment, water is imbibed across the SPM, expanding the osmotic engine, which pushes against the barrier, releasing the drug through the delivery orifice.

**H. Osmotic Bursting Osmotic Pump**

This system is similar to an EOP expect delivery orifice is absent and size may be smaller.

**Mechanism of drug release**

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.

**Advantages**

Varying the thickness as well as the area the semipermeable membrane can control release of drug. This system is useful to provide pulsated release. (Parmar, Vyas and Vaya 28-29)

**I. OROS Push-Stick Technology**

The OROS Push-Stick technology provides the greatest benefit for compounds with low water solubility and dosage greater than 150 mg. It consists of a bilayer capsule shaped tablet.

---

![Figure 1.9: OROS Push-Stick Technology](image-url)
J. Asymmetric membrane osmotic system

Asymmetric membrane (AM) film-coated delivery systems are a unique embodiment of osmotic devices in the use of phase inversion technology to create the semipermeable asymmetric membrane. As with other osmotic pumps, the AM drug delivery system releases the active ingredient by an osmotically controlled mechanism which, when properly constructed, delivers the active agent independently of pH or external agitation. The critical differentiating features that distinguish AM dosage forms from other osmotic devices are the high water permeability and controlled porosity resulting from the spray-coating process. (Kumar and Bhadra 54-59)

K. 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. 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 in to 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.

Mechanism of drug release

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. (Wong; Wong et al.)

1.1.7 Evaluation of Oral Osmotic Drug Delivery Systems

Oral osmotic drug delivery systems can be evaluated for following:

1.1.7.1 Visual inspection

Visual inspection of the film for smoothness, uniformity of coating, edge coverage and luster.
1.1.7.2 Coating uniformity

The uniformity of coating among the tablets can be estimated by determining the weight, thickness and diameter of the tablet before and after the coating.

1.1.7.3 Coat weight and thickness

The coat weight and thickness can be determined from depleted devices following careful washing and drying of the film, using standard analytical balance and screw gauge, respectively.

1.1.7.4 Orifice diameter

The mean orifice diameter of osmotic pump tablet can be determined microscopically using pre calibrated ocular micrometer.

1.1.7.5 In vitro drug release

The in vitro delivery rate of drugs from osmotic systems can be determined using diverse methodologies, including vertically reciprocating shaker, conventional USP dissolution apparatus I and II, flow-through apparatus, etc.

1.1.7.6 Effect of pH

An osmotically controlled release system delivers its contents independently of external variables. To check this, dissolution media with different pH is used.

1.1.7.7 Effect of agitation intensity

In order to study the effect of agitational intensity of the release media, release studies is carried out in dissolution apparatus at various rotational speeds.

1.1.7.8 In vivo Evaluation

As the environment in the intestinal tract of the dog is quite similar to that of the human beings in terms of pH and motility, dogs have been widely used for in vivo delivery rate measurement of drug(s) from oral osmotic drug delivery systems and also to establish In vitro /In vivo correlation (IVIVC). In vivo evaluation can also be performed in healthy human volunteers. Various pharmacokinetic parameters (Cmax, Tmax, AUC and MRT) and relative bioavailability are calculated.
1.1.8 Marketed Products

Table 1.4: List of Marketed Products

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Active ingredient</th>
<th>Design system</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpress LP</td>
<td>Prazosin</td>
<td>Push - Pull</td>
<td>2.5 - 5 mg</td>
</tr>
<tr>
<td>Acutrim</td>
<td>Phenylpropanolamine</td>
<td>Elementary pump</td>
<td>75 mg</td>
</tr>
<tr>
<td>Cardura XL</td>
<td>Doxazosin</td>
<td>Push - Pull</td>
<td>4, 8 mg</td>
</tr>
<tr>
<td>Covera HS</td>
<td>Verapamil</td>
<td>Push - Pull with time delay</td>
<td>180, 240 mg</td>
</tr>
<tr>
<td>Ditropan XL</td>
<td>Oxybutinin chloride</td>
<td>Push - Pull</td>
<td>5, 10 mg</td>
</tr>
<tr>
<td>Dynacirc CR</td>
<td>Isradipine</td>
<td>Push - Pull</td>
<td>5, 10 mg</td>
</tr>
<tr>
<td>Invega</td>
<td>Paliperidone</td>
<td>Push - Pull</td>
<td>3, 6, 9 mg</td>
</tr>
<tr>
<td>Efidac 24</td>
<td>Chlorpheniramine maleate</td>
<td>Elementary Pump</td>
<td>4 mg IR, 12 mg CR</td>
</tr>
<tr>
<td>Glucotrol XL</td>
<td>Glipizide</td>
<td>Push - Pull</td>
<td>5, 10 mg</td>
</tr>
<tr>
<td>Minipress XL</td>
<td>Prazocine</td>
<td>Elementary pump</td>
<td>2.5, 5 mg</td>
</tr>
<tr>
<td>Procardia XL</td>
<td>Nifedipine</td>
<td>Push - Pull</td>
<td>30, 60, 90 mg</td>
</tr>
<tr>
<td>Sudafed 24</td>
<td>Pseudoephedrine</td>
<td>Elementary pump</td>
<td>240 mg</td>
</tr>
<tr>
<td>Volmax</td>
<td>Sabutamol</td>
<td>Elementary pump</td>
<td>4, 8 mg</td>
</tr>
<tr>
<td>Tegretol XR</td>
<td>Carbamazepine</td>
<td></td>
<td>100, 200, 400 mg</td>
</tr>
<tr>
<td>Viadur</td>
<td>Leuprolide acetate</td>
<td>Implantable osmotic systems</td>
<td></td>
</tr>
<tr>
<td>Chronogesic</td>
<td>Sufentanil</td>
<td>Implantable osmotic systems</td>
<td></td>
</tr>
<tr>
<td>Concerta</td>
<td>Methylphenidate</td>
<td>Implantable osmotic systems</td>
<td>18, 27, 36, and 54 mg</td>
</tr>
</tbody>
</table>
1.2 Introduction to Sparingly Water Soluble Drug

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important factor to achieve desired concentration of drug in systemic circulation. Approximately more than 40% of the new APIs are poorly soluble in water. Such drugs possess low oral bioavailability and erratic absorption of the drugs from the GIT due to their low saturation solubility and dissolution rate.

The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. In the other ways, the solubility can also be defined as the ability of one substance to form a solution with another substance.

The solubility of a substance may be described in a variety of ways. The USP/NF generally expresses the solubility in terms of the volume of solvent required to dissolve 1 gram of the drug at a specified temperature.

<table>
<thead>
<tr>
<th>Descriptive terms</th>
<th>Parts of the solvent required for 1 part solute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very soluble</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Freely soluble</td>
<td>1-10</td>
</tr>
<tr>
<td>Soluble</td>
<td>10-30</td>
</tr>
<tr>
<td>Sparingly soluble</td>
<td>30-100</td>
</tr>
<tr>
<td>Slightly soluble</td>
<td>100-1000</td>
</tr>
<tr>
<td>Very slightly soluble</td>
<td>1000-10,000</td>
</tr>
<tr>
<td>Practically insoluble or insoluble</td>
<td>&gt; 10,000</td>
</tr>
</tbody>
</table>

1.2.1 Problems Associated with Sparingly Soluble Drugs

The Biopharmaceutics Classification System (BCS) is not only a useful tool for obtaining waivers for In vivo bioequivalence studies but it also helps in decision making in the drug discovery and early development of new drugs. Relative to highly soluble compounds, BCS class – II drugs which have high permeability and low drug solubility often manifest In vivo consequences, including decreased bioavailability, increased chance of food effect, more
frequent incomplete release from the dosage form and higher interpatient variability. Poorly soluble compounds also present many In vitro formulation obstacles, such as limited choices of delivery technologies and complex dissolution testing with limited or poor correlation to the In vivo absorption. These In vivo and In vitro characteristics and the difficulties in achieving predictable and reproducible In vivo/In vitro correlations are often sufficient to halt development on many newly synthesized compounds due to solubility issues.

Due to short biological half-life, it also requires frequent dosing in large number of patients, which leads to patient non-compliance. Thus, there is a strong clinical need and market potential for a dosage form that will deliver drug in a controlled manner to the patient, thereby resulting in a better patient compliance.(Hite, Turner and Federici 38-40)

1.2.2 Solubilization Techniques

Poorly soluble drugs have motivated the development of new drug delivery technologies to overcome the hindrances to their solubilization through either chemical or mechanical modification of the environment surrounding the drug molecule, or physically altering the macromolecular characteristics of aggregated drug particles. These technologies include two types of methods for solubility enhancement which are listed in Table 1.1.(Puthli et al. ; Hite, Turner and Federici 38-40) It includes conventional as well as novel approaches. These systems are characterized by Phase solubility studies, Drug content analysis, Dissolution rate, Differential Scanning Calorimetry (DSC), X-ray Diffraction study (X-RD), Scanning Electron Microscopy (SEM), Fourier transform infrared (FT-IR) spectroscopy(Mehramizi et al. 812-23; Kanagale et al. 306-11) etc.
Table 1.6: Techniques for Solubility Enhancement

<table>
<thead>
<tr>
<th>Conventional Techniques</th>
<th>Novel Techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle size reduction via comminution and spray drying,</td>
<td>Super critical fluid processing,</td>
</tr>
<tr>
<td>Addition of surfactants and inclusion in cyclodextrin-drug complexes,</td>
<td>Self-emulsifying systems,</td>
</tr>
<tr>
<td>Use of effervescent mixtures, swellable polymer, wicking agent,</td>
<td>Nanosuspension,</td>
</tr>
<tr>
<td>Modification of the crystal habit via polymorphs/pseudomorphs,</td>
<td>Hot melt extrusion,</td>
</tr>
<tr>
<td>Drug dispersion in carriers like eutectic mixtures,</td>
<td>Liquid solid compact</td>
</tr>
<tr>
<td>Solid dispersions,</td>
<td></td>
</tr>
<tr>
<td>Solid solutions,</td>
<td></td>
</tr>
<tr>
<td>pH adjustment and salting-in processes,</td>
<td></td>
</tr>
<tr>
<td>Micronisation</td>
<td></td>
</tr>
</tbody>
</table>

1.3 AIM OF THE PRESENT WORK

Among all newly discovered chemical entities about 40% drugs are lipophilic and fail to reach market due to their poor water solubility. The solubility behavior of drugs remains one of the most challenging aspects in formulation development. A success of formulation depends on how efficiently it makes the drug available at the site of action. Therapeutic effectiveness of a drug depends on the bioavailability and ultimately upon the solubility of drug molecules especially in oral formulation. Poorly water soluble drugs have good permeability but it often requires high dose after oral administration in order to reach therapeutic concentration. The bioavailability of an orally administration drug depends on its solubility in aqueous media over different pH ranges. The insufficient dissolution rate of the drug is the limiting factor in the oral bioavailability of poorly water soluble compounds. Various techniques are used for the improvement of aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrothropy etc. These sparingly soluble drugs having short biological half life are generally developed as controlled release formulation so that dosage frequency can be reduced.
Moreover, it requires to improve the solubility before developing its controlled release formulation. During the past three decades significant advances have been made in the area of novel drug delivery systems. Among the various novel drug delivery systems available in market, oral controlled release (CR) systems hold the major market share. This is due to improved patient convenience and compliance, reduction in fluctuation in steady state plasma level so decrease intensity of local or systematic side effects and increase safety margin of high potency drugs. Controlled release system proved to be a good for drugs having short half-life as it helps in utilization of most of the drug, thus reduce the necessity of total amount of drug administered.

A number of design options are available to control or modulate the drug release from a dosage forms. CR dosage forms mainly of matrix, reservoir or osmotic type. The orally administered drugs, in the form of conventional matrix or reservoir type formulations, poses problems of bioavailability fluctuations due to gastric pH variations. Moreover, the release of drugs from these systems is affected by the hydrodynamic conditions of the body. Osmotically controlled drug delivery systems (OCDDS), a one of the advanced drug delivery system, utilize the principles of osmotic pressure for the controlled delivery of active pharmaceutical ingredient.(Conley, Gupta and Sathyan 1879-92)

Osmotic devices are most promising strategy based system for controlled drug delivery. They are among the most reliable controlled drug delivery system and could be employed as oral drug delivery systems or implantable device. Osmosis is an aristocratic biophenomenon, which is exploited for development of delivery systems with every desirable property of an ideal controlled drug delivery system. Osmotic system utilizes the principles of osmotic pressure for delivery of drug. Delivery of drug from osmotic pumps can be designed to follow true zero-order kinetics and thus high degree of In vitro/In vivo correlation can be achieved. Drug release from these systems is also independent of pH, food and hydrodynamic conditions of the gastro-intestinal tract (GIT) to a large extent, and release characteristics can be easily adjusted by optimizing the parameters of the delivery system. The various products available in the market based on the principle of osmotic pressure includes Teczem (Enalapril and Diltiazem), Tiamate (Diltiazem), Acutrim (Phenylpropanolamine), Efidac 24 (Pseudoephedrine, Chlorpheniramine), Osmosin (Indomethacin), Volmax (Albuterol), Cardura XL (Doxazosin mesylate), Concerta (Methylphenidate), Ditropan XL (Oxybutynin chloride), Dynacirc CR (Isradipine), Glucotrol XL (Glipizide), Minipress XL (Prazosin),
Introduction

Procardia XL (Nifedipine), Altoprev (Lovastatin), Fortamet (Metformin Hydrochloride), Covera-HS (Verapamil) etc.

Osmotic technology is utilized for delivering different categories of drugs by the researchers. These include non-steroidal anti-inflammatory drugs, antipyretics, antihypertensive, anti-diabetic, antipsychotic, anti-parkinsons, anti-histaminic, cough suppressants, anti-asthmatic, antineoplastics, antiviral and antifungal etc. Drugs from non-steroidal anti-inflammatory (NSAID) and anti-hypertensive category falling under BCS class-II drugs were selected for the development of OCDDS due to its short biological half-life (2-6 hrs), high potency, and need for prolonged treatment.

Flurbiprofen, [(+/-) - 2-(2-fluoro-4-biphenylyl) propionic acid] is an important non-steroidal anti-inflammatory BCS Class-II drug, effectively used in the treatment of rheumatoid arthritis, osteoarthritis and ocular inflammatory conditions. (Marsh, Schuna and Sundstrom 10-25; Thaller, Kulshrestha and Bell 642-45) Nicardipine Hydrochloride (NH), a calcium channel-blocking agent, is an effective drug in the management of mild to moderate hypertension, angina pectoris and cerebral disease. These drugs were selected for development of OCDDS in present investigation. (Yüksel, Tinçer and Baykara 145-54) The conventional formulations of these drugs possess problems like frequent dosing, large fluctuation in drug plasma concentration and tolerance development on long term use. Moreover, it may cause adverse gastrointestinal reactions. It also depends on factors such as presence or absence of food, pH and hydrodynamic conditions of the gastro-intestinal tract. This strongly indicates need to develop controlled release formulations for these drugs. Literature survey indicated that no osmotic formulations of selected drugs are available in Indian market. Thus, OCDDS was selected for development of CR formulation of these drugs.

Flurbiprofen and Nicardipine Hydrochloride exhibits poor solubility. In view of this, the study was undertaken to improve its solubility before developing their osmotic formulations. Inclusion complexation using β-CD was chosen as it provides faster drug release, stable and ease in manufacturing because of good compressibility of β-CD.

Osmotic formulations can be developed using various technologies like single and multiple chamber systems. In the present study Controlled Porosity Osmotic Pump (CPOP), Elementary Osmotic Pump (EOP) and Push Pull Osmotic Pump (PPOP) were choosen for selected drugs because these techniques are proved as simple, inexpensive and having industrial feasibility. All these systems rely on semipermeable membrane to function. These
systems were characterized by the different parameters like weight variation, hardness, friability, drug content, and *In vitro* drug release studies etc.

Design of Experiment is adopted as one of the tool for systematically optimization of process and formulation parameters for development of twice a day formulation of selected drugs. To achieve this, the desired drug release was decided i.e. 15 to 20% drug release in 120min, 85 to 90% drug release in 540min and nearly complete drug release in 720min to choose the formulation.

Thus, the aim of the present study was to formulate optimize and characterize osmotically controlled drug release systems for selected drugs using various techniques. Different formulation variables like amount of osmotic agent, amount of osmopolymer, size of delivery orifice, concentration of pore former and effect of weight gain were evaluated for the selection of optimized batch. Optimized batch was subjected stability study as per ICH guidelines. The study also focused comparison of developed formulation made by different technologies for selected drugs and identifying optimized formulation of each drug and performing its *In vivo* study using albino rabbits.

**1.4 References**


Introduction


