INTRODUCTION
Introduction

During the past three decades significant advances have been made in the area of controlled drug delivery. This was, in part, due to the evolving disciplines of biopharmaceutics, pharmacokinetics and pharmacodynamics. In a typical therapeutic regimen, the drug dose and the dosing interval are optimized to maintain drug concentration within the therapeutic window, thus ensuring efficacy while minimizing toxic side effects. Surveys indicated that dosing more than once or twice daily greatly reduces patient compliance. Hence, the primary objective for controlled drug delivery is to maintain drug concentration within therapeutic window, improve patient compliance to the dosage regimen by decreasing dosing frequency, and improve drug efficacy while reducing toxic side effects. A diagrammatic illustration of controlled versus conventional dosage delivery is shown in fig.1.1.

FIGURE 1.1: Simulation of Blood Concentration Profiles resulting from multiple doses of conventional dosage form \(A_1, A_2, A_3\) and \(A_4\) as compared to a single dose of controlled release (zero order) dosage form \(B\).
Numerous technologies have been used to control the systemic delivery of drugs. One of the most interesting uses osmotic pressure as a source of energy. Osmotic pressure has now been used extensively in fabrication of drug delivery systems. This portion will focus on controlled release devices based on the osmotic pressure concept. More emphasis is given to oral osmotic pumps.

**History**

Since the beginning of antiquity, both pharmacy and medicine have sought effective delivery systems for administering beneficial drugs. The first written reference to a delivery system is to the Eber Papyrus, written about 1552 B.C. In 865-925 AD, Arab physician Rhazes invented coated pill. Primeval tablet was described in Arabian manuscripts written by al-Zahrawi, 936-1009 A.D. The earliest application of osmotic pressure to drug delivery was made by Rose and Nelson (1955). The next quantum leap in osmotic dosage forms came in 1972 when Theeuwes (1975) invented elementary osmotic pump. After that many modified osmotic pumps have been invented which enable controlled delivery of many drugs.

**Theory**

**Osmotic Pressure**- Osmotic pressure, like vapour pressure and boiling point is a colligative property of a solution in which a nonvolatile solute is dissolved in a volatile solvent. If cobalt chloride is placed in a parchment sac and suspended in a beaker of water, the water gradually becomes red as the solute diffuses throughout the vessel. In this process of diffusion, both the solvent and solute molecules migrate freely. On the
other hand, if the solution is confined in a membrane permeable only to solvent molecules, the phenomenon known as osmosis (Greek: a push or impulse) occurs, and the barrier that permits only the molecules of one of the components (usually water) to pass through is known as a semipermeable membrane. Osmosis is therefore defined as the passage of the solvent into a solution through a semipermeable membrane. This process tends to equalize the escaping tendency of the solvent on both sides of the membrane. It should be evident that osmosis can also take place when a concentrated solution is separated from a less concentrated solution by semipermeable membrane.

Osmosis in some cases is believed to involve the passage of solvent through membrane by a distillation process, or by dissolving in the material of the membrane in which solute is insoluble. In other cases, the membrane may act as a sieve, having a pore size sufficiently large to allow passage of solvent but not of solute molecules. In either case the phenomenon of osmosis really depends on the fact that the chemical potential of a solvent molecule in solution is less than it exists in pure solvent. Solvent therefore passes spontaneously into the solution until the chemical potentials of solvent and solute are equal.

Osmotic pressure can be measured with the help of a simple experiment using an osmometer (fig. 1.2), one side of which contains a pure solvent, while the other contains a solution. A semipermeable membrane separates the two sides. The solvent will travel from the solvent side to the solution side until such time as the hydrostatic pressure created by the solvent flux is sufficiently high to stop further flux.

The osmotic pressure that is set up as a result of this passage of solvent molecules may be determined either by measuring the hydrostatic head (h) appearing in
the solution or by applying a known pressure that just balances the osmotic pressure and prevents any net movement of solvent molecules into the solution. The latter is preferred technique. Osmotic pressure is defined as the excess pressure, or pressure greater than that above the pure solvent, which must be applied to the solution to prevent the passage of the solvent through a perfect semipermeable membrane.

Flow of solvent depends on following factors: Semipermeable membrane characteristics, differential osmotic pressure between two sides of osmometer, differential hydrostatic pressure between two sides of osmometer, and the difference between osmotic pressure and hydrostatic pressure as the mass (volume) transfer process approaches equilibrium.

Osmotic pressure can also be calculated by using Van’t Hoff and Morse equation:

\[ \pi V = n RT \]  

(Eq.1)
in which $\pi$ is osmotic pressure in atm, $V$ is the volume of solution in liters, $n$ is number of moles of solute, $R$ is gas constant (0.082 liter atm/mole deg) and $T$ is the absolute temperature (Martin, 1994).

Osmotic pressures for concentrated solutions of soluble solutes commonly used in controlled formulations are extremely high, ranging from 28 atm for sodium phosphate up to 500 atm for lactose fructose mixture. Some commonly used osmotic agents are given in Table -1.1.

TABLE 1.1: List of osmotic agents with the osmotic pressure (Thweeus, 1981).

<table>
<thead>
<tr>
<th>Compound or Mixture</th>
<th>Osmotic Pressure (atm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol : Fructose</td>
<td>415</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>356</td>
</tr>
<tr>
<td>Fructose</td>
<td>355</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>Dextrose</td>
<td>82</td>
</tr>
<tr>
<td>Potassium sulfate</td>
<td>39</td>
</tr>
<tr>
<td>Mannitol</td>
<td>38</td>
</tr>
<tr>
<td>Sodium phosphate tribasic – 12 H$_2$O</td>
<td>36</td>
</tr>
<tr>
<td>Sodium phosphate dibasic – 7 H$_2$O</td>
<td>34</td>
</tr>
<tr>
<td>Sodium phosphate dibasic – 12 H$_2$O</td>
<td>31</td>
</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>

These osmotic pressures can produce high water flows across semipermeable membranes. The osmotic water flow across a membrane is given by this equation:

$$\frac{dv}{dt} = \frac{A}{h} \left( L_p \left( \sigma \Delta \pi - \Delta P \right) \right)$$

(Eq.2)
where \( \frac{dv}{dt} \) is the water flow across the membrane of area \( A \), thickness \( h \); \( \Delta \pi \) & \( \Delta P \) are the osmotic and hydrostatic pressure differences, respectively, on either side of the membrane; \( L_p \) is the mechanical permeability; \( \sigma \) is the reflection coefficient (leakage of solute through membrane). In terms of membrane performance and predictability, it is important to select a material whose reflection coefficient is close to 1. Water permeabilities of membranes can vary over a wide range, but most osmotic devices generally use relatively water permeable materials. Cellulosic materials, particularly cellulose acetate, are widely used. Table-1.2 gives list of various polymers for semipermeable membranes. Semipermeable membrane has important role in controlling drug release. Hence, the membrane must meet several performance criteria. First, the material must possess sufficient wet strength (~ 10^5 psi) and wet modulus (~ 10^4 psi) so as to retain its dimensional integrity during the operational lifetime of the device. Second, the polymer membrane must exhibit sufficient water permeability so as to attain water flux rate \( (dv/dt) \) in the desired range. Third, the reflection coefficient (\( \sigma \)), "leakiness" of the membrane to the osmotic agent, should approach the limiting value of 1. Finally, the membrane should be biocompatible.
TABLE-1.2: List of semi permeable polymers with their water vapour transmission rates (WVTR) (Johnson, 1980).

<table>
<thead>
<tr>
<th>Polymers Membrane</th>
<th>WVTR(g/100m²/24hr/mm thick)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyvinyl alcohol</td>
<td>100</td>
</tr>
<tr>
<td>Polyurethane</td>
<td>30-150</td>
</tr>
<tr>
<td>Methyl cellulose</td>
<td>70</td>
</tr>
<tr>
<td>Cellulose acetate</td>
<td>40-75</td>
</tr>
<tr>
<td>Ethyl cellulose</td>
<td>75</td>
</tr>
<tr>
<td>Cellulose acetate butyrate</td>
<td>50</td>
</tr>
<tr>
<td>Polyvinyl chloride (cast)</td>
<td>10-20</td>
</tr>
<tr>
<td>Polyvinyl chloride (extruded)</td>
<td>6-15</td>
</tr>
<tr>
<td>Polycarbonate</td>
<td>8</td>
</tr>
<tr>
<td>Polyvinyl fluoride</td>
<td>3</td>
</tr>
<tr>
<td>Ethylene vinyl acetate</td>
<td>1-3</td>
</tr>
<tr>
<td>Polyesters</td>
<td>2</td>
</tr>
<tr>
<td>Cellophane (polyethylene coated)</td>
<td>&gt;1.2</td>
</tr>
<tr>
<td>Polymethylene fluoride</td>
<td>1.0</td>
</tr>
<tr>
<td>Ethylene propylene copolymer</td>
<td>0.8</td>
</tr>
<tr>
<td>Polypropylene</td>
<td>0.7</td>
</tr>
<tr>
<td>Polyvinyl chloride (rigid)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Classification of Osmotic Pumps

Implantable Osmotic Pumps (Santus, 1995) -

The Rose Nelson Pump - In 1955, two Australian physiologists reported the first osmotic pump. They were interested in delivery of drugs to the gut of sheep & cattle. The pump consisted of three chambers (fig.1.3): a drug chamber with an orifice, a salt chamber with elastic diaphragm containing excess solid salt, and a water chamber. A semipermeable membrane separates the drug and water chamber. 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.

![Diagram of Rose-Nelson Osmotic Pump]

**FIGURE 1.3:** Rose – Nelson Osmotic Pump

The pumping rate of Rose-Nelson pump is given by the equation.

\[
\frac{dm}{dt} = \frac{dv}{dt} C \quad \text{(Eq.3)}
\]

where \(\frac{dm}{dt}\) is the drug release rate, \(\frac{dv}{dt}\) is the volume flow of water into the salt chamber, and \(C\) is concentration of drug into the drug chamber. Substituting eq.2 in eq.3 gives

\[
\frac{dm}{dt} = \frac{A}{Lp (\sigma \Delta \pi - \Delta P)} C \quad \text{(Eq.4)}
\]

These basic equations can be used to describe the behaviour of all the devices described in this chapter.

The osmotic pressure of saturated salt solution is high, in the order of tens of atmosphere, and the small pressure required to pump the suspension of active agent is
insignificant in comparison. Therefore, the rate of water permeation across the semipermeable membrane remains constant as long as sufficient salt is present in the salt chamber to maintain a saturated solution and hence a constant osmotic pressure driving force.

**Higuchi – Leeper Pump** - Design of Higuchi – Leeper pump is described in fig.1.4, it represents the first simplified version of Rose-Nelson pump. It contains a rigid housing and the semipermeable membrane, which is supported on a perforated frame. Rigid housing is divided in two chambers by a movable separator. The benefit over Rose-Nelson pump is that it does not have water chamber, and the device is activated by water imbibed from the surrounding environment. This means the pump can be prepared loaded with drug and then stored for weeks or months prior to use.

![Diagram of Higuchi – Leeper Pump](image)

**FIGURE 1.4 : Higuchi – Leeper Pump**
**Higuchi – Theeuwes Pump** - In early 1970s, Higuchi and Theeuwes developed a simpler form of Rose-Nelson Pump. As shown in fig.1.5, semipermeable wall itself acts as a rigid outer casing of the pump. The device is loaded with drug prior to use. When the device is placed in 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.

![Diagram of Higuchi – Theeuwes pump](image)

**FIGURE 1.5** : Higuchi – Theeuwes pump

**Implantable Mini Osmotic Pump** - This is most advanced version in the category of implantable pumps developed by Alza Corporation. As shown in fig.1.6, it is composed of three concentric layers – the drug reservoir, the osmotic sleeve and the rate controlling semipermeable membrane. The additional component called flow moderator is inserted into the body of the osmotic pump after filling.

The inner most compartment is drug reservoir which is surrounded by an osmotic sleeve, a cylinder containing high concentration of osmotic agent. The osmotic sleeve is covered by a semi permeable membrane. When the system is placed in aqueous

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environment water enters the sleeve through semi permeable membrane, compresses the flexible drug reservoir and displaces the drug solution through the flow moderator. These pumps are available with variety of delivery rates between 0.25 to 10 μl per hour and delivery duration between 1 day and 4 weeks.

**Oral Osmotic Pumps-**

*Elementary Osmotic Pump(Theeuwes, 1975)-* Although Elementary osmotic pump works on same mechanism as the implantable pumps, it is simplest possible form of osmotic pump as it does not require special equipment and technology (fig.1.7). It can be mass-produced economically using ordinary tabletting and coating machine and a facility to drill an orifice.
The elementary osmotic pump consists of an osmotic core containing drug, which is coated with a semi permeable membrane, usually cellulose acetate, with a delivery orifice. The core may or may not contain an osmotic agent depending on the osmotic activity of the drug. When exposed to aqueous environment, the core imbibes water osmotically at a controlled rate through the semi permeable membrane, forming a saturated drug solution inside the system. The membrane being non-extensible, internal volume of the pump remains constant. The system delivers, via the orifice, in any time interval, a volume of saturated solution of drug equal to volume of water uptake. This process continues at a constant rate until all solid drug inside the tablet has been dissolved and only a solution filled shell remains. The residual dissolved drug continues to be delivered, but at a declining rate, until the osmotic pressure inside and outside the pump is equal. The typical release rate obtained from this system is illustrated in fig.1 8. Elementary osmotic pump is most appropriate for delivery of drugs having moderate solubility (50 to 500 mg/ml) in water. It typically delivers 60-80% of its contents at constant rate.
Delivery rate of the drug is dependent on membrane permeability, the osmotic pressure of the core formulation, and the solubility of the drug in question. The delivery rate is independent of the release orifice size as long as the cross sectional area \( A_0 \), is within two critical limits; \( A_{\text{min}} \leq A_0 \leq A_{\text{max}} \). The size of the orifice must be larger than a minimum size, \( A_{\text{min}} \), to minimize hydrostatic pressure within the device. This is a necessary step in achieving zero order drug release. The presence of any significant hydrostatic pressure would decrease the delivery force for drug delivery. In addition, larger hydrostatic pressure could deform the device. The size of orifice must be smaller than a maximum size, \( A_{\text{max}} \), to minimize diffusional contribution to the delivery rate.

The general expression for the solute delivery rate, \( \frac{dm}{dt} \), obtained by pumping through the orifice is described by Rose-Nelson equation that is given below:

\[
\frac{dm}{dt} = \frac{A}{L_p (\sigma \Delta \tau - \Delta P)C} \quad (\text{Eq.4})
\]
As the delivery orifice increases, hydrostatic pressure inside the system is minimized as expressed by the condition $\Delta \pi >> \Delta P$.

When the osmotic pressure of the formulation ($\pi$) is large compared to the osmotic pressure of the environment, $\pi$ can be substituted for $\Delta \pi$. Eq. 4 then reduces to a much simpler expression in which the constant $k$ replaces the product $L_p g$:

$$\frac{dm}{dt} = \frac{A}{h} (-k \pi C)$$  \hspace{1cm} (Eq.5)

Zero-Order Delivery Rate – The release rate from the elementary osmotic pump is zero order from $t = 0$ until a time $t_z$, at which time all of the solid in the core has dissolved and is described by:

$$\left( \frac{dm}{dt} \right)_z = \frac{A}{h} (-k \pi S)$$  \hspace{1cm} (Eq.6)

where $S$ is the solubility, and $\pi_s$ is the osmotic pressure at saturation.

The rate of dissolution of a single compound within the system is much larger than the rate of pumping as given Eq.6. For this reason, the concentration, $C$, can be replaced by the component solubility, $S$, from time $t = 0$ to $t = t_z$.

Nonzero-Order Release Rate – The nonzero-order release rate from the system (Eq.5) is obtained by describing the concentration, $C$, as a function of time. For simplicity, the volume flux into the system is replaced by the symbol $F$:

$$F = \frac{A}{h} (-k \pi)$$  \hspace{1cm} (Eq.7)

and $F_z$ represents the flux during the zero-order time and is related to $F$ by:
By substituting Eq.8 into Eq.5, the nonzero-order release rate as a function of concentration is given by:

\[ \frac{dm}{dt} = \frac{F_s}{S} C^2 \quad \text{(Eq.9)} \]

Beyond t_z, the mass m, of component dissolved into the elementary pump volume, V, is given by:

\[ m = CV \quad \text{(Eq.10)} \]

The change in mass at constant volume V, causes a concentration change, \( dC/dt \), given by:

\[ \frac{dm}{dt} = -V \frac{dC}{dt} \quad \text{(Eq.11)} \]

The delivery rate, \( dm/dt \), can be eliminated between Eqs.9 and 11 as shown by:

\[ -\frac{dC}{dt} = \frac{F_s}{VS} C^2 \quad \text{(Eq.12)} \]

The concentration, C, inside the system is obtained by integrating Eq.12 from time t_z to t, when the concentration changes from S to C:

\[ \int_{S}^{c} dC = -\int_{t_z}^{t} \frac{F_s}{VS} C^2 \, dt \quad \text{(Eq.13)} \]

Solving Eq.13 and rearranging terms result in an expression for the concentration as a function of time:
Substituting Eq.13 into Eq.8 gives the release rate as a function of time, indicating the parabolic decline.

\[
\frac{dm}{dt} = \frac{F_s S}{V} \left[ F_s \left( 1 + \frac{(t-t_z)}{V} \right)^2 \right] 
\]

(Eq.15)

The nonzero - order release rate can also be expressed as a fraction of the zero order rate.

\[
\frac{dm}{dt} = \left( \frac{dm}{dt} \right)_z \left[ 1 + \left( \frac{1}{SV} \right) \left( \frac{1}{dt} \right)_z (t-t_z) \right]^2 
\]

(Eq.16)

The delivery rate discussed in this section is the rate from the elementary osmotic pump when most of the contents are delivered by pumping. When the membrane is not ideally semipermeable, a fraction of the agent is delivered by diffusion through the membrane.

Mass Delivered at Zero Order, \( m_z \), and Zero-Order Delivery Time, \( t_z \) - Fcr a total mass, \( m_0 \), contained in the core of the elementary osmotic pump, only an amount \( m_z \) is delivered at zero order, and an amount \( m_{NZ} \) is delivered at a parabolically declining rate given by Eq.15. The amount \( m_{NZ} \) is the mass that just fills the internal volume of the system with a saturated solution, as shown by:

\[
m_{NZ} = SV 
\]

(Eq.17)
The internal volume, \( V \), of the system containing a pure component is related to the total mass \( m_t \), by the density, \( \rho \), of the core by:

\[
m_t = \rho V \quad \text{(Eq. 18)}
\]

The fraction not delivered at zero order is obtained from Eqs. 17 and 18 and given by:

\[
\frac{m_{NZ}}{m_t} = \frac{S}{\rho} \quad \text{(Eq. 19)}
\]

Since the sum of \( m_{NZ} \) and \( m_z \) is equal to \( m_t \), the fraction of the total mass delivered at zero order can be given by:

\[
\frac{m_z}{m_t} = 1 - \frac{S}{\rho} \quad \text{(Eq. 20)}
\]

The time \( t_z \) at which the mass \( m_z \) is delivered for an ideal system, with zero start up time, is obtained from:

\[
\frac{m_z}{m_t} = \left( \frac{dm}{dt} \right)_z \quad \text{(Eq. 21)}
\]

Combining Eqs. 20 and 21 gives:

\[
t_z = m_t \left( 1 - \frac{S}{\rho} \right) \frac{1}{(dm/dt)_z} \quad \text{(Eq. 22)}
\]

The membrane being semi permeable in nature, does not allow any ion to pass through, it allows only the passage of water, which makes the delivery rate of drug from the system independent of the pH of the environment (fig. 1.9). Since there is no requirement for the system to disintegrate for release of drug to occur and there is no
influence of stirring rate (fig. 1.10) or surfactants on in vitro release rates, the in vivo delivery rate of drug is expected to be the same as that in vitro.

FIGURE 1.9: Effect of pH conditions on in vitro delivery rate profile of sodium phenobarbitone from elementary osmotic pump system in gastric and intestinal fluid USP (without enzymes).

FIGURE 1.10: Effect of hydrodynamic conditions on in vitro delivery rate profile of potassium chloride elementary osmotic pump in water at 37°C.

**Push-pull Osmotic Pump (Wong, 1992a)**- Push pull osmotic pump is a modified elementary osmotic pump through which it is possible to deliver both poorly water-
soluble and highly water-soluble drugs at constant rate. The system resembles a standard bilayer coated tablet (fig.1.11). One layer (depicted as the upper layer), contains drug (accounts for 60-80% of tablet weight) 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 layer imbibes water. The other layer (accounts for 20-40% of tablet weight) (depicted as the lower layer), contains osmotic and colouring agents, polymers 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, using standard film coating equipment and techniques, with a semi permeable membrane. After the coating has been applied, a small hole (orifice) is drilled through the membrane by a laser or mechanical drill on the drug layer side of the tablet. The drug layer can be detected by light sensors (for mass production) or by an eye, which differentiates between the drug and the non-drug layers of the tablet based on colour (from the colourant added to the non-drug layer). A film coat can be applied (for cosmetic purpose or to protect light sensitive drugs) over the cellulose membrane to complete the fabrication.

FIGURE 1.11: The Push – Pull Osmotic pump.
When the system is placed in an aqueous environment, water is attracted into the tablet by an osmotic pressure gradient across the membrane. The gradient develops because of high affinity of the osmotic agents for water and the low water activity in the dry tablet core. The osmotic attractant in the drug layer pulls water into that compartment to form in situ a suspension of drug. The osmotic agent in the non-drug layer simultaneously attracts water into that compartment, causing it to expand volumetrically as shown in fig.1.11. Since the membrane is insoluble and rigid in nature, it maintains constant shape and volume of the system and the expansion of non-drug layer pushes the drug suspension out of the delivery orifice. The delivery orifice is large enough to eliminate the build up pressure within the system and yet not large enough to permit uncontrolled leaching of drug from the orifice.

The operation of the system can be compared to a piston within a cylinder. The non drug layer acts like a piston, pushing almost all the drug suspension out of the orifice as it expands. At the completion of delivery cycle, the membrane shell contains only the expanded non-drug layer.

The drug layer and the non-drug layer act together to substantially ensure that the delivery of drug from the compartment is controlled and constant over a prolonged period of time by two methods. First, the drug layer imbibes external fluid across the wall, thereby forming a dispensable composition, which is substantially delivered at non-zero order rate, without the record composition present, since the driving force decays with the time. Second, the non-drug layer operating by imbibing external fluid across the wall continuously and consequently, increases in volume as well as imbibition area, thereby exerting a force which can be constant, increasing or
decreasing with time (depending on the osmotic formulation) against the drug layer and diminishing its volume, thus directing drug to the passage way at a controlled rate from the compartment. Additionally, as the drug layer is squeezed out, which is delivered from the device, the osmotic composition closely contacts the internal wall and generation constant delivery rate in conjunction with the non-drug layer. The swelling and expansion the non-drug layer, with its accompanying increase in volume, along with the simultaneous corresponding reduction in volume of the drug layer, assures the delivery of drug through the osmotic passageway at a controlled rate over time.

In case of push-pull osmotic pump, the volume rate delivered by the device $F_t$ is composed of two sources; the water imbibition rate by the first composition $F_t$ and the water imbibition rate of the second composition $Q$ wherein:

$$F_t = F + Q \quad \text{(Eq.23)}$$

Since the boundary between the first composition and the second composition hydrates very little during the functioning of the device, there is insignificant water migration between the compositions. Thus, the water imbibition rate of the second composition, $Q$, equals the expansion of its volume:

$$\frac{dv_p}{dt} = Q \quad \text{(Eq.24)}$$

The total delivery rate from the osmotic device is then,

$$\frac{dm}{dt} = F_t \cdot C = (F + Q)C \quad \text{(Eq.25)}$$
wherein $C$ is the concentration of drug in the delivered slurry or solution. Conservation of the osmotic device volume, $V$, and the surface area $A$, gives equations 26 and 27.

$$V = V_d + V_p$$  \hspace{1cm} (Eq.26)

$$A = A_d + A_p$$  \hspace{1cm} (Eq.27)

Wherein $V_d$ and $V_p$ equal the volumes of the first composition and the second composition, respectively, and wherein $A_d$ and $A_p$ equal the surface area in contact with the wall by the first composition and the second composition, respectively. In operation, both $V_p$ and $A_p$ increase with time, while $V_d$ and $A_d$ decrease with time as the device delivers beneficial agent.

The volume of the second composition that expands with time when fluid is imbibed into the compartment is given by eq.28:

$$V_p = \frac{W_H}{W_p}$$  \hspace{1cm} (Eq.28)

wherein $W_H$ is the weight of the fluid imbibed by the second composition, $W_p$ is the weight of the second composition initially present in the device, $W_H/W_p$ is the ratio of fluid to initial solid of the second composition, and

$$V_p = \left[ \frac{W_H}{1 + \frac{W_H}{W_p}} \right]$$  \hspace{1cm} (Eq.29)

wherein $\rho$ is the density of the second composition corresponding to $W_H/W_p$. Thus, based on the geometry of a cylinder, where $r$ is the radius of the cylinder, the area of imbibition is related to the volume of the swollen second composition as follows:

$$A_p = \pi r^2 + \frac{2}{r} \frac{W_p}{\rho} (1 + W_H/W_p)$$  \hspace{1cm} (Eq.30)
The fluid imbibition rates into each composition are:

\[ A_d = A - A_p \]  
(Eq.31)

The fluid imbibition rates into each composition are:

\[
F = \left( \frac{k}{h} \right) (A_d - \Delta \pi_d) 
\]  
(Eq.32)

\[
Q = \left( \frac{k}{h} \right) (A_p - \Delta \pi_p) 
\]  
(Eq.33)

where \( k \) equals the osmotic permeability of the wall, \( h \) equals the wall thickness, \( \Delta \pi_p \) and \( \Delta \pi_d \) are the osmotic gradients for the first composition and the second composition respectively. The total delivery rate, therefore, is equation:

\[
\frac{dm}{dt} = \frac{k}{h} C \left[ \left( \frac{2 \ W_p}{\rho} \right) \left( \frac{2 \ W_p}{\rho} \right) \frac{2 \ W_p}{\rho} \right] (1 + W_{H/W_p}) \Delta \pi_d 
\]  
(Eq.34)

The system typically delivers more than 80% of their contents at a constant rate.

The osmopolymers acceptable for forming first layer (drug layer) of the push pull osmotic pump comprise hydrophilic polymers that are non-cross-linked, or slightly cross-linked, such as with cross-links formed by ionic, hydrogen or covalent bonds. The osmopolymers interact with water and aqueous biological fluids and form a solution or a suspension with high osmotic pressure that are osmotically pumped through exit pores. The osmopolymers can be of plant and animal origin, prepared by modifying
naturally occurring structures, and synthetic polymer osmopolymers. The osmotic potential is proportional to the ionisable group in the osmopolymers chain as evident by the equation:

$$\pi = \frac{RT1C_2}{Mw_2}$$

(Eq.35)

Where $\pi$ is the osmotic pressure generated by the osmotic solute, $R$ is the gas constant, $T$ is the temperature (K), $C_2$ is the osmotic solute concentration in solution (mg/ml), $Mw_2$ is the molecular weight of ionizable species or sites per molecule. If one assumes $C_2$ is about the same for all miscible polymers, then ionisable density (i$Mw_2$) is the determining factor in the osmotic potential for different hydrophilic polymers.

Table 1.3 compares the i/$Mw_2$ values for a group of osmopolymers, depicting that the larger the ionisable density for a polymer, the higher is its osmotic potential which follows the same relative parameters as shown in fig 1.12. The hydration coefficient is the ratio $(W_H/W_P)$ wherein $W_H$ is the weight of water imbibed into the osmopolymers and $W_P$ is the weight of dry osmopolymer. The first layer (drug layer) of push-pull osmotic pump generally exhibits a viscosity about 100 centipoises to 10,000,000 centipoises, when dosage form in use at an animal temperature of 35°C to 45°C (Wong et. al., 1993).
TABLE 1.3 : Physical and chemical properties of osmopolymers

<table>
<thead>
<tr>
<th>Polymer</th>
<th>i</th>
<th>M.W. of repeat unit</th>
<th>Ionizable density (i/M_w^2(\times 10^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorbitol</td>
<td>6</td>
<td>182</td>
<td>3.3</td>
</tr>
<tr>
<td>Polyethylene oxide</td>
<td>1</td>
<td>44</td>
<td>2.27</td>
</tr>
<tr>
<td>Sodium carboxy vinyl polymer</td>
<td>2</td>
<td>94</td>
<td>2.13</td>
</tr>
<tr>
<td>Potassium carboxy vinyl polymer</td>
<td>2</td>
<td>110</td>
<td>1.82</td>
</tr>
<tr>
<td>Carboxy vinyl polymer</td>
<td>1</td>
<td>72</td>
<td>1.39</td>
</tr>
<tr>
<td>Pectin</td>
<td>1</td>
<td>200</td>
<td>0.5</td>
</tr>
<tr>
<td>Hydroxy propyl methyl cellulose</td>
<td>1</td>
<td>201</td>
<td>0.50</td>
</tr>
<tr>
<td>Hydroxy propyl cellulose</td>
<td>1</td>
<td>336 *</td>
<td>0.30</td>
</tr>
</tbody>
</table>

* when molar substitution equals 3.0

**Controlled Porosity Osmotic Pumps** - As it is discussed earlier permeability of semi-permeable membrane plays important role in rate of release of drugs from the osmotic pumps. To increase the permeability of membrane and maintaining its semi-permeable nature two layers of membrane are applied on pumps. The inner membrane is microporous membrane, which is made up of cellulosic materials containing some watersoluble pore forming agents. A semi-permeable membrane covers this layer. When the
system is placed in an aqueous environment the soluble components of first layer of coating dissolve, resulting in a micro-porous membrane, which provides greater flux of water into the system.

**Osmotic Bursting Osmotic Pumps** - This system is similar to an elementary osmotic pump except delivery orifice is absent and size may be small. When it is placed in an aqueous environment, water is imbibed and hydraulic pressure is built up inside until the wall ruptures and the contents are released to the environment. Varying the thickness as well as the area of the semi permeable membrane can control release of drug. This system is useful to provide pulsated release of drug.

**Combination of Effervescent Agents with the Drug (Rastogi et. al, 1995)** - This is a commercially important variation of elementary osmotic pump. Drugs, which are poorly soluble at low pH, may precipitate at the pH of gastric fluid, when such a drug (indomethacin) is delivered through osmotic pump it may precipitate on the orifice affecting its functioning. An effervescent compound such as potassium bicarbonate can be incorporated to overcome this problem. When delivered from the pump with the drug solution, the bicarbonate reacts with acid in the exterior environment generating carbon dioxide. The expansion of gas dispenses the precipitated drug, allowing for rapid absorption of the drug and preventing blockage of the orifice.

**Pump for Insoluble Drugs** - In this system for delivering insoluble drugs, particles of osmotic agents are coated with an elastic semi-permeable membrane. These coated particles are then mixed with the relatively insoluble drug and tableted and coated with
the rigid semi-permeable membrane in usual way. When this system is placed in an aqueous environment, water is drawn through the two-membranes in-turn into the osmotic agent particles, which swell and hydrostatic force delivers the insoluble drug out of the orifice.

Advantages (Rastogi et al., 1995)

Apart from reduced dosing frequency, reduced systemic side effects and improved patient compliance, other unique advantages of osmotic pump are as follows:

1. It delivers drugs at zero order release kinetics. Constant delivery rate is an important specification for chronic treatment.

2. The attainable delivery rate is significantly greater than the rate that can be attained with diffusion based systems of comparable size. This is especially important for cases where large dosage of drugs must be administered.

3. Delivery rate is independent of pH and outside agitation. This therefore suggests that the delivery rate is independent of the variation in pH throughout the GIT (advantage over normal enteric coated tablet) and GI motility.

4. Delivery of drugs takes place in solution/suspension form, which is ready for absorption. Thus it is an in situ prepared liquid dosage form.

5. In vitro delivery rate can be accurately predicted since the system is well described by relevant equation and the delivery rate in GI tract is equal to in vitro delivery rate.

6. It is possible to design an osmotic pump for drugs with wide range of water solubilities.
7. Due to its zero order release profile it can be used in very early stages of drug research, such as drug screening, animal toxicology and pharmacology and initial clinical testing.

Limitations
1. Special equipment is required for making an orifice in the system.
2. Residence time of the system in the body varies with the gastric motility and food intake.
3. It may cause irritation or ulcer due to release of saturated solution of drug.

Present Status and Future Trends
Osmotic drug delivery devices possess potential applications in all vistas. The versatility of osmotic drug delivery system is reflected from table 1.4.

Conclusion
This chapter covers the fundamental principles underlying the application of osmotic pressure in controlled delivery of drugs. Therapeutic value of a controlled release pharmaceutical product largely depends on dosage form technology. Osmotic system technology has been extended to allow rate-controlled, constant drug delivery over a wide range of water solubility. Delivery rates and duration can be designed to limits imposed by GI transit time and absorption capacity. In general these systems made 4- and 3- times-a-day regimens obsolete. Instead they made once-a-day dosing
practical for many agents, including drugs with short half-lives. For these and the other reasons, the future of osmotic technology in drug delivery is bright.

TABLE 1.4: Present day osmotic pumps loaded with drug and their applications

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Type of Device</th>
<th>Application</th>
<th>Disease</th>
<th>Drug</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OROS</td>
<td>Clinical Studies</td>
<td>β₂ receptor in CVS disorders</td>
<td>Metoprolol</td>
<td>Sandberg, 1993</td>
</tr>
<tr>
<td>2</td>
<td>OROS</td>
<td>Clinical Studies</td>
<td>Hypertensive Asthma</td>
<td>Metoprolol</td>
<td>Bauer, 1994</td>
</tr>
<tr>
<td>3</td>
<td>Mini-osmotic pump</td>
<td>Research</td>
<td>Depression</td>
<td>Fluoxamine</td>
<td>Bosker, 1995</td>
</tr>
<tr>
<td>4</td>
<td>Mini-osmotic pump</td>
<td>Research</td>
<td>Vaccine development</td>
<td>Antigen (BSA)</td>
<td>Ikeda, 1993</td>
</tr>
<tr>
<td>5</td>
<td>Mini-osmotic pump</td>
<td>Clinical Studies</td>
<td>Cancer Pain</td>
<td>Hydromorphone</td>
<td>Slate D.L., 1993</td>
</tr>
<tr>
<td>6</td>
<td>Mini-osmotic pump</td>
<td>Research</td>
<td>Neovascularization</td>
<td>VEGF</td>
<td>McKellar, 1994</td>
</tr>
<tr>
<td>7</td>
<td>Mini-osmotic pump</td>
<td>Research</td>
<td>Inflammation</td>
<td>Dexamethasone</td>
<td>Wyatt, 1995</td>
</tr>
<tr>
<td>8</td>
<td>Mini-osmotic pump</td>
<td>Research</td>
<td>Leukemia</td>
<td>Doxorubicin + Verapamil</td>
<td>Katz, 1995</td>
</tr>
<tr>
<td>9</td>
<td>MOTS</td>
<td>Clinical Research</td>
<td>Fungal infection</td>
<td>Nystatin</td>
<td>White, 1995</td>
</tr>
<tr>
<td>10</td>
<td>OROS</td>
<td>Vet. use</td>
<td>Parasitic infestation</td>
<td>Milbemycin</td>
<td>Walduck, 1997</td>
</tr>
<tr>
<td>11</td>
<td>OROS</td>
<td>Clinical Studies</td>
<td>Arrythmias</td>
<td>Verapamil</td>
<td>Pastore, 1995</td>
</tr>
<tr>
<td>12</td>
<td>Mini-osmotic pump</td>
<td>Research</td>
<td>Cancer</td>
<td>5-bromo-2-deoxy uridine</td>
<td>Sule, 1994</td>
</tr>
<tr>
<td>13</td>
<td>Mini-osmotic pump</td>
<td>Research</td>
<td>CV disorders</td>
<td>CV drugs</td>
<td>Catellani, 1998</td>
</tr>
<tr>
<td>14</td>
<td>Mini-osmotic pump</td>
<td>Research</td>
<td>Hyperplasia</td>
<td>EGF</td>
<td>Brown, 1993</td>
</tr>
<tr>
<td>15</td>
<td>GITS</td>
<td>Clinical Studies</td>
<td>Angina</td>
<td>Nifedipine</td>
<td>Okimoto, 1999a</td>
</tr>
<tr>
<td>16</td>
<td>OROS</td>
<td>Research</td>
<td>Schizophrenia</td>
<td>Chloropromazine</td>
<td>Okimoto, 1999b</td>
</tr>
</tbody>
</table>