1.1. INTRODUCTION
In a typical therapeutic regimen the drug dose and dosing interval are optimized to maintain drug concentration within the therapeutic window, thus ensuring efficacy while minimizing toxic effects. Survey indicated that dosing more than once or twice daily greatly reduces patient compliance. So, in recent year considerable attention has been made on the development of novel drug delivery system and the main reason for this shift is relatively low development cost and time required for introducing a novel drug delivery system as compared to a new chemical entity. These products provide significant benefits over immediate release formulation, including greater effectiveness in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to simplified dosing schedule (Verma and Garg, 2001).

Conventional oral drug delivery systems are known to provide an immediate release of drug, in which one cannot control the release of the drug and effective concentration at the target site. The bioavailability of drug from these formulations may vary significantly, depending on factors such as physico-chemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the GI tract, GI motility, etc. (Prescott, 1989).

In the recent years, pharmaceutical research has led to the development of several novel drug delivery systems. The role of drug development is to take a therapeutically effective molecule with sub/optimal physicochemical and/or physiological properties and develop an optimized product that will still be therapeutically effective but with additional benefits such as:

- Sustained and consistent blood levels within the therapeutic window
- Enhanced bioavailability
- Reduced inter-patient variability
- Customized delivery profiles
- Decreased dosing frequency
- Improved patient compliance
- Reduced side effects (Bhatt, 2004)

The drug release can be modified by different ways but the most of novel drug delivery system is osmotic principle. The osmotic systems utilize the principles of osmotic pressure for the delivery of drugs in both the routes oral as well as parenteral (Verma et al., 2002). Oral osmotic systems
include gastrointestinal therapeutic systems while parenteral osmotic systems include implantable pumps.

1.1.1. Historical aspects of the Osmotic Pumps

About 75 years after discovery of the osmosis principle, it was first used in the design of drug delivery systems. Rose and Nelson, the Australian scientists, were initiators of osmotic drug delivery (Rose and Nelson, 1955). In 1955, they developed an implantable pump (Fig. 1.1), 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 semi-permeable 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.

![Fig. 1.1: Rose Nelson Pump](image)

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 \( \frac{dm}{dt} \) = rate of mass transfer

\( \frac{dv}{dt} \) = rate of flow of water in to device and \( c \) = concentration

In general, this equation, with or without some modifications, applies to all other type of osmotic systems.
Several simplifications in Rose-Nelson pump were made by Alza Corporation in early 1970s. The Higuchi-Leeper pump (Fig. 1.2) 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.

![Fig. 1.2: Higuchi-Leeper Pump](image)

Further simplified variant of Rose-Nelson pump was developed by Higuchi and Theeuwes (Fig. 1.3). This pump comprises a rigid, rate controlling outer semi permeable membrane surrounding a solid layer of salt coated on the inside by an elastic diaphragm and on the outside by the membrane. In use, water is osmotically drawn by the salt chamber, forcing drug from the drug chamber.

![Fig. 1.3: Higuchi-Theeuwes Pump](image)

In 1975, the major leap in osmotic delivery occurred as the elementary osmotic pump for oral delivery of drugs was introduced. The pump consists of an osmotic core containing the drug, surrounded by a semi-permeable membrane with a delivery orifice. When this pump is exposed to water, the core imbibes water osmotically at a controlled rate, determined by the membrane...
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Introduction

permeability to water and by the osmotic pressure of the core formulation. As the membrane is
non-expandable, the increase in volume caused by the imbibition of water leads to the
development of hydrostatic pressure inside the tablet. This pressure is relieved by the flow of
saturated solution out of the device through the delivery orifice. This process continues at a
constant rate until the entire 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. Normally, the EOP
(Elementary osmotic pump) delivers 60-80% of its contents at a constant rate, and there is a short
lag time of 30-60 min as the system hydrates before zero order delivery from the EOP is obtained
(Theeuwes, 1975).

1.1.2. Osmosis

Osmosis refers to the process of movement of solvent molecules from lower concentration to
higher concentration across a semi permeable membrane. Osmosis is the phenomenon that makes
controlled drug delivery a reality. Osmotic pressure created due to imbibition of fluid from
external environment into the dosage form regulates the delivery of drug from osmotic device.
Rate of drug delivery from osmotic pump is directly proportional to the osmotic pressure
developed due to imbibition of fluids by osmogen. Osmotic pressure is a colligative property of a
solution in which the magnitude of osmotic pressure of the solution is independent on the number
of discrete entities of solute present in the solution. Hence the release rate of drugs from osmotic
dispensing devices is dependent on the solubility and molecular weight and activity coefficient of
the solute (osmogen). Osmotic pressure is the property of the solution in which the non-volatile
solute is dissolved in a volatile solvent.

The first osmotic effect was reported by Abbe Nollet in 1748. Later in 1877, Pfeffer performed
an experiment using semi-permeable membrane to separate sugar solution from pure water. He
showed that the osmotic pressure of the sugar solution is directly proportional to the solution
concentration and the absolute temperature. In 1886, Vant Hoff identified an underlying
proportionality between osmotic pressure, concentration and temperature and revealed that
osmotic pressure is proportional to concentration and temperature and the relationship can be
described by following equation (Santus and Baker, 1995)

\[ \Pi = \mathcal{O} \ c \ R \ T \]

Where, \( \Pi \) = osmotic pressure
Ø = osmotic coefficient  
C = molar concentration  
R = gas constant  
T = absolute temperature  

Osmotic pressure can be measured by osmometer (Jain, 2006) (Fig. 1.4), one side of which contains pure solvent, while the other contains solution. A semi-permeable membrane separates the two sides. The solvent will travel from the solvent side to the solution side until the hydrostatic pressure created by the solvent flux is sufficiently high to stop further flux. Osmotic pressure may be determined 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 the solvent molecule into the solution.

![Fig. 1.4: Osmometer](image)

1.1.3. Basic components of Osmotic System

1.1.3.1. Drug

Drugs which have short biological half-life and can be used for prolonged treatment are ideal candidate for osmotic systems such as Dilitiazam HCl (McClelland et al., 1991), Carbamazepine, Metprolol (Bauer et al., 1994), Nifedipine, Oxprenolol, and Glipizide (Thombre et al., 1999).

1.1.3.2. Osmotic Agent

Osmotic Agents are the ionic compounds consisting of inorganic salts or hydrophilic polymers. These agents can be classified as follows:

1. Water soluble salts of inorganic acids: Magnesium chloride, magnesium sulfate; lithium, sodium, or potassium chloride; sodium or potassium hydrogen phosphate.
2. Water soluble salts of organic acids: Sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate.

1.1.3.3. Semi-permeable Membrane
An important part of the osmotic drug delivery system is the semi-permeable membrane housing. Therefore, the polymeric membrane selection is key to osmotic delivery formulation. The membrane must possess certain performance criteria.

1.1.3.3.1. Ideal Characteristics of Semi Permeable Membrane (Ghosh and Ghosh, 2011)
The Semi Permeable Membrane should have following characteristics i.e.

1. To maintain its dimensional integrity during the operational lifetime of the system, the material must have sufficient wet strength (~10^3 psi) and wet modulus (10^5 psi).
2. Water permeability of the membrane should be enough so as to maintain water flux rate in the expected range. To determine water flux rates, transmission rate of water vapors can be used.
3. The coefficient of reflection and osmotic agent leakiness should reach the limiting value of unity.
4. The membrane must be biocompatible.

Any polymer that is permeable to water but impermeable to solute can be used as a coating material in osmotic devices. E.g. Cellulose esters like cellulose acetate, cellulose acetate butyrate, cellulose triacetate and ethyl cellulose and Eudragit (Jensen et al., 1995).

1.1.3.4. Plasticizers
The type and amount of the plasticizer used in the coating solution has a significant effect in the formulation of osmotic system. They can change viscoelastic behavior of polymers and these changes may affect the permeability of the polymeric films. Some of the plasticizers used are

- Polyethylene glycols
- Ethylene glycol monoacetate; and diacetate- for low permeability
- Tri ethyl citrate
- Diethyl tartrate or Diacetin- for more permeable films

1.1.3.5. 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. They are characterized by having the ability to undergo physisorption with water. Physisorption is a form of absorption in which the solvent molecules can loosely adhere to surfaces of the wicking agent.
via Vander Waals interactions between the surface of the wicking agent and the adsorbed molecule. The function of the wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of increased surface area. Materials, which suitably for act as wicking agents include colloidal silicon dioxide, kaolin, titanium dioxide, alumina, niacinamide, sodium lauryl sulphate (SLS), low molecular weight poly vinyl pyrrolidone (PVP), bentonite, magnesium aluminium silicate, polyester and polyethylene.

1.1.3.6. Pore forming agent

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 wall 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. For example, alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, 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 and polyols such as alcohols and polyvinyl pyrrolidone can be used as pore forming agents.

1.1.3.7. 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 include methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, n-butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, water etc. 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, 2001).


Osmotic pumps can be classified into following categories:
A. Oral osmotic pumps
A.1 Single Chamber Osmotic Pumps
   Elementary osmotic pump
A.2 Multi Chamber Osmotic Pumps
Push-pull osmotic pump
Osmotic pump with non-expanding second chamber

A.3 Specific Types of Osmotic Pumps
Controlled porosity osmotic pump
Osmotic bursting osmotic pump
Liquid OROS
Delayed Delivery Osmotic device
Telescopic capsule for delayed release
OROS-CT (colon targeting)
Sandwiched oral therapeutic system
Osmotic pump for insoluble drugs
Monolithic osmotic systems
OSMAT
Effervescent activity-based osmotic systems
Mini osmotic pump

Osmotic delivery systems for solids

Type I: Single compartment. In this design, the drug and the osmotic agent are located in the same compartment and are surrounded by the semipermeable membrane (SPM). Both the core components are dissolved by water, which enters the core via osmosis. A limitation is the dilution of drug solution with the osmotic solution, which affects the release rate of the drug from the system. Additionally, water-incompatible or water-insoluble drugs cannot be delivered effectively from a single compartment configuration.

Type II: Multiple compartments. In this design, drug is separated from the osmotic compartment by an optional flexible film, which is displaced by the increased pressure in the surrounding osmotic compartment, which, in turn, displaces the drug solution or suspension. The type II system inherently has greater utility than type I systems and can deliver drugs at a desired rate independent of their solubilities in water. One main advantage of these systems is their ability to deliver drugs that are incompatible with commonly used electrolytes or osmotic agents (Fig. 1.5).

Osmotic delivery systems for liquids
Active ingredients in liquid form are difficult to deliver from controlled release platforms because they tend to leak in their native form. Therefore, liquid active agents typically are enclosed in a
soft gelatin capsule, which is surrounded by an osmotic layer that, in turn, is coated with a semipermeable membrane. When the system takes up water from its surroundings, the osmotic layer squeezes the innermost drug reservoir (Fig. 1.6). The increasing internal pressure displaces the liquid from the system via a rupturing soft gelatin capsule (Sastry et al., 2006).

![Classification of osmotic delivery systems: Types I and II](image1)

**Fig. 1.5: Classification of osmotic delivery systems: Types I and II**

![Osmotic delivery system for delivery of a liquid active agent](image2)

**Fig. 1.6: Osmotic delivery system for delivery of a liquid active agent**

### 1.1.4.1. Elementary Osmotic Pumps

It consists of an osmotic core containing drug, coated with semi-permeable membrane (cellulose acetate), with a delivery orifice (Fig. 1.7). The core may or may not contain osmotic agent depending on the activity of the drug (Theeuwes, 1975).
Fig. 1.7: Elementary osmotic pump

When exposed to aqueous environment, the core imbibes water osmotically at a controlled rate through 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 the drug through the orifice, a volume of saturated solution of drug equal to volume of water uptake. The process continuous until the entire solid drug has been dissolved and only a solution filled shell remains. The residual dissolved drug continuous to be delivered (at a declining rate) until the osmotic pressure inside & outside the pump is equal. It delivers 60-80% of its contents at a constant rate. The release rate obtained from the system is illustrated in graph Fig. 1.8.

Fig. 1.8: Release rate of elementary osmotic pump

Delivery rate of drug is dependent on osmotic pressure of the core formulation and membrane permeability. It is independent of the release orifice as long as the cross sectional area ($A_o$) is within the minimum & maximum i.e., $A_{\text{min}} < A_o < A_{\text{max}}$. The size of the orifice must be larger than the minimum size to minimize the hydrostatic pressure within the device (to achieve zero order release rate). The size of the orifice must be smaller than the maximum size to minimize diffusional contribution (Jain, 2001).
1.1.4.2. Push-Pull Osmotic Pumps

It is a modified elementary osmotic pump (Fig. 1.9) through which both poorly water-soluble and highly water soluble drugs can deliver at a constant rate. This system is same as a standard bilayer coated tablet. Upper layer contains polymeric formulation of drug, osmotic agent and other excipients, forms 60-80% tablet weight. This polymeric osmotic agent can form a suspension of drug in situ. Lower layer consist of osmotic agent, colouring agent, polymers and tablet excipients, forms 20-40% tablet weight. To form a single bilayer core, these layers are formed and joined together by tablet compression. Then this tablet core is coated with the semi permeable membrane. After coating, with the help of laser or mechanical drill a small hole is drilled through the membrane on the upper side of the tablet. On placing the system in aqueous media, water enters into the tablet by osmotic pressure created by osmotic agent in both the layers. The osmotic pressure in the drug layer attracts water inside the compartment to form suspension of drug in-situ. The osmotic agent in the lower layer simultaneously pull water into that compartment, resulting in expansion of volume and the expansion of lower layer deliver the drug suspension out of the delivery orifice.

![Fig. 1.9: Push pull osmotic pump](image)

1.1.4.3. Osmotic pump with non-expanding second chamber

Non-expanding second chamber is another type of multi-chamber devices. This type of system can be divided into two sub groups (Srenivasa et al., 2001).

In first type of system, the second chamber is used to dilute the solution of drug escaping the devices. This is advantageous because it reduces GIT irritation risk as drug leaves as dilute solution, not as a saturated solution. However before the delivery of drug from the device, it must pass through a second chamber. Water is pulled into the second chamber either because of osmotic agent or because it contain, water soluble agents such as sodium chloride. These devices
contain two chambers, in one osmotic agent, such as sugar or a salt like sodium chloride while in another chamber drug is present. The osmotic agent solution from first chamber passes through the hole to the drug chamber where it mixes with the solution of drug before delivery through the semipermeable membrane. This device can be used to deliver insoluble drugs.

### 1.1.4.4. Controlled Porosity Osmotic Pump

The pump can be made with single or multi-compartment dosage form, in either form, the delivery system comprises a core with the drug surrounded by a membrane which has an asymmetric structure, i.e. comprises a thin dense skin layer supported by a porous substructure (Fig. 1.10) (Zentner et al., 1985). The membrane is formed by phase inversion process controlled by the evaporation of a mixed solvent system. Membrane is permeable to water but impermeable to solute and insensitive pore forming additive dispersed throughout the wall. When exposed to water, low levels of water-soluble additive are leached from polymer materials that were permeable to water yet remained insoluble. Then resulting sponge like structure formed the controlled porosity walls of interest and was substantially permeable to both water and dissolved drug agents. Rate of drug delivery depends upon the factors are water permeability of the semi permeable membrane and the osmotic pressure of the core formulation, thickness and total surface area of coating (Zentner et al., 1985). All of these variable are under the control of the designer and do not vary under physiological condition, leading to the robust performance allude to above. The rate of flow (dv/dt) of water into the device can be represented as

\[
\frac{dv}{dt} = \frac{A}{h} k (D_p - D_R)
\]

Where \(dv/dt\) = rate of flow of water in to device

- \(k\) = Membrane permeability
- \(h\) = Thickness of semipermeable membrane
- \(A\) = Area of the membrane
- \(D_p\) = Osmotic pressure difference
- \(D_R\) = Hydrostatic pressure difference
Fig. 1.10: Controlled porosity osmotic pump

1.1.4.5. Osmotic bursting osmotic pumps
This system resembles an EOP except in this, delivery orifice is not present and size can be small. When it comes in contact with an aqueous media, water is imbibed and there is an increase in hydraulic pressure inside until the ruptures of wall is there and the contents are released. Release of drug can be controlled by altering the thickness as well as the area of the semi-permeable membrane. This system is used to provide pulsated release of drug.

1.1.4.6. L-OROS (Liquid Oral Osmotic System)
Alza developed L-OROS to diminish the drug solubility issue. L-OROS deliver the drug in the form of liquid so as to get extended release with high bioavailability (Schultz and Kleinebudde, 1997). Generally three types are there:

i. L-OROS hard cap
ii. L-OROS soft cap
iii. Delayed liquid bolus delivery system

Each system consists of liquid drug layer, an osmotic engine or push layer and a coating of semi-permeable membrane. When it is exposed in aqueous media water crosses the rate controlling membrane and osmotic layer get activated. Hydrostatic pressure is developed due to the expansion of the osmotic layer inside the system causing the delivery of liquid formulation from the delivery orifice. Whereas continuous drug delivery is achieved by hard cap or soft cap L-OROS (Fig. 1.11), to deliver a pulse of liquid drug, the L-OROS delayed liquid bolus drug delivery system are designed. It consists of three layers: a placebo delay layer, a liquid drug layer and an osmotic engine, all coated by rate controlling semi-permeable membrane. The delivery orifice is drilled on the placebo layer end of the capsule shaped device. The placebo is released
first, when the osmotic engine expands, delaying drug layer release from 1 to 10 hours, depending on the permeability of the rate controlling membrane and thickness of the placebo layer.

**Fig. 1.11: L- OROS**

### 1.1.4.7. Delayed Delivery Osmotic Device

These are multi-particulate delayed release systems consist of pellets of active pharmaceutical ingredients (with or without osmogen) coated with semi-permeable membrane. Because of their semi-permeable walls, an osmotic device inherently show lag time before drug delivery begins. Although this characteristic is usually cited as a disadvantage, it can be used advantageously. The delayed release of certain drugs (drugs for early morning asthma or arthritis) may be beneficial. Rapid expansion of membrane after contact with aqueous environment resulted in pore formation and API (active pharmaceutical ingredient) release. The application of this system can be used for poorly water soluble drugs (Theeuwes et al., 1993).

### 1.1.4.8. Telescopic Capsule for Delayed Release

Telescopic capsule consists of two chambers (Fig. 1.12), the first chamber contains the drug and an exit port, and the second chamber contains an osmotic engine. The two sections are separated by a layer of wax like material. In this device, the active agent is placed into one of the chamber either manually or by automatic filling mechanism. The bilayer capsule 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 into the closed end of the cap and the barrier layer exposed towards the cap opening. The open end of the filled vessel is fitted inside the open end of the cap, and the two pieces are compressed together until the cap, osmotic bilayer tablet and vessel fit together tightly. As fluid is imbibed the housing of the dispensing device, the osmotic engine expand and exerts pressure on the slidable connected first and second wall sections. During the delay period the volume of reservoir containing the active agent is kept constant, therefore a
negligible pressure gradient exists between the environment of use and interior of the reservoir. As a result, the net flow of environmental fluid driven by the pressure enter the reservoir is minimal and consequently no agent is delivered for the period.

![Image: Telescopic Capsule](image1)

**Fig. 1.12: Telescopic Capsule**

### 1.1.4.9. OROS – CT (colon targeting)

Single osmotic unit or a unit containing five to six Push-Pull Osmotic Pumps filled in hard gelatin capsule (Fig. 1.13). The osmotic system is enteric coated. Gelatin capsule shell dissolves after coming in contact with GI fluids (Liu and Ku, 2000). Enteric coating on the system prevents entry of fluid from stomach to the system and it dissolves after entering into intestine. The water imbibes into the core and push compartment will swell. At the same time, the flowable gel is formed which is pushed out via delivery orifice at predetermined rate.

![Image: OROS-CT](image2)

**Fig. 1.13: OROS-CT**

### 1.1.4.10. Sandwich oral therapeutic system

It consists of polymeric push layer sandwiched between two layers of drug having two delivery orifices (Fig. 1.14). When this system is placed in the aqueous environment the middle push layer having the swelling agents swell, which results in delivery of drug from the two orifices situated
on opposite sides of the tablet. Thus this system is suitable for the drugs which can cause local irritation to the gastric mucosa (Liu et al., 2000).

**Fig. 1.14: Sandwiched osmotic tablets**

1.1.4.11. Osmotic Pumps for Insoluble Drugs
For the delivery of insoluble drugs, particles of osmotic agent are coated with an elastic semi-permeable membrane. These coated particles are then mixed with insoluble drug and then tableted, coated with rigid semi-permeable membrane. When this system is placed in an aqueous solution, water is drawn through two membranes in-turn into the osmotic agents particles, which swell and hydrostatic force delivers the insoluble drug out of the orifice.

1.1.4.12. Monolithic Osmotic System
Monolithic Osmotic System is composed of a simple dispersion of a water-soluble agent in a polymeric matrix. When this system is placed in the aqueous environment, water imbibes in to system by the active agent which results in rupturing of the polymeric matrix capsule surrounding the drug thus deliver it to the outside environment. Initially, this process occurs at the outer of the polymer matrix, but slowly it proceeds towards the interior of the matrix. This system is suitable only if volume of the active agent is incorporated into the device is up to 20 to 30%, as above this level, leaching of the substance takes place (Padma et al., 2003).

1.1.4.13. OSMAT (Osmotic Matrix Tablet)
It is a novel osmotically driven matrix system, which utilizes the hydrophilic polymers to swell, and gel in aqueous medium forming a semi permeable membrane in-situ releases from such a matrix system containing an osmogen can be modulated by the osmotic phenomenon
OSMAT thus combines both matrix osmotic characteristics resulting in a quantum improvement in drug delivery from swellable matrix system. OSMAT produces controlled drug release with adequate delivery rates in an agitation in dependent manner. Thus OSMAT represents simple, versatile, and easy to fabricate osmotically driven controlled drug delivery system based upon low cost technology.

### 1.1.4.14. Effervescent Activity-Based Osmotic System

This is the variation of elementary osmotic pump. Drugs (indomethacin) which are poorly soluble at low pH may precipitate at pH of gastric fluid may affect the functioning of the pump. An effervescent compound (potassium bicarbonate) is incorporated to overcome this problem. When delivered from the pump with the drug solution, the bicarbonate reacts with acid in the exterior environment producing carbon-dioxide. The expansion of the gas dispenses the precipitated drug. This allows the rapid absorption of the drug and prevents the blockage of orifice (Okimoto et al., 1998).

### 1.1.4.15. Mini Osmotic Pump

This is the most advanced version in the category of implantable pumps developed by Alza Corporation (Fig. 1.15). It is composed of three concentric layers:

- Drug reservoir
- Osmotic sleeve
- Rate controlling semi-permeable membrane

There is an additional component called flow modulator is inserted into the body of the osmotic pump after filling. Drug reservoir 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 system is placed in aqueous environment, water enters through the semi-permeable membrane, which compresses the flexible drug present in drug reservoir. This results in the displacement of drug through the flow modulator. It is available between 0.25-10 ml/h delivery rates for the duration of 1 day to 4 week.
1.1.5. Factors Affecting Drug Release Rate/ Formulation Aspects

1.1.5.1. Solubility

Solubility of the drug selected for osmotic formulation is a very important factor as the solubility is directly proportional to the release kinetics from the osmotic system. Drugs with high and low water solubility do not form a good candidate for osmotic delivery. If needed, the solubility of drug in the core can be modulated by solubility-modifying approaches:

1. Use of swellable polymers: vinyl acetate copolymer, polyethylene oxide have uniform swelling rate which causes drug release at constant rate.
2. Use of wicking agents: These agents may enhance the surface area of drug with the incoming aqueous fluids. E.g. colloidal silicon dioxide, sodium lauryl sulfate, etc.
3. Use of effervescent mixtures: Mixture of citric acid and sodium bicarbonate which creates pressures in the osmotic system and ultimately controls the release rate.
4. Use of cyclodextrin derivatives: They are known to increase solubility of poorly soluble drugs. The same phenomenon can also be used for the osmotic systems (Thombre et al., 1999).
5. Use of alternative salt form: Change in salt form may change solubility.
7. Resin Modulation approach: Ion-exchange resin methods are commonly used to modify the solubility of APIs. Some of the resins used in osmotic systems are Poly (4-vinyl pyridine), Pentaerythritol, citric and adipic acids (Herbig et al., 1995).
8. Use of crystal habit modifiers: Different crystal form of the drug may have different solubility, so the excipient which may change crystal habit of the drug can be used to modulate solubility.

9. Co-compression of drug with excipients: Different excipients can be used to modulate the solubility of APIs with different mechanisms like saturation solubility, pH dependent solubility. Examples of such excipients are organic acids, buffering agent (Verma and Garg, 2004).

1.1.5.2. 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 simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment. Table 1.1 shows osmotic pressure of commonly used solutes in controlled release formulations.

<table>
<thead>
<tr>
<th>Compounds of mixture</th>
<th>Osmotic pressure (atm)</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td>Mannitol-Lactose</td>
<td>130</td>
</tr>
<tr>
<td>Dextrose</td>
<td>82</td>
</tr>
<tr>
<td>Potassium sulphate</td>
<td>39</td>
</tr>
<tr>
<td>Mannitol</td>
<td>38</td>
</tr>
<tr>
<td>Sodium phosphate tribasic.12H₂O</td>
<td>36</td>
</tr>
<tr>
<td>Sodium phosphate dibasic.7 H₂O</td>
<td>31</td>
</tr>
<tr>
<td>Sodium phosphate dibasic.12 H₂O</td>
<td>31</td>
</tr>
<tr>
<td>Sodium phosphate monobasic.H₂O</td>
<td>28</td>
</tr>
</tbody>
</table>

1.1.5.3. Size of Delivery Orifice

For the drug delivery, orifice is one of the most important parts in the membrane. To control the drug delivery from the system, the orifice size must be optimum. For optimum delivery the size
of orifice should be smaller than the maximum size \( A_{\text{max}} \) to minimize the diffusion of solute from the orifice. Due to small size of orifice, the hydrostatic pressure may not be relived because small size can lead to deformation of the system thus resulting in unpredictable drug release. The orifice size range in osmotic pumps ranges from 600µ to 1 mm.

1.1.5.4. Membrane Thickness

Membrane thickness plays an important role in controlling the rate of penetration of water into the osmotic system. By selecting suitable membrane material the permeability of water into the membrane can be increased. A 1000 fold variation in the time of release of the active ingredient is possible by varying the thickness of the membrane. The rate of drug release can be varied by varying the membrane material, while small change up to a 5% can be best achieve by varying the membrane thickness.

1.1.5.5. Use of Wicking Agents

Wicking agents increases the contact surface area of the drug with the incoming aqueous fluid. By creating channels or a network of increased surface area, the wicking agent increases the rate of drug released from the orifice of the osmotic system. The examples of wicking agents are PVP, colloidal silicon dioxide & Sodium lauryl sulphate.

1.1.5.6. Type and Amount of Plasticizer

Plasticizers & low molecular weight diluents are used to modify the physical properties and to improve film forming characteristic of polymers. The plasticizers can convert a brittle and hard polymer into a softer, more pliable material and can make it more resistant to physical and mechanical stress. The low molecular diluents added to dilute the mixture for controlling the viscosity effectively. The permeability of the polymer films can be affected by polymer which results in the change of drug release rate from the osmotic tablets.

1.1.6. Evaluation of Osmotic Pumps

Evaluation of osmotic pumps can be done by two ways:

*In-vitro* evaluation

*In-vivo* evaluation

1.1.6.1. *In-vitro evaluation* (Ozdemir and Sahin, 1997)

**Visual inspection:** Visual inspection of the film for smoothness, uniformity of coating, edge coverage and luster.
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.

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.

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

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 (Swanson et al., 1987).

1.1.6.2. 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 widely been 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) (Kaushal and Garg, 2003). In-vivo evaluation can also be performed in healthy human volunteers. Various pharmacokinetic parameters ($C_{\text{max}}$, $t_{\text{max}}$, AUC and MRT) and relative bioavailability can be calculated.

Marketed Products: Listed in Table 1.2.

Table 1.2: Marketed products

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>API (Active Pharmaceutical Ingredients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efidac 24®</td>
<td>Chlorpheniramine</td>
</tr>
<tr>
<td>Acutrim®</td>
<td>Phenylpropanolamine</td>
</tr>
<tr>
<td>Sudafed 24®</td>
<td>Pseudoephedrine</td>
</tr>
<tr>
<td>Volmax®</td>
<td>Albuterol</td>
</tr>
<tr>
<td>Minipress XL®</td>
<td>Prazocine</td>
</tr>
<tr>
<td>Ditropan XL®</td>
<td>Oxybutynin chloride</td>
</tr>
<tr>
<td>Procardia XL®</td>
<td>Nifedipine</td>
</tr>
<tr>
<td>Glucotrol®</td>
<td>Glipizide</td>
</tr>
<tr>
<td>Covera HS®</td>
<td>Verapamil HCl</td>
</tr>
<tr>
<td>DynaCirc CR®</td>
<td>Isradipine</td>
</tr>
<tr>
<td>Invega®</td>
<td>Paliperidone</td>
</tr>
<tr>
<td>Viadur®</td>
<td>Leuprolide acetate</td>
</tr>
<tr>
<td>Chronogesic™</td>
<td>Sufentanil</td>
</tr>
</tbody>
</table>
Osmotic drug delivery systems for oral and parenteral use offer distinct and practical advantages over other means of delivery. The following advantages have contributed to the popularity of osmotic drug delivery systems.

i. The delivery rate of zero-order is achievable with osmotic systems.

ii. Delivery may be delayed or pulsed, if desired.

iii. Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.

iv. The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.

v. For oral osmotic systems, drug release is independent of gastric pH and hydrodynamic conditions.

vi. The release from osmotic systems is minimally affected by the presence of food in the gastrointestinal tract.

vii. A high degree of in vivo- in vitro correlation (IVIVC) is obtained in osmotic systems.

1.1.8. Concept of Asymmetric Membrane
An asymmetric membrane is a controlled device consists of a drug-containing core surrounded by a membrane, which has an asymmetric structure (Thombre et al., 1999). It is composed of a thin, dense skin layer supported by a thicker, porous substructure layer. The asymmetrical design of membrane combined the advantage of high selectivity of a dense membrane with the high permeation rate of both the porous membrane and thin dense membrane.

1.1.8.1. Features of Asymmetric Membrane Osmotic System
Asymmetric membrane (AM) film-coated delivery systems are unique embodiment of osmotic devices in the use of phase inversion technology to create the semipermeable asymmetric membrane.

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.

AM dosage forms are the high water permeable and controlled porosity resulting from the spray coating process.
A comprehensive model describing drug release from asymmetric membrane dosage form consists of osmotic and diffusional contribution (Amsden et al., 1995). The diffusional contribution is derived from the fact that the asymmetric membrane is not perfectly semipermeable therefore a portion of drug is released by diffusion primarily through pores in the coating the total mass of drug delivered per unit time \( \frac{dm}{dt} \) is modeled by (Donald, 2005)

\[
\frac{dm}{dt} = \frac{dm}{dt}_o + \frac{dm}{dt}_d
\]  
(1)

\( o \) = Osmotic pump  \( d \) = Diffusion  \( t \) = Total

The total drug release profile is described by

\[
\frac{dm}{dt} = \frac{AC}{hP_w \Delta \Pi} + \frac{P_d AC}{h}
\]  
(2)

1.1.8.2. Manufacturing method

Preparation of asymmetric membrane by phase inversion can be accomplished by either wet or dry process (Donald, 2005)

1.1.8.2.1. Dry process: Asymmetric membrane is formed by phase inversion of polymer controlled by the rate of evaporation of volatile solvents in the coating formulation (Philip and Pathak, 2007).

1.1.8.2.2. Wet process: The polymer is dissolved in a solvent system, then cast as a film and immersed into a quench bath of non-solvent for polymer. The solvent from first step is extracted from the cast polymer (Philip and Pathak, 2006).

Phase inversion denotes the process of transforming a polymer in solution to a macromolecular gel. Originally the polymer is dissolved in a solvent system that constitutes a single phase then formation of two interdispersed liquid phases. Further drying results in formation of a primary and secondary gel.

1.1.8.3. Polymers Used to Fabricate Asymmetric Membrane Dosage Form (Donald, 2005)

Asymmetric membrane dosage forms have been fabricated from wide range of polymers including cellulose derivative, polysulfones, polyanamides, polyurethane, polypropylene, poly (vinyl chloride) polyvinyl alcohol, poly (vinylidine fluoride), ethylene vinyl acetate, ethylene vinyl alcohol, poly (methyl methacrylate).

The cellulose derivatives consist of cellulose ester or ethers containing mono-, di-, or triacyl esters. Other cellulose derivatives employed in reverse osmosis membranes have been incorporate into AM dosage forms, such as cellulose nitrate, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate trimelliate,
cellulose acetate methyl sulfonate, cellulose acetate p- toluene sulfonate and cellulose methacrylates.

1.1.9. Nutraceuticals

Nutraceutical is recognized internationally as the singular word that describes the emerging industry of food or food-related substances with potential medical and health benefits. The new word has helped give an identity to this field. The role of nutraceuticals in the treatment and prevention of disease is now being investigated in a wide range of illnesses, including heart disease, cancer, diabetes, arthritis, hypertension, high cholesterol levels, and osteoporosis. The potential benefit of nutraceuticals for anxiety and depression is also being explored.

1.1.9.1. Classification

The food products used as Nutraceutical contain the following except probiotics; all the components are found in fruits, vegetables and different types of herbal foods (Kalia, 2005).

1. Antioxidant
2. Prebiotics
3. Probiotics
4. Polyunsaturated fatty acid
5. Dietary fibres

1.1.9.2. Selected possible uses for Nutraceuticals

The use of nutraceuticals can be found in AIDS, Alzheimer’s disease, anti-aging, anti-cancer, anti-fatigue, anxiety, appetite suppression, arthritis and joint aging, attention deficit disorder, cancer, cardiovascular disease, colon care, chronic fatigue syndrome, depression, diabetes, dyspepsia, energy boosters, erectile dysfunction, immune boosters, inflammatory diseases, memory improvement, menopause, muscle builders, obesity, seasonal affective disorder (SAD).

1.1.9.3. Reason for selecting Nutraceuticals:

Nutraceuticals have the potential to play a role in the prevention and treatment of diseases. The nutraceuticals are preferred due to:

1. Nutraceuticals are positioned at the interface of food and drugs, and provide medical as well as health benefits.
2. Since new molecule is difficult to discover, more expensive and risky than ever before, many pharmaceutical companies are now trying to produce nutraceuticals to which there is undoubtedly a very huge and growing market.
3. Increased healthcare cost with conventional pharmaceuticals.
4. Nutraceuticals are gaining popularity as people are relying on them for safeguarding their health and avoiding side effects associated with drugs as well.
5. Renewable sources.
6. Long history of use and better patient tolerance as well as public acceptance.
7. Local availability.
1.2. Objectives of the Research

Nutraceuticals have opened a door to a potential golden era of medicine. In the intervening years, it has become a part of the standard lexicon in the nutritional field. A nutraceutical is defined as “any substance considered a food, or part of a food, with medical or health benefits including the prevention, treatment or cure of disease.” Such substances include traditional foods, isolated nutrients, plants, dietary supplements (vitamins), genetically engineered “designer” foods, herbs, and processed foods. Naturally occurring substances with the promise of medical and health benefits need an identity, just like pharmaceuticals.

Lycopene is the main carotenoid in tomatoes and tomato products (Clinton et al., 1998) and occurs also naturally in some other fruits and vegetables, guava, watermelon and pink grapefruit (Nguyen and Schwartz, 1999). Among the common dietary carotenoids, lycopene has the highest singlet oxygen capacity in-vitro (Paiva and Russell, 1999, Di et al., 1989). However, the extremely high lipophilicity (log $P = 17.64$) of lycopene resulting in its extremely low aqueous solubility, which is significant barrier to its oral formulation and bioavailability.

Curcumin, a highly pleiotropic molecule with an excellent safety profile targeting multiple diseases with strong evidence on the molecular level, could not achieve its optimum therapeutic outcome in past clinical trials, largely due to its low solubility and poor bioavailability (Basnet and Basnet, 2011). Thus it is hypothesized that oral bioavailability of nutraceuticals can be enhanced by formulating them as osmotic drug delivery system.

Thus in the proposed work, approach will be made to formulate and evaluate osmotically controlled drug delivery system of lycopene and curcumin with enhanced solubility.

1.2.1. Aims & Objectives

The aim of the present research work is to develop a novel osmotically controlled oral formulation of lycopene and curcumin with enhanced solubility and delayed release which may further increase the bioavailability of drugs. The system comprises osmotic controlled release formulations of lycopene and curcumin through osmotically controlled asymmetric membrane capsule, using solubility modulation approach. Thus, the specific objectives are:
1. Formulation and evaluation of osmotically controlled drug delivery system of lycopene with enhanced solubility.
2. Formulation and evaluation of osmotically controlled drug delivery system of curcumin with enhanced solubility.
3. Pharmacokinetic and statistical analysis of developed formulations.
4. Establishment of *in vitro* and *in vivo* correlation (IVIVC).

**Plan of Work**

1. **Preformulation studies**
   - Identification of drugs
   - Calibration curves at different pH
   - Solubility studies at various pH
   - Solubility modulation study
   - Drug - excipient compatibility study using IR spectroscopy
   - Optimization study using central composite design and factorial design

2. **Formulation and Characterization**
   - Osmotically controlled drug delivery system of lycopene
   - Osmotically controlled drug delivery system of Curcumin

3. **Pharmacokinetic analysis of developed formulation in rabbit model**
4. **Establishment of *in-vitro* and *in-vivo* correlation (IVIVC)**
5. **Stability Studies as per ICH Guidelines**