1. INTRODUCTION

One of the purposes for the development of controlled release (CR) preparations is to find a way to obtain ideal blood drug concentration. Now a day a lot of CR products, such as matrix tablets, osmotic pump, transdermal drug delivery systems and so on, have been developed and appeared in the market. Among all these preparations controlled release membrane preparations (CRMP), whose drug release rate are controlled mainly by membrane coating the solid cores outside, are regarded as excellent CR dosage form.¹

Limitations of preparation:²,³
The preparation of controlled-release dosage forms is subject to several variables of considerable importance. The oral administration route remains the most popular, in spite of a number of problems. This include

- The potential for chemical degradation under various pH conditions in the gastrointestinal tract.
- The influence of gastric emptying and
- Its dependence on food.

Factors affecting controlled release dosage form

1) Dose:
The amount of drug in oral controlled-release dosage form is approximately two or three times greater than the amount of oral conventional dosage forms.

2) Aqueous solubility:
The drug solubility in water is a very important factor that affects its incorporations into oral pharmaceutical dosage forms. The drugs with high or low solubility are not chosen for this kind of pharmaceutical forms.

3) Partitions coefficient:
It explains the ability of a drug to cross the biological membranes and interaction with the receptor. As a first approximation, the more effectively a
drug crosses membranes, the greater is its activity. Drugs with a partition coefficient that is either extremely higher or lower are poorer candidates for formulation into controlled release dosage forms.

1) PKa:
   It allows to determine the un-ionized form of a drug and together with the partition coefficient O/A, allow expecting its absorption.

2) Drug stability:
   The drug must be stable under biological fluids. Otherwise, it is necessary to use methods avoiding its contact with the site of gastrointestinal tract where instability has occurred.

3) Molecular weight:
   The ability of a drug to diffuse through polymeric membrane, is a function of its diffusion coefficient. Drugs with molecular weights greater than 500-700 Daltons have a lower diffusion coefficient, which makes their use in controlled-release forms difficult.

4) Biological half-life:
   It is principal limitation, although it is difficult to define upper and lower limits for the value of half-live of a drug that best suits it for controlled release formulation.
   It is accepted that a drug with a half-life between 2 and 6 hours must be used.

5) Absorption:
   A rapid rate of absorption of the drug relative to its release is essential if the system is to be successful.

6) Distribution:
   Drugs with the high apparent volume of distribution, which in term influence the rate of elimination for the drug, are poor candidates for controlled release.

10) Metabolism:
    Drug, which is extensively metabolized is suitable for controlled release system.

11) Therapeutic Index (TI):
    The release rate of a drug with narrow therapeutic index should be such that the plasma concentration attained is within the therapeutically safe and effective range.
This is necessary because such drugs have toxic concentration nearer to their therapeutic range.

**OSMOTICALLY DRIVEN ORAL DRUG DELIVERY SYSTEMS:**

In recent years considerable attention has been focused on the development of novel drug delivery systems (NDDS). Among various NDDS available in the market, per oral controlled release (CR) systems hold the major market share because of their advantages over others. These system are capable of delivering the drug in a predetermined time and rate thus maintaining the peak plasma level in therapeutic level for a long time period. These dosage forms increases the patient compliance by reducing the dosage frequency. However, drug release from oral controlled release dosage forms may be affected by pH, GI motility and presence of food in the GI tract.

To overcome these drawback osmotically controlled oral drug delivery systems (OCODDS) is developed. Which utilize osmotic pressure as the energy source for the controlled delivery of drugs. Drug release from these systems is independent of pH 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.

"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. In1884, Hugo de Vries invoked osmotic concepts to understand the contraction of the contents of plant cells placed in solutions of high osmotic pressure, where the cell membrane acts as a semipermeable membrane. The osmotic pressure difference between inside and outside environments causes osmotic water loss and results in plasmolysis. In 1886, Van’t Hoff identified an underlying proportionality between osmotic pressure, concentration, and temperature in Pfeffer’s experiment. Later, he revealed a relationship between osmotic pressure and solute concentration and temperature that was similar to the ideal gas equation, where pressure is proportional to concentration.
and temperature. According to Van’t Hoff’s equation, the osmotic pressure in a dilute solution is equal to the pressure that the solute would exert if it were a gas occupying the same volume. Osmotic pressure, a colligative property, depends on the concentration of solute (neutral molecule or ionic species) that contributes to the osmotic pressure. Solutions of different concentrations having the same solute and solvent system exhibit an osmotic pressure proportional to their concentrations. Thus a constant osmotic pressure, and thereby a constant influx of water, can be achieved by an osmotic delivery system that results in a constant release rate of drug. Therefore, zero-order release, which is important for a controlled release delivery system when indicated, is possible to achieve using these platforms. In 1974, Theeuwes and Higuchi applied the principle of osmotic pressure to a new generation of controlled drug delivery devices with many advantages over other existing controlled drug delivery systems. The first of these devices, the elementary osmotic pump, is considered a typical delivery system that operates on osmotic principles.6

1.1 ADVANTAGES OF OSMOTICALLY CONTROLLED ORAL DRUG DELIVERY SYSTEM7-8

- They typically give a zero order release profile after an initial lag time. • Deliveries may be delayed or pulsed if desired.
- Drug release is independent of gastric pH and hydrodynamic condition.
- Increase safety margin of high potency drug due to better control of plasma level.
- Maximum utilization of drug enabling reduction in amount of dose administration.
- The release mechanisms are not dependent on drug.
- A high degree of in-vitro and in vivo correlation.
- Improved patient compliance due to less frequent drug administration
The rationale for this approach that the presence of water in g.i.t. is relatively constant, at least in terms of the amount required for activation and controlling osmotically base technologies.

Limitations of preparation: 9-10

The preparation of controlled-release dosage forms is subject to several variables of considerable importance. The oral administration route remains the most popular, in spite of a number of problems. This include

- The potential for chemical degradation under various pH conditions in the gastrointestinal tract.
- The influence of gastric emptying and its dependence on food.
- If the coating process is not well controlled there is a risk of film defects, which results in dose dumping
- Size of hole is critical and expensive as compared to conventional tablets.

1.2 OSMOTICALLY DRIVEN ORAL DRUG DELIVERY SYSTEM:

Osmotic pressure was reported in 1880s by Vant Hoff, Netherlands physical chemist who won the first Nobel Prize in chemistry in 1901. The first device employing osmotic pressure as energy source to deliver active in active ingredients was reported in 1950s. Because pharmaceutical agent can be delivered at approximate zero-order rate over a long period by osmotic pressure, there has been increasing interest in the development of osmotic device in the past two decades.

The elementary osmotic pump (EOP) was firstly introduced by Theeuwes in 1970s. Disadvantage of the generic EOP is that it is only suitable for water-soluble drugs.

The two-layer push-pull osmotic tablet, which is able to deliver water insoluble drugs, was appeared in 1980s.11 Table 1.1 denotes major historical benchmarks and development in osmotic drug delivery.
### 1.2.1 Major Benchmarks in osmotic drug delivery system

Table 1.1: Benchmarks in osmotic drug delivery system

<table>
<thead>
<tr>
<th>Year</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1748</td>
<td>First report of osmosis</td>
<td>(Banker, 1987).</td>
</tr>
<tr>
<td>1877</td>
<td>Quantitative measurement of osmotic pressure</td>
<td>(AMartin., 1993)</td>
</tr>
<tr>
<td>1955</td>
<td>First osmotic pump by Rose-Nelson developed pump for pharmaceutical research</td>
<td>(Rose et al, 1995)</td>
</tr>
<tr>
<td>1973</td>
<td>Higuchi- Leeper introduced a new version of Rose-Nelson pump with certain modification</td>
<td>(Santus et al, 1995)</td>
</tr>
<tr>
<td>1973</td>
<td>Osmotically powdered agent dispense device with filling means.</td>
<td>(Theeuwes, 1984)</td>
</tr>
<tr>
<td>1975</td>
<td>Introduced the first oral osmotic pump i.e. EOP. It was the major the major mile stone in the field of oral osmotic drug delivery system.</td>
<td>(Cortese et al, 1982)</td>
</tr>
<tr>
<td>1976</td>
<td>Patent granted on the design of Alzet osmotic pumps which later extensively used as an experimental research tool in laboratory animal.</td>
<td>(Theeuwes et al, 1984)</td>
</tr>
<tr>
<td>1979</td>
<td>Osmotic bursting drug delivery device.</td>
<td>(Chein et al, 1984)</td>
</tr>
<tr>
<td>1982</td>
<td>Patent issue for an osmotic system which consist of a layer of a fluid swell able hydro gel to deliver insoluble to very insoluble to very insoluble drug.</td>
<td>(Corteses, et al, 1984)</td>
</tr>
<tr>
<td>1984</td>
<td>First report of combination therapy by use of push pull osmotic pump.</td>
<td>(Theeuwes et al, 1984)</td>
</tr>
<tr>
<td>1985</td>
<td>Controlled porous osmotic pump was developed from which drug is leached out from the coating, eliminating the need of complicated laser drill procedure.</td>
<td>(Zentner et al, 1991)</td>
</tr>
<tr>
<td>1986</td>
<td>Patent issue claiming a delivery system for controlled administration of drug to ruminants.</td>
<td>(Mishra et al, 2006)</td>
</tr>
<tr>
<td>1989</td>
<td>Developed of Push Pull osmotic pump of Nefedipine (Procardia XL) by Pfizer which was the largest selling cardiovascular product in US market until 1995</td>
<td>(Mishra et al, 2006)</td>
</tr>
<tr>
<td>1995</td>
<td>Patent to an osmotic dosage form for liquid drug delivery. The system consist of an outside semi permeable wall, middle osmotic active layer, capsule containing an active agent and an orifice for delivery of the agent.</td>
<td>(Mishra et al, 2006)</td>
</tr>
<tr>
<td>1999</td>
<td>Asymmetric membrane capsule is introduced to deliver the drug through the osmotic pressure. Journal of Applied Pharmaceutical Science, 01 (02); 2011: 38-49</td>
<td>(Mishra et al, 2006)</td>
</tr>
<tr>
<td>2000</td>
<td>DUROS Leuropolid implants i.e. Viadur approved as first implantable osmotic pump for</td>
<td>(Mishra et al, 2006)</td>
</tr>
</tbody>
</table>
1.3 PRINCIPLE OF OSMOSIS

An osmotic system releases a therapeutic agent at a predetermined, zero order delivery rate based on the principle of Osmosis, which is movement of a solvent from lower concentration of solute towards higher concentration of solute across a semi-permeable membrane.\(^{12}\) After administration of osmotic system, water is imbibed into the core osmotically through semi permeable membrane resulting in development of hydrostatic pressure that pumps drug containing solution or suspensions out of the core through one or more delivery ports. The delivery from the system is controlled by the water influx through semipermeable membrane.

Water influx into osmotic system can be described by the following equation.\(^{13}\)

\[
\frac{dv}{dt} = A \theta \Delta \pi / \tau \\
\]

where,

\(dv/dt\) - Water influx,

\(A\) - The membrane area,

\(\tau\) - The thickness of membrane.

\(\theta\) - Osmotic permeability in \(cm^2.cm/cm^3.atmm\)

\(\Delta \pi\) - Osmotic pressure difference between the two solutions on either side of membrane

Vant Hoff’s equation, which suggests proportionality between osmotic pressure, concentration and temperature. According to the Vant Hoff’s equation, the osmotic pressure of the dilute solution will be equal to the pressure the solute would exert if it were a gas occupying the same volume.

\[
\pi V = nRT \\
\]

\(^{12}\) Mishra et al, 2006

\(^{13}\) Mishra et al, 2006
Where,
\( \pi \) - stands for osmotic pressure in atmosphere,
\( V \) - stands for volume of solution in liters,
\( n \) - Stands for the number of moles of solute,
\( R \) - Stands for the gas constant (0.082 liter atm/ mole degree), and
\( T \) - Stands for absolute temperature

**1.4 TYPES OF OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEMS**

Based on their design and the state of active ingredient, osmotic delivery systems can be classified as follows:

**1.4.1. Osmotic delivery systems for solids**

*a) 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 as shown in figure 2.
b) 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.

![Classification of osmotic drug delivery systems](image1)

Figure 1.2: Classification of osmotic drug delivery systems

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.

1.4.2. Osmotic delivery systems for liquids.

Active ingredients in liquid for mare 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. The increasing internal pressure displaces the liquid from the system via a rupturing soft gelatin capsule as shown in figure 1.3.

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

Figure 1.3: Osmotic drug delivery system for delivery of liquid active agent
1.4.3 Elementary osmotic pump (EOP).

OROS represents the oral osmotically driven dosage forms developed by ALZA. In the OROS elementary osmotic pump, a tablet core of drug is surrounded by a semipermeable membrane that has one or more openings. After ingestion, the core draws water through the semipermeable membrane from the gastrointestinal (GI) surroundings. The imbibed water dissolves the drug, which is expelled through the orifice in a zero-order fashion as shown in figure 1.4. The semipermeable membrane for OROS typically is composed of cellulose acetate. The membrane is nonextendable and preserves the physical dimensions of the dosage form. Drug delivery is zero order until the solid portion of the core is exhausted. Release will then occur in non-zero-order fashion, declining parabolically. The driving force that draws water into the system is the osmotic pressure difference between the outside environment and the saturated drug solution. Therefore, the osmotic pressure of the drug solution must be greater than the GI osmotic pressure. Hence the elementary osmotic pump is suitable for drugs with solubility greater than about 2 to 10% wt. Because a thick membrane is required to preserve the shape of the core, the water permeation rate can be unacceptably low, particularly if the drug is moderately soluble and possesses low osmotic pressure. Different modifications are used to alleviate the limitations associated with delivery from an EOP. One method involves the use of composite structures that form a microporous layer for the easy penetration of water and a relatively thin semipermeable membrane. The use of bicarbonate salts to prevent blocking of orifice, buffers to modify drug solubility and addition of osmotic agents to the core represent other modifications that can be explored.

![Figure 1.4: Drug release mechanism from osmotic tablet](image-url)
Release kinetics in elementary osmotic pumps

The elementary osmotic delivery system consists of an osmotic core containing drug and, as necessary, an osmogen surrounded by a semipermeable membrane with an aperture as shown in figure 5. 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. 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 non-equilibrium thermodynamics, which describes the volume flux \( \frac{dV}{dt} \), across the semipermeable membrane in the form of the following equation

\[
\frac{dV}{dt} = \left( \frac{A}{h} \right) L_P (\sigma \Delta \pi - \Delta P)
\]  

(1.3)

Where,

\( \Delta \pi \) and \( \Delta P \) = osmotic and hydrostatic pressure differences, respectively, across the membrane

\( L_P \) = mechanical permeability

\( \sigma \) = reflection coefficient, which accounts for leakage of solute through the membrane

\( A \) = surface area of the membrane

\( h \) = membrane thickness
The corresponding solute delivery rate $\frac{dm}{dt}$ can be expressed as follows:

$$\frac{dm}{dt} = \left( \frac{A}{h} \right) L_{fr}(\sigma \Delta \tau - \Delta P)C$$

Where,

$C$ is the solute concentration in the delivered fluid.

**1.4.5 Push-pull osmotic pump:**

It is a modified elementary osmotic pump. It can be used for delivery of drugs having extremes of water solubility, i.e. both poorly water-soluble and highly water soluble drugs at a constant rate. It is a bilayer tablet coated with a semipermeable membrane. Drug along with osmogen is present in the upper compartment where as lower compartment consists of polymer osmotic agents. The drug compartment is connected to the outside environment via a delivery orifice. After coming in contact with the aqueous environment, polymeric osmotic layer swells and pushes the drug layer as shown in figure 1.6 thereby delivering the drug in the form of a fine dispersion via the orifice.
1.4.6 Multiparticulate delayed release system:

It consists of pellets of drug with or without osmogent coated with a semipermeable membrane. These pellets, after coming in contact with the aqueous environment, imbibe water osmotically, which results in a rapid expansion of the membrane leading to the formation of pores and drug release.

1.4.7 Osmotic bursting osmotic pumps:

In these systems, delivery orifice is absent. 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. This osmotic bursting device can be employed to control drug release by varying the thickness as well as the area of the semipermeable membrane.

1.4.8 Combination of effervescent agents with the drug:

This is a commercially important variation of EOP. Drugs, which are poorly soluble at low pH, may precipitates at the pH of gastric fluid, when such drug (indomethacin), is delivered through osmotic pump it may precipitate on the orifice affecting its function. 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 gas. The expansion of gas dispenses the precipitated drug, allowing for rapid absorption of the drug in the stomach.

1.4.9 Pump for insoluble drugs:

In this system for delivering insoluble drugs, particles of osmotic agent are coated with an elastic semi-permeable membrane, these particles are then mixed with the relatively insoluble drug and compressed into tablet 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.
1.4.10 Controlled porosity osmotic pump:

It contains water-soluble additives in the coating membranes, which after coming in contact with water, dissolves resulting in an in-situ formation of a microporous membrane. The resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from these systems was found to be primarily osmotic, with simple diffusion playing a minor role. The release rate from these types of systems is dependent on the coating thickness, level or leachable components in the coating, solubility of the drug in the tablet core, and osmotic pressure difference across the membrane, but is independent of the pH and agitation of the release media.

1.5 COMPONENTS OF OSMOTIC SYSTEMS

The major formulation components of a typical osmotic delivery system include drug, osmotic agents, and a semipermeable membrane.

1.5.1 Osmotic components

Table 1.2: Compounds that can be used as an osmogen

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inorganic acids</td>
<td>lithium sodium or potassium chloride; Lithium, sodium or potassium sulphate; Sodium or potassium hydrogen phosphate etc.</td>
</tr>
<tr>
<td>Water-soluble salts of Carbohydrates</td>
<td>Sodium and potassium acetate, Arabinose, ribose, xylose, glucose, fructose, galactose, mannose, sucrose, maltose, lactose, raffinose, etc.</td>
</tr>
<tr>
<td>Water-Soluble amino acids</td>
<td>Glycine, leucine, alanine, methionine, etc</td>
</tr>
<tr>
<td>Organic polymeric osmogens</td>
<td>Sodium carboxy methylcellulose, HPMC, Hydroxyethyl methyl cellulose, cross-linked PVP, Polyethylene oxide, carbopols, polyacrylamides, etc.</td>
</tr>
<tr>
<td>Organic acids</td>
<td>magnesium succinate, sodium benzoate, sodium Citrate, sodium ascorbate, etc.</td>
</tr>
<tr>
<td>Inorganic acids</td>
<td>lithium sodium or potassium chloride; Lithium, sodium or potassium sulphate; Sodium or potassium hydrogen phosphate etc.</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>

Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers. Osmotic agents can be any salt such as sodium chloride, potassium chloride, or sulfates of sodium or potassium and lithium. Additionally, sugars such as glucose, sorbitol, or sucrose or inorganic salts of carbohydrates can act as osmotic agents. Hydrophilic polymers encompass osmopolymers, osmogels, or hydrogels. These materials 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.

**Semipermeable membrane–forming polymers for osmotic pumps**

An important part of the osmotic drug delivery system is the semipermeable membrane housing. Therefore, the polymeric membrane selection is key to the osmotic delivery formulation. The membrane should possess certain characteristics, such as impermeability to the passage of drug and other ingredients present in the compartments. The membrane should be inert and maintain its dimensional integrity to provide a constant osmotic driving force during drug delivery. Numerous polymers are currently available to form semipermeable membranes. One class includes cellulosic polymers such as cellulose ethers, cellulose esters, and cellulose ester-ethers. Examples of this group include cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, and mono-, di-, and tricellulosealkanlates. Additional semipermeable membrane–forming polymers are selected from the group consisting of acetaldehyde dimethyl cellulose acetate, cellulose acetate ethyl carbamate, cellulose dimethyl amino acetate, semipermeable polyamides, semipermeable polyurethanes, or semipermeable sulfonated polystyrenes.

The cellulosic polymers have a degree of substitution (DS) of 0 to 3 on the anhydro glucose unit. The DS is the number of hydroxyl groups present on the anhydro glucose unit being replaced by a substituting group. Examples of this group
include cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, and mono-, di-, and tricellulose alkanylates. Cellulose acetate is available in different grades, such as cellulose acetate having a DS of 1 to 2 and an acetyl content of 21 to 35 percent or cellulose acetate having an acetyl content of 32 to 39.8 percent. Other forms of cellulose polymers with a more specific substitution are cellulose propionate with a DS of 1.8, a propyl content of 39.2 to 45 percent, and a hydroxyl content of 2.8 to 5.4 percent or cellulose acetate butyrate with a DS of 1.8, an acetyl content of 13 to 15 percent, and a butyrate content of 34 to 39 percent. Moreover, the semipermeable membrane may consist of a mixture of cellulose acetates, alkanylates, or acrylates with different degrees of substitution.

**Flux-regulating agents**

Delivery systems can be designed to regulate the permeability of the fluid by incorporating flux-regulating agents in the layer. Hydrophilic substances such as polyethyleneglycols (300 to 6000 Da), polyhydricalcohols, polyalkylene glycols, and the like improve the flux, where as hydrophobic materials such as phthalates substituted with an alkyl oralkoxy (e.g., diethyl phthalate or dimethoxyethylphthalate) tend to decrease the flux. Insoluble salts or insoluble oxides, which are substantially water-impermeable materials, also can be used for this purpose.

**Plasticizers**

To give the semipermeable membrane flexibility, plasticizers such as phthalates (dibenzyl, dihexyl, or butyl octyl), triacetin, epoxidizedtallate, or tri-isocytlltrimellitate are added. In the design of osmotic controlled release systems, these plasticizers help to modulate and achieve the required release rate.

1.6 KEYPARAMETERS THAT INFLUENCE DESIGN OF OCODDS

1.6.1 Orifice size:

To achieve an optimal zero-order delivery profile, the cross sectional area of the 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 deform the membrane and affect the zero-
order delivery rate. Therefore, the cross-sectional area of the orifice $S_o$ should be maintained between the minimum and maximum values. Typically, a diameter of about 0.2 mm through a membrane of 0.2-mm thickness is needed to maintain a delivery rate on the order of 10 mg/h for water-soluble compounds.

The minimum cross-sectional area can be estimated from the following equation:

$$S_{min} = 5 \left[ \left( \frac{L}{P_{max}} \right) \mu \left( \frac{dV}{dt} \right) \right]^{1/2}$$

where $dV/dt =$ volme flux through the orifice

$L =$ length of the orifice (usually the same as the thickness of the membrane)

$\mu =$ viscosity of the drug solution flowing through the orifice

$P_{max} =$ maximum tolerated hydrostatic pressure difference across the membrane before the occurrence of deformation of the housing.

The maximum cross-sectional area of the orifice is obtained by specifying that the diffusional contribution to the release rate must be smaller than a fraction $f$ of the zero-order pumping rate and is defined by the following equation:

$$S_{max} = \frac{M_{rZ} f L}{D_s C_s}$$

Where,

$M_{rZ}$ is the amount of the drug delivered in zero-order fashion,

and $D_s$ is the drug diffusion coefficient in the permeating solvent. In practice, a fraction smaller than 0.025 generally is necessary to minimize diffusional contributions.

Some of the reported processes to create delivery orifice in the osmotic system are:
• Laser drilling
• Use of modified punches
• Use of pore formers
• Use of mechanical driller

1.6.2 Solubility

Drugs should have sufficient solubility to be delivered by osmotic delivery. In the case of low-solubility compounds, several alternate strategies may be employed. Broadly, the approaches can be divided into two categories. First, swellable polymers can be added that result in the delivery of poorly soluble drugs in the form of a suspension. Second, the drug solubility can be modified employing different methods such as cocompression of the drug with other excipients, which improve the solubility. For example, cyclodextrin can be included in the formulation to enhance drug solubility. Additionally, alternative salt forms of the drug can be employed to modulate solubility to a reasonable level.

Approaches to deliver drugs having extremes of solubility:

• Co-compression of drug with excipient.
• Use of encapsulated excipient
• Use of swellable polymers
• Use of effervescent mixtures
• Use of cyclodextrin derivative
• Resin modulation approach
• Use of alternative salt form
• Use of crystal habit modifiers
• Use lyotropic crystals
• Use of wicking agents
1.6.3 Osmotic pressure

Osmotic pressure, like vapor pressure and boiling point is a colligative property of a solution in which a non volatile solute is dissolved in a volatile solvent. For controlling the drug release from these systems, it is important to optimize the osmotic pressure gradient between inside compartment and the external environment. If a drug does not possess sufficient osmotic pressure an osmogent can be added in the formulation. Some of the drugs does not posses sufficient osmotic pressure, an osmogent can be added in the formulation. Some of the compounds that can be used as osmogent are listed in table 1. Polymeric osmogents are mainly used in the fabrication of push pull osmotic pumps and other modified devices for controlled release of drugs with poor water solubility.

These are swellable, hydrophilic polymers that interact with the aqueous fluids and swell or expand to an equilibrium state. These polymers have a capacity to retain a significant portion of the imbibed water within the polymer structure. It is possible to confirm the contribution of osmotic pressure in drug release from osmotic system by conducting the release studies in media of different osmotic pressure. The release rates obtained can be plotted against the osmotic pressure difference across the device wall. Using this approach, release of potassium chloride from controlled porosity osmotic pump was studied in aqueous media of different and inverse relation was found between the two. A linear relationship was obtained confirming osmotic release from the system.

1.6.4 Semipermeable membrane

An important part of the osmotic drug delivery system is the semipermeable membrane housing. Therefore, the polymeric membrane selectionis key to the osmotic delivery formulation. The membrane should possess certain characteristics, such as impermeability to the passage of drug and other ingredients present in the compartments. The membrane should be inert and maintain its dimensional integrity to provide a constant osmotic driving force during drug delivery. Numerous polymers are currently available to form semipermeable membranes. One class includes cellulosic polymers such as cellulose ethers, cellulose esters, and cellulose ester-ethers. Examples of this group include cellulose acylate, cellulose diacylate, cellulose
triacylate, cellulose acetate, cellulose diacetate, and mono-, di-, and tricellulose
alkanlylates.

1.7 ARTHRITIS

(from Greek *arthro-*-, joint + -itis, inflammation; plural: arthritides) is a form of joint
disorder that involves inflammation of one or more joints. There are over 100
different forms of arthritis. The most common form, osteoarthritis (degenerative joint
disease), is a result of trauma to the joint, infection of the joint, or age. Other arthritis
forms are rheumatoid arthritis, psoriatic arthritis, and related autoimmune diseases.
Septic arthritis is caused by joint infection. The major complaint by individuals who
have arthritis is joint pain. Pain is often a constant and may be localized to the joint
affected. The pain from arthritis is due to inflammation that occurs around the joint,
damage to the joint from disease, daily wear and tear of joint, muscle strains caused
by forceful movements against stiff painful joints and fatigue.

1.7.1 Classification

There are several diseases where joint pain is primary, and is considered the main
feature. Generally when a Arthritis person has "arthritis" it means that they have one
of these diseases, which include:

a) Osteoarthritis
b) Rheumatoid arthritis
c) Gout and pseudo-gout
d) Septic arthritis
e) Ankylosing spondylitis
f) Juvenile idiopathic arthritis
g) Still's disease

Joint pain can also be a symptom of other diseases. In this case, the arthritis is
considered to be secondary to the main disease; these include: Psoriasis (Psoriatic
arthritis), Reactive arthritis, Ehlers-Danlos Syndrome, Haemochromatosis, Hepatitis

1.7.2 Signs and symptoms

Regardless of the type of arthritis, the common symptoms for all arthritis disorders
include varied levels of pain, swelling, joint stiffness, and sometimes a constant ache
around the joint(s). Arthritic disorders like lupus and rheumatoid can also affect other
organs in the body with a variety of symptoms. Inability to use the hand or walk Malaise and a feeling of tiredness Weight loss Poor sleep Muscle aches and pains Tenderness Difficulty moving the joint It is common in advanced arthritis for significant secondary changes to occur. For example, in someone who has limited their physical activity: Muscle weakness, Loss of flexibility, Decreased aerobic fitness These changes can also impact on life and social roles, such as community involvement.

Disability
Arthritis is the most common cause of disability in the USA. More than 20 million individuals with arthritis have severe limitations in function on a daily basis. Absenteeism and frequent visits to the physician are common in individuals who have arthritis. Arthritis makes it very difficult for individuals to be physically active and many become home bound. It is estimated that the total cost of arthritis cases is close to $100 billion of which nearly 50% is from lost earnings. Each year, arthritis results in nearly 1 million hospitalizations and close to 45 million outpatient visits to health care centers. Arthritis can make it very difficult for an individual to remain physically active, contributing to an increased risk of obesity, high cholesterol or vulnerability to heart disease. Individuals with arthritis are also at increased risk of depression, which may be related to fear of worsening symptoms.

Diagnosis
Diagnosis is made by clinical examination from an appropriate health professional, and may be supported by other tests such as radiology and blood tests, depending on the type of suspected arthritis. All arthritides potentially feature pain. Pain patterns may differ depending on the arthritides and the location. Rheumatoid arthritis is generally worse in the morning and associated with stiffness; in the early stages, patients often have no symptoms after a morning shower. Osteoarthritis, on the other hand, tends to be worse after exercise. In the aged and children, pain might not be the main presenting feature; the aged patient simply moves less, the infantile patient refuses to use the affected limb. Elements of the history of the disorder guide diagnosis. Important features are speed and time of onset, pattern of joint involvement, symmetry of symptoms, early morning stiffness, tenderness, gelling or locking with inactivity, aggravating and relieving factors, and other systemic
symptoms. Physical examination may confirm the diagnosis, or may indicate systemic disease. Radiographs are often used to follow progression or help assess severity.

**Osteoarthritis**

Osteoarthritis is the most common form of arthritis. It can affect both the larger and the smaller joints of the body, including the hands, feet, back, hip, and knee. The disease is essentially one acquired from daily wear and tear of the joint; however, osteoarthritis can also occur as a result of injury. Osteoarthritis begins in the cartilage and eventually causes the two opposing bones to erode into each other. Initially, the condition starts with minor pain during activities, but soon the pain can be continuous and even occur while in a state of rest. The pain can be debilitating and prevent one from doing some activities. Osteoarthritis typically affects the weight-bearing joints, such as the back, spine, and pelvis. Unlike rheumatoid arthritis, osteoarthritis is most commonly a disease of the elderly. More than 30 percent of women have some degree of osteoarthritis by age 65. Risk factors for osteoarthritis include prior joint trauma, obesity, and a sedentary lifestyle. Osteoarthritis, like rheumatoid arthritis, cannot be cured, but one can prevent the condition from worsening. Physical therapy to strengthen muscles and joints is very helpful. Pain medications are widely required by individuals with osteoarthritis. For some patients, weight loss can reduce the stress on the joints. When the disease is far advanced and the pain is continuous, surgery may be an option. Unlike rheumatoid arthritis, joint replacement does help many individuals with osteoarthritis.

**Rheumatoid arthritis**

Rheumatoid arthritis is a disorder in which the body's own immune system starts to attack body tissues. The attack is not only directed at the joint but to many other parts of the body. In rheumatoid arthritis, most damage occurs to the joint lining and cartilage which eventually results in erosion of two opposing bones. Rheumatoid arthritis often affects joints in the fingers, wrists, knees and elbows. The disease is symmetrical (appears on both sides of the body) and can lead to severe deformity in a few years if not treated. Rheumatoid arthritis occurs mostly in people aged 20 and above. In children, the disorder can present with a skin rash, fever, pain, disability, and limitations in daily activities. Often, it is not clear why the rheumatoid arthritis occurred. With earlier diagnosis and aggressive treatment, many individuals can lead
a decent quality of life. The drugs to treat rheumatoid arthritis range from corticosteroids to monoclonal antibodies given intravenously. The latest drugs like Remicade can significantly improve quality of life in the short term. In rare cases, surgery may be required to replace joints but there is no cure for the illness.

**Lupus**
This is a common collagen vascular disorder that can be present with severe arthritis. Other features of lupus include a skin rash, extreme photosensitivity, hair loss, kidney problems, lung fibrosis and constant joint pain.

**Gout**
Gout is caused by deposition of uric acid crystals in the joint, causing inflammation. There is also an uncommon form of gouty arthritis caused by the formation of rhomboid crystals of calcium pyrophosphate known as pseudogout. In the early stages, the gouty arthritis usually occurs in one joint, but with time, it can occur in many joints and be quite crippling. The joints in gout can often become swollen and lose function. Gouty arthritis can become particularly painful and potentially debilitating when gout cannot successfully be treated. When uric acid levels and gout symptoms cannot be controlled with standard gout medicines that decrease the production of uric acid (e.g., allopurinol, febuxostat) or increase uric acid elimination from the body through the kidneys (e.g., probenecid), this can be referred to as refractory chronic gout.

**Treatment**
There is no cure for either rheumatoid or osteoarthritis. Treatment options vary depending on the type of arthritis and include physical therapy, lifestyle changes (including exercise and weight control), orthopedic bracing, medications. Joint replacement surgery may be required in eroding forms of arthritis. Medications can help reduce inflammation in the joint which decreases pain. Moreover, by decreasing inflammation, the joint damage may be slowed.

**Physical and occupational therapy**
In general, studies have shown that physical exercise of the affected joint can have noticeable improvement in terms of long-term pain relief. Furthermore, exercise of
the arthritic joint is encouraged to maintain the health of the particular joint and the overall body of the person. Individuals with arthritis can benefit from both physical and occupational therapy. In arthritis the joints become stiff and the range of movement can be limited. Physical therapy has been shown to significantly improve function, decrease pain, and delay need for surgical intervention in advanced cases. Exercise prescribed by a physical therapist has been shown to be more effective than medications in treating osteoarthritis of the knee. Exercise often focuses on improving muscle strength, endurance and flexibility. In some cases, exercises may be designed to train balance. Occupational therapy can provide assistance with activities as well as equipment.

**Medications**

There are several types of medications that are used for the treatment of arthritis. Treatment typically begins with medications that have the fewest side effects with further medications being added if insufficiently effective. Treatment also depends on the type of the arthritis. For example, the first-line treatment for osteoarthritis is acetaminophen (paracetamol) while for inflammatory arthritis it involves non-steroidal anti-inflammatory drugs like ibuprofen etc.