CHAPTER I

INTRODUCTION

Oral ingestion is one of the oldest and most extensively used route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is little or no control over release of the drug, and effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses. This kind of dosing pattern results in constantly changing, unpredictable, and often sub- or supra-therapeutic plasma concentrations, leading to marked side effects in some cases. Moreover, the rate and extent of absorption of drug from conventional formulations may vary greatly, depending on factors such as physicochemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the gastrointestinal(GI) tract, GI motility, and so on. Uncontrolled rapid release of drug may also cause local GI or systemic toxicity. Better dosage design and delivery can minimize many of these problems. Ideal oral drug delivery systems should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled release(CR) delivery systems provide a uniform concentration/ amount of drug at the absorption site and thus, after absorption, allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration. However, drug release from oral CR dosage forms may be affected by pH, GI motility, and the pressence of food in the GI tract. An appropriately designed osmotically controlled oral drug delivery system(OCODDS) can be a major advance toward overcoming some of these problems. Drug delivery from these systems is not influenced by the different physiological factors within the gut lumen, and the release characteristics can be predicted easily from the known properties of the drug and the dosage form.(Verma, Mishra, and Garg, 2000)

The first device to employ these principles to deliver active ingredients was the Rose-Nelson pump, developed in the 1950s. The first significant commercial osmotic devices were developed at Alza and initially marketed in the 1970s. Such devices included both tablets for oral delivery of human pharmaceuticals and implantable pumps used primarily for animal studies.(Herbig et al., 1995)

Osmotic systems generally consist of an osmotically active core surrounded by a rate-controlling, semipermeable coating. The osmotic pressure of the agent inside the system draws water through the semipermeable coating, forming a saturated aqueous solution inside the device. Water is drawn into the device osmotically and dissolves the agent, forming saturated solution of the agent. Because the membrane is nonextensible, the increase in volume caused by the imbibition of water raises the hydrostatic pressure inside the system slightly. This pressure is relieved by a flow of saturated agent solution out of the device through one or more delivery ports. This process continues at a constant rate until all the solid agent inside the system has been dissolved and only a solution filled shell remains. This residual dissolved agent continues to be delivered but at a declining rate. Cellulose acetate has been known to form semipermeable membranes(SPMs) and is the most widely used polymer for osmotic drug delivery. The deliverly port could be made by a laser beam, mechanical drill or pore-forming agent.

The purpose of this study in using capsule as osmotically active core because it has some advantages, easy taking and production. Another purpose is to investigate the possibility of the osmotically system in capsule. However, there are many factors effecting drug release, for example, the thickness of semipermeable membrane, osmotic pressure, level of pore-forming agent etc. PEG 400 were used as pore forming agent. The effect of PEG and film thickness on lag time and drug release were investigated. Osmotically active core capsule was coated with cellulose acetate using fluidized bed coater.

This study differs from reported paper (Thombre et al,1998) using hard gelatin capsule as shell for osmotic system, constructed cellulose acetate membrane or semipermeable membrane by spraying with fluidized bed coater, and PEG400 controlling ingress of water and releasing of drug. In the contrary, Thombre et al

(1998) reported asymmetric membrane capsules. The capsule wall was made by a phase inversion process in which the membrane structure was prescipitated on stainless steel mold pins by dipping the mold pins into a coating solution containing a polymer-solvent-nonsolvent system followed by dipping into a quench solution. The asymmetric membrane wall was composed of a thin dense region supported on a thicker porous region. The transport of water through an asymmetric membrane is faster than that through a dense membrane.

Objective of this study.

1. To investigate the possibility of using hard gelatin capsule as osmotically active core.
2. To characterize the effect of following factors on drug release : size and position of orifice, type and amount of plasticizer, thickness of cellulose acetate film, type and amount of osmotic agent.
3. To investigate the effect of dissolution testing condition on drug release : rotating apparatus, tonicity and pH of dissolution medium.

Literature review

Sustain released dosage forms are developed for a variety of reasons such as increasing patient compliance, reducing unexpected toxic effect due to high peak concentration and improvement of treatment efficiency because of the less fluctuation in drug delivery. In addition, they imply predictable and reproducible drug release kinetics as well.(Chien et al.,1983)

There are many attempts that have recently been made in developing new techniques for drug delivery. These techniques can regulate the rate of drug delivery, sustain the duration of therapeutic action, and/or target the delivery of drug to a tissue. These advancements lead to the development of the drug delivery systems with the following biomedical benefits.

1. Control administration of a therapeutic dose at a desirable delivery rate
2. Maintain constant drug concentration within an optimal therapeutic level for prolonged duration of treatment.
3. Maximize efficacy-dose relationship.
4. Reduce adverse side effects.
5. Minimize the needs of frequent dose intake
6. Improve patient compliance.

Based on the science and engineering of drug delivery, these technical advancements can be categorized into the following approaches

1. Controlled Drug Release by Diffusion Process.
   - 1.1 Membrane permeation controlled drug delivery.
   - 1.2 Matrix diffusion controlled drug delivery.
   - 1.3 Microreservoir dissolution controlled drug delivery.
2. Controlled Drug Release by Activation Process.
   - 2.1 Osmotic pressure activated drug delivery
   - 2.2 Hydrodynamic pressure activated drug delivery.
   - 2.3 Vapor pressure activated drug delivery.

2.4 Machanic activated drug delivery

2.5 Magnetic force activated drug delivery.

2.6 Ultrasound activated drug delivery.

2.7 Iontophoresis activated drug delivery.

2.8 pH activated drug delivery.

2.9 Ion activated drug delivery

2.10 Swelling activated drug delivery

2.11 Hydrolysis activated drug delivery.

2.12 Enzyme activated drug delivery.

Mechanical pumps were among the first reliable controlled release delivery systems and were developed as methods of infusing drugs. More recent pumps have been small enough to be made implantable. These implantable pumps are generally used to deliver insulin or heparin. It is these implantable mechanical pumps that will be discussed in this chapter.

The development of osmotic pumps is more recent. Osmotic effects are often a problem in controlled release diffusion-controlled devices, as osmotic inhibition of water by water-soluble agents causes the devices to swell or dilute the active agent. However, in recent years researchers have produced a series of devices in which this effect has been used as a driving force for controlled release systems. These devices have been used as implantable systems and in simple oral tablet formulations.

1. Basic osmotic principles.

The first report of an osmotic effect dates to Abbe'Nollet(1748), but Pfeffer(1877) obtained the first quantitative measurements. The form of Pfeffer's experiment is shown in Figure 1. A membrane permeable to water but impermeable

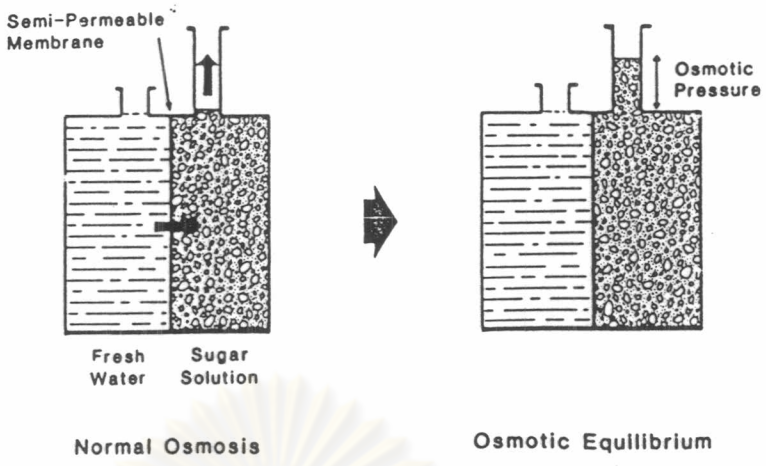

Figure 1: A schematic illustration of osmotic flow and the attainment of osmotic equilibrium.

to sugar is used to separate a sugar solution from pure water. A flow of water then takes place into the sugar solution that cannot be halted until a pressure π is applied to the sugar solution. Pfeffer showed that this pressure, the osmotic pressure π of the sugar solution, was directly proportional to the solution concentration and absolute temperature. Within a few years, van't Hoff had shown the analogy between these results and the ideal gas laws by the expression.

$$\pi = n_2 RT \qquad (1)$$

where n_2 is the molar concentration of sugar (or other solute) in the solution, R is the gas constant, and T the absolute temperature(Santus and Baker,1995).

The van't Hoff equation remains a useful expression for calculating the osmotic pressures of solutes across perfect semipermeable membranes and is quite accurate for low solute concentrations. But if the membrane is not completely semipermeable and allows some passage of solute as well as solvent, the osmotic pressure calculated by Eq(1) will be higher than the experimental value. Deviations from this ideal equation also occur with Concentrated solutions. Osmotic pressures can be obtained to a good approximation from vapor pressure measurements by using the expression

$$\pi = \frac{RT}{v} \ln \left(\frac{\rho_0}{\rho}\right) \quad (2)$$

where ρ_0 is the vapor pressure of the pure solvent, ρ is the vapor pressure of the solution, and v is the molar volume of the solvent. Since vapor pressures are usually much easier to measure than osmotic pressures, this expression is often used.

Osmotic pressure for soluble solutes are extremely high, as shown in the osmotic pressures of solutes commonly used in controlled release pharmaceutical formulations, displayed in Table 1. These high osmotic pressures can produce high water flows across semipermeable membranes.

Table1 : Osmotic pressures of saturated solutions of common pharmaceutical Solutes(Zentner et al.,1990)

Compound or Mixture	Osmotic Pressure (atm)
Lactose-Fructose	500
Dextrose-Fructose	450
Sucrose-Fructose	430
Mannitol-Fructose	415
Sodium chloride	356
Fructose	335
Lactose-Sucrose	250
Potassium chloride	245
Lactose-Dextrose	225
Mannitol-Dextrose	225
Dextrose-Sucrose	190
Mannitol-Sucrose	170
Sucrose	150
Mannitol-Lactose	130
Dextrose	82
Potassium sulfate	39
Mannitol	38
Sodium phosphate tribasic.12H_2O	36
Sodium phosphate dibasic.7 H_2O	31
Sodium phosphate dibasic.12 H_2O	31
Sodium phosphate dibasic.anhydrous	29
Sodium phosphate monobasic. H_2O	28
lactose	23

The osmotic water flow across a membrane is given by the equation

$$\frac{dV}{dt} = \frac{A\theta\Delta\pi}{l} \quad (3)$$

where *dV/dt* is the water flow across the membranes area *A* and thickness l, whose permeability is θ, Δπ is the osmotic pressure difference between the two solutions on either side of the membrane. This equation is only strictly true for completely permselective membranes - that is, membranes permeable to water but completely impermeable to the other solutes in the solution. When this is not the case, the osmotic pressure term must be modified by a factor σ, known as the Staverman reflection coefficient. However, the difference between solute and water permeabilities through almost all membranes used in osmotic devices is sufficiently large that we can make the approximation σ =1 for these membranes. Water permeabilities can vary over a wide range, but most osmotic devices generally use relatively water-permeable materials. Cellulosic polymers, particularly cellulose acetate, are widely used. Typical values for the osmotic water permeability of cellulosic membranes are from 1×10^{-2} to 1×10^{-4} cm^3 mil/cm^2 hr atm.

Small osmotic pumps of this form are sold under the trade name Alzet® (from Alza). They are frequently used as implantable controlled release delivery systems in experimental studies of the effects of continuous administration of drugs. The device has a volume of approximately 170 μL and the normal delivery rate is 1 μ L/hr. Because the delivery rate is fairly slow, the delivery port is made in the shape of a long thin tube to minimize diffusional loss of drug from the device.

Bittner et al.(2000) reported to the impact of co-solvents and the composition of experimental formulations on the pump rate of the ALZET® osmotic pump. The water-miscible co-solvents polyethylene glycol 400 (PEG400), N-methyl-2-pyrrolidone(NMP), and N, N- dimethylacetamide (DMA) exhibit the potential to increase the solubility of poorly water-soluble compounds and therefore they represent promising vehicles for compound delivery using osmotic pumps in early discovery experiments. 1-week pumps were filled with mixtures of either the co-solvents with water(60:40, v/v), with PEG400, or with PEG400/water mixtures of different concentrations. Using the various PEG400/water mixtures, the amount of

co-solvent in the formulation had no significant impact on the overall release profile. By contrast, the use of PEG400 resulted in a significant decrease in the pump rate.

Pope et al. (1985) reported that ivermectin, a potent antiparasitic agnet with activity against internal and external parasites, was delivered to cattle at a controlled zero-order rate for 35 days via orallyadministered, specially weighted, ALZET 2 ML4 osmotic pumps. Prolonged retention within the ruminoreticulum can be achieved by controlling either the density of the formulation or the size of the delivery device. The delivery device or formulation can be maintained in the ruminoreticulum for days, weeks, months, or years.

ELEMENTARY OSMOTIC PUMP

An important further simplification of the original Rose-Nelson concept is the osmotic tablet also developed by Theeuwes(1975) and shown in Figure 2. This device eliminates the separate salt chamber; an active agent having a suitable osmotic pressure is formed into a tablet by a simple tableting machine. The tablet is then coated with a semipermeable membrane, usually cellulose acetate. A small orifice is then drilled through the membrane coating.

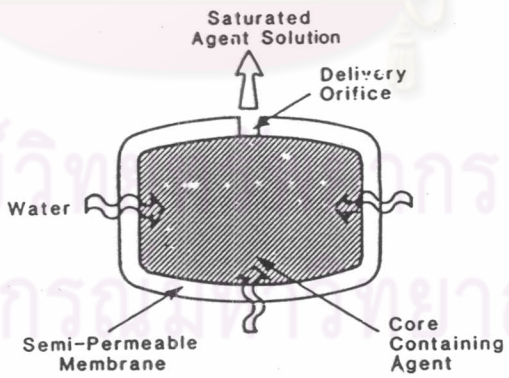

Figure 2 : The Theeuwes elementary osmotic pump.

When this tablet is placed in an aqueous environment, the osmotic pressure of the agent inside the tablet draws water through the semipermeable coating,

forming a saturated aqueous solution inside the device. Water is drawn into the device osmotically and dissolves the agent, forming saturated solution of the agent. Because the membrane is nonextensible, the increase in volume caused by the imbibition of water raised the hydrostatic pressure inside the tablet slightly. This pressure is relieved by a flow of saturated agent solution out of the device through the small orifice. Thus, the tablet acts as a small chemical pump in which water is drawn osmotically into the tablet through the membrane wall and then leaves as a saturated agent solution via the orifice. This process continues at a constant rate until all the solid agent inside the tablet has been dissolved and only solution-filled shell remains. This residual dissolved agent continues to be delivered but at a declining rate.

The elementary osmotic pump was developed by Alza under the name OROS®, and has been commercialized for a number of drugs(Santas and Baker,1995). The first product, Osmosin® (controlled release indomethacin) (Anongmous, 1985), Indosmos® tablet was withdrawn a year after launching because of side effects including bleeding and perforation of the intestinal tract (Santas and Baker, 1995 ; Wilson and Hardy, 1985). Florence, et al.(1984) showed that the external polymeric film of the Osmosin® tablet bound strongly to glass and to the porcine esophagus when partially hydrated.

Theeuwes (1975) studied the delivery rate of KCl from elementary osmotic pump system. From this study, the characteristics of elementary osmotic pump system can be summarized as follow:

The mode of operation of the elementary pump is well understood, and the in vitro delivery rate from the system can be accurately predicted.

The fraction of drug delivered at zero order can be predicted from the compound solubility and core density.

The delivery rate is independent of (a) the pH of the environment, (b) the agitation of the environment, and (c) the size of the orifice for orifice within the predictable range.

Theeuwes et al.(1983) reported the principles of an elementary osmotic pump, systems were designed to deliver indomethacin in solution at a constant rate. Delivery rates were independent of pH, method of measurement, and stirring rate.

Ozdemir and sahin(1997) reported that ibuprofen elementary osmotic pumps were prepared and sodium chloride and polyethylene glycol 6000 were used as osmotic agent. The tablets were coated with a mixture of cellulose acetate and polyethylene glycol400 by the use of a modified fluidized bed apparatus. Delivery orifices on the coated tablets are produced using a microdrill.

Prabakaran et al (2003) reported diltiazem hydrochloride elementary osmotic pump. Its solubility is high. Diltiazem hydrochloride elementary osmotic pump had shown higher release rate. Drug entrapment in polymer matrix or addition of release retardant materials(various polymers) can reduce the release rate of drug. Ingredients of the system were optimized for parameters like drug:polymer ratio and amount of osmogent, for the desired release pattern.

The controlled porosity osmotic pump.

The pumps can be made with single or multiparticulate dosage forms. The core is surrounded by a rate-controlling water-insoluble wall made from a polymer that is permeable to water but impermeable to solute and a pH-insensitive pore-forming additive dispersed throughout the wall.

When the system comes in contact with a gastrointestinal aqueous environment, the coat's water-soluble component dissolves, leaving pores in the membrane. Water diffuses into the core through the microporous membrane and establishes an osmotic gradient that controls drug release. Substances such as sodium chloride, urea, and potassium chloride have been used as water-leachable components in the coating. The factors that control the release rate in these systems are coating thickness, the level of water-leachable component in the coating, solubility of the drug and the osmotic gradient across the coating(Kaushai and garg, 2003).

Gondaliya and Pundarikakshudu (2003) reported that Diltiazem HCl is released from a controlled-porosity osmotic pump predominantly by osmosis. Glycerin used as a pore fomer at a 20%(by weight) concentration of the polymer that contained 35%(by weight) water-insoluble plasticizers showed a zero-order release kinetic. The drug release rate decreased with an increase in dibutylphthalate and triethylcitrate concentration, however,the release rate increased with an increase in the PEG-400 concentration.

Verma and Garg (2004) reported that extended release formulation of glipizide were developed based on osmotic technology. Drug release was directly proportional to the initial level of pore former, but inversely related to the membrane weight. The release from the developed formulations was independent of pH and agitational intensity of the release media, assuring the release to be farily independent of pH and hydrodynamic conditions of the body. Glipizide release from the developed formulations was inversely proportional to the osmotic pressure of the release media.

Okimoto et al (1999) reported that sulfobutyl ether-β-cyclodextrin, $(SBE)_{7m}$- β-CD, which acts as both a solubilizer and as an osmotic agnet. Chlopromazine free base(CLP) was chosen as a model drug for this study. The CLP release profile from an OPT prepared from a core tablet composed of a 1:10 molar ratio of CLP to $(SBE)_{7m}$- β- CD was pH-independent, and was controlled by modulating the membrane thickness of the OPT. Another cyclodextrin, hydroxypropyl- β-cyclodextrin(HP- β- CD), and a sugar mixture of lactose and fructose resulted in pH-dependent release at the same molar ratio. In addition to serving as a solubilizer and osmotic agent, $(SBE)_{7m}$- β- CD can also serve as the controlling agent for pH independent release of CLP from OPTs.

Verma et al (2003) reported that extended release formulations of isosorbide mononitrate, based on osmotic technology. Drug release data from isosorbide mononitrate formulations fitted well into zero-order kinetics, indicating the release to be drug load independent. Membranes were found to develop pores/channels after coming win contact with the aqueous environment; the number of pores being dependent on the initial level of pore former in the membrane. Drug release and the

burst strength of the exhausted shells were found to be dependent on the level of pore former.

Appel and Zentner (1991) reported that using modified ethylcellulose lattices for microporous coating of osmotic tablets. Urea as a pore-forming agent, was added to ethyl cellulose latex, aquacoat, to increase the release rate of drugs from coated osmotic tablets. Modified lattices were used to coat KCl and diltiazem HCl tablets. Scaning electron microscopy (SEM) showed that the urea was eluted from the coat in aqueous solution leaving a porous coating.

Makhija and Vavia (2003) reported that pseudoephedrine was chosen as model drug with an aim to develop a controlled release system. Sodium bicarbonate was used as the osmogent. Cellulose acetate(CA) was used as the semipermeable membrane. Different channeling agents tried were diethylphthalate(DEP), dibutylphthalate(DBP), dibutylsebacate(DBS) and polyethyleneglycol 400 (PEG400). It was found that drug release rate increased with the amount of osmogent due to the increased water uptake, and hence increased driving force for drug release. This could be retarded by the proper choice of channeling agent in order to achieve the desired zero order release profile.

Lindstedt et al.(1989) reported that ethyl cellulose were semipermeable. The permeability of ethyl cellulose was very low, only about one tenth of that of cellulose acetate, but was increased by incorporating hydroxypropyl methylcellulose (HPMC) in the film composition. Cores of potassium chloride(KCl) coated with mixtures of ethyl cellulose and up to 24% HPMC were shown to release their content mainly through osmotic pumping.

Push-pull osmotic pumps.

These pumps are in the form of a two-layer tablet with a drug and push layer. The drug layer comprises the diluents and low molecular weight polymers in addition to the drug. The push layer is constructed of a higher molecular weight osmopolymer and an osmagent. Polymers that can be used include sodium carboxymethyl cellulose, polyoxyethylene, and hydroxypropyl methylcellulose.

When the system comes in contact with an aqueous environment, both layers absorb water. The lower compartment, which does not have an orifice, swells and pushes against the diaphragm. Consequently, the upper chamber contracts, thereby delivering the drug through the orifice as a solution or a suspension. The drug layer in this device constitutes 60-80% of the tablet weight, and the osmotic polymeric layer constitues 20-40%. The devices are capable of delivering drugs with solubility extremes(Kaushai and garg, 2003).

Asymmetric membrane for osmotic drug delivery.

To increase coating permeability further, a new type of osmotic tablet was developed jointly at Bend Research, Inc., and Pfizer. Inc., that consists of a homogeneous tablet core coated with an asymmetric-membrane film. These films are similar to a symmetric membrane made for reverse osmosis or ultrafiltration applications, in that the coating consists of a porous substrate with a thin outer skin. These coatings can be used to make osmotic drug delivery formulations that offer several significant advantages over conventional osmotic tablets. High water fluxes can be achieved using asymmetric coating, facilitating osmotic delivery of drugs with low solubilities and enabling higher release rates. The permeability of the coating to water can be adjusted by controlling the membrane structure. In addition, the porosity of the skin can be controlled, minimizing the time lag before drug delivery begins and allowing the drug to be release from a large number of delivery ports; these ports do not have to be formed in a separate step. In addition, these asymmetric-membrane coatings can be applied to capsules and multi-particulate dosage forms (Herbig et al, 1995).

Thombre et al.(1999) reported that the asymmetric membrane capsule is a controlled drug delivery device which consists of a drug-containing core surrounded by a membrane which has an asymmetric structure. It has a relatively thin, dense region supported on a thicker, porous region. The drug is released over a prolonged duration by diffusion through the capsule walls and/or via osmotic pumping, i.e., by convection through pores in the capsule walls.

Thombre, DeNoto, and Gibbes(1999) reported to delivery of glipizide from asymmetric membrane capsules using encapsulated excipients. The asymmetric membrane capsule can be used to deliver a poorly water soluble drug with a pH sensitive solubility such as glipizide. In order to obtain the desired delivery duration, the drug was solubized with the use of a pH-controlling excipient. In the case of the asymmetric membrane capsule, it was shown that this limitation could be overcome by encapsulating the pH-controlling excipient in a membrane and including the coated excipient in the asymmetric membrane capsule core to prolong its availability within the core. Thus, prolonged release of glipizide could be obtained with the asymmetric membrane capsule.

Prabakaran et al.(2003) reported to osmotically regulated asymmetric capsular systems for simulaneous sustained delivery of anti-tubercular drug. Sustained release asymmetric membrane capsular systems were developed for simultaneous oral delivery of rifampicin and isoniazid sodium in order to reduce the problems associated with the multi drug therapy of tuberculosis. Dense semipermeable membrane systems provided controlled release of both drugs but were devoid of initial burst release of isoniazid. To overcome these drawbacks, a modified asymmetric system was developed by adding appropriate amount of hydrophilic polymer mixture with isoniazid. The system provided satisfactory sustained release of rifampicin and isoniazid with initial burst release may be sufficient to achieve minimum effective concentration in blood.

Delivery rate (Theeuwes, 1975)

The delivery rate of agent from the EOP system is controlled by the solvent influx across the semipermeable membrane which inturn carries the agent to the outside. The equation which describes the volume flux , dV/dt , across semipermeable membrane is

$$\frac{dV}{dt} = \frac{AL_p(\sigma\Delta\pi - \Delta P)}{h} \qquad (4)$$

where $\Delta\pi$ and ΔP are the osmotic and hydrostatic pressure differences, respectively between the inside and outside of the system; L_p is the mechanical permeability; σ is the reflection coefficient; A is the membrane area; and h is the membrane thickness.

The general expression for the solute delivery rate, dm/dt, obtained by pumping through the orifice is described by

$$\frac{dm}{dt} = \frac{dV}{dt} C \qquad (5)$$

where C is the concentration of compound in the dispensed fluid expressed per unit volume of solution.

Substituting Eq. 4 in Eq. 5 results in Eq. 6, which most broadly describes the solute delivery rate

$$\frac{dm}{dt} = \frac{A}{h} L_p(\sigma\Delta\pi - \Delta P) C \qquad (6)$$

As the delivery orifice increases, hydrostatic pressure inside the system is minimized as expressed by the condition $\Delta\pi >> \Delta P$

When the osmotic pressure of the formulation (π) is large compared to the osmotic pressure of the environment, π can be substituted for $\Delta\pi$. Eq. 6 then reduces to a much simpler expression in which the constant k replaces the product $L_p\sigma$

$$\frac{dm}{dt} = \frac{A}{h} k\pi C \qquad (7)$$

The release rate from the EOP is zero order from $t = 0$ until a time t_z at which time all of the solid in the core has dissolved.

$$\frac{dm}{dt_z} = \frac{A}{h} k\pi_s C \qquad (8)$$

S is the solubility, and π_s is the osmotic pressure at saturation.

The rate of dissolution of a single compound within the system is much larger than the rate of pumping as given by Eq. 8. For this reason, the concentration, C, can be replaced by the component solubility, S, from time t = 0 to t = t_z.

The nonzero-order release rate from the system (Eq.7) is obtained by describing the concentration, C, as a function of time. For simplicity, the volume flux into the system is replaced by the symbol F;

$$F = \frac{A}{h} k\pi \qquad (9)$$

and F_s represents the flux during the zero-order time and is related to F by

$$\frac{F_s}{F} = \frac{\pi_s}{\pi} = \frac{S}{C} \qquad (10)$$

By substituting Eq. 10 into Eq. 7, the nonzero-order release rate as a function of concentration is given by

$$\frac{dm}{dt} = \frac{-F_s C^2}{S} \qquad (11)$$

Beyond t_z, the mass, m, of component dissolved into the EOP volume, V, is given by

$$m = CV \qquad (12)$$

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

$$\frac{dm}{dt} = \frac{VdC}{dt} \qquad (13)$$

The delivery rate , dm/dt , can be eliminated between Eqs. 11 and 13 as shown by

$$\frac{-dC}{dt} = \frac{F_s C^2}{VS} \qquad (14)$$

The concentration , C , inside the system is obtained by intrgrating Eq. 16 from time t_z to t , when the concentration changes from S to C.

$$-\int_S^C \frac{dC}{C^2} = \frac{F_s}{VS}\int_{tz}^{t} dt \qquad (15)$$

Solving Eq 15 and rearranging terms result in and expression for the concentration as a function of time:

$$C = \frac{VS}{V+F_s(t-t_z)} \qquad (16)$$

Substituting Eq. 16 into Eq. 11 gives the release rate as a function of time, indicating the parabolic decline:

$$\frac{dm}{dt} = \frac{F_s S}{[1+ F_S/V(t-t_z)]^2} \qquad (17)$$

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

$$\frac{dm}{dt} = \frac{(dm/dt)_z}{[1+(1/SV)(dm/dt)_z (t - t_z)]^2} \quad (18)$$

The delivery rate discussed in this section is the rate from the EOP when most of the contents are delivered by pumping. When the membrane is not ideally semipermeable, a fraction of the agent is delivered by diffusion through the membrane. The case involving both pumping and diffusion is treated in the different way.

The most important application of these devices is for oral drug delivery, where typically all the drug in the tablet must be delivered within 10 to 20 hours as the tablet passes through the gastrointestinal system. Using available coating materials, this type of delivery time requires that rather soluble drugs be used, in order to provide osmotic pressures sufficient for drug delivery. Typically the solubilities of drugs delivered by these pumps are at least 10 to 15 wt% and usually much more, examples of these drugs are sodium indomethacin, potassium chloride (KCl), metoprololol, and acetazolamide.

These elementary osmotic pumps are the basis of a series of controlled release oral drug delivery formulations developed by Alza under the name Oros®. Conventional high-speed tableting machinery and coating machinery are used to form the devices, and the small hole is formed by a laser drilling system connected to a conventional tablet labeling machine.

Size of delivery orifice

The size of the delivery orifice must satisfy two conditions

1. It must be smaller than a maximum size. A_{max} to minimize the contribution to the delivery rate made by solute diffusion through the orifice.

2. It must be sufficiently large, above a minimum size, A_{min} to minimize hydrostatic pressure inside the system, that would affect the zero-order release rate in the following ways. Hydrostatic pressure within the system not only decreases the osmotic influx but also it can increase the volume of the system. During the time

that the system volume is increasing, the out flow would be smaller than the in flow, resulting in a depressed delivery rate.

Mathematically, these two conditions can be expressed by $A_{min} \leq A_0 \leq A_{max}$, where the cross-sectional area of the orifice, A_0, is large than or equal to a minimum value and smaller than or equal to a maximum value.

The size of passageway of osmotic devices was showed in U.S.Patent 3,916,899. A passageway in the wall for dispensing agent from the device, passageway having a maximum cross-section area, A_s, defined as

$$A_s = \frac{L}{F} \times \frac{Q_P}{t} \times \frac{1}{DS} \qquad (19)$$

Wherein L is the length of the passageway, Q_p/t is the mass of agent dispensed from the device per unit time, D is the diffusion coefficient of agent in the dispensed solution, S is the solubility of agent in the fluid and F has a value of from 2 to 1000, passageway having a minimum area, A_s,defined by

$$A_s = \left[\frac{Lv}{t} \times 8 \times \frac{\P\eta}{\Delta P} \right]^{1/2} \qquad (20)$$

Wherein L is the length of the passageway, (v/t) is the volume of agent solution dispensed per unit time, Π is 3.14, η is the viscosity of the solution being dispensed and ΔP is the hydrostatic pressure difference between the inside and the outside of the compartment and having a value of up to about 20 atmospheres.

Material in osmotic pump systems

Osmogent

Osmogents are the osmotically effective compounds that are inorganic or organic compounds, which exhibit an osmotic pressure gradient against an external fluid across wall and film(Theeuwes F, 1978). The osmogent in the compartment acts by imbibing fluid to concentrate solution and then expand in volume with a

corresponding collapse of compartment. The example of salts osmogents are as follows: magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium chloride, sodium carbonate, etc. Some osmogents are carbohydrates, such as, raffinose, sucrose, glucose, sodium alginate, gum etc. The osmogent is usually present in an excess amount and it can be in any physical form such as crystal, pellet, tablet, strip, powder, film or granule.

Semipermeable membrane(Theeuwes,1978 ; Theeuwes,1975)

Film use in this system should be polymer that possesses good semipermeability property, rigid and not flexible. The examples of this type of polymer are cellulose acetate, cellulose triacetate, polyurethane, polyethylene and polyamide. Polymer selection is base on water vapor transmission rate through the film in unit of g/100 square inch /24 hr / 1 mm of film thickness which is shown in Table (Theeuwes F, 1975)

Ozturk et al (1990) studied of the mechanism of drug release from pellets coated with an ethylcellulose-based pseudolatex widely accepted for use as a sustained release coating for pharmaceuticals the release from phenylpropranolamine HCl pellets coated with an ethylcellulose-based film appears to be a combination of osmotically driven release and diffusion through the polymer and/or aqueous pores.

Zhang et al (2003) reported that hydroxypropylmethylcellulose and the mixture of Eudragit RS and RL were applied as the swelling layer and semipermeable outer coat, respectively. The osmotic active agent induces a continuous water influx resulting in a rapid expansion of the membrane. The subsequent formation of fractures leads to a fast drug release after an initial lag time. All the results obtained in the present study indicated that both diffusion and osmotic pumping effect were involved in drug release from the device, but the latter was more dominant.

Cellulosic polymer

Cellulose as Figure 3 , the structure-forming element of plant cells, is one of the most abundant of all organic polymers and has been an important chemical raw material for more than a hundred years. Its use as a membrane material dates back to Fick. In controlled release applications, cellulosic membranes are widely used in applications requiring a membrane permeable to relatively polar hydrophilic active agents. Because of their high water permeability, these membranes are also used in osmotic pumping devices. Microporous cellulose triacetate films have also been investigated as monolithic dispersions for volatile oils and fragances.

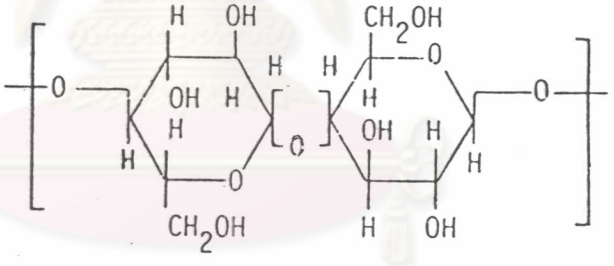

Figure 3 : Structure of cellulosic polymers.

Polymers of this type are widely used in food, cosmetic, and pharmaceutical industries. In pharmaceutics, these polymers are mainly used as coating agent. Cellulose is a polysaccharide consisting of glucose repeat units. There are three free hydroxyl groups per sugar, and all can be substituted. Non-enteric cellulose esters include polymers that are pH-independent solubility profile in water. Examples of polymers, this type are cellulose diacetate (commonly known as cellulose acetate,

CA), cellulose triacetate(CTA) and cellulose acetate butyrate(CAB). The acetyl content in the cellulose deacetate and triacetate should not be less than 29.0 and not more than 44.8 %. For cellulose acetate phthalate(CAP) acetyl content should be between 21.5% and 26.07%, and the amount of phthalyl group should be between 30.0 % and 36.0 %. CAP is soluble in pH 6.2 and higher, therefore it is used as an enteric coating

Cellulose acetates are-prepared by treating cellulose with a mixture of acetic acid and acetic anhydride in the presence of sulfuric acid as a catalyst(Kumer and Banker, 1993). The reaction is generally allowed to proceed to substitute all three hydroxyl groups. The fully substituted triester derivative is then hydrolyzed to give the desired level of substitution. Cellulose phosphate is produced by reaction of cellulose with phosphoric acid in molten urea or with a mixture of phosphoric acid and phosphorus pentaoxide in alcohol, followed by isolation as a sodium salt. (Kumer and Banker, 1993). Various grades of cellulose acetates commercially available, and their degree of substitution(DS) values, molecular weights, molting points, and glass transition temperatures(Tg), are listed in Table 2.

Table 2. Physicochemical properties of cellulose acetate(Kumer and Banker, 1993).

Grade	Acetyl/hydroxyl content	m.p.	T_g	Manufacturer
CA-435-75s	43.5/0.9	204-99	-	Eastman
CA-439-60s	39.5/4.0	240-60	186	Eastman
CA-398-3	39.8/3.5	230-50	180	Eastman
CA-398-6	39.8/3.5	230-50	182	Eastman
CA-398-10	39.8/3.5	230-50	185	Eastman
CA-398-30	39.7/3.5	230-50	189	Eastman
CA-320-5	32.0/9.0	232-54	209	FMC
CA-398-10	39.8/3.4	212-50	191	FMC
CA-435-75s	43.7/0.9	286-306	179	FMC

Solubility of cellulose acetate in organic solvents varies with the level of substitution as well as its distribution in the product. Pure cellulose, despite its free hydroxyls, does not dissolve in water, because of its high crystallinity. Substitution of the hydroxyl groups with, for example, acetyl groups, decreases crystallinity by reducing the regularity of the polymer chains and increases the interchain hydrogen bonding. As the acetate content is increased, the polymer's water sorption increases until the polymer becomes water soluble at 13 wt% acetyl. Further substitution makes the polymer more hydrophobic, and the polymer again becomes water insoluble at approximately 19 wt% acetyl. The fully substituted triacetate has a relatively low water sorption of 10wt%. In principle, any degree of substitution of cellulose is possible, giving a very large range of properties.

The preparation of osmotic pumping devices often requires membranes with very high water permeabilities. Cellulose acetate membranes are used in this application because the water permeability is high and can be easily adjusted by varying the degree of acetylation of the polymer. The permeability of these membranes can be increased further by adding plasticizers to the polymer to increase the water diffusion coefficient or by adding hydrophilic flux enhancers, which increase the water sorption of the membrane. Some hydrophilic plasticizers serve both purposes. The water permeability is increased more than fourfold by the addition of the PEG 400'.

Pore-former

Pore-former is used in making delivery orifices on the surface of osmotic pump tablets. The objective of pore-former is to make numerous delivery orifices due to inconsistency in the release of drug of single delivery orifice cause by clotting of the orifice

Pore-former should possess good solubility property. Such pore-former are sucrose, sorbital, urea and polyethylene glycol. Upon contact with dissolution fluids, the pore formers leached out rapidly to form a multiporous rate-controlling membrane through which the drug diffused in a zero-order fashion.

The pore-former can be a solid or a liquid. The term liquid, for this invention embraces semi-solid, and viscous fluids. The pore-formers can be inorganic or organic. Solid additives include alkali metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulfate etc. Water may be used as the pore-former.The pore-former include organic compounds such as saccharides. The saccharides include the sugars sucrose, glucose,fructose and water soluble polysaccharides. Also, sorbitol, mannitol, organic aliphatic and aromatic oils,including diols and polyols(Zentner et al., 1990)

Solvent

Solvents suitable for manufacturing the wall of the osmotic device include members selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatic, aromatics, heterocyclic solvents and mixtures(Zentner et al., 1990)

Platicizer

Typical plasticizers are those selected from the group consisting of phthalates, phosphates, citrates , polyethylene glycol etc. (Zentner et al., 1990)

Rao and Diwan (1997) reported that permeability of cellulose acetate (CA) free films casted from chloroform solution containing different plasticizers to developing a suitable rate controlling membrane for transdermal use. Dibutyl phthalate (DBP), polyethylene glycol 600 (PEG600) and propylene glycol(PG) were used as plasticizers at a concentration of 40%w/w of dry polymer weight. Permeability characteristics of free films were studied using the drugs such as diltiazem hydrochloride and indomethacin. The films plasticized with PEG600 showed higher permeability for both drugs compared with other film. The order of decrease of permeability of plasticized films with plasticizers is PEG600>PG>DBP

Polyethylene glycol

Polyethylene glycols are a series of water soluble synthetic polymers, the repeating unit being oxyethylene(-OCH_2CH_2-) with either end of the chain comprising and hydroxyl group. The general structure is ($HOCH_2(CH_2OCH_2)$m CH_2OH) where m is an average number of oxyethylene group, i.e., PEG 400, m=8.7 or PEG 4000, M = 69-84. The available molecular weight fractions lie between approximately 200 to several million, the polymers ranging from viscous liquids at room temperature from 200 to 700, semisolids from 1,000 to 2,000 and wax-like solids form 300 to 100,000 above which the solids are resinous and form strong thermoplastic films. The molecular weight range used for solid dispersion lies between approximately 3,000 to 20,000(Craig, 1990)

Polyethylene glycol can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol. Animal studies have also been performed using polyethylene glycol as solvents for steroids in osmotic pumps.

In film coating, solid grades of polyethylene glycol are also widely used as plasticizer in conjunction with film forming polymers. The presence of PEG, especially liquid grades, in film coats tends to increase their water permeability and may reduce protection against low pH in enteric coating films.

Propranolol hydrochloride

Propranolol hydrochloride is a non-selective β-adrenergic blocking agent (Reynolds, 1994).

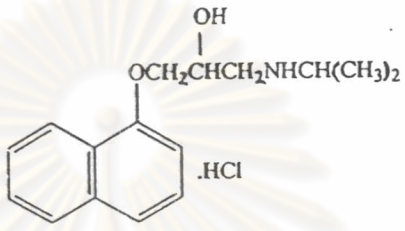

Figure 4 : The structure of propranolol hydrochloride.

Empirical Formula : $C_{16}H_{21}NO_2HCl$

Molecular weight : 295.8

Chemical Name : (1)(+/-)1-Isopropylamino-3-(1-naphthalenyoxy)-2-propanol
(2)1-{(1-methylethy)amino}-3-(1-naphthalenyoxy)-2-propanol

Description : white to off white, crystalline powder, odorless with a bitter taste. It absorbs less than 1% of water at 25°C at relative humidity up to 80%

Melting Point : melts in the range 163° to 166°C

Dissolution Constant : pKa 9.5 (24°C)

Partition Coefficients : in octanol/aqueous buffer pH 7.4 is 1.2

Solubility

Propranolol hydrochloride is soluble 1 in 20 of water and 1 in 20 of ethanol; slightly soluble in chloroform and practically insoluble in ether.

Stability

Propranolol Hydrochloride is affected by light. In aqueous solutions, it decomposes with oxidation of the isopropylamine side chain, accompanied by reduction in the pH and discoloration of the solution. Solutions are most stable at pH 3.0 and decompose rapidly under alkaline conditions.

Propranolol hydrochloride is almost completely absorbed after oral administration. Dosage is 20 mg. to 2 gm. Daily in divided doses. Peak plasma concentration is achieved at approximately two hours in fasting patient. It is highly bound to plasma proteins about 85-95% but it has short plasma half-life 3-4 hours and rapidly hepatic metabolism after oral administration, therefore;it needs several times(3-4 times)by oral regimen.