CHAPTER I

INTRODUCTION

Sustained release products are made for improved treatment of patients such as avoiding patients compliance problems, employing less total drug reliance, i.e. minimize or eliminate local and systemic side effects, less potentiation or reduction in drug activity with chronic use, and minimize drug accumulation with chronic dosing, and improved efficiency in treatment, i.e. cure or control of conditions more promptly, improved control of conditions such as less fluctuation in drug level.

The conventional products often produce plasma fluctuations that exceed the maximum safe therapeutic level and decline below the minimum effective level. The ratio of these two levels is the therapeutic index (TI). The development in sustained products aims at designing a system with a zero order that produces the optimal plasma concentration. It producing controlled therapy index is smaller than the therapeutic index of a drug. The requirements for drug properties of sustained products are short half-life and its narrow therapeutic index.

Propranolol hydrochloride is almost completely absorbed after oral administration. It has a narrow therapeutic index at constant condition in plasma at 20 - 50 μg/ml. It is about 85 - 95 % bound to plasma proteins but it has short plasma half-life of 3 - 4 hours (Evans, 1973) and rapid hepatic metabolism after administration. Therefore, it will needs 3 - 4 times that of oral regimen. Thus, it has been made in sustained release preparation in order to attain those advantages as described.

Elementary osmotic pump is a method of controlling the release rate of the drug. It is a single unit dosage form and the release rate is independent of gastrointestinal pH or motility (Theeuwes, 1983). The elementary osmotic pump comprises a solid core, semipermeable film coating and passageway, as shown in Figure 1.

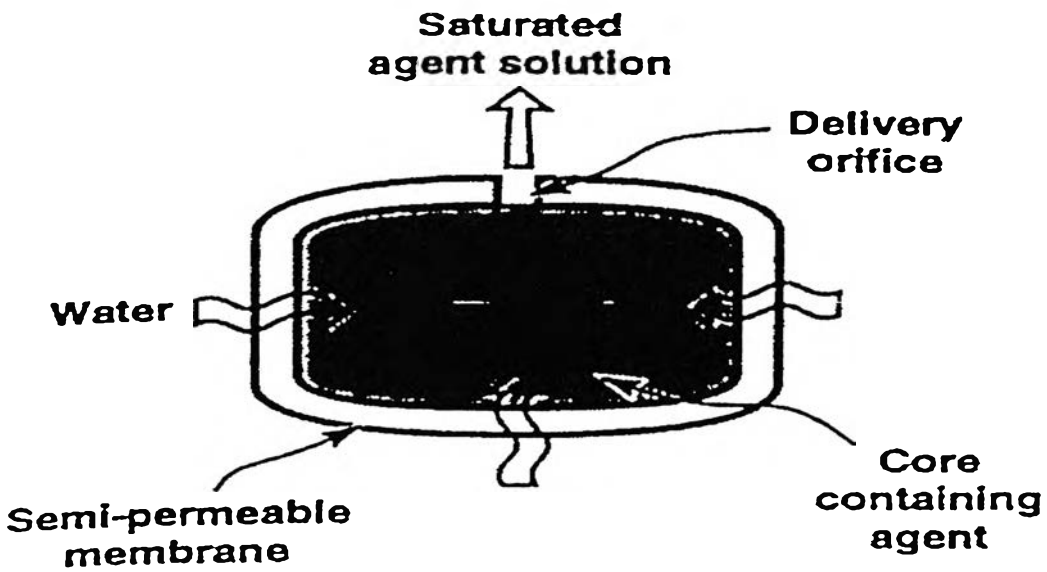

Figure 1(a) The basic structure of elementary osmotic pump(Theeuwes and Ayer, 1978).

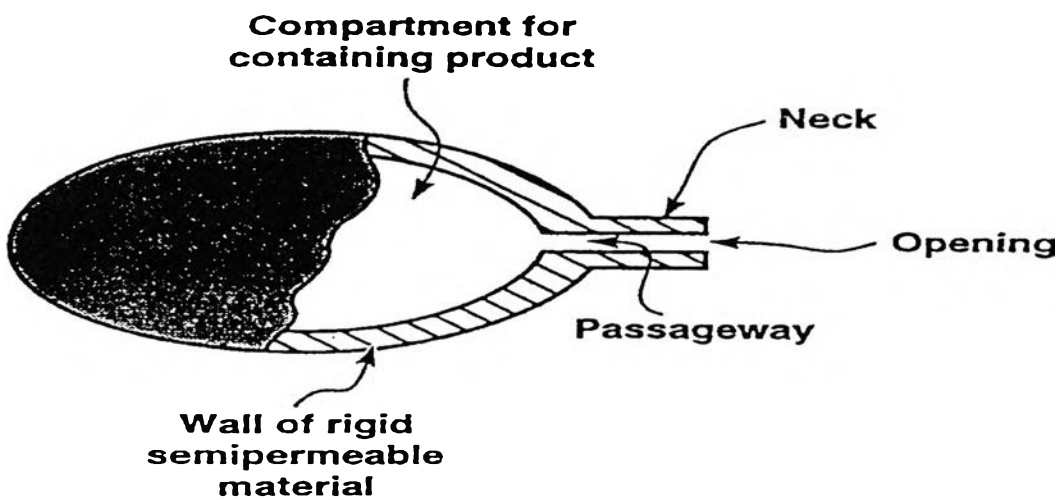

Figure1(b) The basic structure of elementary osmotic pump (Theeuwes and Ayer, 1978).

The release rate is dependent on the properties of core tablets, membrane area, thickness of film coating, and permeability of film, as shown in equation 1.

$$dM / dt = [A. Lp.\sigma.\pi.C] / h \quad \ldots\ldots(1)$$

where

dM / dt	is release rate
A	is surface area
Lp	is mechanism permeability
σ	is reflection coefficient
π	is osmotic pressure
C	is concentration of compound in the dispensed fluid
h	is films thickness

In this study, preparations of propranolol hydrochloride sustained release tablets were produced as osmotic pump systems. The tablets were manufactured in three steps using simple machines, first the drug was compressed into tablets. The tablets were then film coated by a coating machine. Lastly a microdrilling machine was used to make an exit passageway on the tablets.

Cellulose acetate derived from cellulosic polymer group was used as semipermeable film former. Polyethylene glycol 400 and 4000 were used as hydrophilic plasticizer and flux enhancer, respectively. Dibutyl phthalate was selected as hydrophobic plasticizer. Various osmotic agents such as lactose, mannitol, sodium chloride and sucrose were incorporated in the core tablets.

Objective of the study

1. To prepare propranolol hydrochloride microporous osmotic pump tablets using cellulose acetate as semipermeable film former.

2. To study the effect of film formulation; polyethylene glycol 400, polyethylene glycol 4000 and dibutyl phthalate on the physicochemical properties and the release of drug from osmotic pump tablets.

3. To study the effect of osmotic agents in core tablets: lactose, mannitol, sodium chloride and sucrose on the release of drug from osmotic core tablet.

4. To study the effect of size of passageway on the release of drug from osmotic pump tablets.

LITERATURE REVIEWS

1. Controlled-Release drug delivery systems

Sustained-release dosage forms are developed for a variety of reasons such as they may improve patient compliance, reduce unexpected toxic effect due to high peak concentration and improve efficiency in treatment because of the less fluctuations in drug level. Controlled-release drug administration means not only prolonged duration of drug delivery, as in sustained-release and prolonged release, but also implies predictability and reproducibility of drug release kinetics (Chien, 1983). In the exploration of oral controlled drug administration, one encounters three areas of potential challenge :

1. Drug delivery system : Development of a visible drug delivery system which is capable of administering a therapeutic agent at a programmed rate for a duration required for optimal treatment.

2. Gastrointestinal transit time : Prolongation of the gastrointestinal residence time, so the drug delivery system developed can reside at the vicinity of absorption site for sufficient long period of time to deliver all the drug loading dose.

3. Hepatic first-pass elimination : If the drug is subjected to an extensive hepatic "first-pass" elimination, preventive measures should be developed to minimize the extent of hepatic "first-pass" metabolism.

Osmotic pressure-controlled drug delivery system is one of those new drug delivery systems for oral controlled drug administration. Review of literature has

revealed the recent development of a number of novel drug delivery systems which could be utilized for the controlled administration of drugs in the alimentary canal. These potential developments can be outlined and discussed as below literature.

2. Basics of osmotic pump technology

The osmotic pump system is made by basic osmosis theory and the release rate of it is higher than the drug diffusion rate (Theeuwes, 1975). In 1748 Abbe Nollet showed osmosis phenomenon in two compartments with semipermeable membrane (not permeable to solute but it is permeable to solvent or water), water moved from low chemical potention to high chemical potention. Eventually it stopped when the hydrostatic pressure (Gravity) pushed an equal amount of water back to in equilibrium status. The phenomenon of osmosis moves water across semipermeable membrane towards the region of highest chemical potention (solute concentration) and water is passes spontaneously into the high chemical potention of both compartments were equal (Martin, 1983), as shown in Figure 2.

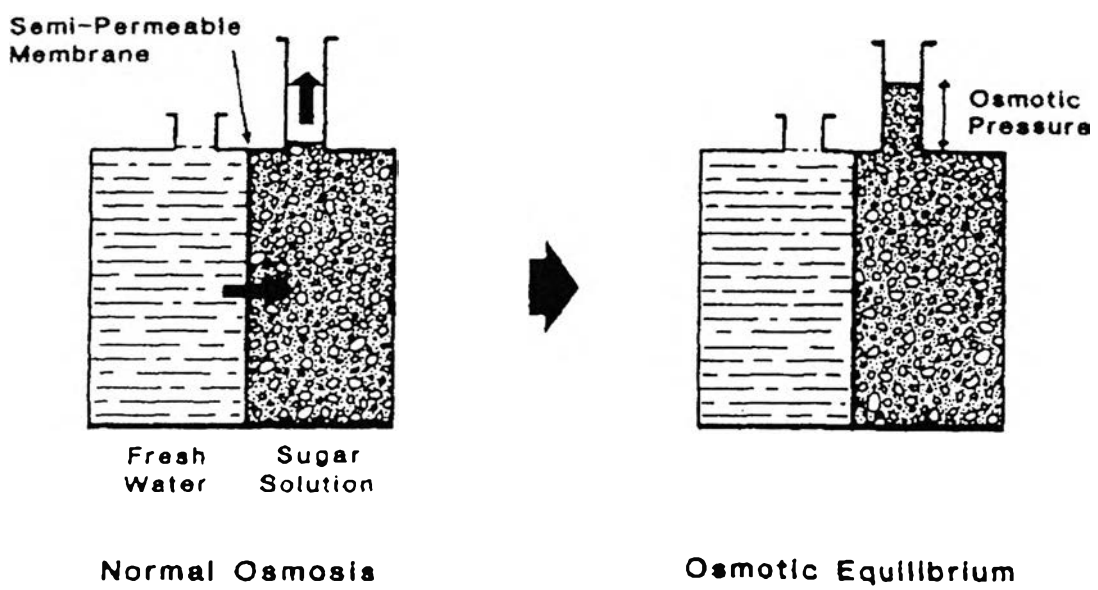

Figure 2 Model of osmosis phenomenon (Baker,1987).

In 1877 Pfeffer made the first qualitative measurements of osmotic pressure. He coated porous clay cups with ferrocyanide to make a "membrane" that allowed water to diffuse freely while sucrose solution diffused very slowly. The clay cups were rigid and could withstand a lot of pressure. He found that the osmotic pressure (P) was proportional to temperature (K) and to the concentration of the solute.

In 1866 Van't Hoff recognized in Pfeffer's data a proportionality between osmotic pressure, concentration and absolute temperature and suggested a relationship that corresponded to the equation for an ideal gas.

Van't Hoff had shown the analogy between solutions and gases and that the osmotic pressure in dilute solution was equal to the pressure that the solute would exert if it were a gas occupying the same volume, as shown in Figure 3. The equation is

$$\pi V = nRT \quad \text{.....(2)}$$

in which

π is the osmotic pressure in atm

V is the volume of the solution in liters

n is the number of moles of solute

R is the gas constant equal to 0.082 liter.atm/mole degree

T is the absolute temperature (K).

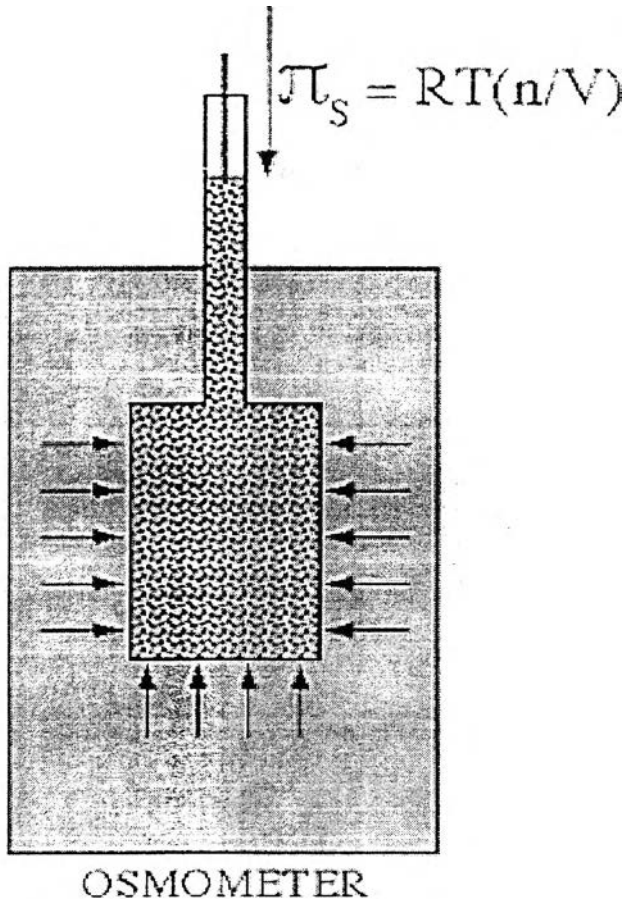

Figure 3 Model of basic osmometer (Martin, 1993).

Observation (Pharmaceutical index, Ed 12)

In reality the above equation is a limiting law applying to dilute solutions, and it simplifies into this form from a more exact expression (equation 2) only after introducing a number of assumptions that are not valid for real solution as the osmotic pressure of solute molecules are exerting pressure on the membrane, just as gas molecules create a pressure by striking the walls of vessel. It is more correct, however, to consider the osmotic pressure as resulting from the relative escaping tendencies of the solvent molecules on two sides of the membrane. Equation 2 can be expressed as

$$\pi = (n / V) . RT = CRT \quad \ldots\ldots (3)$$

in which

C is the concentration of the solute in moles per liter (Molarity).

Morse and others (Martin, 1983) have shown that when the concentration is expressed in molarity rather than molality, the results compare more in approximate with the experimental finding. The Morse equation is

$$\pi = RTm \quad \ldots\ldots (4)$$

Molarity (Osmolarity) is the concentration expressed as moles of solute particle per liter of solution. The osmolarity may be calculated from osmolarity or by summing the particle concentration of each constituent.

Molality (Osmolality) is the concentration of a solution expressed as moles of solute particle per kilogram of water. The osmolality of solution can be determined using an osmometer, which measures either freezing point depression or vapor pressure.

The permeability of water across the semipermeable membrane is proportional to the osmotic pressure difference across the film (Athayde, U.S. Patent 5,257,987). The osmotic pressures for soluble solutes are extremely high, as shown in the osmotic pressure of solutes commonly used in controlled release pharmaceutical formulations, displayed in Table 2 (Theeuwes and Ayer, U.S. Patent 4,077,407).

Table 1 Osmotic pressures of saturated solutions of common pharmaceutical solutes (Baker, 1987).

Compound or Mixture	Osmotic Pressure (atm)
Sodium chloride	356
Fructose	355
Potassium chloride	245
Sucrose	150
Dextrose	82
Potassium sulfate	39
Mannitol	38
Sodium phosphate tribasic	36
Sodium phosphate dibasic	31
Sodium phosphate monobasic	28

These high osmotic pressure can produce high water flows across semipermeable films. The osmotic water flow across a film is given by the equation

$$dV / dt = [A.Lp.(\sigma.\Delta\pi - \Delta P)] / h \quad (5)$$

in which

dV / dt is the volume flux

A is membrane area

h is membrane thickness

Lp is mechanism permeability

σ is reflection coefficient

$\Delta\pi$ is osmotic pressure different, between the inside and outside of system

ΔP is hydrostatic pressure, between the inside and outside of system.

Observation (Baker, 1987)

This equation is strictly for the use of completely permeable selective membrane i.e. membranes permeable to water but completely impermeable to the osmotic agent. The basic concept of osmosis can be used to provide explanation of the osmotic systems such as Rose-Nelson pump, Higuchi-Leeper pump, Higuchi-Theeuwes pump, and Elementary osmotic pump.

2.1 Rose-Nelson pump

The Rose-Nelson pump consists of three chamber : a drug chamber, a salt chamber containing excess solid salt, and a water chamber. The drug and water chambers are separated by a rigid semipermeable membrane, as shown in Figure 4.

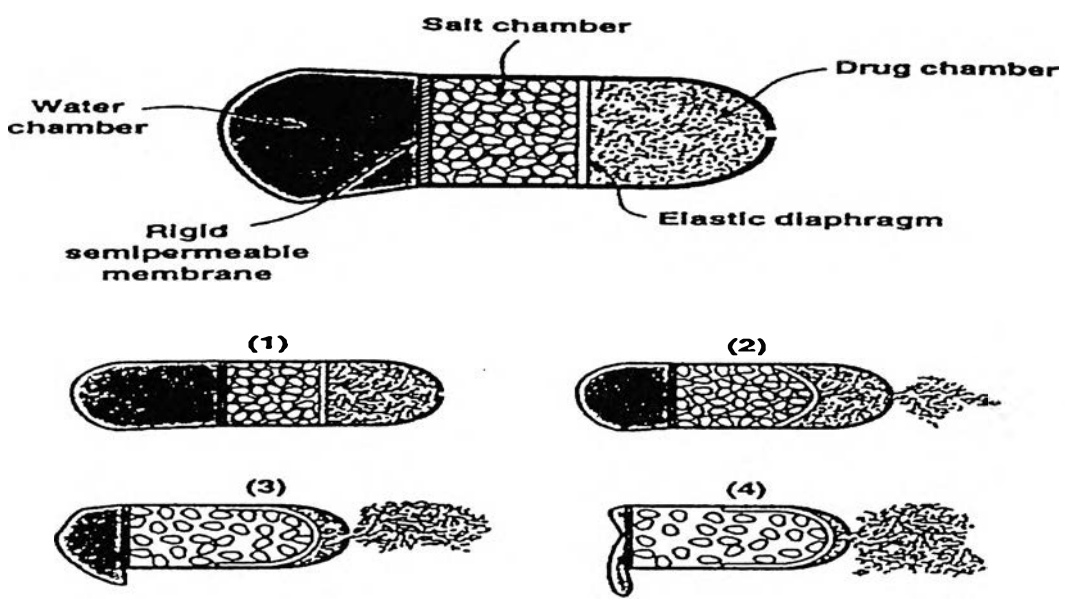

Figure 4 Model of Rose-Nelson pump (Baker, 1987).

The pump is worked by the difference in osmotic pressure across the membrane, which moves water from the water chamber and increases water flow volume. This distends the latex diaphragm separating the salt and drug chamber, thereby pumping drug out of the device. The pumping rate of the Rose-Nelson pump is given by the equation

$$dMt / dt = (dV / dt) . C \quad \ldots\ldots(6)$$

where

dMt / dt is the drug release rate

dV / dt is volume flux of water into the salt chamber

C is the concentration of drug in the drug chamber.

Substituting equation 5 into equation 6 results in equation 7, which describes broadly the solute delivery rate.

$$dMt / dt = [A.Lp. (\sigma.\Delta\pi - \Delta P).C] / h \quad \ldots\ldots(7)$$

As the delivery orifice increases, hydrostatic pressure inside the system is minimized as expressed by condition $\Delta\pi >>> \Delta P$. When the osmotic pressure of the formulation (π) is largely compared to the osmotic pressure of the environment, π can be substituted for $\Delta\pi$. The equation is then reduced to a much simple expression in which the constant " k " replaces the product " Lp.σ ".

$$dM / dt = (A.k.\pi.C) / h \quad \ldots\ldots(8)$$

2.2 Higuchi-Leeper pump

The Higuchi-Leeper pump has no water chamber, and the device is activated by water imbibed from the surrounding environment, as shown in figure 5.

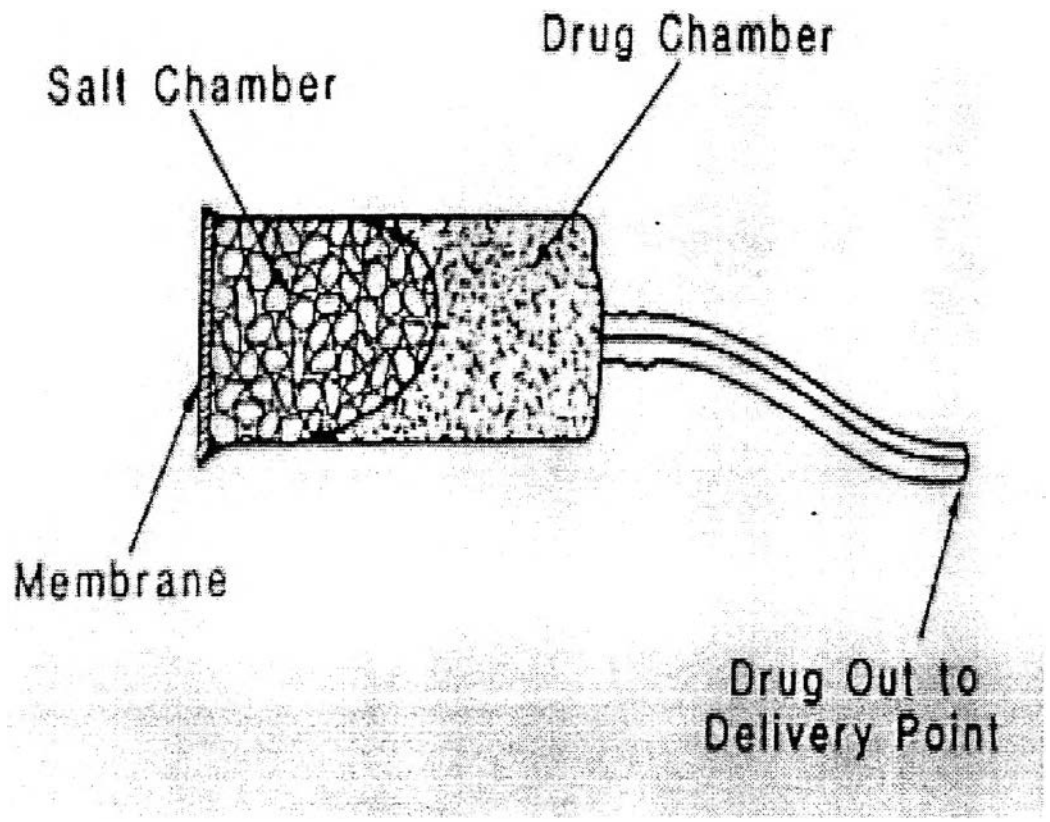

Figure 5 Model of Higuchi-Leeper pump (Baker, 1987).

This pump is activated when it is swallowed or implanted in the body. It was prepared load with drug(s) and then stored for weeks or months prior to use. The pump is contains a rigid housing, and the semipermeable membrane is supported on a perforated frame. This type of pump usually has a salt chamber containing a fluid solution with excess solid salt.

2.3 Higuchi-Theeuwes pump

In the Higuchi and Theeuwes pump device, it comprises a rigid semipermeable membrane (outer) surrounding a solid layer of salt coated on the inside by an elastic diaphragm and on the outside by the membrane, as shown in Figure 6.

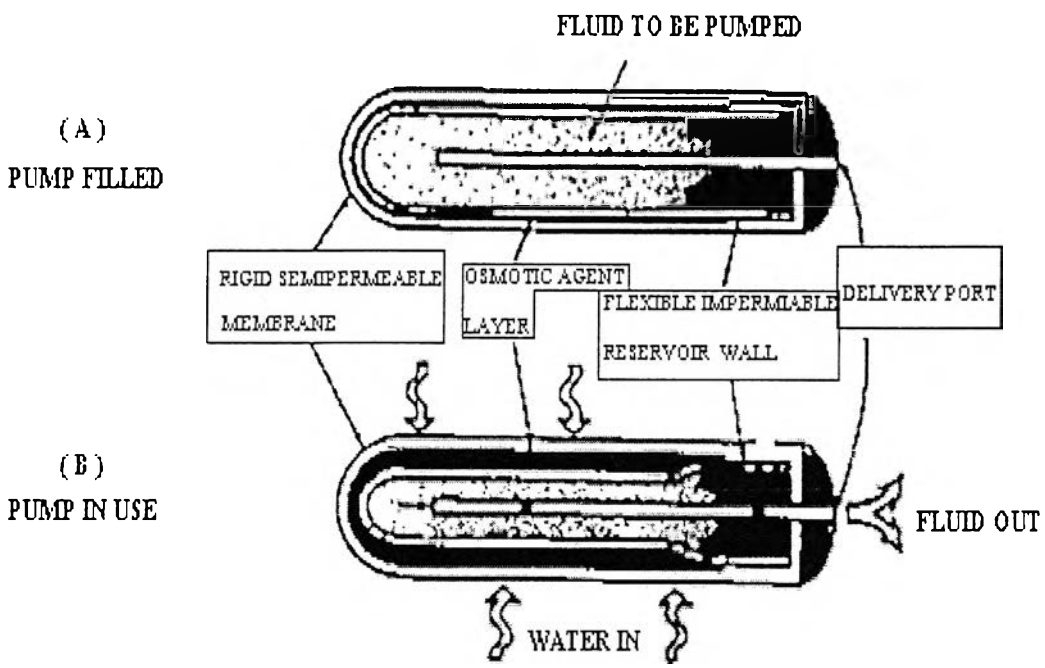

Figure 6 Model of Higuchi-Theeuwes pumps. (Baker,1987)

In use, water is osmotically drawn by the salt through the semipermeable membrane. This water increases the volume of the salt chamber, forcing drug from the drug chamber. The pumps are frequently used as implantable controlled release delivery systems in experiment studies of the effects of continuous administration of drug(s). The device has a volume of approximately 170 μl and the normal delivery rate is 1 μl / hr.

Figure 7 Insertion of osmotic pump delivery system. (Baker,1987)

In Figure 7, one of the devices is shown being implanted in a laboratory rat. 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. The delivery pattern obtained with one of these devices is shown in Figure 8.

They are sold under the trade name "Alzet®" (for animal laboratory) and "Osmet®" (for human laboratory). They are made by Alza's Corporation

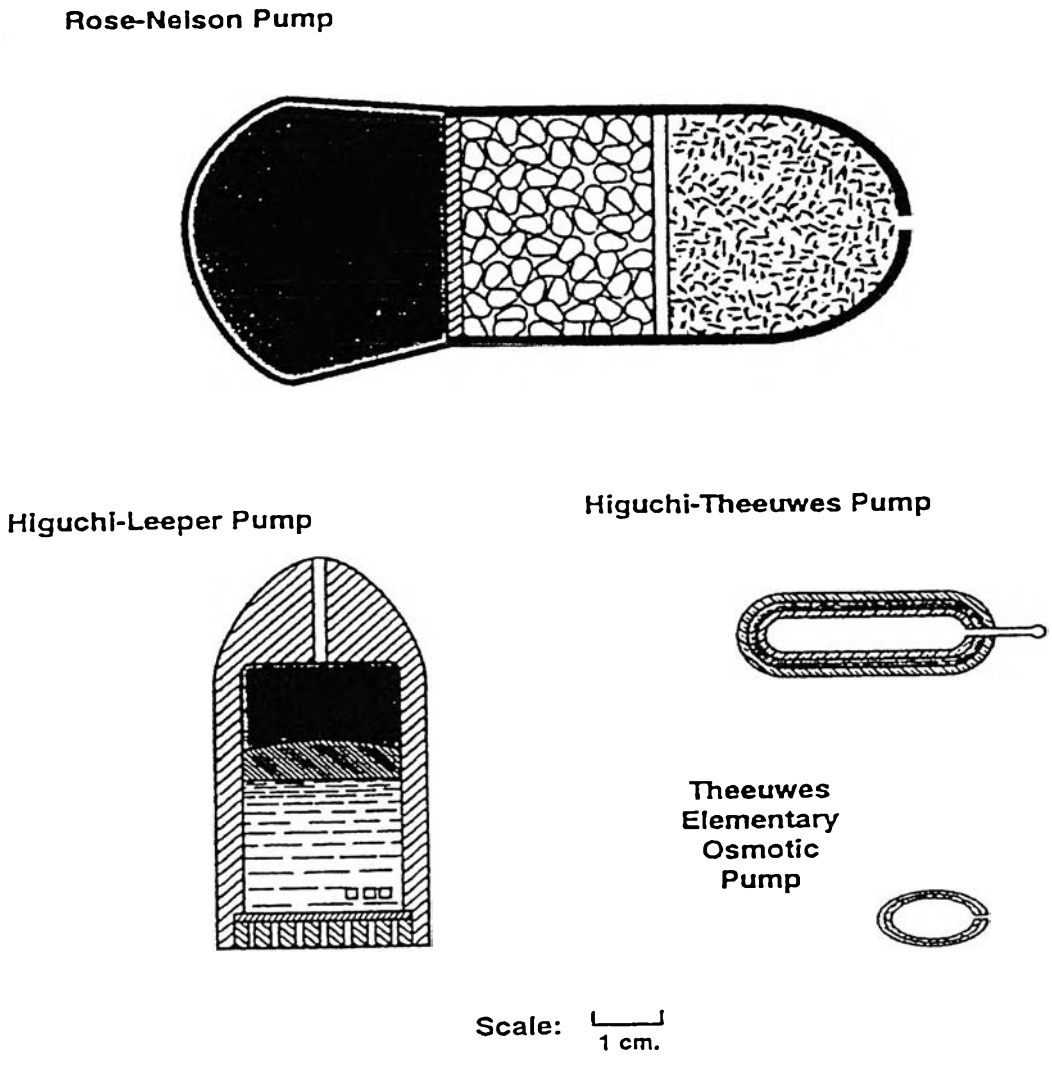

Figure 8 Comparative size of osmotic devices (Zentner, 1989).

2.4 Elementary osmotic pump

In 1974 Theeuwes made first elementary osmotic pump. This device is derived from basic concept of Rose-Nelson pump, but it separates the salt chamber by using the drug itself as the osmotic agent. The device is formed by compressing a drug having a suitable osmotic pressure into a tablet using a tablet machine. The tablet is then coated with a semipermeable membrane, usually cellulose acetate, and a small hole is drilled though the membrane coating. The device is really a coated tablet with a hole and

represents, in a sense, the ultimate simplification of the original Rose-Nelson device. When this tablet is placed in an aqueous environment, the osmotic pressure of the soluble drug inside the tablet draws water though the semipermeable coating, forming a saturated saturated aqueous solution inside the device. The membrane is non-extensible, and the increase in volume caused by the imbibition of water raises the hydrostatic pressure inside the tablet slightly. This pressure is relieved by a flow rate agent solution via the orifice. This process continues at a constant rate until all the solid drug inside the tablet has been dissolved and only a solution-filled shell remains. This residual continues dissolving the drug to be delivered, but at a declining rate, until the osmotic pressure inside and outside the tablet is equal. The driving force to draw water into the device is caused by difference in osmotic pressure between the outside environment and a saturated drug solution. The pumps were developed by Alza's Corporation under the name "OROS®", and have been commercialized for a number of drugs. The technology got off to a rather rocky start, with the first product, Osmosin® (Controlled release indomethacin), being withdrawn a year after launching of the blockbuster, billion-dollar product-controlled-release nifedipine (Procardia XL® in the United States, Adalat CR® in Europe). Related products include Actrium® (phenylpropanolamine, once-daily, over-the-counter appetite suppressant tablets.), Covera-HS™ (verapamil hydrochloride, once-daily controlled-onset extended-release (coer-24™) tablets for the treatment of hypertension and angina pectoris.) Minipress XL® (prazosin, once-daily extended release tablets for the treatment of hypertension. Introduced in France under the trade name Alpress LP®.), and Volmax® (salbutamol, extended release tablets for relief of bronchospasm in patients with reversible obstructive airway disease.). A number of other drugs, include glipizide (Glucotrol XL®, once-daily extended release tablets used adjunct to diet for the control of hyperglycemia in patient with non-insulin-dependent diabetes mellitus.), diltiazem, gemfibrozil and isradipine. Trademark are used to identify products and services of ALZA Corporation and its client companies: ALZET®

is trademark of ALZA Corporation; Adalat CR® is trademark of Bayer AG; Volmax® is trademark of Glaxo Holdings; Acutrium® is a trademark of Novartis; Alpress®, Glucotrol XL®, and Procardia XL® are trademarks of Pfizer Inc.; COER-24™ and Covera-HS™ are trademarks of G.D. Searle & Co.

2.5 Novel elementary osmotic pump

For the first OROS® product in the early 1980s, many attempts were made to expand the range of drugs that could be delivery by this type of osmotic delivery. In particular, the device illustrated in figure 1 (a) and 1 (b) is limited to the delivery of relatively soluble drugs, generally with solubilities of greater than 2 - 5 % w/v. One approach to the problem, discovered relatively early on, was the development of multichamber tablets.

These multichamber tablets can be divided into two main categories (devices with a second expandable osmotic chamber and devices with a non-expanding second chamber), depending on whether one chamber expands into other or whether the chambers are rigid, maintaining their volume throughout the period of operation. These concepts are particularly interesting and valuable because it allows delivery of drug with limited solubility such as nifedipine.

2.6 Devices with a second expandable osmotic chamber

These devices tablets are comprises with two chambers separated by an elastic or removable barrier, as shown in Figure 9.

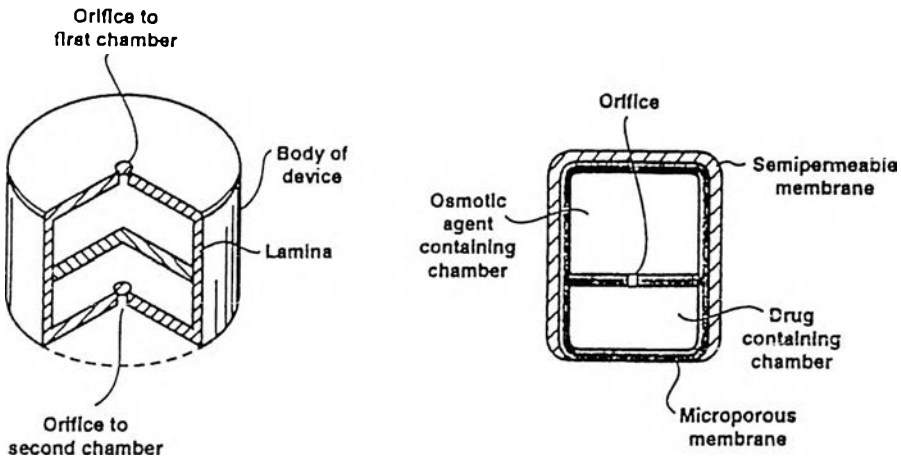

Figure 9 Model of devices with a second expandable osmotic chamber (Zentner, 1989).

The first model of two-chamber device was obtained as early as 1978, but more than 10 years were to pass before the first product using this concept was produced. The problem, of course, was to create the technology to produce the small tablets shown in Fig 10.

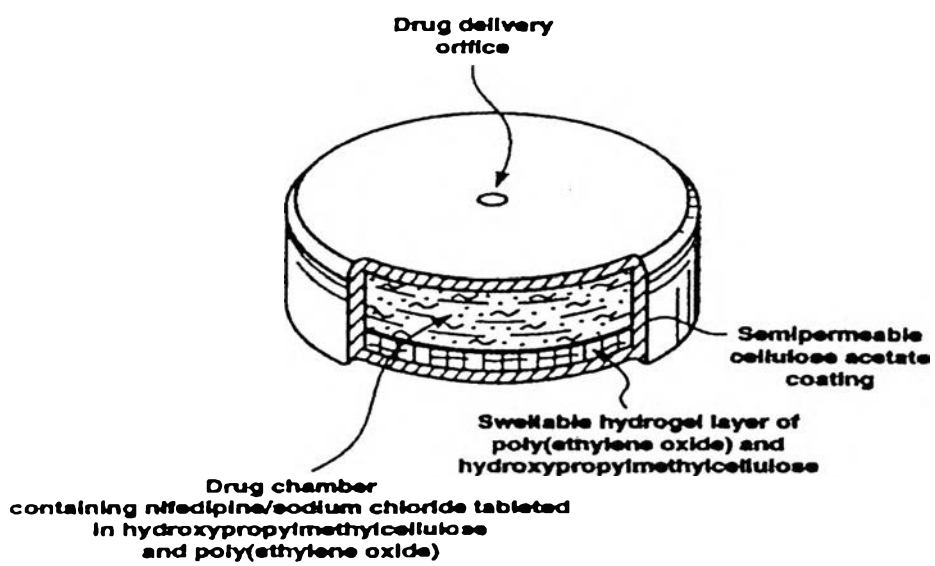

Figure 10 Model of Adalat CR® (Procardia XL®) (Zentner, 1989).

In the large qualities with the reliability and low cost required for a successful pharmaceutical product. One issue was to find a method of suspending the drug in a matrix that would have a sufficient osmotic pressure to draw water through the membrane to the drug chamber. This matrix would also, when hydrated, have to be fluid enough to be pushed easily through a small hole by the small pressure generated by elastic diaphragm but perfect devices were to incorporate finely dispersed drug in a hydrogel. Many of the useful hydrogel polymers were ionic materials such as sodium carboxylmethylcellulose, in which the ionizable groups provided most the osmotic pressure required to draw water through the semipermeable membrane. These polymers, when dry, could be compressed into the tablets with conventional machinery, but when hydrated, became fluid gels easily extrudable through the small delivery hole of the tablet and able to drive both dissolved and suspended drug to the body. Method of forming the barrier separating the drug chambers were used of crosslink osmotic hydrogels that were able to draw water into the salt chamber and then to expand to from a hydraulic piston to push the drug from the tablet. This concept ultimately led to the major product Procardia XL® (Adalat CR ®). This device has an external semipermeable membrane, cellulose acetate, with a laser-formed passageway. The drug chamber contains the drug, nifedipine, and hydroxylpropylmethylcellulose and poly(ethylene oxide) together with a small amount of sodium chloride to assist in drawing water into the chamber. The swellable hydrogel chamber is a mixture of poly(ethylene oxide) and hydroxylpropylmethylcellulose. The two-layered tablet is made with a special tablet press, such as Manestry Layerpress. The drug-containing composition is fed into the cavity mold of the press and compressed into a solid layer. The second osmotic (hydrogel) layer is fed into the cavity overlaying the compressed layer and pressed into a solid layer to form a two-layer core. The core is then coated using a conventional coating machine, and the drug delivery hole is formed in the tablet with a laser drill. In use, the delivery of nifedipine from the osmotic device is carried

out by imbibition of fluid by the drug chamber composition in situ, and delivery of the suspension through the passageway. Concurrently, imbibition of fluid by second hydrogel layer causes this layer to swell and cooperate with the first composition to drive the drug through the passageway. The osmotic device may be considered as a cylinder, with the second composition expanding like the movement of a piston to aid in delivering the agent from the device.

2.7 Devices with a non-expanding second chamber

These devices are containing a non-expanding second chamber. They can be divided into two subgroups, depending on the function of the second chamber. In first devices, the second chamber is used to dilute the drug solution leaving the device. This is useful because in some cases, if the drug leaves the oral osmotic device as a saturated solution, irritation of the gastro-intestinal tract is a risk. This was, for example, the problem that led to withdrawal of Osmosin®, sodium indomethacin. The concept of devices is shown in Figure 11.

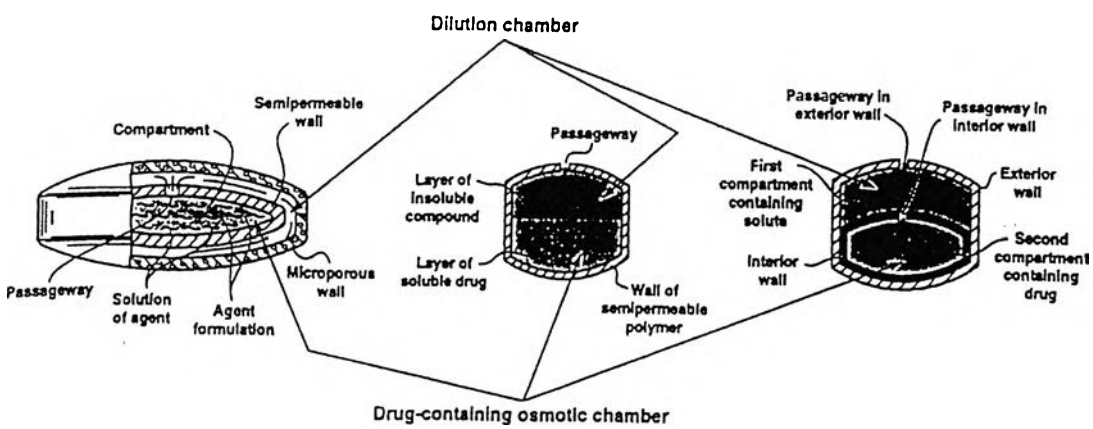

Figure 11 Model of devices with a non-expanding second chamber (Zentner, 1989).

The devices consist of a normal drug-containing OROS® tablet from which drug is released as a saturated solution. However, before the drug can escape from the device, it must pass through a second chamber. Water is also drawn osmotically into this chamber either because of the osmotic pressure of the drug solution or because the second chamber contained a water-soluble dilution, such as sodium chloride. Examples of the category of non-expanding multichamber devices were showed in U.S. Patent 4,439,196, 4,449,983, 4,455,143, 4,449,983 and 4,455,143 were showed the simplest devices of this type. The devices, which is essentially two separate simple OROS® tablets formed into a single tablet, is illustrated in Figure 11. Both drugs are delivered simultaneously. They are more sophisticated and consist of two rigid chambers. The first chamber contains a biologically inert osmotic agent, such as sugar or a simple salt like sodium chloride; the second chamber contains the drug. In use, water is drawn into both chambers through the surrounding semipermeable membrane. The solution of osmotic agent formed in the first chamber where it mixes with the drug solution before exiting through the surrounding the drug chamber. This device could be used to deliver relatively insoluble drugs.

2.8 Method of preparation of passageway

Developing the high speed machinery to produce the holes of the precise size and reliability required must have been a major challenge to the developers of this technology. In the laboratory, a simple mechanical drill can be used to drill tablets at a speed of 10 - 20 tablets/min, but in commercial operations, tablets must be produced at rates in the range 1000 - 10000 tablets/min (Theeuwes, Saunders and Mefferd, 1977). The design of a laser-drilling system, the first and still the most wildly used method of producing these tablets on a large scale. Laser has been used prior to 1978 to bore holes, for example in baby-bottle nipples and lasers were known to have enough energy to drill

the hole required in an osmotic tablet. However, to obtain the required processing speeds, the laser must be able to drill a hole in a tablet moving under the laser head at high speed. By focusing the laser at the tablet and pulsing the laser beam at the appropriate frequency, holes can be drilled in slowly moving tablets. But as the speed is increased, the hole becomes elliptical because of movement of the tablet during the laser firing time. Above a certain speed, drilling a hole is impossible. The solution to the problem, is an optical tracking system, which causes the laser beam to oscillate at the same speed as the tablet, firing at each tablet in succession. High-speed machines incorporating this system have been built. It is believed that most the OROS® tablets on the market are produced using this laser-drilling technology, but other approaches continuous to be developed. For example, U.S. Patent 4,271,113 describes a method of forming the osmotic passageway, in which that tablet is indented prior to coating. The indentation produces a recess that is only partially covered during subsequent coating of the tablet, thus forming the hole, More recently, a method has been U.S. Patent 5,071,607 for forming outlet passageway through the films.

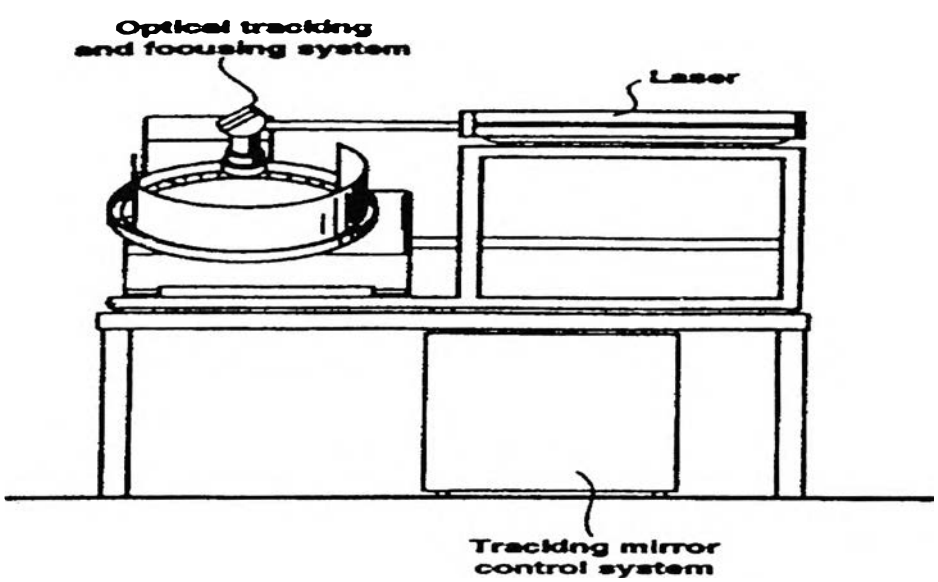

Figure 12 The laser drill machine (Theeuwes, Saunders and Mefferd, 1977).

The process comprises laser drill machine moving the tablets in succession along a predetermined path at a predetermined velocity, tracking the moving tablets seriatim at the velocity with a laser of wavelength which is absorbable by the walls and firing the laser during the tracking, the laser beam dimensions at the wall, the laser power and firing duration being such as to cause the laser beam to heat and pierce the wall to the extent that an outlet passageway 4 to 2000 μ in diameter is formed in the wall.

In preferred embodiments of the above process: the path is circular; the tracking is done by reflecting the laser beam from an oscillating mirror such that the beam repeatedly sweeps a predetermined section of the tracking is positioned at a distance from the lens such that the laser beam is diverging at its point of contact with wall.

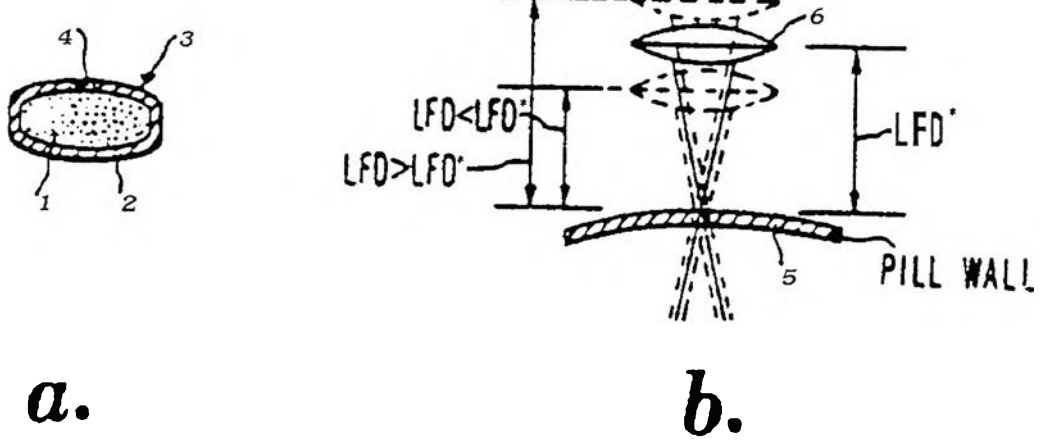

Figure 13 Method of laser-drilling osmotic tablets (Theeuwes, Saunders and Mefferd, 1977).

Figure 13a showed tablets (**3**) having an inner core (**1**) surrounded by a wall (**2**) having an outlet passageway (**4**). The core must comprise a material which is an osmotically effective solute. In this respect it may comprise an active agent, such as a drug, which is itself an osmotic attractant or an active agent which itself is either an

osmotically effective solute or one admixed with an inert osmotically effective solute additive such as an organic salt or a sugar. The wall is formed at least in part of a semipermeable material, that is, it is permeable to the inward passage of water from the environment of use. The wall is usually between about 0.1 to 2000 microns thick. Since the wall functions as a pump housing it must maintain its integrity (not distend or disintegrate substantially) over the dispensing lifetime of the tablets. Materials from which osmosis and reverse osmosis membranes are made be used to make the wall. An apparatus or indexes such as that used in the pharmaceutical industry to print trademarks or other designations on tablets are used to place the tablets under the laser beams. The tablets are tracked by the apparatus and the laser is activated by a magnetic button.

The laser is adapted to pulse mode operation and the duration for which beam (7) is emitted will depend on the pulse setting of the laser. Duration in the range of 0.1 to 10 milliseconds will usually be employed. Beam (7) is transmitted by the tracking mechanism onto the surface of the moving tablets (3) and moves with the moving tablets. The energy of the beam is absorbed by the material of wall (2) of the tablets, causing the material to heat and ultimately be pierced by the beam, thus forming passageway (4).

Assuming efficient absorption of the laser beam by the material of the wall, the size of the passageway will depend upon the laser power, firing duration (pulse time), thickness of the wall and the dimensions of the beam at the wall also affect the shape of the passageway and are a function of the distance between focusing lens (6) and the wall.

In Figure 13b, the distance between the lens and the wall is generally designated **LFD** (lens focusing distance), with **LFD*** designating the **LFD** which is equal to the

focal length of the lens. When **LFD** is equal to greater than **LFD*** the wall is struck with a biconvergent beam causing the passageway to be frustoconical in shape rather than cylinder by a divergent beam which, it has been found, forms a generally cylindrical hole. For this reason it is desirable that **LFD** is equal to or greater than **LFD***.

2.9 Film's composition (Theeuwes and Ayer, U.S. Patent 4,077,407 and 4,160,020)

U.S. Patent 4,077,407 and 4,160,020 covered the materials for preparing of coating film. The film composition is comprised (1) at least one wall forming material permeable to an external fluid and impermeable to an active ingredient or a mixture of agent and an osmotically effective compound that exhibits an osmotic pressure gradient across the wall against the external fluid blended with at least one or more of the following wall forming materials, (2) a stabilizing material that imparts physical and chemical integrity to the wall and more particularly gives the wall inertness towards the agent, (3) a flux enhancer that promotes the permeability of fluid through the wall, (4) a plasticizer that gives flexibility to the wall, and (5) a dispersant useful for blending the materials into an operative integral composite wall. The wall's integrity or inertness to agents in the compartment, and to fluids and other compounds in the environment of use can be precisely regulated by selected the ingredients blended into the wall forming blend. The fluid permeability of the wall can be regulated in a like manner.

Polymers which are useful as wall forming are those by cellulose esters such as mono-, di-, and tri-cellulose acrylates. The stabilizing material and wall forming stabilizing material include polymers that impart integrity to the final wall in the presence of drug and in the environment of use, which environments include the

gastrointestinal tract. These polymers are cellulose derivatives such as cellulose acetate acetoacetate, cellulose acetate chloroacetate, cellulose acetate phthalate, etc. The expression " flux enhancer agent " as used herein means a compound that when added to a semipermeable wall forming material assists in regulating the fluid permeability or liquid flux through the wall.

The flux enhancer in some embodiments also can increase the flexibility of the wall. The flux enhancers include : (1) polyhydric alcohols and derivatives, such as polyalkene glycols of the formula $H(O\text{-alkylene})_n OH$ wherein the bivalent alkylene radical is straight or blanched chain and has from 1 to 10 carbon atoms and n is 1 to 5000 or high ; (2) poly-α,ω-alkylenediols wherein the alkylene is straight or branched chain 2 to 10 carbon atoms such as poly-1,3-propanediol, poly-1,4-butanediol, poly-1,5-pentanediol and poly-1,6-hexanediol ; and (3) ester and polyesters of alkylene glycols of the formula $HO(alkylene\text{-}o)_n H$ where the divalent alkylene radical includes the straight chain and isomeric groups having 2 to 6 carbons and n is 1 to 14.

Usually, 0.001 part up to 50 parts of flux enhancer can be used to achieve the desired results, with a preferred range consisting of 0.1 part up to 30 parts of enhancer for 100 parts of wall forming material. Exemplary plasticizers suitable for the purpose include both cyclic plasticizers and acyclic plasticizers. Typical plasticizers are those selected from the group consisting of phthalates, phosphates, citrates, adipates, etc. Generally, 0.01 to 50 parts, preferably 2 to 30 parts, of a plasticizer or a mixture of plasticizer are incorporated into 100 parts of wall forming material.

Dispersants useful for the process act by regulating the surface energy of materials to improve their blending into the composite. The dispersants can be anionic, cationic, nonionic or amphoteric, and they include anionics such as sulfated esters, amides,

alcohols, ethers and carboxylic acids; sulfonated aromatic hydrocarbons, aliphatic hydrocarbons, esters and ethers; acrylated amino acids and peptides; and metal alkyl phosphates; cationic dispersants such as primary, secondary, tertiary and quaternary alkylammonium salts; acrylated polyamines; and salts of heterocyclic amines, arylamonium dispersants such as esters of polyhydric alcohols; alkoxylated amines; polyoxyalkylene; esters and ethers of polyoxyalkyalkylene glycols; alkanolamine fatty acid condensates; and dialkyl polyoxyalkylene phosphates; and ampholytics such as betamines, and the amino acids.

2.10 Size of passageway (Theeuwes, 1975)

The size of passageway of osmotic devices was showed in U.S. Patent 3,916,899. The size of passageway can easily be ascertained from the immediate equation wherein the maximum size of the passageway is

$$As / h = Qp / (F.t.DS) \quad \text{.....(9)}$$

where

As is the cross-sectional area of the passageway

h is the length of the passageway and for a device with a passageway through a membrane it corresponds to the thickness of the membrane

D is the diffusional coefficient of the active agent in the solution osmotically attracted into the device

F is the ratio of mass of active agent delivered per unit time

Conveniently stated as Qp / t, to the mass of agent or drug Qd / t delivered per unit time through the solution in the passageway in the absence of any measurable osmotic pumping so the ratio of $F = Q(p/t) / Q(d/t)$ is always at least 2 and preferably greater than 10 and usually in the preferred range of 10 to 1000. The size of passageway is constructed with a minimum size so that the size is sufficiently large to prevent hydrostatic pressure ΔP buildup in a device. This minimum size can be determinated, for example a cylindrical passageway by the following equation:

$$As = [(LV.8\pi.\eta) / (t.\Delta P)]^{1/2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (10)$$

where

As is the cross-sectional area of the passageway

π is 3.14

η is the velocity of the solution in the passageway leaving the device

ΔP is hydrostatic pressure difference between the inside and the outside of the device, at which the device osmotically pumps agent without substantially deforming or rupturing the wall of the device and it is preferably less than 20 atmospheres

L is the length of the passageway

V / t is the volume released per unit time.

The osmotic devices are made with at least one passage way. The number of passageways for any device is easily ascertained as $As \geq N.Ah$ where As is as previously defined as the total cross-sectional area of the passageway and it is equal to or large than the number of passageways N times the area Ah for N indicated passageways.

The size of passageway must be smaller than a maximum size to minimize the contribution to the delivery rate made by solute diffusion through the passageway and larger than a minimum size, 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 decrease the osmotic influx as seem in equation 5, but also it can increase the volume of the system. During the time that the system volume is increasing, the outflow would be smaller than the inflow, resulting in a depressed delivery rate.

3. Model drug

Sustained release dosage forms are of great interest for the formulation of an oral drug containing an active ingredient with short half-life in plasma and narrow therapeutic range. They offer a way to reduce the number of administration. In recent year, many drug entities has been developed into sustained release products. Propranolol is one of the drug candidate prepared in such dosage forms.

The structural formulae of propranolol hydrochloride is given in Figure 15 along with its molecular weight, It is white or off-white, odorless or almost odorless, crystalline powder with bitter taste. It is commercially available as hydrochloride salt. It is soluble 1 in 20 of water and of alcohol, slightly soluble in chloroform and practically insoluble in ether.

In aqueous solution, propranolol decomposes with oxidation of the isopropylamine side-chain, accompanied by a reduction in pH and discoloration of the solution. Its solution is most stable at pH 3 and decomposes rapidly in alkali medium.

Das and Kenneth (1987) reported stability of propranolol hydrochloride extemporaneous suspension and solution which compounded from propranolol tablet and injection, respectively. Both of dosage form, content of propranolol hydrochloride almost equal the initial content which not significant after kept in room temperature at least 238 days because pH of suspension and solution was in pH range 2.8 - 4.0 which provided maximum stability of propranolol hydrochloride.

The study by Henrry (1986) reported the stability of propranolol solution heated at pH 2 and 6 but at pH 8.5, it was found that the drug degraded and changed to strawcolors. This report supports the degradation of propranolol hydrochloride in alkali medium as previously mentioned.

Propranolol hydrochloride has pharmacological action similar to those of other β-blocker for treatment hypertension, cardiac arrhythmia, angina pectoris, prophylactic after recovery from myocardial infection, treatment symptomatic condition from hyperthyroidism and prophylactic the headache from migraine.

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 (Evan, 1973) and rapidly hepatic metabolism after oral administration, therefore; it needs several times (3 - 4 times) by oral regimen.

Propranolol has narrow therapeutic range at constant condition in plasma 20-50 μg/ml (Niebergall, Sugita and Schnaare, 1974). The apparent volume of distribution 182 liters are large than volume of total water in body (52 liters, approximately 50 liters

in 70 kg body weight), it means drug is highly deposit or bound to tissue. The clearance is 637 ml/min result in rapidly excretion (Lee and Robinson, 1978).

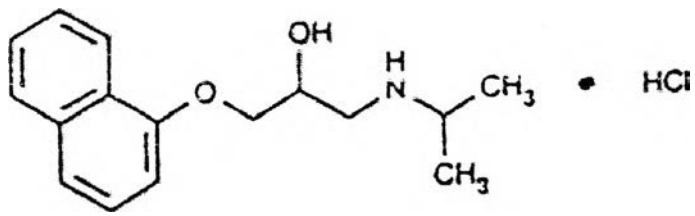

Figure 14 Chemical structure of propranolol hydrochloride (Lund, 1994).

Bodmeier and Paeratakul (1990) prepared film contained propranolol hydrochloride by dissolving the drug in the aqueous colloidal polymer dispersion of Eudragit ®RS30D and study action of drug content, plasticizer content, method of film preparation and storage humidity. The result showed that the addition of the more hydrophilic Eudragit ®RL30D increased the permeability of the films. The amount of water-soluble plasticizer, triethyl citrate added had a pronounced effect on drug release. The release was rapid at low high plasticizer concentration because of incomplete coalescence of latex and leaching of the plasticizer.

Kelbert and Bechard (1992) evaluated a cellulose acetate (CA) latex as coating material for controlled release products. Propranolol hydrochloride tablet formulations were coated with cellulose acetate (CA) latex dispersion to examine film-forming properties, propranolol release, and the effects of flux enhancers on drug release. Film permeability of the drug was low. Films containing 40 % sucrose and 10 % polyethylene glycol 8000 (PEG 8000) provided the best release characteristics in terms of small lag time and drug release profile. It was postulated that drug mass transport occurred mainly within the porous CA structure and the responsible mechanism was a

combination of molecular diffusion/osmotic pressure via water transport into the porous CA membrane. Plasticizer loss during drying was demonstrated and related to the change in release seen with drying time.

Ganga et al. (1992) studied the propranolol hydrochloride release form the hydrophilic matrix tablets containing different ratio of Na-CMC and HPMC.

Hosny et al. (1994) prepared and evaluated the controlled release characteristics of propranolol hydrochloride beads. Eudragit ®RS100 was used as release controlling material and beeswax was used as overcoating. Drug loading efficiency and their dissolution behavior in 0.1 N HCL were studied. The result showed that the coating level of the polymer, particle size of the beads and overcoating with beeswax played major role in determining the release rate of the drug from coated beads.

4. Film-former used in coating formulation

Cellulose, 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 of drug delivery system. In controlled release applications, cellulose 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.

Cellulose is a polysaccharide consisting of glucose repeat units. There are three free hydroxyl groups per sugar, and all can be substituted.

Cellulose acetate

Pure cellulose, despite its free hydroxyls, dose 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.

Cellulose acetate is an tasteless and odorless, free flowing, white to light tan colored, fibrous or flaky. Its structural formula is shown in Figure 15. It is soluble in cyclic ethers, ester, ether alcohols, ketones and certain solvent mixtures (methanol-acetone, acetone-ethanol, dichloromethane-methanol, etc.) with magnificent characteristics of cellulose acetate in film coating system, many experiments then come cross.

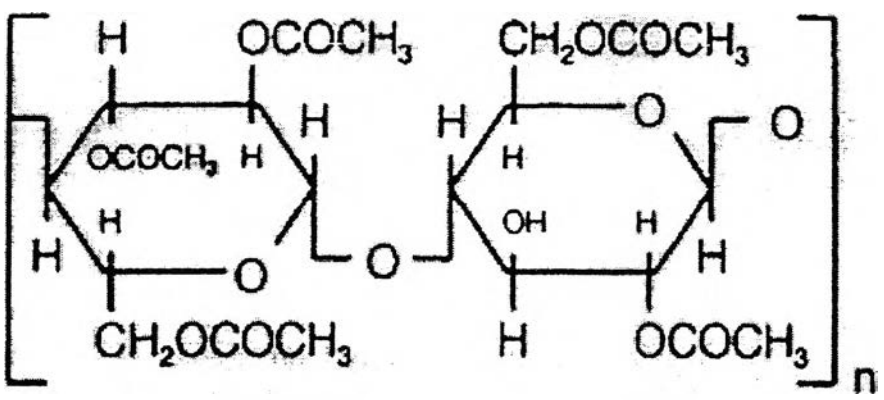

Figure 15 Chemical structure of Cellulose Acetate (Wade and Weller, 1994).

Many application are applied to control drug delivery systems. Many utililizations involve with the mixture of cellulose acetate. Some outstanding implementations are as followed:

Savage and Rhodes (1995) reviewed history of sustained-release coatings and the reasons why 3 materials, cellulose acetate, ethylcellulose, and methacrylic acid copolymers have dominated this technology. Result were showed that cellulose acetate had properties that made it very suitable to be used as the main film former in film coatings that were applied for controlled-release purpose.

Phuapradit et al. (1995) developed in vitro method for optimization of the membrane formulation. Polymeric membranes were prepared and evaluated for mechanical properties and permeability to a model drug, theophylline. Cellulose acetate and ethylcellulose membranes were effective in preventing the diffusion of theophylline. It was concluded that the test methods may be used to quantify the parameters for changes in compositions that could be used to optimize a polymeric membrane formulation.

Guo, Robertson, and Amidon (1991) investigated the influence of physical aging on mechanical properties of polymer free films. The prediction of long-term aging effects on the water permeability and dissolution rate of polymer film-coated tablets was also studied. Cellulose acetate (CA), ethylcellulose (EC), and hydroxypropyl methylcellulose phthalate (HPMCP) were used as tablet film coatings and studied to determine the effects of physical aging on water permeation of CA and EC, mechanical properties of EC and dissolution of HPMCP. Water permeabilities of CA and EC and dissolution rate of HPMCP decreased with physical aging time after being quenched from above glass transition temperatures (Tg) to temperatures below Tg. The decrease in free volume of the polymers seen during aging was accompanied by decreased transport mobility. The effects of long-term aging on polymer dissolution rates and water permeabilities were estimated from a linear double-logarithmic relationship between mobility properties and aging time. It was concluded that, following quenching

from Tg and annealing in the sub-Tg range, the water permeability and dissolution rate of polymer film-coated tablets decreased with aging.

Guo, Robertson, and Amidon (1992) also investigated thermodynamic aspects of the disappearance of antiplasticization in slightly plasticized polymer films at high temperature, using cellulose acetate films and varying concentrations of polyethylene glycol 600 to demonstrate the relaxation activation energy.

Guo et. al., (1993) investigated effects of plasticizers on water permeation and mechanical properties of cellulose acetate : antiplasticization in slightly plasticized polymer film. Results showed that at 37 °C, water permeability decreased with increasing plasticizer levels to a minimum and then increased with higher plasticizer levels. Low plasticizer levels decreased permeability by antiplasticization. Antiplasticization arose from an interaction between polymer and plasticizer molecules and decreased the molecular mobility of the polymer. This was confirmed by mechanical measurements of polymer free films at this temperature. However, above the glass transition temperature, polymer films contained enough energy to overcome the interaction between polymer and plasticizer and the antiplasticization effect disappeared. It was concluded that the water permeability of cellulose acetate decreased to a minimum at low plasticizer levels and then increased with increasing plasticizer due to antiplasticization.

Guo et. al., (1994) investigated theoretical and experimental study of additive effects of physical aging and antiplasticization on the water permeability of polymer film coatings. To investigate the effects of aging and antiplasticization on the water transport of cellulose acetate film-coated tablets, several cellulose acetate solutions containing 0 - 20 % triacetin as a plasticizer were prepared and sprayed over sorbitol

tablets and stored for up to 20 hours at 37 °C. Tablets were then evaluated for water permeability. Results indicated that the water permeability of cellulose acetate film-coated tablets decreased with both physical aging time and plasticizer level.

Appel, Clair, and Zentner (1992) formulated and optimized a modified microporous cellulose acetate latex coating for osmotic pumps. The effect of 4 formulation variables (plasticizer level, pore former level, cure time, and cure temperature) on the in vitro potassium chloride release rate and coat burst strength using a full 24 factorial experimental design was studied to determine the importance of coating formulation and processing variables on a modified microporous cellulose acetate (CA) latex coating for osmotic pumps. Potassium chloride core tablets were coated with a CA latex formulation containing a plasticizer (triacetin) and a pore-forming agent (urea) and coated tablets were cured at elevated temperatures. Urea content was the most important variable, followed by triacetin content and cure time. Cure temperature did not influence the results. Response surfaces generated with the experimental values were used to predict a formulation that would have both a high release rate and a high burst strength. This formulation was prepared and tested both in vitro and in vivo in dogs. The in vitro release rate and burst strength results agreed with those predicted by the model.

Chowdary and Ratna (1992) prepared and evaluated of cellulose acetate microcapsules. To obtain sustained release microcapsules of diclofenac, the drug was microencapsulated with cellulose acetate by an emulsification method to produce spherical microcapsules; the microcapsules were evaluated for size distribution, drug content uniformity, wall thickness, surface characteristics, and drug release properties. The method employed was found to give discrete, spherical, and free flowing cellulose acetate microcapsules of diclofenac. The microcapsule sizes could be readily separated.

Size distributions were found to be log-normal. Drug content was found to be uniform in a batch of microcapsules. Diclofenac release from the microcapsules was slow and spread over extended periods of time. Good correlation between percent coat material, wall thickness, and release rates was observed. Drug release was governed by diffusion rate and followed first order kinetics. Blends of microcapsules with different wall thickness gave a good sustained release profile very close to the theoretical sustained release profile needed for diclofenac.

Mahieux, Arnaud, and Chaumeil (1992) studied the influence of acacia gum on mechanical and chemical properties in free cellulose acetate films. The influence of 3 formulations containing acacia gum at concentrations of 0 %, 50 %, and 75 % on the mechanical and chemical properties of free cellulose acetate films that were used as membranes in gastrointestinal diffusion systems was investigated. The mechanical toughness and the physical aspects were influenced by operating conditions and by the relative air humidity. The increase of relative humidity from 0 % to 75 % decreased the mechanical toughness and the color film changed from clear to opaque white. The presence of acacia gum decreased the mechanical toughness and the water vapor transmission rate and increased the film water solubility in proportion to the acacia gum concentrations. It was concluded that the cellulose acetate films become more sensitive to hydrolysis in the presence of acacia gum.

Sinko, Yee, and Amidon (1991) predicted of physical aging of controlled release coatings by application of the relaxation coupling model to glassy cellulose acetate. The effect of physical aging on both the water transport properties and the mechanical properties of glassy cellulose acetate was investigated. The results indicate a reduction in the mechanical rate of relaxation as well as a reduction in the water permeability as the glass ages. A model that described the low frequency relaxation behavior of

condensed, amorphous systems was used to qualify the mechanical relaxation data. Predictions from the model correlated closely with the observed water permeability reductions and thus indicate that the transport properties of glassy polymers were dependent on the structure of the glass. It was concluded that this approach may provide further insight into the effects of nonequilibrium behavior on pharmaceutically important properties that may serve as a basis for predicting aging and permeability changes in controlled release dosage forms.

Chowdary and Vijaya-Ratna (1990) prepared and evaluated of cellulose acetate microcapsules theophylline. Theophylline was microencapsulated with cellulose acetate. Results showed that controlled drug release was dependent on cellulose acetate content and microcapsule size. Good correlation was found between percent coating and the time for 50 % drug release. Drug release was found to be of a diffusion type and release followed first order kinetics.

Sprockel, Prapaitrakul, and Shivanand (1990) studied the permeability of cellulose polymers. Water vapor transmission rates (WVTR) were studied through solvent cast polymer films prepared from derivatives of cellulose acetate, cellulose acetate propionate and Cabufucon A® (cellulose acetate butyrate). Results showed that rates were influenced by relative humidity, the substituent type and the extent of substitution. Increasing the relative humidity from 32 - 90 % increased the WVTR 3 - 5 times, depending on the polymer used. The WVTR increased in the order of butyrate\ LT / propionate\ LT / acetate. An increase in the extent of substitution with acetyl and/or butyryl groups resulted in an exponential decline in the WVTR.

Bindschaedler, Gurny, and Doelker (1987) studied mechanically strong films produced from cellulose acetate latexes. The prerequisites for mechanically strong films

produced from cellulose acetate latexes, such as choice of water soluble plasticizers possessing some degree of volatility, were discussed.

Bindschaedler, Gurny, and Doelker (1987) studied osmotic water transport through cellulose acetate membranes produced from a latex system. Results showed that physicochemical properties of cellulose acetate aqueous colloidal dispersions used in the production of latex film coating systems were described which show a wide range of permeabilities, dependent on the choice of the plasticizer and processing conditions.

Allen, DeMarco, and Kwan (1972) evaluated the process of coating cellulose acetate film by spray method. The apparatus was constructed to permit systematic variations in factors affecting film formation by spraying. The utility and applicability of the proposed methodology were demonstrated in experiments in which the effects of spray rate, spray distance, and film substrate on the tensile strength, modulus of elasticity, apparent density, and water vapor permeability of cellulose acetate films were investigated.

5. Plasticizer

5.1 Dibutyl phthalate

Dibutyl phthalate is a clear, colorless, oily liquid. It is practically odorless, or with a very slight aromatic odor and a bitter, disagreeable taste. Dibutyl phthalate was used as a plasticizer for film coating on tablets, beads and granules at concentrations of 10 - 30 % by weight of polymer. It very soluble in acetone, benzene, ethanol (95 %) and ether; soluble1 in 2500 of water. It is incompatible with strong oxidizing materials. The structure formula of dibutyl phthalate was shown in Figure 16.

$C_{16}H_{22}O_4$

Figure 16 Empirical formula of Dibutyl Phthalate (Wade and Weller, 1994).

Mu, Zhang, and Zhu (1994) studied the effect of plasticizers on water vapor permeability of free film of hydroxypropyl methylcellulose phthalate (HPMCP). Results showed that lowest permeability was observed for hydroxypropyl methylcellulose phthalate film containing 10 % dibutyl phthalate or castor oil. As the plasticizer content increased to over 10 %, permeability became larger than that of pure hydroxypropyl methylcellulose phthalate film. The addition of talc reduced film permeability.

Maul and Schmidt (1995) investigated the effects of plasticizers on drug release of film-coated pellets. Results showed that drug release from films plasticized with dibutyl phthalate was slower than from films prepared with triethyl citrate. It was concluded that dibutyl phthalate was more suitable for Eudragit L-30D coatings than triethyl citrate.

5.2 Polyethylene glycol (macrogol, PEGs)

PEG was polymer between ethylene oxide and water. Liquid form appears as clearly, colorless, slight odor, dissolve with water, ethylene alcohol and other glycols. Solid form appears as white or creamy, dissolve in water and ethyl alcohol melting point 40 - 60 °C depend on polymer weight. Special characteristic of PEG was liquid like substances but dissolve in water. Polyethylene glycol divided in 2 form

1. Liquid PEG s (Grade 200 - 600)
2. Solid PEG s (Grade > 1000)

The structure formula of PEG was shown in Figure 17.

$$HOCH_2 (CH_2OCH_2)_n CH_2OH$$

Figure 17 General empirical formula of PEGs (Wade and Weller, 1994).

Guo, et al. (1993) studied plasticization of cellulose acetate with three different molecular weight of polyethylene glycol and triacetin. This study focused on the plasticization-induced changes in the water permeation and mechanical properties. Results indicated that at 37 °C, the water permeability of cellulose acetate was decreased with increasing plasticizer to a minimum and then to increase with higher concentrations of plasticizer. Low plasticizer concentrations caused a decrease in water permeability by antiplasticization. Antiplasticization across from an interaction between the polymer and the plasticizer molecules and decreased the molecular mobility of the polymer. This effect was confirmed by mechanical measurements of polymer free films at the same experiment temperature.

Theeuwes and Ayer (1978) studied permeability of cellulose acetate films. Results showed that the permeability of film could be increased by adding polyethylene glycol M.W. 400.

Lim and Wan (1994) were studied the effect of plasticizers on the properties of polyvinyl alcohol films. The effects of plasticizers propylene glycol, glycerin (glycerol), and polyethylene glycol 600 on the morphology and water resistance of

polyvinyl alcohol films were studied. Differential scanning calorimeter showed that crystallite formation in the films was affected to different degrees by the plasticizers. The plasticizers reduced the degree of crystallinity in the films and lowered crystalline melting temperatures probably by introducing defects into the crystal lattice. This, coupled with leaching of plasticizers from the film when immersed in distilled water, lowered water resistance of the films. The effects of plasticizers were also related to the compatibility of plasticizers and polyvinyl alcohol. It was concluded that the incorporation of plasticizers into polyvinyl alcohol films increases film flexibility, thereby lowering water resistance and enhancing aqueous solubility.

Guo et. al., (1994) investigated the formation of plasticizer channels in plasticized polymer films. The effects of 0 - 40 % polyethylene glycol 600 on the sucrose permeability, void volume, and morphology of cellulose acetate free films were studied. Sucrose permeability decreased with increasing polyethylene glycol to a minimum and increased dramatically in the presence of over 30 % polyethylene glycol. Decreased sucrose permeability with increasing plasticizer at low plasticizer levels was attributed by the antiplasticization effect, and increased sucrose permeability at high plasticizer levels was explained by the formation of plasticizer channels. Void volume and morphology studies supported the assumption that plasticizer channels were formed by high levels of plasticizer. It was concluded that plasticizer channels were formed in polymer films containing high concentrations of polyethylene glycol, resulting in increased sucrose permeability.

Jain, Vyas , and Dixit (1990) were prepared salbutamol delivering transdermal dosage form based on osmo-regulatory principle. The development and the in vitro and in vivo evaluation of a transdermal delivery system of albuterol (salbutamol) that releases the drug according to zero order kinetics were described. In vivo studies were

performed in 12 asthmatic subjects who were randomized to receive 4 mg albuterol (Asthaline) tablet every 6 hours or a single transdermal patch. The delivery of the drug from the system was affected by osmotic phenomenon when sodium chloride was used as an osmogent. To establish the desired release rate polyethylene glycol 4000 (PEG 4000) was used as the channeling agent in rate controlling membranes of cellulose acetate. The forced expiratory volume and drug plasma concentration were monitored periodically in patients. The results showed that the transdermal albuterol system could be used successfully with improved therapeutic response and holded promise for clinical studies.

6. Solvent

6.1 Methanol (Methyl alcohol)

It appear as a clear, colorless mobile and volatile liquid with a slight characteristic odor. It has a burning taste and absorbs water rapidly from air. It has melting point 34 - 36 °C and boiling point 212 °C. It very soluble in ethanol (95 %), chloroform and ether; very slightly soluble in glycerin; partially insoluble in water.

6.2 Methylene chloride (Dichloromethane)

It appears as a clear, colorless, mobile and volatile liquid with chloroform-like odor. It has specific gravity 1.318 - 1.322, melting point -95 °C and boiling point 39.5 - 40.5 °C. It is soluble in about 50 parts of water and miscible with alcohol and ether. Its vapor is not explosive when mixed with air.