CHAPTER I

INTRODUCTION

A type of drug delivery systems had been previously developed to release drugs for extended periods by an osmotic pumping mechanism. Osmotic systems generally consist of an osmotically active core surrounded by a rate controlling, semipermeable coating. Water is imbibed into the core through the semipermeable coating, creating a osmotic pressure that pumps a drug-containing solution or suspension out of the core through one or more delivery ports. Constant rate of drug release that are independent of pH or agitation in the receptor solution are characteristics of osmotic drug delivery system because the factors affecting release kinetics are typically independent of these variables.

The first osmotic tablets consisted of tablets coated with dense semipermeable coating with a hole drilled through the coating through which the drug was delivered (Theeuwes, 1975). This is still the principal type of coating used in commercial osmotic devices. Additional formulation had been developed that consist of dense semipermeable coatings containing leachable materials (Zentner et al., 1985; U.S. patent no. 4,687,660). The leachable materials dissolve out of the coating during use, forming drug-delivery ports. These osmotic tablet formulations are well-suited for soluble drugs and core excipients with high osmotic pressures. However, for drugs with low solubility investigations to overcome this problem have been reported by several researchers. Incorporation of excipients that modulate the solubility of diltiazem hydrochloride within the core could be one approach to control the release of drug (McClelland et al., 1991). Use of polymer coated buffer component to modulate the drug solubility within the core was described (U.S. patent no. 4,755,180). Swellable polymers could be utilized for delivery of drug having poor aqueous solubility (U.S. patent no. 4,992,278)

The choice of rate-controlling membrane was an important aspect in the formulation development. The coating was able to resist the pressure within the device. However, this might be problematic in cases where the drug was having low

osmotic pressure because of which incomplete/ slow drug release may take place (Verma et al., 2002) Selecting membrane that have high water permeabilities could be a solution to this problem. The use of cellulose acetate, ethyl cellulose had been reported (Lindstedt et al., 1989; U.S. patent no. 4,673,405).

In recent years chitosan has gained increasing interest in the pharmaceutical field due to its favorable biological properties such as biocompatibility, biodegradability and lack of toxicity together with its wide availability, low cost and high versatility of use (Felt et al., 1998; Dodane and Vilvivalam, 1998) Due to its cellulose-like chemical structure, chitosan exhibits good filmable property. Various pharmaceutical applications of chitosan film have been proposed (Cervera, et al., 2004; Zhang and Bai, 2003; Shu and Zhu, 2002; Felt et al, 1998; Nakatsuka and Andrady, 1992; Remunan-Lopez and Bodmeier, 1996). The poor solubility of fabricated chitosan acetate film was detected when stored under accelerated conditions, as an alternative approach to prepare the insoluble films from various chitosan salts by moist heat treatment (Ritthidej et al., 2000). Thus, chitosan as one of the most interesting natural polymers which provided high water permeability and could be easily adjusted by exposure to accelerated condition could be used as film former on osmotic delivery system to give a constant drug release throughout the desired interval.

Objective of this study

1. To prepare propranolol hydrochloride osmotic pump tablets with chitosan acetate as a film former

2. To study the effect of different molecular weight and sources of chitosan on the properties of propranolol hydrochloride film coated tablets.

3. To examine the effect of temperature and moisture content on sustained release characteristic of propranolol hydrochloride film coated tablets.

4. To study the effect of various amount of osmotic agent in core tablet and molality of dissolution medium on the release of propranolol hydrochloride from osmotic pump tablets.

5. To investigate the effect of orifice on the release of drug from osmotic pump tablets.

Literature review

General background on Chitosan

The history of chitosan dates back to the last century, when Rouget discussed the deacetylated form of chitosan in 1859. During the past 20 years, a substantial amount of work has been published on this polymer and its potential use in various applications (Dodane and Vilivalam, 1998).

Chitosan is a copolymer of β-(1→4)-linked 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose. This polycationic biopolymer is generally obtained by alkaline deacetylation from chitin, which is the main component of the exoskeleton of crustaceans, such as shrimps (Qurashi, Blair and Allen, 1992). The main parameters influencing the characteristics of chitosan are its molecular weight (MW) and degree of deacetylation (DD), representing the proportion of deacetylated units (Berth, G. et al., 1998). These parameters are determined by the conditions set during preparation. Moreover, they can be further modified. For example, the DD can be lowered by acidic depolymerisation.

Chitosan is currently receiving a great deal of interest for medical and pharmaceutical applications (Merwe, S.M. et al., 2004; Thanou, Verhoef and Junginger., 2001). The main reasons for this increasing attention are certainly its interesting intrinsic properties. Indeed, chitosan is known for being biocompatible allowing its use in various medical applications such as topical ocular application, implantation or injection. Moreover, chitosan is metabolized by certain human enzymes, especially lysozyme, and is considered as biodegradable. In addition, it has been reported that chitosan acts as a penetration enhancer by opening epithelial tight-junctions. Due to its positive charges at physiological pH, chitosan is also bioadhesive, which increases retention at the site of application. Chitosan also promotes wound-healing and has bacteriostatic effects. Finally, chitosan is very abundant, and its production is of low cost and ecologically interesting (Berger et al., 2004)

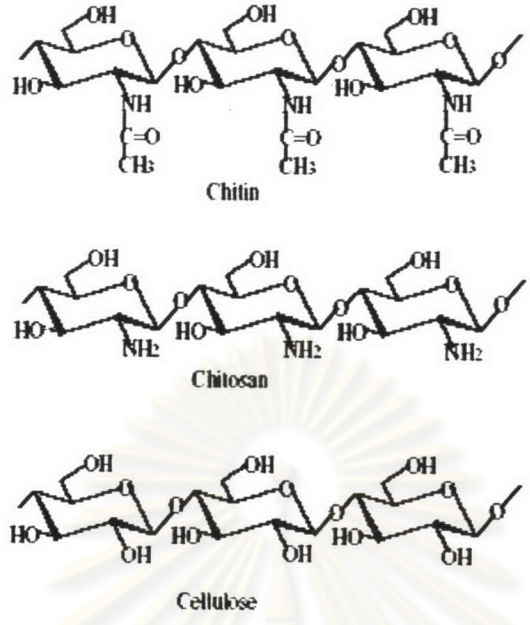

Figure 1 Molecular structures of chitin, chitosan and cellulose

Mechanical Properties of Chitosan Film

Due to glycosidic linkage and long polymeric chain like cellulose, chitosan exhibits the property as a filmable material (Cervera, N.F. et al.,2004; Zhang and Bai, 2003; Phaechamud, T. et al., 2000). Neutralized chitosan acetate membrane showed higher values of stress, strain and modulus than cellulose acetate membrane. The thermoelastic and equilibrium stress-strain properties of chitosan film slightly crosslinked with glutaraldehyde had a higher stress than expected and this result was attributed to an energetic component of the tensile force caused by hydrogen bonding interactions and/or to strain-induced crystallization (Andrady and Xu, 1997). As mentioned by many researchers, mechanical properties of chitosan film were notably affected by some factors as followed (Srinivasa, P.C. et al., 2004; Ritthidej, G.C. et al., 2000; Phaechamud, T. et al, 2000).

A. Effect of Electric Charge

Electric charge generated and utilized during casting of chitosan acetate film caused a parallel orientation of chitosan molecules due to its cationic nature of polymeric chain. In addition, this cast film showed the break point after yielding by stretching. This behavior was reported close to the inter-macromolecular sliding during elongation. Additionally, the estrangement of the diffracting planes in powder X-ray diffractogram confirmed that the orientation of chitosan film was changed by an electric charge (Ikeda et al., 1996).

B. Effect of Irradiation

An attempt to sterilize the products produced from chitosan was described. The gamma irradiation was arisen as one of such method. Gamma irradiation reduced the mechanical strength of the neutralized chitosan film as a result of polymeric chain scission, whereas the films after exposure to moist heat at temperature 121°C under the pressure of 15 lb/in^2 (as using in autoclaving process) retained their original tensile strength to a greater extent, though the film elongation rates were considerably lowered. However, Lim and Koo (1998) suggested that gamma irradiation might be an attractive sterilization method since the biocompatibility of neutralized chitosan acetate film was not affected by this irradiation dose of 25 kGy. While Lim, Khor and Koo (1998) reported that gamma irradiation in air enhanced both the Young's modulus and the tensile strength of film but not significantly altered the percent strain at break point or the energy to break point, and this irradiation in anoxia did not exhibit significant changes in mechanical properties.

C. Effect of Temperature and Moisture

Ritthidej, G.C. et al. (2000) demonstrated that the extent of changes in mechanical strength and permeability of neutralized chitosan acetate films was influenced by temperature and moisture content of the heat applied. Dry heat treatment at 120°C lowered the strain at break point, but the Young's modulus remained relatively unchanged. The autoclaved film showed the weakest mechanical properties, but showed the lowest permeability to indomethacin compared to film

heated in air or in anoxia. The investigators claims that the autoclaving process might induce rearrangement of molecular chain which did not allow for chain slippage during stretching, but was structured enough to reduce the permeability of drug through the film. Maillard-type reaction was also mentioned that it was the cause of discoloration of chitosan film during heat treatment (Srinivasa, P.C. et al., 2004).

The longer moist heat treatment and an increase or longer of acyl group or lower amount of hydroxyl group in solvent molecule would decrease in % water sorption and dissolution of treated film. The water sorption capacity of the polymer was probably determined the nature of functional groups of the polymer. The highest hydrate capacity were increased by the hydroxyl, amide and ester group, meanwhile that of the ≡C–, $-CH_2-$, $-CH_3$ and $-C_2H_5$ functional group were several orders of magnitude lower Phaechamud, 1999).

The Composition of Chitosan Coated Film

A. Chitosan Salt Film

There was different interaction between chitosan and acids in solution, and during film fabrication the chitosan molecules had distinctive spatial configulation, the mechanical properties of various chitosan salt films was distinctive as mentioned by Kawada et al (1998) who revealed that chain conformation of chitosan in crystal depended on the kinds of aqueous acid solution which utilized as solvent for film fabrication. Additionally, because of the solid state nature and high MW of citric and malic acids, the amount of acid loading was rather high and thereby these two acids had a tendency to interfere the closeness or linkage between polymeric chains and thus the mechanical properties of chitosan film in these salt forms were lower than those of chitosan acetate and propionate films (Phaechamud, 1999).

B. The Plasticizer and Hydrophobic Substance

Unplasticized chitosan acetate film was brittle. There was the necessary for auxiliary agent comprised primarily of plasticizer, which provided the plastic with required elasticity and stabilized to prevent breakdown of the polymer at elevated temperature. Hydrophilic plasticizer could not extend drug release. This result should be related to the volatility of plasticizer during heat treatment (Singh and Khan 1997). Castor oil at concentration of 15% was reported for plasticizing (Phaechamud, 1999). In addition, other hydrophobic substance was incorporated in chitosan acetate film in order to develop the sustainable drug release. This material was magnesium stearate. An incorporation of plasticizer in chitosan acetate film containing magnesium stearate 45% could prolong medicament release. This evidence might relate to the effect of incorporation plasticizers on reducing the electrostatic repulsion of protonated amine groups and thus reducing the film hydration. In addition, castor oil was attributed to the formation of a more continuous film especially after moist heat treatment. It might be due to the efficiency of rather long molecule of castor oil to penetrate through chitosan and stearate chains. The introduction of castor oil in chitosan acetate for preparation of polyurethane-chitosan interpenetrating polymer networks had also been notified by Gong et al (1998).

C. The Colorant

Chitosan could act as filmable material due to its glycosidic linkage like cellulose. It exhibited good film forming capacity. However, Millard-type reaction was mentioned that it was the cause of discoloration of chitosan film during heat treatment (Srinivasa, et al., 2004). For this reason, Color was another additive that used in this coating system. The charge interaction between anionic dye molecules and $-NH^{3+}$ group on chitosan chain could be occurred between chitosan and other dyes (sunset yellow, poncear 4R and tartrazine). The presence of positive charge on molecule of brilliant blue and its influence especially in acidic environment might provide enough repulsion force to decrease the charge interaction between sulfonate groups of dye and protonated amine groups of chitosan. Owing to the presence of positive charge on structure and high water solubility, the tolerance to coagulate with chitosan should be higher than other dyes (Phaechamud, T. et al., 2000)

Film coating

Film coating has increased in popularity for a number of reasons. The film process is simpler, and therefore easier to automate. In addition, moisture involvement can be avoided, if necessary, through the use of nonaqueous solvents. Moreover, distinctive identification tablet marking are not obscured by film coats.

There are now many synthetic polymeric materials available for film coating, many of which meet all the requirements of a good film former. These include lack of toxicity and a suitable solubility profile for film application and upon ingestion, together with the ability to produce a tough, yet elastic film even in the presence of powdered additives such as pigments. The film must, of course, be stable to heat, light, and moisture and be free from undesirable taste or odor (Porter, Bruno and Jackson, 1982).

Two major groups may be distinguished: a) materials that are nonenteric and for the most part cellulose derivatives and b) materials that can provide an enteric effect and are commonly esters of phthalic acid. Within both groups it is general practice to use a mixture of materials to give a film with the optimum range of properties. They may contain a plasticizer that, as the name implies, prevents the film from becoming brittle with consequent risk of chipping. Because they essentially function by modifying polymer-to-polymer molecular bonding, the choice of plasticizer is dependent upon the particular film polymer. Like so many other facets of tablet coating, there is no substitute for properly designed experimental trials in developing a robust procedure (Swarbrick and Boylan, 1996).

The nature of the solvent system may markedly influence the quality of the film, and, to optimize the various factors, mixed solvents are usually necessary. More specifically, the rate of evaporation, and hence the time for the film to dry, has to be controlled within fine limits if a uniform smooth coat is to be produced.

However, as a result of increasing regulatory pressures against undesirable solvents, there has been a pronounced trend toward aqueous film coating. Many of the same polymers can be used, but it may be necessary to employ lower molecular

weight grades due to their high viscosity in aqueous systems. Alternatively, water-insoluble polymers may be dispersed as a latex (emulsion) or pseudo-latex (suspension) in an aqueous media. This approach permits high solids content without attendant high viscosity problems. However, acceptable film forming in these systems is dependent upon coalescence or agglomeration. In the case of pseudo-latices, this agglomeration requires a soft particle, and thus a high concentration of plasticizer in the system, to ensure formation of a continuous film (Banker and Rhodes, 2002)

Osmotically Controlled System

A. Osmosis

Solvent from a solution of lower concentration will move spontaneously to a higher concentration solution across an ideal semi-permeable membrane, which is permeable to solvent but impermeable to solute. This phenomenon is called osmosis. The flow of solvent can be reduced by applying pressure to the higher concentration solution side of the membrane. At a certain pressure, equilibrium is reached so that the movement of water ceases. This pressure is called the osmotic pressure, which is solely a property of the solution. If a pressure greater than the osmotic pressure is applied to the higher concentration side, the flow of solvent will be reversed, i.e., the solvent now moves from the higher concentration solution to the lower concentration solution. This phenomenon is called reverse osmosis. Osmotic pressure may be considered a measure of the difference between the nature of the solution and the pure solvent. Osmotic pressure can be successfully used in drug delivery systems by confining it in a mechanical device and concentrating the pressure at a single site (Kim, C. et al., 2000).

When equilibrium is reached, the chemical potentials of the pure solvent (or dilute solution), μ_A^*, and the concentrated solution, μ_A, are equal,

$$\mu_A^* (p) = \mu_A (x_A, \pi + p) \qquad \text{(Eq.1)}$$

where x_A is the concentration of solute, π is the osmotic pressure, and p is the experimental pressure. The right-hand side of equation (1) can be rewritten in terms of the pure solvent by:

$$\mu_A\ (x_A, \pi + p) = \mu_A^*\ (\pi + p) + RT \ln\ x_A \qquad \text{(Eq.2)}$$

where R and T are the gas constant and temperature, respectively. However, we may express the chemical potential of the concentrated solution only due to solvent:

$$\mu_A^*\ (\pi + p) = \mu_A^*\ (p) \int_p^{\pi+T} + V_m\, dp \qquad \text{(Eq.3)}$$

where V_m is the volume of solvent. Substitution of equations (2) and (3) into (1) yields:

$$-RT\ln(1-x_A) = \int_p^{\pi+p} + V_m\, dp \qquad \text{(Eq.4)}$$

For the dilute solutions, $\ln(1-x_A) = -x_A$. If constant molar volume of the solvent is assumed, then from equation (4) the van'Hoff equation is obtained:

$$\pi V = nRT \qquad \text{(Eq.5)}$$

The osmotic pressure caused by solutes is very high and that from an ionic salt is much higher than that from a nonionic solute. Theoretically the osmotic pressure of an ionic salt is given by:

$$\pi V = inRT \qquad \text{(Eq.6)}$$

where i is the number of ions that compose the salt.

B. Elementary Osmotic Pump System (OROS®)

After experimenting with several osmotic pressure driven drug delivery system, Alza Corporation developed the OROS® elementary pump shown in Fig. 2. This system is prepared by compressing drug powder into a hard tablet, coating the tablet with cellulose derivatives to form a semi-permeable membrane, and then drilling an orifice in the coating with a laser (Cardinal, J.R., 1988).

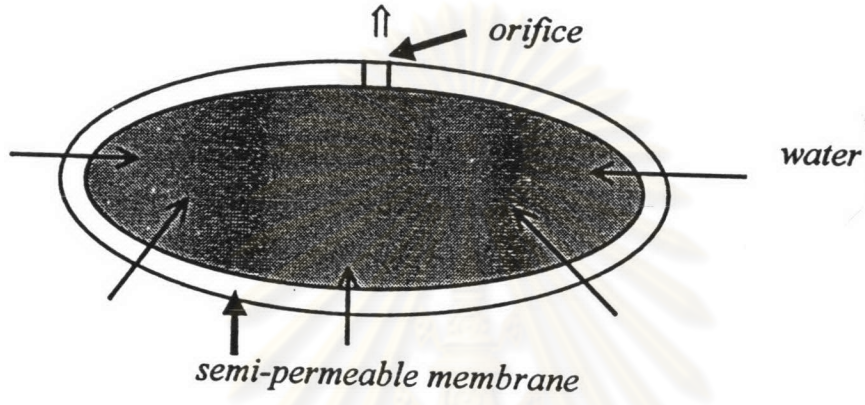

Figure 2 The elementary osmotic pump

The volumetric flow of solvent (water) across the semi-permeable membrane is given by the non-equilibrium thermodynamics of the reverse osmosis process as:

$$\frac{dV}{dt} = \frac{A}{h} L_p(\sigma\Delta\pi - \Delta p) \qquad \text{(Eq.7)}$$

where $\Delta\pi$ and Δp are the osmotic and hydrostatic pressure difference, respectively, between the high and low concentration sides of the membrane, L_p is the permeability coefficient of the semi-permeable membrane, σ is the reflection coefficient, A is the membrane surface area, and h is the membrane thickness.

The solute delivery rate, *dm/dt*, is equal to the product of the volume flow rate and drug concentration written as:

$$\frac{dm}{dt} = \frac{dV}{dt}C \qquad \text{(Eq.8)}$$

where C is the solute concentration in the outgoing fluid. When the osmotic pressure inside the membrane is very large compared to the pressure outside the membrane and $\Delta\pi >> \Delta p$, equation (7) simplifies to:

$$\frac{dV}{dt} = \frac{A}{h}L_p\sigma\pi = \frac{A}{h}k\pi \qquad \text{(Eq.9)}$$

where k = σL_p

Zero-order rate and mass delivered at zero-order: As long as the undissolved drug remains in the osmotic tablet, the release rate is zero-order. If the concentration of the drug is equal to the drug's solubility in water, C_s, and the osmotic pressure generated by this saturated solution is π_s, then

$$\left(\frac{dm}{dt}\right)_z = \frac{A}{h}k\pi_s C_s \qquad \text{(Eq.10)}$$

The time for which drug is delivered under zero-order conditions is given by:

$$t_z = m_t(1 - \frac{C_s}{\rho})\frac{1}{(dm/dt)_z} \qquad \text{(Eq.11)}$$

where t_z is the time at which all of the solid in the core has been dissolved.

The total mass in the core, m_t, is the sum of the mass delivered at zero-order, m_z, and the mass delivered at non-zero-order rate, m_{nz}, after which the entire solid drug has dissolved, given by:

$$m_{nz} = C_s V \qquad \text{(Eq.12)}$$

$$m_t = \rho V \qquad \text{(Eq.13)}$$

where V and ρ are the volume and density of the osmotic tablet, respectively. Combining equations (12) and (13) gives:

$$\frac{m_z}{m_t} = 1 - \frac{C_s}{\rho} \qquad \text{(Eq.14)}$$

Non-zero release rate: As soon as all of the solid has dissolved, the solute concentration drops below saturation, and the osmotic pressure and the drug delivery rate decline as a function of time.

From t_z and afterwards, the delivery rate (non-zero order) is described by:

$$\left(\frac{dm}{dt}\right)_{nz} = \frac{\left(dm/dt\right)_z}{\left[1 + \frac{1}{C_s V}\left(\frac{dm}{dt}\right)_z (t - t_z)\right]^2} \qquad \text{(Eq.15)}$$

which indicates that the release rate declines parabolically with respect to time. The concentration at time t after t_z is calculated by:

$$C = \frac{C_s V}{V + (t - t_z)F_s} \qquad \text{(Eq.16)}$$

where $F_s = AL_p\pi / h$

An advantage of the osmotic pump delivery device is that the delivery rate is not influenced by physiological and experimental conditions. Due to the semi-permeable membrane, ions do not readily cross over but water does. The permeation of water through the membrane is not dependent upon stirring rate because water permeation is a property of the membrane and the osmotic pressure gradient across it.

With this consideration, even a drug with a pH-dependent solubility can be delivered at a constant rate regardless of the pH of the delivery medium.

However, with this type of device there is a problem in delivering drug with low water solubility because the osmotic pressure generated by the drug solution is not sufficient to drive the drug release. As a result, the percentage of the total mass delivered at zero-order is less with a drug of low solubility. In this case, osmogents, such as glucose and NaCl, are added to the device to increase the osmotic pressure. In order to maintain a zero-order rate for a given release period, the ratio of drug to osmogent must be equal to the ratio of the solubility of drug to osmogent. However, if the drug solubility is too low (i.e. < 1%) and the amount of drug to be administered is large, the usefulness of the elementary osmotic pump device is limited due to the tablet size needed to accommodate the amount of drug. Other modifications of the osmotic pump have been developed to address this situation and are discussed in the next section.

Alternatively, a highly water-soluble drug may allow a higher percentage of drugs to be delivered at zero-order, but the length of delivery is short because the drug concentration quickly falls below saturation. For this situation, a solubility modulated osmotic pump device has been developed to increase the duration of delivery time while maintaining a reasonable zero-order rate (Kim, C., 2000).

C. Micro-Porous Osmotic Pumps (MPOP)

Fabricating an osmotic pump with a single orifice is a costly process because the hole must be produced consistently with laser drill. Zetner et al. developed an osmotic pump device based upon a micro-porous membrane rather than a non-porous semi-permeable membrane as shown in Figure 3.

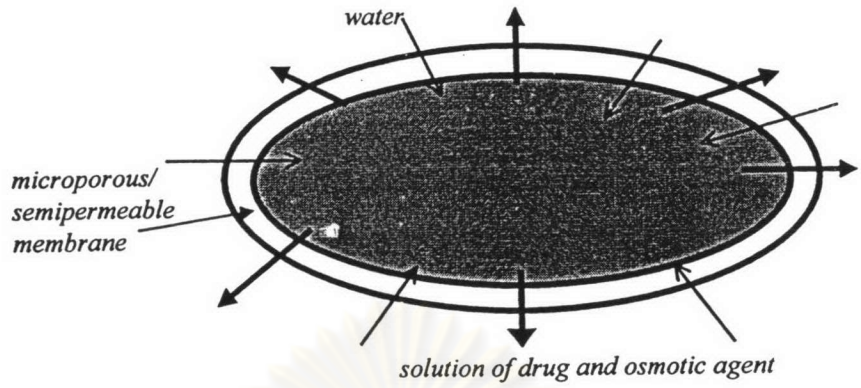

Figure 3 Schematic diagram of the porosity controlled osmotic pump

In this device, drugs, as well as water, freely diffuse through the membrane. A fraction of the drug and the osmogent diffuses through the micro-porous membrane. Incorporating water-soluble substances in the coating solution (i.e. polyethylene glycol and lactose) forms the micro-porous structure of the membrane. Upon contact with water, the water-soluble substances from the membrane leach out, leaving behind a micro-porous morphology. This device delivers drug by both osmotic pressure and diffusion mechanisms (Makhija and Vavia, 2003). The delivery rate of drug is expressed by:

$$\left(\frac{dm}{dt}\right)_z = \frac{A}{h}k\pi_s C_s + \frac{A}{h}PC_s \qquad \text{(Eq.17)}$$

where P is the permeability of the membrane. A rigorous mathematical interpretation of the non-zero release rate for both the osmotic pump and membrane diffusion has been presented by Theeuwes and is expressed by:

$$t - t_z = \frac{Vh}{AP}\ln\left[\frac{F_s\frac{C}{C_s} + \frac{AP}{h}}{\left(F_s + \frac{AP}{h}\right)\frac{C}{C_s}}\right] \qquad \text{(Eq.18)}$$

The non-zero order delivery rate is given by:

$$\frac{dm}{dt} = \frac{F_s}{C_s} C^2 + \frac{A}{h} PC \qquad \text{(Eq.19)}$$

As indicated in equation (17), the release rate is controlled by:1) the level of leachable additives incorporated into the membrane which affect membrane permeability, 2) the nature of the polymer membrane, 3) the thickness and surface area of the membrane, 4) the solubility and osmotic pressure of the core, and 5) the drug load in the core. The most common polymers used for the micro-porous membrane are cellulose acetate, ethyl cellulose and Eudragit®LS and RS. A scanning electron microscope showed that the micro-porous membrane is a sponge-like structure consisting of numerous open and closed pores that form an interconnected network structure (Chien, Y.W., 1983).

D. Push-Pull

As mentioned in the previous section, the simple OROS® system is well suited for a moderately water-soluble drug. For a poorly water-soluble drug (<1%), the delivery rate is very slow because of the small osmotic pressure gradient. Even if an osmogent is incorporated into the core, the osmotic pressure gradient is not increased enough to affect a sufficient delivery rate because the ratio of drug to osmogent concentration is not equal to the ratio of drug solubility to osmogent concentration. To deal with this problem, Alza developed another osmotic pump system shown in Fig. 4. This device consists of two compartments: a water-swellable polymer layer and a drug layer. The core is coated with a non-porous semi-permeable membrane. When the "push-pull" device is in contact with water, both layers pull water from the dissolution medium. Due to the low solubility of the drug, a drug suspension is produced in the top layer while a hydrophilic polymer in the bottom layer expands toward the top layer to push the suspended drug through the orifice (Kim, C., 2000).

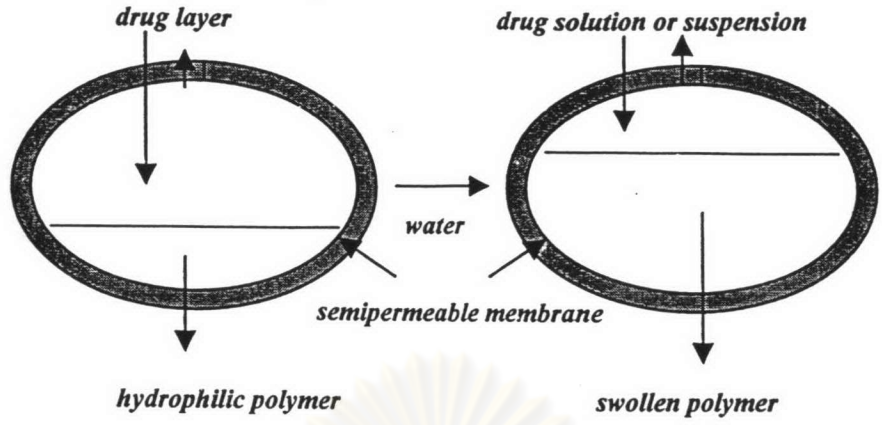

Figure 4 Schematic diagram of the push-pull osmotic pump

Factors Affect the Drug Release

As reported by several researchers, drug release from osmotic pumps was notably affected by some factors as followed

A. Solubility

The kinetics of osmotic drug release is directly related to the solubility of the drug within the core. Highly water soluble drug would demonstrate a high release rate that would be zero-order for a small percentage of the initial drug load. However, it is possible to modulate the solubility of drug within the core. Some of the approaches that have been used to delivery drug having extremes of solubility are:

McClelland et al (1991) reported co-compression of drug with excipients of a highly water-soluble drug, diltiazem hydrochloride. Because of very high water-solubility, the majority of drug fraction was release predominantly at a first-order rather than the desired zero-order rate. The solubility of diltiazem hydrochloride was reduced by incorporation of sodium chloride into the core tablet formulation. The modification resulted in more than 75% of the drug to be released by zero-order kinetics over a 14-16 h period. Herbig et al (1995) reported osmotic delivery of

doxazosin, which has pH-dependent solubility. Tablet cores contain drug, along with organic acids (succinic and adipic acid) to increase the solubility of doxazosin within the core. Use of polymer coated buffer components to modulate the drug solubility within the core is described in U.S. patent no. 4,755,180. Swellable polymer can be utilized for osmotic delivery of drug having poor aqueous solubility is reported in U.S. patent no. 4,992,278 for carbamazepine, theophylline, acetylsalicylic acid and nifedipine.

B. Osmotic Pressure

For controlling the drug release from osmotic system, it is important to optimize the osmotic pressure gradient between inside compartment and the external environment. It is possible to achieve and maintain a constant osmotic pressure by maintaining a saturated solution of osmotic agent in the compartment. If a drug does not possess sufficient osmotic pressure, an osmogent can be added in the formulation (Verma, R.K., 2002)

C. Delivery Orifice

Osmotic delivery systems contain at least one delivery orifice in the membrane for drug release. The size of delivery orifice must be optimized in order to control the drug release from osmotic system. If the size of delivery orifice is too small, zero-order delivery will be affected because of development of hydrostatic pressure within the core. This hydrostatic pressure may not be relieved because of the small orifice size and may lead to deformation of delivery system, thereby resulting in unpredictable drug delivery. On the other hand, size of delivery orifice should not also be too large otherwise; solute diffusion from the orifice may take place (Theeuwes, F., 1975). Drug release from osmotic system is not affected by the size of the delivery orifice within certain limits as reported from osmotic pumps of nifedipine was studied as a function of orifice diameter and no significant differences were found in the release profiles for orifice diameter ranging from 0.25 to 1.41 mm (Liu, Khang, Rhee

and Lee, 2000). However, Ramadan and Tawashi (1987) reported that under turbulent flow conditions and high rotating speeds, the orifice size has a significant effect.

D. Membrane Charteristics

The choice of a rate-controlling membrane is an important aspect in the formulation development of oral osmotic systems. To ensure that the coating is able to resist the pressure within the device, thickness of membrane is usually kept between 200 and 300 μm (Santus and Baker, 1995). However, this may be problematic in cases where the drug is having low osmotic pressure because of which incomplete/ slow drug release may take place (Verma, R.K., 2002).

Propranolol Hydrochloride

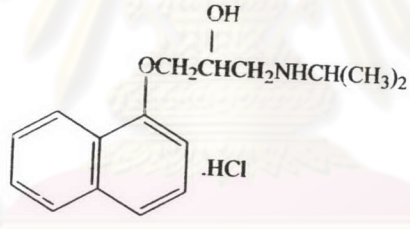

Figure 5 The structure formula of propranolol hydrochloride

Chemical name of propranolol hydrochloride is (±)1-Isopropylamino-3-(1-naphthyloxy)propan-2-ol hydrochloride. The empirical structure is $C_{16}H_{21}NO_2HCl$ with molecular Weight 295.8. Propranolol HCl is white or almost white crystalline powder, odorless, nonhygroscopic and bitter taste. It has melting point at 163-166°C. It is classified as water soluble drug. It is soluble in 20 parts of water and slightly soluble in chloroform, and practically insoluble in ether (Reynold, 1994).

This model drug is a beta blocker clinically used in the treatment of hypertension and to improve the tolerance to exercise in patients with angina pectoris.

It has been given for the prevention of re-infarction. It is also used in the treatment of cardiac arrhythmias and it is often effective in supraventricular tachyarrhythmias (John, 1990).

In aqueous solution, the oxidation of the isopropylamine side chain, accompanied with the reduction in the pH of the solution decomposed the compound. This drug is most stable at pH 3 and decomposes rapidly under alkaline condition. Propranolol HCl is sensitive to light, but stable to heat. It should be preserved in well-closed containers. The USP requires the preparations to be protected from light (The United States Pharmacopeial Convention, 1990)

Release Mechanism

The liberation of medicament from prepared dosage form is mostly detected from the dissolution test. The release behavior can be observed from the amount of drug released and time profile. In general, the obtained release profiles contain elementary information exemplified the structure and mechanisms of a delivery device on a microscopic scale. Possibly, interactions and other subtle relationships between encapsulated component and its carrier can be obviously known. More detailed information on the microstructure and properties of the selected device appears to be necessary to understand the release mechanisms. Ideally, the release profiles can be corrected to understand the microstructure of the carrier; hence, the manufacturer can predict the release characteristic and can design the device with the more desired release pattern.

Additionally, practical methods such as optimization techniques combined with above data will be useful in designing or construct the desired drug delivery system (Gopferich, 1996). The mathematical model is developed to describe the drug release behavior and is also useful for aiding the understanding of delivery system. The development is based on a composite of geometrical shape to predict drug release.

The Release Model

For this study, the selected mathematical models were zero order, first order, Higuchi and power law expression models. Each mathematical model consists of independent and dependent variables, constants and parameters that have to be related or estimated.

A. Zero Order

An ideal controlled release system is one which can manipulate the medicament released at constant rate until the system is exhausted. The drug transport through the membrane by simple diffusion should provide the constant release rate. Mathematically, the release rate from this device is expressed as:

$$dW_t/dt = k \qquad \textbf{(Eq.20)}$$

where k is a constant; W_t is the mass of drug released and t is the time.

This release pattern is called zero-order release model. If the drug diffusion is the major release mechanism, the release rate should be directly proportional to the drug solubility.

B. First Order

The first order model selected for the case of the release rate is proportional to the mass of drug contained within the device. The release rate could be expressed as:

$$dW/dt = k(W_o - W) \qquad \text{(Eq.21)}$$

where W_o is the mass of drug in the device, W is the drug remaining in device and k is the rate constant. On rearrangement, this model can be express as:

$$W = W_o e^{-kt} \qquad \text{(Eq.22)}$$

In case of coated dosage form, typically, constant drug release can be achieved up to about 70-80% of drug release after which the release rate will decline. Presumably, the gradually decline rate of a constant-thermodynamic activity reservoir system in late stage of drug release is due to the decreased drug concentration inside the device below the saturation level resulting in a loss of thermodynamic activity and release rate. This release behavior can be described as first order characteristic (Porter and Jambhekar, 1995).

C. Higuchi's Model

Higuchi (1963) introduced a mathematic model for the drug released from an inert matrix by plotting the percentage of drug liberated as a function of the square root of time:

$$F = K(t)^{(1/2)} \qquad \text{(Eq.23)}$$

where F is the fraction of drug released, t is the time and K is the release constant defined as:

$$K = [((D\varepsilon)/\tau)(2A - \varepsilon C_s)C_s] \qquad \text{(Eq.24)}$$

where D is diffusion coefficient, ε and τ are the porosity and tortuosity factor of matrix respectively, A is the amount of drug in the matrix (weight/volume) and C_s is the solubility of drug.

The level of film coating sometimes related to the change in release mechanism. The drug release from incompletely coated bead at low levels of Aquacoat could be describe with the square root of time model, while that from high level of coating appeared to be best described by zero order. Samani et al (1999)

applied this model as one of release models to study the release kinetic of atenolol from film-coated tablets.

D. Power Law Expression

The kinetics of drug liberation can be analyzed by the following commonly used exponential equation:

$$F = K(t)^n \qquad \text{(Eq.25)}$$

while F is the fraction of drug released up to time t, K denotes as a constant incorporating the structure and geometric characteristics of the release device and n is the release component indicative of the mechanism of release (Ritger and Peppas, 1987).

The relationship between the diffusion exponent n and the corresponding release mechanism is dependent upon the geometry employed as presented in Table 1. Chen and Hao (1998) applied this equation to analyze the release mechanism of verapamil released from insoluble gelatin capsule.

Table 1 **Diffusional exponent and mechanism of drug from various non-swellable** and swellable controlled release systems.

Diffusional Exponent (n)			Drug Release Mechanism
Thin film	Cylindrical Sample	Spherical Sample	
0.5[a]	0.45[a]	0.43[a]	Fickian Diffusion
0.5<n<1.0[a]	0.45<n<1.00[b] 0.45<n<0.89[c]	0.43<n<1.00[b] 0.43<n<0.85[c]	Anomalous (non-Fickian Transport)
1.00[a]	1.00[b] 0.89[c]	1.00[b] 0.85[c]	Case-II Transport

*a: in case of both non-swellable and swellable controlled release system; b: in case of non-swellable controlled release system; c: in case of swellable controlled release system.

G. Weibull equation

Weibull equation was originally designed to apply for a large variety of distribution such as yield strength of fibres and steels, size of beans and insects. This expression consists of a set of parameters related to scale, location, and shape. The Weibull equation has been applied successfully to various common types of dissolution curves and useful involving the quantitative interpretation of dissolution data. When applied to release data, the Weibull equation expresses the fraction of cumulative drug release, F, at time t, by:

$$F = 1 - e^{\wedge}\left(\left(-\left(t/Td\right)^{\wedge} B\right)\right) \qquad \text{(Eq.26)}$$

where $Td=A^B$, A is the scale parameter, B is the shape parameter and Td denotes the time interval when 63.2% of drug has been dissolved. The shape parameter, B, characterizes the curve as exponential when $B=1$ and sigmoidal curve when $B>1$. Recz, Dredan, Antal and Gondar (1997) mentioned about shape parameter as $B \cong 1$ refers to first-order dissolution kinetics and $B>1$ indicates the palallel moving courses in adding to diffusion (disintegration, erotion).

Although the constant k is one of the measures of the drug release rate, it should not be used for comparison because different kinetics is usually involved in different test conditions (Talukdar et al., 1996). Therefore, to characterize the drug release rate in different experimental conditions, relative dissolution time (RDT) was calculated from dissolution data by using following equation (Brockmeier and Hattingberg, 1982).

$$\text{RDT} = \frac{ABC}{M_{\infty}} \qquad \text{(Eq.27)}$$

This equation was calculated based on that for determining mean dissolution time. The diagrammatic of dissolution profile for explaining RDT calculation is illustrated in Figure 6

ABC was calculated indirectly by subtracting total area ($M\infty$ multiplied with time function) with area under dissolution curve (AUC). The trapezoidal method was used to calculate AUC.

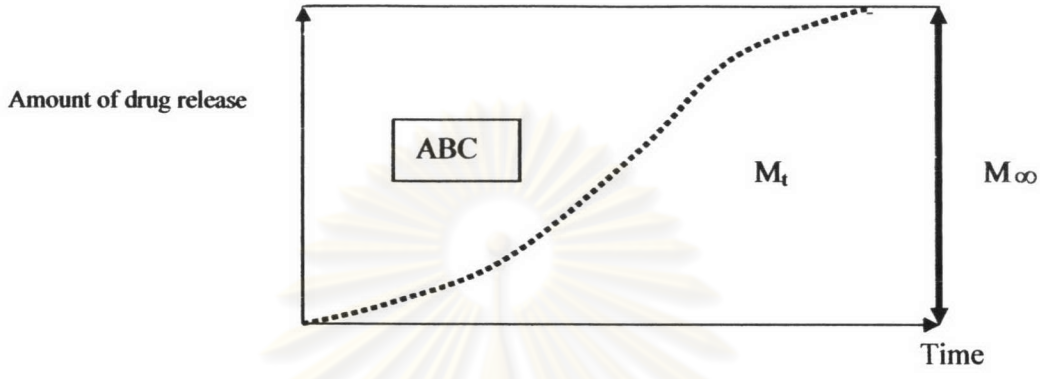

Figure 6 Diagrammatic of dissolution profile for explaining RDT calculation. ABC is area between upper line ($M\infty$) and the dissolution curve; $M\infty$ is maximum drug release at infinite time and M_t is amount of drug release at any time t.