Chapter I

General Background

Introduction

Chitosan is a natural polymer obtained by partial or complete deacetylation of chitin. Chitin and chitosan are manufactured commercially in large scale from the outshell of crustaceans (shrimp and crab). In Thailand, chitin and chitosan have been produced for commercial purpose using shrimp shell as the starting material.

The applications of chitin and chitosan in pharmaceutical system have been widely investigated. Chitin and chitosan have been tested for distintegrant efficacy both in direct compression technique (Sawanayagi, Nambu, and Nagai,1982) and in wet granulation (Kawashima, et al., 1985). Chitin and chitosan were observed to be useful in enhancement of dissolution of poorly soluble drugs by grinding or kneading the drugs with these polymers (Sawayanagi, Nambu, and Nagai, 1982).

Chitin and especially chitosan were evaluated for their use in controlled release preparations. Miyasaki, Ishi, and Nadai (1981) prepared controlled release gel systems using dried gel of chitin and

chitosan. Direct compression matrix tablets of both water soluble and water insoluble drugs using chitosan as a vehicle were prepared by Miyazaki, Ishi and Nadai, 1981. It was reported that when chitosan was used alone in a tablet formulation did not impart sustained release preparation at low concentration. When it was used in a concentration of 50% of tablet weight, a non-erosion type matrix system was formed. If more prolonged release was required, the combination with some type of polymer was needed. Chitosan was also applied in manufacture of sustained release matrices, by wet granulation technique and by coating granules(Kawashima, 1985).

There are several methods that have been used to achieve the preparation oral sustained release dosage forms. A matrix system is a popular method due to its easiness, convenience, cost saving and copability of mass-producion, It can be prepared by several methods. For example, it can be compressed directly from the powdered mixture of drug and polymer or tableting microcapsules or solid dispersed particle prepared with polymers. The latter method imparts the more precisely controllable and predictable drug release rate to the resultant tablets. Spray drying is a useful method for this processing since it can both simplify the process and shorten the processing time. In addition, it offers a mean for obtaining powders with predetermined properties such as particle size and shape (Broadhead et al., 1992).

There has been a renewed interest in the use of spray drying to modify the release characteristics of the pharmaceutical product

(Bodmeier and Chang, 1988 ; Takeuchi et al., 1987 : Wan et al, 1990; Takeuchi et al., 1989 ; Leesawat , 1991).

The advantage of spray drying process in preparation of sustained release matrices areas follows: uniform distribution of polymer and drug content, reproducibility of drug release characteristics within batch to batch , provision of directly compressible co-spray dried powder with free flowing,and low amount of polymer required (Leesawat, 1991).

This work reports another feasibility study on application of chitosan in conjuction with the use of spray drying technique to prepare sustained release matrices.

Chitosan with different degree of deacetylation would have different fundamental physical properties such as solubility, viscosity and rheology(Jaiyongka, 1993). Therefore, chitosan in this experiment were prepared by deacetylation under various reaction time would have differences in degree of deacetylation. then, prepared matrices of chitosan were prepared with propranolol HCl as model drug by spray dry technique. Release characteristics of matrices in buffer pH 1.5 and buffer pH 6.8 were evaluated according to USP XXII.

Objectives of this study:

The aims of this study are :

1.   To investigate the feasibility of preparing co-spray dried powder of propranolol hydrochloride and chitosan having different degree of deacetylation and examine the physico-chemical properties of these co-spray dried powders.

2.   To study release characteristics of matrices prepare from co-spray dried powder of propranolol hydrochloride and chitosan in dissolution medium having different pH and investigate the model and mechanism of drug release from matrices.

3.   To explore data as a guide for developing propranolol hydrochloride controlled release matrices according to compendial specification.

4.   To modify the release characteristics of co-spray dried of propranolol hydrochloride and chitosan matrices by incorporation of cellulose polymer.

Literature Review

Physical Approaches to Controlled Release Dosage Form

There are five methods that are widely used to achieve the preparation of oral sustained release dosage forms.

1. Diffusion system

Basic theory of this system is that diffusion entails the movement of the drug molecules from a region of higher concentration to one of a lower concentration. The release rate of drug from this system is determined by its diffusion through a polymer. There are two types of the diffusion systems.

1.1 Reservoir type

This type occurs as a core of drug surrounded by a polymeric membrane. Methods that have been used to develope reservoir type devices are as follows (Hui and Robinson, 1987). Both the press coating and air suspension techniques have been used to apply insoluble polymeric materials to enclose a containing drug core in tablets, while the microencapsulation process is a commonly used procedure to coat drug particles to be incorporated into tablets or capsules.

If the encapsulating material is selected properly, diffusion will be the controlling process.

Some materials used as the membrane barrier coat, alone or in combination, are hardened gelatin, methyl or ethylcelluloses, polyhydroxymethacrylate, hydroxypropylcellulose, polyvinylacetate and various waxes.

1.2 Matrix type (Baker, 1987)

In matrix devices the material to be released is dispersed uniformly throughout the rate controlling polymer medium. The release profile is then determined by the loading of dispersed agent, the nature of the components, and the geometry of the device. Thin spots, pinholes and other similar defects, which can be serious problems with reservoir systems, do not substantially alter the release rate from matrix devices.

This, together with the case with which dispersions can be compounded (by milling and extruding; for example), results in low fabrication cost.

There are two principal categories of matrix device. If the active agent is dissolved in the polymer medium, the device is call a matrix solution. A device of this kind is often used when the active agent is a liquid, some polymer(for example, polyvinylchloride)

can easily dissolve up to 20% or more of these liquid.

If the active agent has a more limited solubility in the polymer medium, then only a portion of the agent is dissolved in the polymer medium and the remainder is dispersed as small particles throughout the polymer. A device of this type is called a matrix dispersion.

1.2.1 Matrix solution

One method of preparing a matrix device containing dissolved active material is to equilibrate it with the material : for example the device may be soaked in a neat liquid or a concentrated solution. Release kinetics of this method can be calculated by two equations (Heller, 1987). Equation 1, which is known as the early time approximation, holds true for the first 60% of the release rate, after which it is calculated from Equation 2, which is known as the late time approximation

$$\frac{dM_t}{dt} = 2M_x \left[\frac{D}{\pi l^2 t} \right]^{1/2} \tag{1}$$

$$\frac{dM_t}{dt} = \frac{8DM_x}{l^2} \exp \frac{\pi Dt}{l^2} \tag{2}$$

where L = the thickness of device

D = the diffusion coefficient

Mx = the total amount of active agent dissolved in the polymer

Mt = the amount released at time t

As equation 1 shows, release rate decreases as $t^{1/2}$ over the firs 60% of the release ; over the remainder of the release the rate decays exponentially according to equation 2.

1.2.2 Matrix dispersion

The second type of matrix system consists of a dispersion of solid active agent in a rate-limiting polymer matrix. As with matrix solution system, the release varies with the geometry of the device ; it also varies with agent loading. Matrix dispersion systems are of three types, depending on the volume fraction of agent in matrix.

At low loading levels of agent (0-5 vol %), the release of the compound involves dissolution of the agent in the polymer medium followed by diffusion to the surface of the device. These devices are called simple matrix dispersions.

A slightly higher loading levels (5-10 vol %), the release mechanism is more complex, since the cavities remaining from the loss of material near the surface are filled with fluid

imbibed from the external environment, and these cavities provide prefered pathways for the escape of material remaining within the device. At these loading levels, the cavities are not connected to form continuous pathways to the surface, but they may increase the overall apparent permeability of the agent in the device. These devices are called complex matrix dispersions.

When the loading of dispersed agent exceeds 20 volume %, the cavities left by the loss of material are sufficiently numerous to form a continuous channel to the surface of the matrix. In this case, the majority or all of the active agent is released by diffusion through these channels. These type of device is called monolithic matrix system, or simply matrix system. The solubility and diffusivity of the dispersed agent in the fluid filling the channels determines its rate of release

The three types of matrix dispersion are:

1.2.2.1 Simple monolithic dispersions

When the active agent concentration isin the range of 0-5 volume %, the release rate from these systems ca be described by asimple Higuchi model. The model is shown schematically in Figure 1.

Polymer Matrix

Solution

Dispersed
and
Dissolved

Dissolved
Only

C_0

Solution
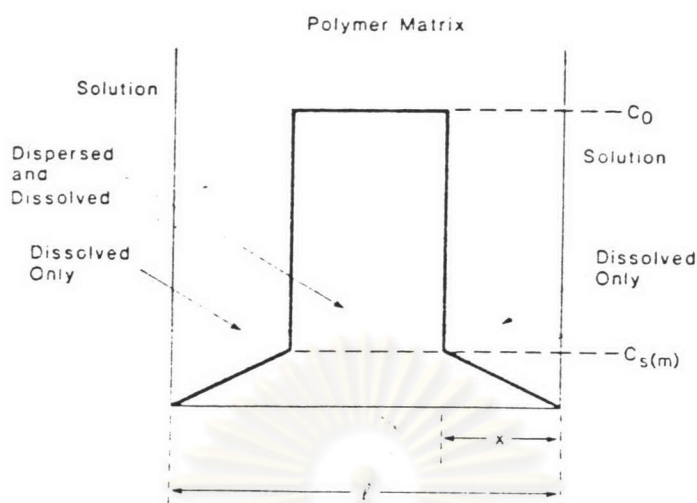
Dissolved
Only

$C_{s(m)}$

x

ℓ

Figure 1 A cross section through a polymer matrix initially

containing dispersed solid agent (Baker, 1987)

This model assumes that solid agent in the surface layer of the device dissolves in the polymer matrix and diffuses from the device first. When the surface layer becomes exhausted of agent, the next layer begins to be depleted. The surface between the region containing dispersed agent and the region containing only dissolved agent thus moves into the interior as a front. The validity of the model developed by Higuchi (1961) has been experimentally demonstrated numerous times by comparing the predicted release rate calculated from the model with the actual experimental release rate. The release kinetics have been derived by Higuchi.

$$dM_t/dt = \frac{A}{2} \left[\frac{2DC_{s(m)}C_o}{t} \right]^{1/2} \qquad \text{for } C_o \gg C_{s(m)} \qquad (3)$$

where M_t = the amount released at time t

         A   = the total area of device

         D   = the diffusion coefficient

$C_{s(m)}$ = the solubility of the agent in the polymer
            matrix

C_o = the total concentration of agent
           (dissolved plus dispersed)

t   = time

1.2.2.2 Complex monolithic dispersion

The Higuchi model is generally a good predictor of agent release for matrix polymer dispersions containing low levels (< 5 %) of active material. However, at higher loadings, deviations from the expected release profile occur. The rate of release is still proportional to $t^{1/2}$ but has a higher value than the model predicts. As discribed ealier, this is due to the presence of fluid-filling cavities created by dissolution and diffusion of particles near the surface, which increase the system's permeability to most substance. At low loading, the permeability extrapolates to the value obtained by independent membrane permeability experiments, in accordance with the simple Higuchi model. However, at high loadings of material, the apparent permeability increase because of the high permeability of the cavities left behind by the released active agent. Thus, equation 3 may be modified for the complex matrix dispersion to

$$dM_t/dt = \frac{A}{2} \left[\frac{2DC_s(m)C_o}{t} \cdot \frac{1+2C_o/\bar{\rho}}{1-C_o/\rho} \right]^{1/2} \qquad (4)$$

where ρ is the density of the permeant

1.2.2.3 Monolithic matrix system

At loadings of active agent above approximately 15 to 20 volume %, all the agent particles dispersed in the polymer matrix are in contact with one another. The release mechanism for this type of monolithic matrix system is illustrated in Figure 2. As shown in the figure, the active agent is released by diffusion through the water-filled pores that form as water is imbibed from the surface of the device to replace the active agent that leaches out.

The mathematical description of release from this type of system exactly matches equation 3 previously derived for simple matrix dispersions, the only difference being substitution of the appropriate expression for the permeability term DK in these equation. In this case, release is through the pores formed by dissolution of the agent, and thus the appropriate substitution for the partition coefficient is

$$K = \epsilon \qquad (5)$$

to reflect the fact that, although the fluid inside the membrane pores is the same as the surrounding solution, only a volume fraction ϵ of the membrane is filled with this fluid. The appropriate substitution for the diffusion coefficient is
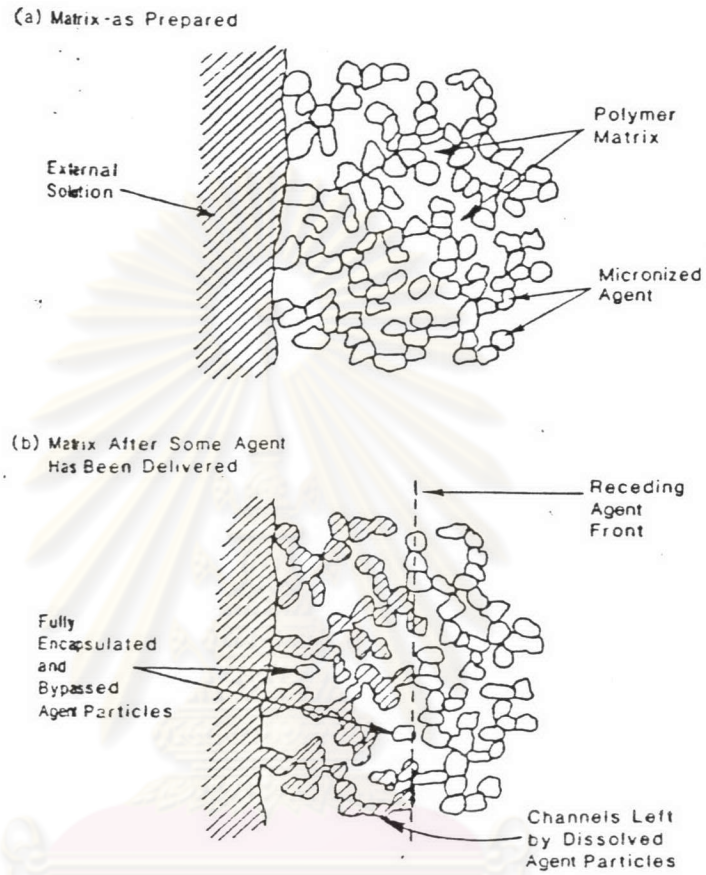
(a) Matrix-as Prepared

Polymer
Matrix

External
Solution

Micronized
Agent

(b) Matrix After Some Agent
Has Been Delivered

Receding
Agent
Front

Fully
Encapsulated
and
Bypassed
Agent Particles

Channels Left
by Dissolved
Agent Particles

Figure 2 Agent release mechanism for a monolithic matrix system

$$D \quad = \quad \frac{D_w}{\tau} \quad\quad (6)$$

where Dw is the diffusion coefficient of the agent in the fluid (water) filling the matrix pore and τ is a term reflecting the entire distance the agent must on average diffuse to escape from the device. Thus, the Higuchi model expression for release from a monolithic slab is

$$dM_t/dt \quad = \frac{A}{2} \left[\frac{2D_w \mathcal{E} C_s C_o}{\tau t} \right]^{1/2} \quad\quad (7)$$

2. Dissolution systems

A drug with a slow dissolution rate will yield an inherently sustained blood level. In principle, then, it would seem possible to prepare sustained release product by decreasing the dissolution rate of drug which are highly water-soluble. This can be done by preparing an appropriate salt or derivative, by coating the drug with a slowly soluble material, or by incorporating it into a tablet with a slowly soluble carrier. Ideally the surface area available for dissolution must remain constant in order to achieve a practice.

The dissolution process can be considered diffusion-layer-controlled, where the rate of diffusion from the solid surface to the bulk solution through an unstirred liquid film is the rate-determining step. In this case the dissolution process at steady state is described by the Noyes - Whitney equation :

$$dC/dt = KdA(Cs-C) = (D/h)A(Cs-C) \qquad (8)$$

where dC/dt = the dissolution rate

Kd = the dissolution rate constant

A = the total surface area

Cs = the saturation solubility of the solid

C = the concentration of solute in the bulk solution

The above equation predicts a constant dissolution rate if the surface area, diffusion coefficient, diffusion layer thickness and concentration difference are kept constant. However, as dissolution proceeds, all of these parameters may change, especially surface area.

Two common formulations relying on dissolution to determine release rate of drug are shown in Figure 3. Most of the products fall into two categories : encapsulated dissolution systems and matrix dissolution systems.

Encapsulated dissolution system can be prepared either by coating particles or granules of drug with varying thicknesses of slowly soluble polymers or by microencapsulation. The most common method of microencapsulation is coacervation, which involves addition of a hydrophillic substance to a colloidal dispersion. The hydrophillic substance, which acts as the coating material, can be selected from a wide variety of natural and synthetic polymers including shellacs, waxes, starches, cellulose acetate phthalate (or butyrate) or polyvinylpyrrolidone. Once the coating material dissolves, all of the drug inside the microcapsule is available immediately for dissolution and absorption. Thus, drug release can be controlled by adjusting the thickness and dissolution rate of the coat. The thickness can be varied from less than $1 \mu m$ to $200 \mu m$ by changing the amount of coating material from 3 to 30% of the total weight.

Matrix dissolution device are prepared by compressing the drug with a slowly soluble polymer carrier into a tablet. There are two general methods of preparing drug-polymer particles : congealing and aqueous dispersion methods. In the congealing method, drug is mixed with the polymer or wax material and either cooled and screened or spray-congealed. In the aqueous dispersion method , the drug - polymer mixture simply is sprayed or placed in water and the resulting particles are collected.
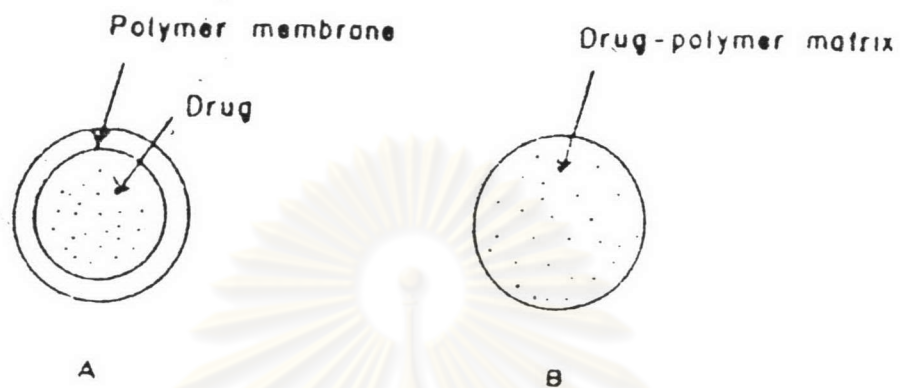
Polymer membrane

Drug-polymer matrix

Drug

A

B

Figure 3 Systems using dissolution

Osmotic delivery orifice

Semi-permeable
membrane
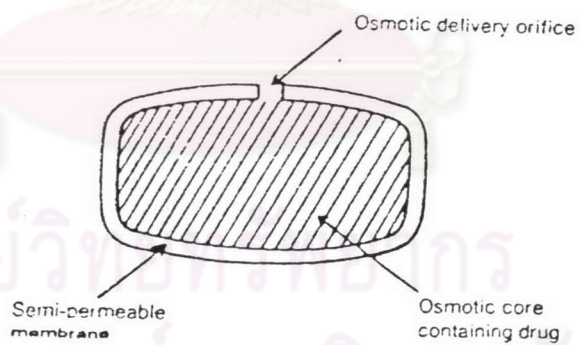
Osmotic core
containing drug

Figure 4 System using osmotic pump

3. Osmotic systems

Osmotic pressure can be employed as a driving force to generate a constant release of drug provided a constant osmotic pressure is maintained and a few other features of the physical system are constrained. Consider a tablet consisting of a core of drug surrounded by a semipermeable membrane containing a small orifice, as shown in Figure 4. The membrane will allow free diffusion of water, but not drug. When the tablet is exposed to water or any fluid in the body, water will flow into the tablet due to osmotic pressure difference and the volume flow rate, dv/dt, of water into the tablet is

$$dV/dt = (kA/h)(\Delta\Pi - \Delta P) \qquad (9)$$

where k, A and h are the membrane permeability, area and thickness, respectively, $\Delta\Pi$ is the osmotic pressure difference and ΔP is a hydrostatic pressure difference. If the orifice is sufficiently large, the hydrostatic pressure difference will be small compared to the osmotic pressure difference, and equation (9) becomes

$$dV/dt = (kA/h)\Delta\Pi \qquad (10)$$

Thus, the volume flow rate of water into the tablet is determined by permeability, area and thickness of the membrane. The drug will be pumped out of the tablet through the orifice at a controlled rate , dM/dt, equal to the volume flow rate of water into the tablet multiplied by the drug concentration , C_s :

$$dM/dt \quad = (dV/dt)C_s \tag{11}$$

The advantage of the osmotic system is that it requires only osmotic pressure to be effective and is essentially independent of the environment. The drug release rate can be predetermined precisely regardless of pH change through the GI tract. Some materials used as the semipermeable membrane include polyvinyl alcohol, polyurethane, cellulose acetate, ethylcellulose and polyvinyl chloride.

4. Ion-Exchange Resins

Ion-exchange resins are water insoluble crosslink polymers containing salt forming groups in repeating positions on the polymer chain. Drug is bound to the resin by repeated exposure of the resin to the drug in the chromatographic column, or by prolonged contact of the resin with the drug solution. Drug release from the drug resin complex depend on the ionic environment, i.e pH and electrolyte concentration within the GI tract as well as properties of the resin.

Drug molecules attached to the resin are released by exchanging with appropriately charged ion in the GI tract followed by diffusion of the free drug molecule out of the resin. The rate of diffusion is controlled by the area of diffusion, diffusional pathlength and extent of crosslinking in the resin. A further modification of release rate can be made by coating the drug complex.

$$Resin^+ - Drug^- + X^- \longrightarrow Resin^+ - X^- + Drug^-$$

or

$$Resin^- - Drug^+ + Y^+ \longrightarrow Resin^- - Y^+ + Drug^+$$
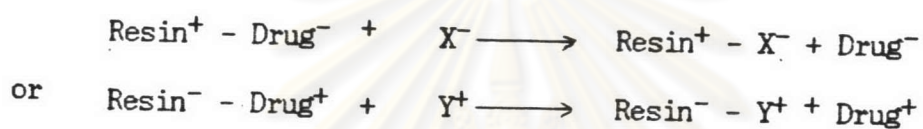
where X^- and Y^+ are ions in the GI tract

5. Prodrugs

A prodrug is a compound formed by chemical modification of a biologically active compound which will liberate the active compound *in vivo* by enzymatic or hydrolytic cleavage. The primary purpose of employing a prodrug for oral administration is to increase intestinal absorption or to reduce local side effects.

The most popular method to obtain sustained release dosage forms is to prepare in matrix system, due to its easiness, convenience , cost saving and capability mass-production.

Chitosan

There has been considerable interest in recent years in developing controlled or sustained drug delivery systems using chitosan. Chitosan has been examined extensively by the pharmaceutical industry in Japan and the US for its potential in controlled drug delivery system. The polymer cationic character together with its potential reactive groups give chitosan unique properties for utilisation in controlled release technologies. In addition, both the biocompatibility and biodegradability have been well established.

Chitosan [a (1,4)-2 amino -2-deoxy- β-D-glucan] is easily prepared from chitin by N-deacetylation with alkali. The degree of deacetylation can be varied according to deacetylation process, there are many factors - such as concentration of alkali used, reaction time, temperature, atmospheric condition and size of chitin particles (Hyes, 1978).

A unique characteristics of chitosan is that it is insoluble in water and common organic solvents but soluble in acid solution. Muzzelli,1977 has reported that chitosan is soluble in aqueous solution of formic, acetic, citric, pyruvic, and lactic acids as well as in glycolic, maleic, malonic, tartaric and many other acids.

Application of Chitosan to Oral Controlled Release Preparations

Miyasaki, Ishii and Nadai (1981) reported the use of chitin and chitosan as vehicle for indomethacin and papaverine hydrochloride. Sustained release of the drugs from the dried gel was obtained. Drugs dispersed in the chitosan gels were released at a constant rate (zero-order).

Kawashima, et al. (1985)prepared of a prolonged release tablet of aspirin with chitosan. The parameters controlling the drug release rate were the chitosan content in the tablet, the physical state of chitosan used for granulation i.e. liquid solution or gel, and the pH of the dissolution test solution. When the chitosan solution was used for agglomeration, the drug release rate of the resultant tablet was faster than when the gel was used. The drug release became more prolonged with increasing chitosan content in the tablet or with decreasing pH of the dissolution test solution.

Sawayanagi, Nambu and Nagai (1982) reported the use of chitosan as a vehicle for sustained-release preparation of water soluble drug, propranolol hydrochloride, by direct compression. Zero-order controlled release was obtained.

Nigalaye , et al. (1990) prepared a hydrocolloidal matrix system containing complexes of chitosan. Chitosan was investigated for

preparation of sustained release tablets of theophylline by direct compression and examined in vitro. It was found that when chitosan is used in a concentration of more than 50 % of tablet weight, an insolable non-erosion type matrix was formed. Tablets prepared with a chitosan concentration of less than 33% were fast releasing. Chitosan used in a concentration of about 10 % acted as a disintegrant and the drug was dissolved within an hour.

Citric acid slowed down the release rates of chitosan based theophylline tablets. Theophylline tablets using carbomer-934P as a sustained release base were evaluated. Carbomer 934P in lower concentrations forms an erosion type matrix. In order to produce a twenty-four hour sustained release tablet, more than 10 % concentrationof carbomer-934P is needed.Combination with chitosan and carbomer-934 produced slow releasing tablets. A hydrocolloidal erosion type matrix was formulated using chitosan, carbomer-934P and citric acid. Only 10 % chitosan was needed to prepare theophylline sustained release tablets in these mixtures (Nigalaye, et al., 1985)

Further studies examined the use of chitosonium malate(salt of chitosan) as a matrix in sustained-release tablet of furosemide by direct compression and wet granulation technique by Akbuga (1993). It was found that when the concentration of chitosonium malate increased, the rate of release of the drug decreased. Chitosonium malate showed sustained-release properties even at low concentrations. When the

release data were filled to the simple power law equation , the mode of drug release was of the non-Fickian and super case II types.

Thanoo, Sunny and Jayakrishnan (1991) prepared cross-linked chitosan microsphere by the glutaraldehyde cross-linking of an aqueous acetic acid dispersion of chitosan in paraffin oil using dioctylsodiumsulphosuccinate as a stabilizing agent. Microspheres were prepared by incorporating theophylline, aspirin or griseofulvin. Drug incorporation efficiencies exceeding 80 % could be achieved for these drugs. *In vitro* release studies of these drugs were carried out in simulated gastric and intestinal fluids at 37 °C. It was observed that the drug release rates were influenced by the cross-linking density, particle size and initial drug loading in the microsphere, it offers an opportunity to manipulate these parameters to obtain a nearly zero order release from the matrix.

Miyazaki, et al. (1988) prepared sustained release of indomethacin from chitosan granules by cross-linking procedure compared with conventional capsules in beagle dogs. The granules produced a sustained plateau of the drug in term of reducing the peak in plasma concentration and maintenance of drug concentration in plasma, the chitosan granules were superior to conventional capsules.

Shiraishi, et al. (1993) reported that controlled release of indomethacin by chitosan-polyelectrolyte complex. The effects of the molecular weights of chitosan hydrolysates on the release and

absorption rate of indomethacin from gel beads were examined. The release rate of indomethacin decreased with increasing of molecular weight and indomethacin content. The release of indomethacin depended upon the dispersion of the indomethacin solid particle in the beads, as well as the porosity, tortousity and surface area of the matrix. The plasma concentration of indomethacin after oral administration of chitosan gel beads to beagle dogs exhibited the sustained release pattern. With increasing molecular weight of chitosan, the AUC and Cmax were decreased, while MAT was increased. A good correlation was observed between the molecular weight of chitosan or dissolution rate constant and the MAT or AUC. The results revealed that the chitosan gel beads composed of chitosan hydrolysate, of molecular weight 25000, might be the best for the sustained release preparation of indomethacin. It was suggested that the absorption of other drugs could be controlled by the proper solution of chitosan hydrolysate of optimal molecular weight and predicted from *in vitro* dissolution test.

Kawashima, et al. (1985) proposed a novel method for the preparation of controlled-release theophylline granules coated with a polyelectrolyte complex of sodium polyphosphate-chitosan. The theophylline granules containing sodium tripolyphosphate were stirred in hydrochloride solution of chitosan. During the mixing, the dissolved sodium tripolyphosphate in the granule moved to the surface and reacted with the chitosan, resulting in the formation of polyelectrolyte complex film. The factors affecting the drug content, the particle size, and the coating film thickness of the resultant

coated granules were determined. The theophylline content in the coated granule decreased with increasing content ratio of sodium tripolyphosphate to theophylline in the original granule and with increasing chitosan concentration in the coating solution. The coated granule size increased with increasing chitosan concentration in the coating solution and with decreasing agitation speed. The coating -film thickness increased with an increase in the chitosan concentration, the pH of the coating solution, and the sodium tripolyphosphate to theophylline content ratio in the original granule The drug-release pattern of the coated granules followed zero-order kinetics and the release rates were significantly reduced compared with that of the original granule.

Release Patterns of Controlled Release Systems

The pattern of delivery achieves by a controlled release system can vary over a wide range , but most release profiles categorized into three types :

1. Zero-order release pattern
2. Square-root-time release pattern
3. First-order release pattern

1. Zero-order release pattern

An ideal controlled release device is one which can deliver the drug at a constant rate until the device is exhausted of

active agent. Mathematically, the release rate from this device is given as

$$\frac{dMt}{dt} = k \tag{12}$$

where
k = zero-order constant

t = time

Mt = the mass of active agent released

2. Square-root-of-time release pattern (Higuchi model)

The second common release pattern, frequently referred to as square-root-of-time or $t^{1/2}$ release, provided compound release that was linear with the reciprocal of the square root of time. The release rate then given as

$$\frac{dMt}{dt} = \frac{k}{\sqrt{t}} \tag{13}$$

The release pattern of this type can be described by Higuchi equation (Higuchi, 1963)

$$Q = \left[\frac{D\epsilon(2A-\epsilon Cs)\ Cst}{\tau}\right]^{1/2} \tag{14}$$

where   Q   =   the amount of drug released per unit surface area

D =   the diffusion coefficient of the drug in the release medium

ϵ =   the porosity of the matrix

τ =   the tortousity of the matrix

A =   the total amount of drug present in the matrix per unit volume

C_s =   the solubility of drug in the release medium

t =   time

The assumptions made derived Equation 14 are as follows.

1. The system is in perfectly sink condition

2. A pseudo-steady state is maintained during release

3. Drug particles are quite small than those in matrix

4. Drug particles are uniformly distributed in the matrix

5. A is greater than C_s or ϵC_s

6. The diffusion coefficient remains constant

In general, Higuchi 's equation is usually desired and used as in equation :

$$Q = kt^{1/2} \tag{15}$$

where   k   =   Higuchi constant

Therefore , the plot of amount of drug released from matrix versus square root of time should be increased linearly if drug release from the matrix is diffusion controlled.

3. First-order release pattern

The release rate in first order model was proportional to active agent contained within device. The rate was then given as

$$\frac{dMt}{dt} = k(Mo-Mt) \qquad (16)$$

where   Mo   =   initial amount of drug

Mt   =   amount of drug released

k   =   first-order rate constant

First-order pattern can be predicted by equation 17 by plotting the log of the drug left against time (Schwartz, et al, 1968). The initial carvature can be attributed to the presence o f surface drug and can be ignored.

$$\log W = \frac{kt}{2.303} + \log Wo \qquad (17)$$

where   W   =   amount of drug left

Wo   =   initial amount of drug

k   =   first order constant

t   =   time

Since both first-order and square root of time plots are acceptably linear, a more stringent test was developed to distinguish between the mechanisms. The use of the predicted rate equations corresponding to equation 14 and 17 can be used for this purpose as shown by the following treatment (Schwartz, et al., 1968).

Equation 14 (square root of time) can be reduced to

$$Q' = KS t^{1/2} \qquad\qquad (18)$$

where Q' = amount released = $Q*S$

S   = surface area

$$K = \left[\frac{D\epsilon(2A - \epsilon C_s)C_s}{\tau} \right]^{1/2} \qquad\qquad (19)$$

by differentiation of the above reduced equation and appropriate substitution , Eq. 20 can be obtained

$$\frac{dQ'}{dt} = \text{rate} = \frac{K^2 S^2}{2Q'} \qquad\qquad (20)$$

which indicates that the rate will be inversely proportional to the amount of drug release, Q. The rate predicted by first-order kinetics, however, is given by the following relationship :

$$\frac{dQ'}{dt} = rate = kWo-kQ' \tag{21}$$

The plots of rates of release versus $1/Q'$ were linear , indicating that the release was fitted with Higuchi model . If the plots of rates of release versus Q' were linear , indicating that first order model was obtained.

Release Mechanisms of Controlled Release Systems

A simple, semiempirical equation (22) can be used to analyze data of controlled release of drug under perfect sink conditions. The general form of this equation is given by Peppas (1985).

$$\frac{M_t}{M_\infty} = kt^n \tag{22}$$

where M_t/M_∞ = the fractional release of drug

t = the release time

k = a constant incorporating structure and geometric
characteristics of the controlled release device

n = the release exponent, indicative of the mechanism
of drug release

Use of equation 22 for the analysis of drug release data has to be done judiciously since violation of the assumptions under which this equation was obtained may lead to unfortunate conclusions about the mechanism of release.

Equation 22 may be used only for systems where the drug diffusion coefficient is clearly concentration-independent. In the case of release from slabs the exponent n will give information about the transport mechanism according to table 1, of course, the same equation can be used to analyze drug release from spheres and cylinders.

Table 1 Interpretation of diffusional release mechanisms from drug release data from thin polymeric films.

Release exponent (n)	Drug transport mechanism	Rate(dM_t/dt) as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous (non-fickian) transport	t^{n-1}
1.0	Case-II transport	Zero-order(time dependent) release
n>1.0	Super-Case-II	t^{n-1}

The exponent n may take values only greater than 0.5. Therefore, if one obtains n < 0.5 , this is a clear indication of statistical analysis problem. In addition, for determination of the exponent n one must use only the initial portion of the release curve (Mt/M∞ < 0.6).

Finally, equation 22 has been proposed for use with systems where drug diffusion occurs through the polymeric structure (network). Use of this equation to analyze data of drug release from porous systems will probably lead to n < 0.5 since the combined mechanisms (diffusion partially through a swollen matrix and partially through water-filled pores) will shift the release exponent toward smaller values.

The exponential dependence of the amount of drug released , Mt/M∞, on time, t, as described by equation 22 can be still used for the analysis of swelling-controlled release systems (e.g. system based on hydroxypropyl methyl cellulose, poly vinyl alcohol, poly (2-hydroxyethyl methacrylate) , etc.) as long as these systems swell only moderately in the penetrant (water,biological fluid). A first estimate of applicability of this equation in swellable system is that the system does not swell more than 25 % of its original volume (Ritger and Reppas, 1987 a)

Case-I (Fickian diffusion) and Case II solute release behavior in swelling-controlled release systems are unique in at each

can be described in term of a single parameter. Case I transport is described by a diffusion coefficient, while case-II transport is described by a characteristic relaxation constant. Non-Fickian behavior, by comparison, requires two or more parameters to discribe the coupling of diffusion and relaxation phenomena.

In order to evaluate the dependence of the value of n on geometry, equation 22 was applied to the first 60 % of the fractional release curve for Fickian diffusion and Case-II transport from a cylinder. Fickian diffusion and Case-II transport from a cylinder are defined by n = 0.45 and 0.89 respectively. For Fickian diffusion and Case-II transport from a swellable sphere the exponent take the values of n = 0.43 and 0.85 respectively. Table 2 summarize the range values of the diffusional exponent n and the related transport mechanism for each geometry (Ritger and Peppas , 1987 a).

A valve of n=1 , however , means that the drug release is independent of time, regardless of the geomtry. Thus, zero-order release can exist for any geometry ; only for slabs does this release coincide with Case-II transport.

Table 2 Diffusion exponent and mechanism of diffusional release from
various swellable controlled release system

Diffusion exponent,n			Drug release
Thin film	Cylindrical sample	Sperical sample	mechanism
0.5	0.45	0.43	Fickian diffusion
0.5<n<1.0	0.45<n<0.89	0.43<n<0.85	Anomalous (non-Fickian)transport
1.0	0.89	0.85	Case-II transport

In non-swellable matrices, in order to evaluate the
dependence of the value of n on geometry, equation (22) was applied
to the first 60 % of the fractional release curve for Fickian
diffusion from a cylinder and sphere. Fickian diffusion are defined
by $n = 0.45$ and $n = 0.43$ from a cylinder and sphere respectively
(Ritger and Peppas , 1987 b).

The relationship between the diffusional exponent n and
the corresponding release mechanism is clearly dependent upon the
geometry employed as shown in Table 3. A valve of $n = 1$, however,
means that the drug release is independent of time , regardless of
the geometry. Thus, zero-order release can exitst for any geometry.

Table 3 Diffusion exponent and mechanism of diffusion release

from various non-swellable controlled release systems

Diffusional exponent,n			Drug release
Thin film	Cylindrical sample	Spherical sample	mechanism
0.50	0.45	0.43	Fickian diffusion
0.50<n<1.00	0.45<n<1.00	0.43<n<1.00	Anomalous (non-Fickian) transport
1.0	1.0	1.0	Zero-order release