# Chapter I

## General Background

### Introduction

Theophylline has been used as a bronchodilator in the treatment of asthma. The relatively narrow safety margin of drug range is commonly stated to be either 5 to 20 μg/ml or 10 to 20 μg/ml which created many problems and its use remained limited(Weinberger and Riegelman, 1974). The first problem of theophylline, if the dosage interval is too long, each single dose must be higher. This implies that the upper border of therapeutic concentration is easily exceeded, increasing the risk of toxic manifestation. Due to the long interval, the rapid elimination of theophylline leads to low concentration before the next dose is taken and reoccurrence of symtoms may be the result. With more frequent medications, each dose is smaller, but the interval between doses may be so short as to interfere with normal activities such as sleep etc. A second problem with frequent medications, is that the patient forgets or decides not to take the drug at the prescribed times of the day, especially if the asthma does not cause much discomfort at that time. The most significant factor in increasing medical awareness of theophylline is the development of controlled release preparations of drug. Indeed, one of the main purposes of the controlled release is to improve safety and minimize side effects of drug by reducing fluctuations in drug levels.

Matrix type tablet as well as coated tablets and particles has been reported as an useful controlled release dosage form with coating polymers. It can be prepared by several methods. For example, it can be compressed directly from the powdered mixture of drug and polymers or tableting microcapsules or solid dispersed particles prepared with polymers. The latter method imparts the more precisely controlled and predictable drug release rated to the resultant tablet, because the active ingredients are coated with or embedded in various polymers with characteristic permeability and solubility properties, such as retarded and enteric properties. The ease with which matrices can be compounded(by direct compression and wet granulation, for example), results in low fabrication costs. This, together with thin spots, pinholes, and other similar defects, which can be a serious problem with reservoir systems, do not substantially alter the release rate from matrices. This reduces requirement for quality controlled. These advantages often outweigh the less desirable declining release rates of common matrices.

Various dosage forms with controlled drug release characteristics have been generally developed, but the controlled release theophylline matrices which prepared from co-spray dried technique is rarely reported and developed. Recently , an ambitious shift has been made from the use of organic solvents to the use of aqueous film-forming polymers because of avoiding explosion hazard and toxicity associated with solvent system and several water dispersing polymers have become commercially available for sustained release coating. Takeuchi, Handa, and Kawashima(1989) reported that they could prepare the controlled release theophylline tablet with

acrylic polymers in compress system by using spray-drying technique in aqueous system. Theophylline microspheres for matrix tablet were prepared in various aqueous polymer systems using spray-drying technique. They found that completely enteric function was observed with drug-to-polymer ratio of 1:3 using Eudragit L30D or L100-55. Tablet with Eudragit E30D formulated at the 2-40% level showed good sustained drug release which was throughly independent of pH of dissolution media. In each tablet, the controlled release was attributed to continuous and well dispersed polymer matrix formed by spray-drying and subsequent compressing process.

It was seen that the previous publication was concerned with the investigation on the methacrylates polymers and no report has been found on the use of cellulose derivatives to prepare sustained release matrices by spray drying technique. In this study,therefore, cellulose derivatives were employed and channeling agents were incorporated in formulations so that the release rate of the drug could be modified. Cellulose derivatives of various types were selected according to their difference in properties and release mechanisms. The use of cellulose derivatives in this study could be classified into three types:

1. Water soluble cellulose: Methocel E4M which release mechanisms are gradual solution and swelling with erosion.

2. Water-insoluble cellulose: Ethylcellulose which release mechanisms are diffusion and dialysis.

3. pH-dependent cellulose: Hydroxypropylmethylcellulose phthalate whose release mechanisms are according to pH, pH dependent erosion and diffusion at low pH.

Ease of compression, their ability to accommodate large percentage of drug and negligible of the processing variable on release rates are some of the other reasons for their popularity.

The term so called "channeling agent" is coined by Sanghavi, Kamath, and Amin(1990) to describe a highly water-soluble material, such as PEG 4000, Polyvinylalcohol(PVA) and Polyvinylpyrrolidone (PVP), that is mixed with a less soluble active agent in the matrix. These have a significant effect on the release rate, because channeling agent is then rapidly leached from the system to form the pore structure, which then allows the active agent to diffuse out faster than it would have done otherwise and also the diffusion of dissolution medium into the matrix is facilitated. They reported that channeling agent led to multiplicity of matrices which followed the same release kinetics. The channeling agent might be called "porosigen" according to the report by Cararelli(Baker, 1987) in which ammonium sulfate and lactose were used in his experiment.

Objectives of this study:

On the basis of the rationale mentioned above, the objectives of this research are, therefore,

1. to study the spray drying technique in preparation of co-spray dried theophylline-polymer and co-spray dried theophylline-polymer-channeling agent for making matrices and examine the physico-chemical properties of these co-spray dried powders.
2. to study some physical properties of these matrices.
3. to study the effect of type and amount of different polymers and/or channeling agent, also the pH of dissolution medium on the release of drug from matrices.
4. to investigate the model and mechanism of drug release from matrices.
5. to explore this lab-scale data as a guide for developing theophylline controlled release matrices on production scales.

## Literature Reviews

### 1. Theophylline

Theophylline is a dimethylated xanthine. Its structure is similar to the other xanthine derivatives, i.e. , caffeine and theobromine, which are commonly found in coffee, tea, cola beverages and chocolate. Although it is present in natural sources, theophylline is available commercially by total synthesis.

#### 1.1 Physico-Chemical properties:(Cohen, 1975)

Chemical name : 1H-Purine-2,6-dione,3,7-dihydro-1,3-dimethyl-,mono or anhydrous; 1,3-dimethylxanthine

Empirical formula : $C_7 H_8 N_4 O_2$

Structural formula :

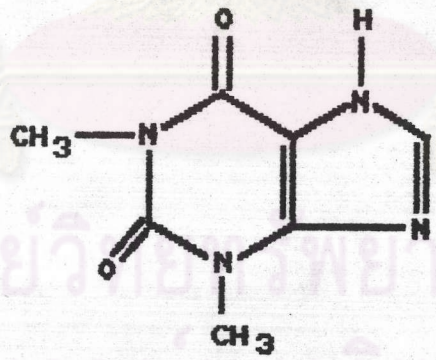

Figure 1. Chemical Structure of Theophylline.

Molecular weight : Theophylline monohydrate 198.18
Theophylline anhydrous 180.17

Description : white, odorless, crystalline powder with a bitter taste. Its saturated aqueous solution is neutral or slightly acid to litmus.

Solubility : 8.3 mg/ml in water, 12.5 mg/ml in ethanol, 11.6 mg/ml in chloroform, and freely soluble in solutions of alkali hydroxides and ammonia.

Melting range : 269°C - 274°C

Stability : Theophylline is stable in air. Its solutions are generally quite stable over the entire pH range. Strongly alkali solutions(pH>12) showed decomposition after several weeks. Theophylline will precipitate from aqueous solutions if pH drops below 9 unless presents in concentration less than the water solubility.

1.2 Pharmacokinetics and Toxicity

The theophylline therapeutic plasma concentration range is commonly stated to be either 5 to 20 µg/ml or 10 to 20 µg/ml. The results are obtained from several investigation (Weinberger and Bronsky, 1974; Benet and Massond, 1984, cited by Sanghavi, Kamath, and Amin, 1990). Toxic reactions occur in 75 % of patients with plasma theophylline concentration over 25 µg/ml, but are uncommon between 15 and 25 µg/ml. They are absent when the concentrations are below 15 µg/ml(Jacobs, Senior, and Kessler, 1976). The concentration under 20 µg/ml is accepted to be safe by these investigators(Jacobs, Senior, and Kessler, 1976; Jenne et al., 1972). Adverse effects associated with plasma concentrations above 20 µg/ml included nausea, vomitting, diarrhea, abdominal pain, headache, irritability, and insomnia(Jacobs, Senior, and Kessler, 1976; Jenne et al., 1972.). Seizures, brain damage, cardiac arrhythmias and death occur at higher levels(above 40 µg/ml)(Hendeles et al., 1977).

Several reports suggested that the concentration-time profiles of theophylline can be well described by a one-compartment open model with first-order absorption and first-order elimination(Gal et al., 1978; Welling et al., 1975, Malee Sae Jung, 1989). Theophylline plasma concentration after the oral administration at any time t can be then described according to the following equation(Gibaldi and Perrier,1982)

$$C = \frac{K_a F X_0}{V(K_a - K)}.(e^{-Kt} - e^{-K_a t}) \qquad (1)$$

C = drug plasma concentration at any time t.

F = fraction of the administration dose ($X_0$) that is absorbed.

V = apparent volume of distribution of drug in the body.

$K_a$,K = first order rate constants for absorption and elimination, respectively.

The theophylline pharmacokinetic parameters summarized by Malee Sae Jung(1989) for Thai subjects is presented in Table 1.

Table 1. Pharmacokinetic parameters of theophylline in 4 different group after oral administration of 2.4 mg/kg body weight of theophylline.

| Group | V(L/kg) | K($Hr^{-1}$) | $K_a$ |
|---|---|---|---|
| Nonsmoking males | 0.484 | 0.0787 | 4.55 |
| Nonsmoking females | 0.380 | 0.0790 | 4.97 |
| Smoking males | 0.457 | 0.1020 | 5.73 |
| Children | 0.417 | 0.1327 | 4.63 |

1.3 Usual Dosage of Theophylline(The United Pharmacopeial convention, 1980)

1.3.1 Oral-Standard rapidly absorbed oral formulation : Capsules, Tablets, and Liquids.

For an acute attack not requiring parenteral therapy:

**Usual adult dose:** Initially, 4.8 mg/kg follow by a maintenance dose of 2.4 mg/kg every six hours, adjust as necessary to control symptoms with a usual optimal dosage of approximately 4.8 mg/kg every six hours.

**Usual pediatric dose:** Initially, 6.4 mg/kg follow by a maintenance dose of 4 mg/kg every six hours, adjust as necessary to control symptoms with a usual optimal dosage of approximately 6.4 mg/kg every six hours.

Note: The oral liquids are recommended for use in acute attacks since they produce therapeutic serum levels more

rapidly than the solid dosage forms.

1.3.2 Oral-Extended-Release Tablets and Capsules.

**Usual adult dose:** Initially, 4 mg/kg every eight to twelve hours, adjust as necessary up to 8 mg/kg every eight hours.

**Usual pediatric dose:** same as usual adult dose.

2. Commercial Controlled Release Theophylline Products.

The informations on the composition and release mechanism of wide variety of theophylline products in the presently marketplace have been reported as follow(Shangraw, 1988):

**Aerolate**(R) is composed of enteric coated beads designed to simply bypass the stomach.

**Slophylline Gyrocaps**(R) (manufactured by Cord Laboratories and marketed by William H. Rorrer,Inc.) consists of inert sugar seeds coated with various combinations of drug and shellac.

**Slo-Bid**(R) (William H. Rorrer,Inc.) is a modification of an earlier sustained release product, Slophylline, which is also marketed by Rorrer. The shellac-theophylline matrix beads of Slophylline are coated with an ethyl cellulose film which is slightly modified to assure increased permeability as residency time in the GI tract progresses. Thus the product becomes more of a diffusion controlled rather than a pH controlled release system.

**Elixophyllin**(R) (Berlex Lab Inc.),**Theovent**(R) (Schering Corp.) and

**Theobid**(R) (Glaxo,Inc.) : All of these products are made by KV Laboratories and appear to be identical in composition and release pattern. This product used coating of shellac, stearic acid and castor oil to slow dissolution of the theophylline.

**Bronkodyl-SR**(R) (Winthrop-Breon Lab.) and **Theophyll SR**(R) (McNeil Pharmaceutical) These also to be identical products made by Cord Laboratories and primarily involve the use of shellac as the rate delaying coating material.

**Theolair SR**(R) (Riker Laboratories,Inc.) and **Respid**(R) (Boehringer Ingelheim) are identical sustained release tablets in which theophylline is granulated with cellulose acetate phthalate and compressed into a non-disintegrating tablets.

**Labid**(R) (Norwich Eaton Pharmaceuticals Inc.) is a long acting dye free tablet in which anhydrous theophylline is distributed in a blend of Carbomer(polymer of acrylic acid crosslinked with a polyalkenyl polyether) and sucrose, slugged and then compressed into non-disintegrating tablets from which release is pH dependent.

**Nuelin**(R) (Riker)(Buckton, Ganderton, and Shah, 1988) which consisted of waxy non-disintegrating bed, the surface of which is coated with cellulose acetate. The tablet undergoes surface erosion.

**Quibron**(R) (Mead Johnson Lab.) is one of the most unique and interesting sustained release products of theophylline as it contains almost no excipient(95% drug). The patent describes a granulation of anhydrous theophylline with 5% hydroxypropyl methyl cellulose which is blended with 0.5% magnesium stearate and compressed

(Shangraw, 1988). The release depends upon the very slow dissolution rate of theophylline from a nondisintegrating surface. The geometry and scoring is also unique. The tablets are long and plate-like providing scoring in both halves and thirds. The plate-like geometry results in a gradual change of surface area with time, thus providing a more uniform dissolution rate.

**Theodur**$^{(R)}$ (Key Pharmaceuticals,Inc.) is certainly the most successful of all the sustained release theophylline products. Its relatively uniform release pattern over a 12-18 hour period of time and it commercial popularity has made it the standard against which all other sustained release theophylline products are compared. Theodur however is also one of the most complicated products in terms of both formulation and method of manufacture. It is a combination of coated beads embedded in a slowly disintegrating matrix. The theophylline is coated onto sugar beads which are then enclosed in various coating of lipid material(glyceryl monostearate, cetyl alcohol, beeswax) and /or an acid polymer cellulose acetate phthalate. The beads are then compressed into a slowly disintegrating waxy type matrix containing additional drug. The release depends upon the type and thickness of the coating, nature of the tablet matrix and the geometry and hardness of the tablets. In spite of its complexity, Theodur$^{(R)}$ has established a record of constant drug delivery, which is not substantially affected by food and pH. This product is identical to the Sustaire$^{(R)}$ which is produced by Roering under license from Key.

**Theo-Dur**$^{(R)}$ **Sprinkle** (Key Pharmaceuticals,Inc.) consists of beads contained within a capsule which could be opened and the contents

emptied into food for ease of administration. However, it should be noted that the beads in the Sprinkle product are not the same beads used in the Theodur tablet. Instead, Key Pharmaceuticals has chosen to utilize one of the more modern diffusion controlled ethyl cellulose coating as the release mechanism. This system is described in the article (Gonzalez and Golub, 1983) which depicts the partially empty and empty shells of the microspheres as the theophylline dissolves and diffuses out from them.

**Theo-24**(R) (Searle Pharmaceuticals Inc.) is the first product introduced into the marketplace for 24 hours dosing. Since its introduction there has been considerable controversy as to the appropriateness of such a dosing schedule in the regulatory agencies, the medical community and the courts. Although the promotional literature describing the sustained release beads(Probeads(R)) is quite elaborate the company will not provide any information on the composition of the product or to explain how the beads are designed to "prolong transit time". It does appear to be a diffusion controlled coated bead type product which utilizes either shellac or cellulose acetate phthalate which is pH dependent. Subsequent studies have shown that the product does release drug at a more rapid rate when given with food than taken on an empty stomach.

**Uniphyll Tablets**(R) (Purdue Frederick) is the most recent sustained release product to receive FDA approval for 24 hours dosing. These tablets consist of granules of theophylline which have been prepared with hydroxypropyl methylcellulose. The granules are coated with cetyl alcohol and then compressed into non-disintegrating tablets. As the cetyl alcohol is partially digested, the hydrophilic granules

are exposed to water which cause them to swell and the theophylline slowly dissolved out of the HPMC gel.

Controlled release theophylline products in Thailand(Oo-Koh, 1990.) are in two dosage forms and five brand names. The details are shown in the Table 2.

Table 2. Controlled release theophylline products in Thailand

| Trade name | Dosage form | Dose(mg) | Manufacturer | Distributor |
|---|---|---|---|---|
| Theodur | Tablet | 200,300 | Astra | Olic |
| Quibron-T/SR | Tablet | 300 | Mead Johnson | Bristol-Myers |
| Nuilin SR | Tablet | 250 | Riker Lab | A F T |
| Theo-24 | Capsule | 200,300 | Searle | Diethelm |
| Theolan | Capsule | 200,300 | Elan | S.Charoen Bhaesaj |

3. Matrix Devices.

The literature about the matrix system was well documented by Baker(1987). A matrix system, as the name implies, consists of drug distributed homogeneously throughout a polymer matrix as represented in Figure 2.

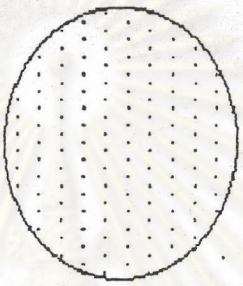

Figure 2. Matrix Device.

When the term "matrix device" is used without qualification, it typically means that the polymer it contained does not chemically disintegrate. If the polymer does erode, the device-although actually a type of matrix device is referred to as an erodible, bioerodible, or biodegradable system.

Matrix systems have the advantage of generally being easier and less expensive to produce than reservoir systems. In addition, because they do not have a polymer covering that can suddenly break, there is no danger of an abrupt release of a large amount of drug.

There are two principal categories of matrix device. If the active agent is dissolved in the polymer medium, the device is called a *matrix solution*. A device of this kind is often used when

the active agent is a liquid; some polymers can easily dissolve up to 20% or more of these liquids. If the active agent has a more limited solubility in the polymer medium, then only a portion of 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.*

### 3.1 Matrix Solution

One method of preparing a matrix devices containing dissolved active material is to equilibrate it with the material: for example, the device may be soaked in neat liquid or a concentrated solution. If the active constituent is dissolved homogeneously in the polymer matrix and it is assumed, for simplicity, that one planar surface was available for release, the amount of drug delivered will be obtained by solving Fick's second law of diffusion.

### 3.2 Matrix dispersion

The second type of matrix system consists of a dispersion of solid active agent in a rate-limiting polymer matrix. The characteristics of matrix dispersion system are listed in Table 4(Grass IV and Robinson, 1990). Matrix dispersion systems are of three types, which would be described latter, depending on the volume fraction of agent in matrix.

Table 3. Characteristics of matrix diffusion systems

| | |
|---|---|
| Description | Homogeneous dispersion of solid drug in a polymer mix |
| Advantages | Easier to produce than reservoir devices<br>Can deliver high-molecular-weight compounds |
| Disadvantages | Cannot obtain zero-order release<br>Removal of remaining matrix is necessary for implanted system |

At low loading levels of agent(0-5 volume percent), the release of the compound involves dissolution of the agent in the polymer medium followed by diffusion to the surface of the device. We will call these devices *simple matrix dispersion.*

At slightly higher loading levels(5-10 volume percent), 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 preferred pathways for the escape of material remaining within the device. At those 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. We will call these devices *complex matrix dispersions.*

When the loading of dispersed agent exceed 20 volume percent, the cavities left by the loss of material are sufficiently numerous to from a continuous channel to the surface of the matrix. In this case, the majority of all of the active agent is released by

diffusion through these channels. We will call these types of device *monolithic matrix systems* or *simply matrix systems*. The solubility and diffusivity of the dispersed agent in the fluid filling the channels determines its rate of release.

Release from these matrix dispersion systems can be described by percolation theory. The concept behind percolation theory can be conveniently illustrated in a two-dimensional grid in which some of the sites are randomly occupied, as shown in Figure 3. (Baker,1987.) The empty sites represent the polymer matrix while the filled sites are the active agent particles. At low loading, as in the simple dispersion case, the active agents are well separated. At higher loading, as in the complex dispersion case, some small islands of interconnected particles grow, while at even higher loading these islands grow in size and connected to form extended pathways. At loadings above a certain critical value, continuous channels permeate the grid, and almost all the agent particles are connected to the channels. This is the matrix system. For the two-dimensional grid illustrated in Figure 3, the critical value at which almost all particles are in contact with one another is an agent volume fraction of 0.45, but in three-dimensional matrix the critical loading value above which a continuous network formed in only 0.15(Zaller, 1977, cited by Baker,1987).

The three types of matrix dispersion are:

3.2.1 Simple matrix dispersion

When the active agent concentration is in the

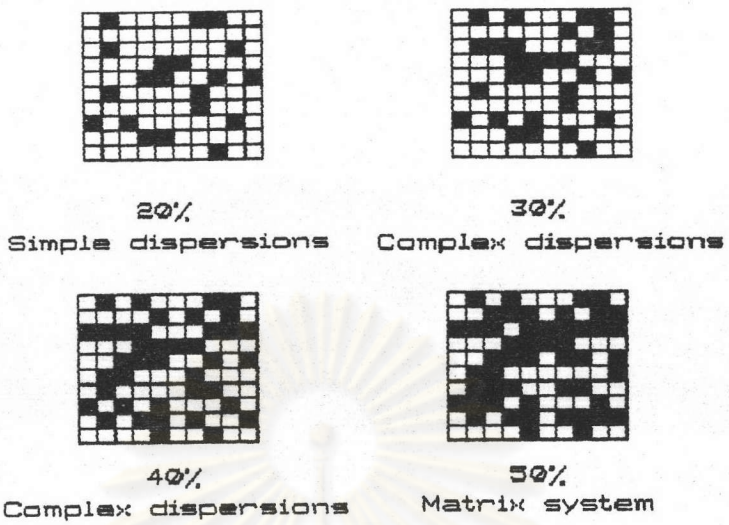


Figure 3. A Two-Dimensional Representation of a Random Distribution of Agent Particles(filled squares) in a Polymer Matrix. Agent Loading of 20,30,40,and 50% are Shown.(Baker,1987)

range of 0-5 volume percent, the release rate from these systems can be described by a simple Higuchi model(Higuchi, 1961). 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 interface between the region containing dispersed agent and the region containing only dissolved agent thus moves into the interior as a front. The release kinetics for such a system have been solved and the appropriate equation is as follows:

$$\frac{dM_t}{dt} \sim \frac{A}{2}\left(\frac{2DC_{s(m)}C_0}{t}\right)^{\frac{1}{2}} \quad for\ C_0 >> C_{s(m)} \qquad (2)$$

where $M_t$ = the mass of drug released at time t

A = the total area of the slab(both sides)

D = agent diffusion coefficient

t = time

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

$C_0$ = the total concentration of agent(dissolved plus dispersed) initially present

The release is proportional to the square root of times.

### 3.2.2 Complex matrix 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 loading, deviations from the expected release profile occur. The rate of release is still proportional to the square-root of time but has a higher value than the model predicts. As described earlier, this is due to the presence of fluid-filling cavities created by dissolution of particles near the surface, which increase the system's permeability to most substances. At high loading doses, the drug can form a continuous capillary network throughout the polymer and release is governed by drug leaching through this region. Thus equation 2 may be modified for the complex matrix dispersion to

$$\frac{dM_t}{dt} = \frac{A}{2}\left(\frac{2DC_{s(m)}}{t} \cdot \frac{1+\frac{2C_0}{\rho}}{1-\frac{C_0}{\rho}}\right)^{\frac{1}{2}} \qquad (3)$$

where $\rho$ is the density of permeant

### 3.2.3 Monolithic matrix systems

At loading of active agent above approximately 15-20 volume percent, all the agent particles dispersed

in the polymer matrix are in contact with one another. The active agent is released by diffusion through the water-filled pores that are formed 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 2 previously derived for simple matrix dispersions, the only difference being substitution of the appropriate expression for the permeability term DK in this 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

$$K = \varepsilon \qquad (4)$$

to reflect the fact that, although the filled inside the membrane pores is the same as the surrounding solution, only a volume fraction $\epsilon$ of the membrane is filled with this fluid.

The appropriate substitution for the diffusion coefficient is

$$D = \frac{D_w}{\tau} \qquad (5)$$

where $D_w$ is the diffusion coefficient of the agent in the fluid filling the matrix pores and $\tau$(tortuosity) 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

$$\frac{dM_t}{dt} = \frac{A}{2}\left(\frac{2D_w \varepsilon C_s C_0}{\tau t}\right)^{\frac{1}{2}} \qquad (6)$$

4. Method of Preparing Matrix.

Matrices are usually much easier to produce than reservoir systems, principally because they do not require a perfectly regular and defect-free rate controlling membrane. The methods used to produce these devices include solution casting of active agent dispersions, cooling active agent melt dispersions, extrusion, rubber milling, plastisol dispersions, and polymerizing prepolymer active agent dispersions. The choice of technique depends on the active agent and the polymer used.

In tablet matrix systems, the matrix is in the form of compressed compact containing an active ingredient, lubricant, filler or binder. The matrix may be tableted from wet-massed granules or by direct compression.

Casting of a dispersion or solution of active agent in suitable polymer casting is one very simple technique, especially for applications requiring relatively small or thin devices. However, the dispersed active agent may settle and aggregate during the time required to evaporate the solvent. Casting the film onto a cold plate eliminates this problem.

Another useful technique for preparing a matrix dispersion from a polymer is rubber milling followed by calendering

or melt extrusion. If rubber milling or extrusion equipment is unavailable or if the sample size is too small to allow the use of such equipment, an ordinary laboratory press can be used. First, a thin film of the polymer is formed and dusted with the active agent. The film is then rolled and melt pressed a second time, and then it is rerolled and pressed several times until a uniform dispersion is produced. The dispersion can be formed into simple shapes by injecting molding or into continuous rods by extrusion.

The preparation of poly(vinyl chloride) plastisol dispersions uses extremely simple technique. Typically 100 parts of a poly(vinyl chloride) plastisol grade resin of particle size 50-100 μm are mixed with 30 to 80 parts of a suitable plasticizer such as di(2-ethylhexyl)phthalate. A smooth cream is obtained, to which the required amount of active agent is then added. The mixture is then briefly degassed under a slight vacuum to remove air bubbles, after which it is poured into a mold and heated in an oven at between 130 and 180 °C for approximately ten minutes. During this heating step, the PVC particles dissolve, and on subsequent cooling a PVC solid solution forms. This can still retain a solid form while containing up to 50 weight percent of the liquid plasticizer-active material mixture. In general, the nonpolymeric content should not exceed 50 weight percent if the device was to retain good mechanical properties. These plastisols are especially useful for preparing matrices containing dissolved hydrophobic liquids. Similar techniques can be used with silicone rubber or polyurethane prepolymer dispersions.

5. Controlled Parameters of the Matrix System

Technological factors influencing release from controlled release matrix tablets can be stated as; choice of polymer as matrix material, polymer concentration, drug loading, formulation additives, channeling agents, and shape factors. Especially no significant difference is observed in drug release patterns from hydrophilic matrix tablets of differing density and different hardness (Capan,1989).

The release of drug from a controlled release matrix tablets may be controlled by varying the following parameters:

1. Choice of matrix material
2. Amount of drug incorporated in matrix
3. Matrix additives
4. Matrix shape

5.1 Choice of Matrix Material

The matrix material should be met the selection criteria in Table 4(Pillai, Babar, and Plakogiannis, 1988).

Table 4. The criteria in selection polymers for matrix development

| |
|---|
| 1. Molecular weight, glass-transition temperature, and chemical functionality of the polymer must allow the proper diffusion and release of the specific active agent. |
| 2. Polymer functional group should not react chemically with the active agent. |
| 3. The polymer and its degradation product must be nontoxic. |
| 4. The polymer must not decompose during the entire shelf-life. |
| 5. The polymer must be easily manufactured or fabricated into a desired product. |
| 6. The cost of polymer should not be expensive as to make controlled drug release devices very expensive. |
| 7. It should be readily available. |

Cellulose is the most abundant of all organic materials. It is a naturally occurring substance that has always been an important part of the diet of human beings. Cellulose and its derivatives meet the above criteria. In addition, they have many different types and have several properties. They can be classified into the following categories.

1. Water soluble hydrophilic polymers
2. Water insoluble polymers ( pH independent )
3. Water soluble or dispersible acidic polymers ( pH dependent )

A water soluble cellulose that widely used in controlled release is hydroxypropyl methylcellulose(HPMC). HPMC is cellulose ethers which may be used as the basis for hydrophilic matrices for controlled release oral delivery. HPMC is an odorless, tasteless white or creamy-white fibrous or granular powder. It is soluble in cold water, forming a viscous colloidal solution, insoluble in alcohol, ether and chloroform but soluble in mixture of methylalcohol and methylene chloride. HPMC is very stable in dry conditions. Solutions are stable at pH 3.0-11.0. It is incompatible in extreme pH conditions and with oxidizing materials. Human and animal feeding studies have shown to be safe. HPMC can be used as film- former, thickening agent, protective colloid, emulsifier, suspending agent and stabilizer. High viscosity grades are used to retard the release of water soluble drugs.

Hogan(1989) explained the operative principle for controlling the release of drug from this matrix tablets is that on exposure to aqueous fluids, the tablet surface became wet and the polymer started to partially hydrated to form a gel layer. An initial burst of soluble drug from this layer may be released. There followed an expansion of the gel layer when water permeated into the tablet, the thickness of the gel layer was increased resulting the diffusion of soluble drug through the gel barrier. Concomitantly the outer layers became fully hydrated and dissolved, a process generally referred to as erosion. Water continued to penetrate towarded the tablet core until it had dissolved.

A water insoluble cellulose that is popularly used is ethylcellulose. Recently, ethylcellulose aqueous dispersions are

available. Surelease(R) is one of these products. Surelease(R) (Chang, Hsiao, and Robinson, 1987; Ghebre-Sellassie et al., 1988) is a completely plasticized aqueous polymeric dispersion that consists of ethylcellulose in ammoniated water and is prepared by phase inversion. The product is a milky liquid in which dibutyl sebacate and oleic acid are incorporated within the dispersed polymeric system during the manufacturing process. Ammoniated water is used to help stabilize the dispersed polymer. In addition, the dispersion contains fumed silica, which acts as an antiadherent and facilitated the application of Surelease(R) during the coating process. The total solid content of Surelease(R) is 25%, 70% of which is ethylcellulose. In conclusion, 100 g.of Surelease(R) has 17.5 g.of ethylcellulose.

Ethylcellulose is the ethyl ether of cellulose and can contain 44.0 and 51.0 percent of ethoxy groups. Ethylcellulose is resistant to alkali, both dilute and concentrated, and also to salt solutions. It can withstand dilute acids for a limited period of exposure. It is subject to oxidative degradation in the present of sunlight or UV light at elevated temperatures. Ethylcellulose is incompatible with paraffin wax and microcrystalline wax. It is presented as a non-toxic substance.

The applications of ethylcellulose in controlled release systems are as followed,

A. Retarding Agent in Matrix.

Drug blending and wet granulation with a solvent such as alcohol produce a tablet which tends to exhibit poor

dissolution. In tablet preparations of water soluble drugs such as acetaminophen and theophylline(Shaikh, Abidi, and Block, 1987A) and sparingly water soluble drugs such as ibuprofen and indomethacin (Shaikh, Abidi, and Block, 1987B), tablets are prepared by direct compression of solid dispersion of ethylcellulose as carrier prolonged drug release. In both cases the prolongation of drug release is primarily associated with an increase in amount of ethylcellulose rather than the variation of viscosity grade. Matrix containing metoclopramide as an active drug and ethylcellulose as a matrix polymer showed a linear relationship between the amount of drug dissolved and the square-root of time(Stamm and Tritsch, 1986).

Ethylcellulose used in combination with HPMC and corn starch produce a sustained release granule of nifedipine and a linear relationship up to above 40% release is obtained based on the Higuchi equation(Kohri et.al., 1987).

B. Coating Material

Ethylcellulose by itself forms a water insoluble film coating. Caffeine and salicylic acid incorporated into ethylcellulose films exhibited the diffusion controlled release. The release of indomethacin from granules could be retarded by ethylcellulose-glycerylmonostearate film and the relase of drug appeared to follow a first order kinetics(Sarisuta and Sirithunyalug, 1988).

Microcapsules of theophylline with ethylcellulose are prepared by coacervation technique using silicon dioxide as separant. Tablets are prepared from microcapsules,

microcapsules with theophylline fat embedded granules, and microcapsules with HPMC 4000. The release of drug from microcapsules follows a first order kinetics whereas that from all tablet formulations is a diffusion controlled model(Parab, Oh, and Ritschel, 1987).

Microcapsules of captopril coated with ethylcellulose 9,14, 93, and 300 cps. can be directly compressed into tablet. The release pattern is achieved first order kinetic according to Higuchi's equation(Singh and Robinson, 1988).

The common pH dependent soluble cellulose is hydroxypropyl methylcellulose phthalate(HPMCP). HPMCP is chemically and physically stable at ambient conditions for at least 3 to 4 years, and at 40 °C /75% relative humidity for 2 to 3 months. Specific incompatibilities are unknown. HPMCP can be used alone or in combination with other soluble or insoluble binders in the preparation of granules with sustained drug release properties. The release rate is pH dependent. The degree of substitution determined its properties as shown in Table 5(American Pharmaceutical Association, 1986).

Table 5. Degree of substitution in various grade of HPMCP.

| Substituted groups | Content(%) | | |
|---|---|---|---|
| | HP-45 | HP-50 | HP-55 |
| Methoxy groups | 19-24 | 20-25 | 18-22 |
| Hydroxypropyl groups | 5.5-9.5 | 5-10 | 4-9 |
| Carboxybenzoyl groups | 18.5-21.0 | 20-24 | 27-35 |

The degree of alkyloxy and carboxybenzoyl substitution determined its polymer properties and in particular the pH at which it dissolved in aqueous media.

## 5.2 Amount of Drug Incorporated in Matrix

The influence of the amount of drug incorporated in matrix is interesting and of practical importance in the field of controlled release tablets. This can be a very important factor, as frequently it is desirable to produce several tablet concentrations of the same drug and matrix to provide a variety of dosage schedules. By doing this, the tablet concentration dependency must first be determined.

Desai, Simonelli and Higuchi(1965) showed that the slope of the release curve should be proportional to the square root of the amount of drug in tablet as it appears raised to the first power under the square root sign.

Fessi et al.(1982) have shown that several systems of low loading type obeyed the Higuchi square root equation, such that the slope is approximately proportional to the initial drug loading.

The deviation at very high drug loading(>30%) can be attributed to interparticle contact. The interparticle contact leads to the formation of channels in the membrane through which the drug can be leached. The full detail had been reviewed in the part of matrix device.

## 5.3 Matrix Additives

Matrix additives or formulation additives further modify release rates. Simple molecules, for example, insoluble diluents such as tribasic calcium phosphate or water solubles

diluents such as lactose may modify release rates. Lapidus and Lordi(1968) showed that the addition of lactose increased the release rate of chlorpheniramine more than the equivalent amount of calcium phosphate. The observed divergence can be explained by the difference in solubility of the diluents and their subsequent effects on tortuosity factor. As the water-soluble diluent dissolved, it diffused outward and decreased the tortuosity of the diffusion path of the drug. On the other hand, the tricalcium phosphate did not diffuse outward, but rather became entrapped within the matrix and effected an increase in release of drug only by the fact that its presence necessarily decreased the gum concentration. Since the drug was more water soluble, the desired release rate was obtained by utilizing tribasic calcium phosphate as matrix additive.

Several investigators have described the incorporation of additives, such as channeling agents, into the matrix and improved drug release. Emori, Ishizaka and Koishi(1984) showed that the release of phenacetin from a wax matrix was improved by the addition of an acrylic acid polymer. Increasing the amount of polymer increased the release rate of phenacetin due to the formation of pores and channels in the matrix resulting from leaching of the polymer. Dakkuri, Butler and Deluca(1978) indicated that the utilization of povidone as a channeling agent in the formulation of a sustained-release tripelennamine hydrochloride core significantly influenced drug release. It appears that channel formation is the mechanism underlying the increase in the drug dissolution rate from cores containing the polymer.

Parab, Oh and Ritscel(1986) have shown that the addition of varying amount of mannitol or hydroxypropyl methylcellulose into the wax matrix improve theophylline release. In addition, Ritschel and Udeshi(1987),cited by Capan(1989), examined the influence of the channeling agents from theophylline matrix tablets prepared with acrylic resin. No difference in the amount of drug released, was found when lactose or dextrose were added to the internal phase before granulation. However, addition of dextrose after granulation into the external phase resulted in a small increase in the amount of drug released.

Cameron and McGinity(1987) examined the release of theophylline from matrix tablets containing a acrylic resin polymer as the retardant substance. Release rates are more rapid when microcrystalline cellulose is the filler excipient and the slowest when calcium sulfate is used as the diluent. More recently, the influence of matrix additives on the drug release rate of theophylline was investigated by Aerde and Remon(1988). They investigated the influence of lactose as a soluble diluent on the release rate of theophylline from a modified starch matrix tablet. The addition of 10% lactose seemed not to influence the release rate. On the contrary, increasing the amount of lactose from 10% to 20% and 30%(W/W) did change the release profile. During the first hour of release a burst effect, releasing about 30% of drug for a matrix with 20% lactose and about 40% of drug for a matrix with 30% lactose was seen. This can be attributed to erosion of tablet's outer layers and delayed installation of an integer gel matrix. As the water-soluble diluent dissolves and diffuses, a decreased tortuosity and a

higher drug release rate are expected.

5.4 Tablet Shape

Influence of shape factors on kinetics of drug release from matrix tablets were investigated by several workers(Brophy and Deasy,1987; Jambhekar and Cobby,1985; Jambhekar, Makoid and Cobby,1987). Higuchi(1963) was the first to derive an expression describing the release of drug through a unit tablet surface. The basic Higuchi equation may be modified, to described drug release from cylindrical tablets.

Ford, Rubinstein, and Hogan(1985.) demonstrated that compaction pressure variations little affected the dissolution rate from promethazine-HPMC matrix tablets and also that surface area of tablet was related to HPMC content and may influence release rates. In fact a linear relationship exists between release rate and surface area. Consequently the results indicate that for maximum maintenance of controlled release, tablet matrices should be as near spherical as possible to produce minimum release rates.

It is often difficult to get uniform release of a drug from a conventionally shaped matrix, such as a sphere or cylinder. The reason is that drug molecules near the surface escape from the device much more rapidly than do drug molecules near the center, which must travel a greater distance to reach the surface.

To overcome this problem, it will be necessary to select a geometry that compensated the increase in diffusional distance with a corresponding increase in surface area for

dissolution. Langer and coworkers(Sanders, 1985) have developed a device known informally as the "Cantaloupe Matrix". In this system, the device is shaped like half a cantaloupe from which the seeds have been removed. The outside of the device is coated with an impermeable plastic, except in the concave portion resembling the cavity of a cantaloupe. The drug, which is distributed uniformly throughout the matrix, can leave the device only through the concave region, which has a smaller surface area than the opposite side of the device, which corresponds to the outside of a cantaloupe.

Because of this special geometry, the release of the drug is essentially constant. In this configuration, the arc length and thus the number of drug molecules increase with increasing distance from the matrix opening. Hence, although drug molecules farthest from the opening have the greatest distance to travel, there are more drug molecules in this region available to traverse this distance.

6. The Analysis of Dissolution Data of Controlled Release System.

6.1 The Release Mechanism of Controlled Release System.

In order to analyze the mechanism of the drug from the matrices, the dissolution data may be analyzed using the semi-empirical equation of Peppas(1985) given below

$$\frac{M_t}{M_\infty} = kt^n \qquad (7)$$

where $M_t/M_\infty$ is the fraction of drug released up to time t

t is the release time

k is a constant incorporating structural and geometric characteristics of the controlled device

n is the diffusional release exponent indicative of the mechanism of release

The determination of the exponent n is valid for the first 60% of the total released drug($M_t/M_\infty \leq 0.6$), which also applied only to the early times of release.

Clearly, a desirable mechanism for many applications is that which leaded to n equals 1, which characterized zero-order release behavior. Table 6 summarized the general dependence of n on the diffusional mechanism(Peppas,1985).

Table 6. Interpretation of diffusional release mechanisms from drug release data from thin polymer film.

| Release exponent(n) | Drug transport mechanism | Rate 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-independent)release |
| n > 1.0 | Super-Case-II transport | $t^{n-1}$ |

The empirical Equation 7 could be modified for application to non-planar geometries. The relationship between the diffusional exponent n and the corresponding release mechanism is clearly dependent upon the geometry employed as shown in table 7(Ritger and Peppas,1987A).

In non-swellable matrices, the values of n are 0.45 and 1.00 for Fickian and Case-II transport, respectively. Case II transport is a special case readily identified and characterized by the constant velocity of the moving solvent front and the resulting linear weight gain with time. However, its characteristics are not as well understood, nor are they as fundamental in origin as those of Fickian diffusion(Tyle, 1990). When the value of n is > 0.45 and < 1.00, the release was said to be non-Fickian (Ritger and Peppas, 1987A). A value of n=1, however, mean that the drug release is independent of time, regardless of the geometry. Thus, zero-order release can exist for any geometry.

Table 7. Diffusional exponent and mechanism of diffusional release from various non-swellable controlled release systems.

| Diffusional Exponent, n | | | Drug Release Mechanism |
|---|---|---|---|
| Thin Film | Cylindrical Sample | Spherical Sample | |
| 0.5 | 0.45 | 0.43 | Fickian Diffusion |
| 0.5 <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 |

In swellable controlled release systems, Case-I(Fickian diffusion) and Case-II solute release behaviors are unique in that each can be described in terms of a single parameter. Case-I transport is described by a diffusion coefficient, while Case-II transport was described by a characteristic relaxation constant. Non-Fickian behavior, by comparison, required two or more parameters to describe the coupling of diffusion and relaxation phenomena.

In swellable matrices, when the system did not swell more than 25% of its original volume, the values of n are 0.45 and 0.89 for Fickian and Case-II transport, respectively. When the value of n is >0.45 and <0.89, the release was said to be non-Fickian (Ritger and Peppas,1987B). When the value of n was greater than that of the Case-II transport, the release was said to be Super Case-II transport. Table 8 summarized the range of values of diffusional exponent n, and the related transport mechanism for each geometry(Ritger and Peppas,1987B). A value of n=1, mean that the drug release was independent of time, regardless of geometry. Thus, zero-order release can exist for any geometry; only for slabs did this release coincide with Case-II transport.

Table 8. Diffusional exponent and mechanism of drug from various swellable controlled release systems.

| Diffusional Exponent, n | | | Drug Release Mechanism |
|---|---|---|---|
| Thin Film | Cylindrical Sample | Spherical Sample | |
| 0.5 | 0.45 | 0.43 | Fickian Diffusion |
| 0.5 <n< 1.00 | 0.45 <n< 0.89 | 0.43 <n< 0.85 | Anomalous (non-Fickian) Transport |
| 1.0 | 0.89 | 0.85 | Case-II Transport |

Hogan(1989) examined the dissolution curves of the drugs promethazine hydrochloride, aminophylline and propranolol hydrochloride with differing HPMC quantity and concluded that as the polymer fraction increase, the dissolution of the drug decrease. The kinetics of drug release can be investigated by using Equation 7. The promethazine and diazepam matrices appear slightly higher values of n at low HPMC content. The values of n are similar(0.65-0.71) for highly soluble drugs promethazine hydrochloride, aminophylline and propranolol hydrochloride and additional theophylline(0.64). The values of n for these drugs are close to the values predicted for diffusional release. The n values for the two poorly soluble drugs are 0.82 and 0.9 for diazepam and indomethacin, respectively. Thus the values of n obtained for indomethacin and diazepam merely emphasized that release for these drugs is not Fickian-controlled and indicates large contribution by tablet erosion to drug release. The anomalous behavior for tetracycline matrices with a value of n=0.45 emphasized the complexity of release of this drug. Peppas(1985) did not interpret n values of $n<0.5$ but stated that such occurrences are an indication of statistical analysis problems or are due to diffusion through a polymeric network where diffusion occur partially through a swollen matrix and partly through water-filled pores. It is possible that tetracycline hydrochloride undergoes a complexation reaction with HPMC in the gel state in the hydrating matrix, retarding its release.

## 6.2 The Release Pattern of Controlled Release System.

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

### 6.2.1 Zero-order model

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

$$\frac{dM_t}{dt} = k \qquad (8)$$

where k is a constant, t is time, and the mass of active agent released was $M_t$. This pattern of release is called zero-order release model.

### 6.2.2 Square-root-of-time model(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

$$\frac{dM_t}{dt} = \frac{k}{\sqrt{t}} \qquad (9)$$

In contrast to first-order release, the release rate here remained finite as the device approached exhaustion.

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

$$Q = [\frac{D\varepsilon}{\tau}.(2A-\varepsilon C_s)C_s]^{\frac{1}{2}} \qquad (10)$$

where Q = weight in grams of drug released per unit surface area

D = diffusion coefficient of drug in the release medium

$\epsilon$ = porosity of the matrix

$\tau$ = tortuosity of matrix

Cs= solubility of drug in the release medium

A = concentration of drug in the tablet, expressed as g/ml

The assumptions made deriving Equation 10 are as follows.

1. A pseudo-steady state is maintained during release

2. A >> C s , i.e., excess solute is present

3. The system is in perfectly sink condition in which C is approximately to zero at all time.

4. Drug particles are much smaller than those in the matrix

5. The diffusion coefficient remains constant

6. No interaction between the drug and the matrix occurs

For purposes of data treatment, Equation 10 is usually reduced to

$$Q = k_H t^{\frac{1}{2}} \qquad (11)$$

where $k_H$ was Higuchi constant. Therefore, the plot of amount of drug released from matrix versus the square root of time should be increased linearly if drug release from the matrix is diffusion controlled. Although the above equation was based on release from a single face, it may be used to describe diffusion-controlled release from all surface matrix.

In order to further verify that the release followed Higuchi model, Higuchi equation was converted into logarithmic form as

$$\log Q = \log k_H + \frac{1}{2}\log t \qquad (12)$$

The plot of log Q versus log t must not only yield a straight line, but must have a slope of 0.5.

### 6.2.3 First-order model

The first-order pattern was the third common type of the release model. The release rate in this case was proportional to the mass of active agent contained within the device. The rate was then given as

$$\frac{dM_t}{dt} = k(M_0 - M_t) \qquad (13)$$

where $M_o$ was the mass of agent in the device at t=0. On rearrangement, this gave

$$\frac{dM_t}{dt} = kM_0 \exp^{-kt} \qquad (14)$$

In first-order model, therefore, the rate declined exponentially with time, approaching a release rate of zero as the device approached exhaustion.

On the assumption that the exposed surface area of matrix decreased exponential with time, Wagner(1969) suggested that drug release from most controlled-release matrices could be described by apparent first order kinetics, thus:

$$A_t = A_0 e^{-k_1 t} \qquad (15)$$

where $k_1$ = first order release constant

$A_o$ = initial amount of drug

$A_t$ = amount of drug remaining in the matrix at time t

Simplifying and taking the logarithm of Equation 15 yielded

$$\log A_t = \log A_0 - \frac{k_1 t}{2.303} \qquad (16)$$

First order pattern can be predicted by plotting the logarithm of the percent of drug remaining against time. If first order model, linear relationship were obtained. Sa, Bandyopadhyay, and Gupta (1990) reported that the initial curvature of the plot may be

obtained because of the presence of surface drugs and they suggested to be ignored.

Since both the square-root-of-time release and first order release plots were linear, as indicated by correlation co-efficient, it was necessary to distinguish between the models. The treatment was based upon use the differential forms of the first order and square root-time equations(Schwartz, Simonelli, and Higuchi,1968).

For Higuchi model, the rate will be inversely proportional to the total amount of drug release in accordance with equation(Sa, Bandyopadhyay, and Gupta, 1990)

$$\frac{dQ'}{dt} = \frac{k_H^2 S^2}{2Q'} \qquad (17)$$

where Q′=Q*S (S is the surface area of matrix). The rate predicted by first-order model was given by:

$$\frac{dQ'}{dt} = kA_0 - kQ' \qquad (18)$$

where $A = A_0 - Q'$. This indicated that rate will be proportional to Q′. The rates of release were determined by measuring the slopes at different points on the percent of drug release versus times curves.

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 operative.

The release pattern for each classes of device is illustrated in Figure 4(Baker, 1987). The release patterns of Zero-Order, Square-root time, and First-Order are depicted(Equation 8, 9, and 13) respectively.

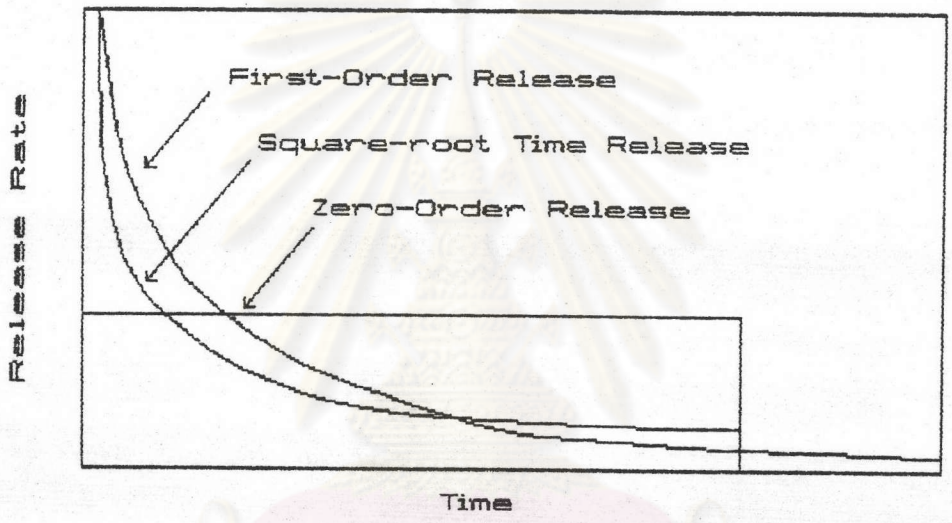


Figure 4. Zero-order, First-order, and Square-Root Time Release Patterns from Devices Containing the Same Initial Active Agent Content.