STUDY OF POLYMER HYDRATION AND DRUG RELEASE:

TEXTURE ANALYSIS AND MODEL EVALUATION

BY

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ABSTRACT

Swellable matrix tablet is a monolithic system for oral drug delivery. Active pharmaceutical ingredients (APIs) and hydrophilic polymers are mixed together and compressed into a tablet preparation for modified drug release. The drug delivery system has been extensively utilized in clinical applications, because it offers structural simplicity, low-cost manufacturing, and desirable drug delivery capacity.

Hydrophilic polymers in a swellable matrix tablet hydrate quickly to form a hydrogel layer on the exterior of the dosage once in contact with water or biologic fluid. The resultant hydrogel serves as a barrier to regulate water permeation into the matrix and drug diffusion from the preparation. It is therefore important to understand how the polymer is hydrated and what mechanism exists between hydrogel formation and drug dissolution from a swellable matrix tablet.

In this thesis, a TA texture analyzer was utilized to monitor and characterize matrix swelling properties during dissolution process. Multiple regression models were employed to analyze the quantitative relationship between drug dissolution or hydrogel thickness and major formulation factors (polymer ratio, drug solubility). Modified release matrix tablets were prepared using four APIs with a range of aqueous solubility, i.e., acetaminophen (ACE), chlorpheniramine (CHL), ibuprofen (IBU), and pseudoephedrine hydrochloride (PSE). Two hydrophilic polymers, polyethylene oxide (PEO) and hydroxypropyl methylcellulose (HPMC) were selected and tested as primary matrix polymers for the formulations.

It was found from the experiments that multiple regression models were capable of describing the relationship between drug dissolution and major formulation factors for both PEO and HPMC matrix preparations. The regression models developed provided satisfactory prediction of drug release from PEO and HPMC matrix tablets, which could further aid in formulation development and optimization.

Texture analysis was a simple and straightforward operation that enabled the collection of directly measurable data for formulation design and optimization. The multiple regression modeling approaches that were developed and validated were also accurate and practical. It would be possible for formulation scientists to predict influences of matrix polymers on drug release characteristics and to optimize drug release profiles using the methodology described in the thesis.

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DEDICATION

To my dedicated wife, Dachuan Zhang and my loving daughters, Amy and Sarah.

To my parents, Mr. Liangyin Li and Mrs. Juanyun Yu.

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LIST OF ABBREVIATIONS

ACE:	Acetaminophen
API:	Active pharmaceutical ingredient
AUC_{TA}:	Area under the force-probe travel distance curve
CHL:	Chlorpheniramine
CLSM:	Confocal laser scanning microscope
CRS:	Controlled release system
Cryo-SEM:	Cryogenic scanning electron microscope
DE:	Dissolution efficient (%)
$DT_{50\%}$:	Time required for 50% of the drug dose to be released
GB:	Glyceryl behenate NF
HPLC:	High performance liquid chromatography
HPMC:	Hydroxypropyl methylcellulose
IBU:	Ibuprofen
LSI:	Light scattering imagining
SMC:	Silicified microcrystalline cellulose
MCC:	Microcrystalline cellulose
NMI:	Non-medicinal ingredient
NMR:	Nuclear magnetic resonance
PEO:	Polyethylene oxide
PSE:	Pseudoephedrine hydrochloride
PVA:	Polyvinyl alcohol
PVP:	Polyvinylpyrrolidone
SDC:	Self-diffusion coefficients

Chapter 1

Introduction

1.1. Modified Drug Release Systems

Appropriate drug dosage forms and novel drug delivery systems are essential keys to therapeutic successes in clinical practice. For the past century, these preparations as well as their manufacturing techniques have been thoroughly investigated and significantly improved. Innovative drug delivery systems have not only optimized therapeutic efficacy of drug molecules, but have also extended patent protection span of numerous chemical entities. As a result, the approach by which a drug substance is delivered can subsequently influence its effectiveness and therapeutic outcomes. It has been a well-accepted fact that a medication can be administered by different routes and the resultant effects could be quite variable. For example, drug compounds that have either a steep dose-response relationship or a narrow therapeutic window should be formulated in appropriate dosage forms in order to achieve optimal therapeutic benefits. A drug concentration above or below the ideal therapeutic window could lead to undesirable or even lethal consequences in clinical practice. Drug release from a conventional preparation such as a tablet or a capsule is normally immediate and direct. Drug blood concentrations can easily reach maximal peak, followed by a sharp decline to sub-therapeutic level. In order to maintain an effective drug concentration for a prolonged period of therapy time, frequent drug dosing is generally required. While dosing at 3-4 times daily was quite common five decades ago, newer medications require less frequent administration and lower drug doses owing to the availability of various novel drug delivery systems [Langer and Wise, 1984, Grassi and Lapasin, 1996]. This trend has been embraced by healthcare professionals, consumers, and pharmaceutical manufacturers,

because the new technology can not only improve convenience in drug administration and monitoring, but can also minimize potential adverse drug effects in patients of long-term medication usage.

The primary design objective of a controlled release system (CRS) is to maintain a relatively constant drug concentration in the blood or target tissues for an extended period of time. By delivering drug content in a modified release manner through specialized dosage forms, it is possible to extend drug retention in the body and to optimize therapeutic outcomes with less frequent dosing. Subsequently, adverse effects and/or toxicity of the medications are also minimized because of less fluctuating blood concentration range [Robinson and Lee, 1987]. *Figure 1.1* demonstrates the theoretical differences in plasma drug concentrations from repeated administration of a conventional dosage form and a single administration of a controlled release preparation, respectively. The therapeutic benefit of a steady drug concentration from a CRS is clearly desirable.

Under ideal circumstance, a CRS should release a portion of the drug dose immediately after the administration, in order to reach effective therapeutic concentration rapidly. Afterwards, drug release should follow a well-defined profile at a steady rate to maintain stable drug concentrations within the therapeutic window and to sustain drug effects for a prolonged period of time. Since drug absorption and distribution are directly related to the amount of drug molecules available *in vivo*, steady and reproducible drug release from a CRS would contribute to well-controlled drug delivery, subsequently leading to fewer concentration fluctuations and adverse drug effects. In addition, certain novel drug delivery systems are able to target medications to specific tissues or organs;

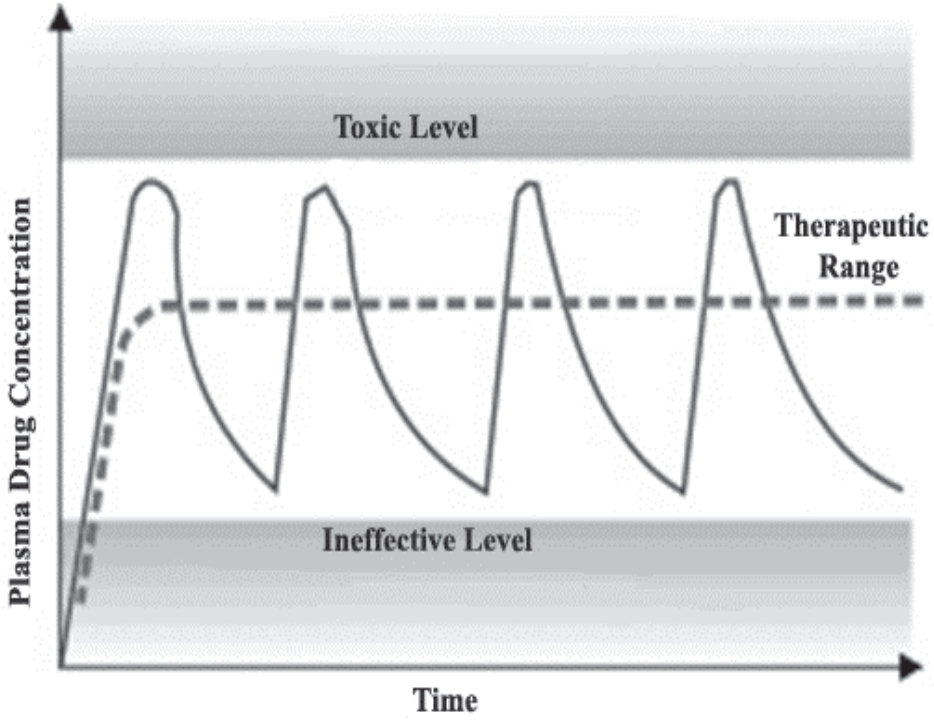


Figure 1.1. Comparison of plasma drug concentration between a conventional dosage form (solid line) and a controlled release dosage form (dashed line)

this would localize the required drug concentrations to the intended targets and minimize the loss of drug effectiveness in the general circulation. Specific drug targeting is particularly desirable in anticancer therapy, since most anticancer drugs are highly toxic and capable of killing both tumor and healthy cells without specific discrimination. To direct controlled drug delivery to tumor cells by using a unique preparation, drug concentrations at the localized sites would be significantly increased and therapeutic outcomes hence greatly improved. Numerous approaches of specific drug targeting have been proposed or tested for clinical practice for some time [Lübbe et al., 1996, Alexiou et al., 2000, Meyer et al., 2001, Plank et al., 2003, Lammers et al., 2008].

One of the most beneficial advantages of the CRS is its ability to improve patient compliance in drug administration. Patients with chronic disease conditions commonly require long-term drug therapy. Use of conventional, immediately-release dosage forms would involve frequent drug administration on a daily basis, and failure to follow regular administration regimens could result in sub-therapeutic outcomes in some patients. The application of a CRS in clinical practice both minimizes drug administration frequency, and reduces the incidence of drug adverse effects and/or toxicity. Consequently, therapeutic outcomes can be significantly enhanced and/or improved.

The invention and application of novel drug delivery systems also provides valuable opportunities for the pharmaceutical industry to manufacture various drug products and to meet different therapeutic requirements of the medications. Controlled release technology and pharmaceutical materials have been dramatically developed and improved over the past five decades. There are now many categories of innovative

preparations available to patients and consumers. Among them solid modified release dosage forms such as tablets and capsules have remained as the most commonly used preparations. Even though there is little difference in appearance from conventional dosage forms, the drug release characteristics from a modified release tablet are completely different from those of an immediate-release counterpart. Three types of modified release tablets possess various drug release mechanisms. The reservoir-type systems rely on the polymeric coating enclosed around the tablet core to control the intake of water and the dissolution of drug substances (*Figure 1.2*). Osmotic pump is a

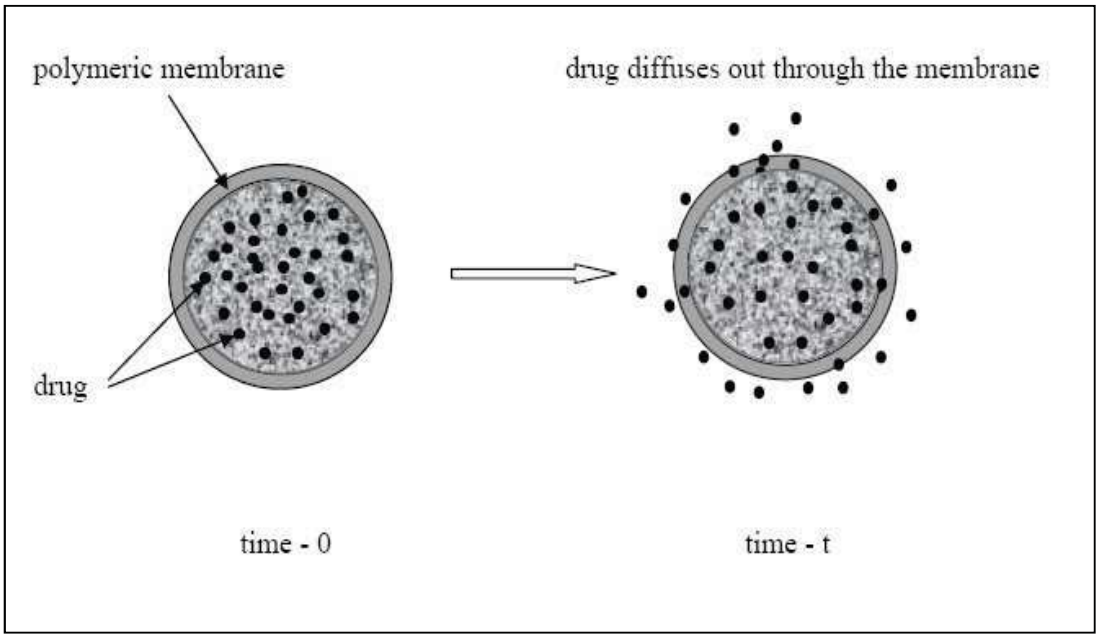


Figure 1.2. Schematic representation of a typical reservoir-type drug delivery system

specialized type of reservoir delivery system, from which the drug release is regulated by osmotic pressure produced by a special chemical substance (*Figure 1.3*). Matrix-type tablets are also known as monolithic devices; the active ingredients are homogeneously dispersed throughout a rate-controlling polymeric matrix. Drug dissolution from a matrix tablet is controlled by the combination of drug diffusion and polymer erosion (*Figure 1.4*). This is one of the most commonly used modified release tablet formulations because of their simple and versatile manufacturing possibility.

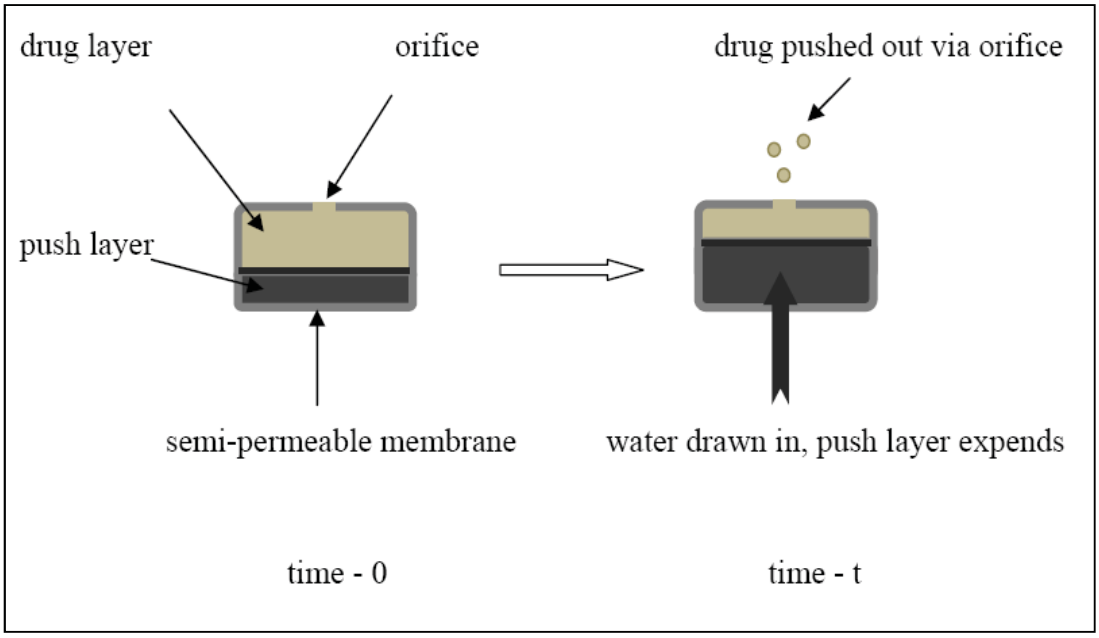


Figure 1.3. Schematic representation of a typical osmotic pump drug delivery system

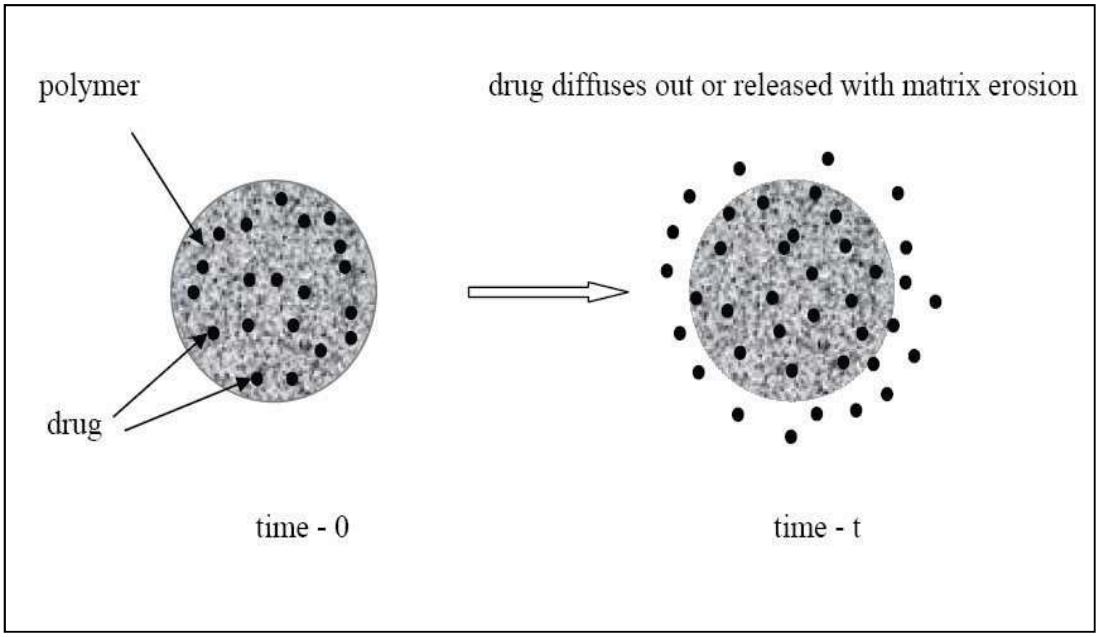


Figure 1.4. Schematic representation of a typical matrix-type drug delivery system

1.2. Swellable Matrix Preparation

Swellable matrix tablets are one of the most common and practical CRS for pharmaceutical applications [Tyle, 1990, Amidon et al., 2000, Wise, 2000]. Since they were first introduced, numerous matrix-based drug delivery systems have been developed and patented. The manufacturing techniques as well as polymeric excipients suitable for matrix dosages have also been improved and perfected over the years. Compared to other

CRS preparations, matrix systems possess several advantages in terms of tablet configuration and large-scale manufacture. As a fundamental CRS, the capacity of drug loading in a matrix system is flexible by directly mixing hydrophilic polymers with the active ingredient. Desirable drug release profiles are also achievable by changing the type and proportion of matrix polymers in the formulation [Colombo et al., 1995]. There is little risk of "dose dumping" for matrix CRS in the gastrointestinal tract, because the polymeric matrix only allows water penetration and drug diffusion, and there is no exterior coating for potentially accidental breakage. In addition, large-scale preparation of swellable matrix tablets is generally straightforward and cost-effective in comparison to reservoir-type tablets. Industrial processing may involve mixing and direct compression of different powder mixtures; no complicated coating processing is required. Consequently, the cost and product choice are acceptable to both the pharmaceutical manufacturers and the consumers. This further makes matrix CRS a desirable dosage choice for new drug development and assessment.

1.2.1. Drug Release Mechanisms

Even though tablet preparations all look similar in exterior appearance, they may possess very different structural configurations and drug release mechanisms. Once a solid tablet is in contact with a biological fluid in the gastrointestinal tract, drug release from the preparation is regulated by how the fluid gets into the dosage form and how the active ingredient behaves in a solution.

A dry swellable matrix tablet has a solid and integrated core structure prior to application. This configuration is also known as the glassy state. Under this condition the active ingredient and matrix components are homogenously mixed, and no drug movement or diffusion takes place within the matrix core [Lee, 1987]. Once the tablet matrix is in contact with a liquid, the hydrophilic polymer absorbs the solvent and hydrates quickly. Subsequently the swelling of polymeric network initiates, and the structure of matrix exterior changes from a glassy state to a rubbery state [Kararli et al., 1990, Ju et al., 1995]. The transition of the matrix polymer from a glassy state to a rubbery state creates a hydrogel layer that serves as a barrier to regulate fluid penetration into the tablet core and drug diffusion from the dosage form [Peppas, 1987, Colombo et al., 2000]. This swelling progression of the polymeric matrix results from the disruption of hydrogen bonds among polymer chains [Fyfe and Blazek, 1997, Kiil and Dam-Johansen, 2003]. When water molecules penetrate into a solid matrix, they insert themselves into the hydrogen bonds between adjacent polymer chains. As more and more water molecules penetrate and spread the polymeric chains, the binding forces of the matrix are gradually reduced. The hydrophilic polymer starts to gain rotational freedom and to take more space, consequently leading to swelling and hydration of the tablet matrix. The drug molecules that are embedded in the tablet matrix will then dissolve and diffuse through the polymer networks by generating a concentration gradient and producing a modified drug release rate. Since the hydrophilic polymer is water-soluble, the exterior hydrogel layer will also dissolve slowly from the outside surface at a constant or modified rate while more water is permeating. The rate and degree of polymer erosion

are dependent on the type and amount of polymer and other excipients present in the preparation. The solubility of an active ingredient may also contribute to matrix hydration and erosion. Eventually, the solid matrix will hydrate completely and release the entire drug content from inside (*Figure 1.5*). As a result, drug release from a swellable matrix tablet is controlled by two simultaneous mechanisms, i.e., erosion or attrition of the outermost, least consistent hydrogel layer, and dissolution of an active ingredient in the medium and diffusion of the drug molecules through the hydrogel layer [Feely and Davis, 1988]. It is possible to design and formulate swellable matrix tablets to achieve reproducible and predictable drug dissolution properties. Molecular diffusion is dependent on both the concentration gradient and the diffusional distance. A high drug loading in the tablet matrix and reasonable drug solubility would create a favorable drug concentration gradient in the hydrogel layer, which facilitates rapid drug diffusion and dissolution. Under this circumstance, the diffusion mechanism will become dominant in subsequent drug release while the hydrogel layer remains relatively stable. If drug solubility is low, however, drug release from a swellable matrix system will be regulated predominantly by polymeric hydration and surface erosion. In addition, when drug diffusion becomes practically negligible in a matrix tablet, drug release will achieve approximately zero-order kinetics. In general, drug release from a majority of swellable matrix tablets relies on a combination of polymer swelling, drug diffusion and polymer erosion. Therefore, parameters such as solvent penetration, polymer hydration and erosion, drug solubility, and drug diffusion will govern drug release from these delivery systems.

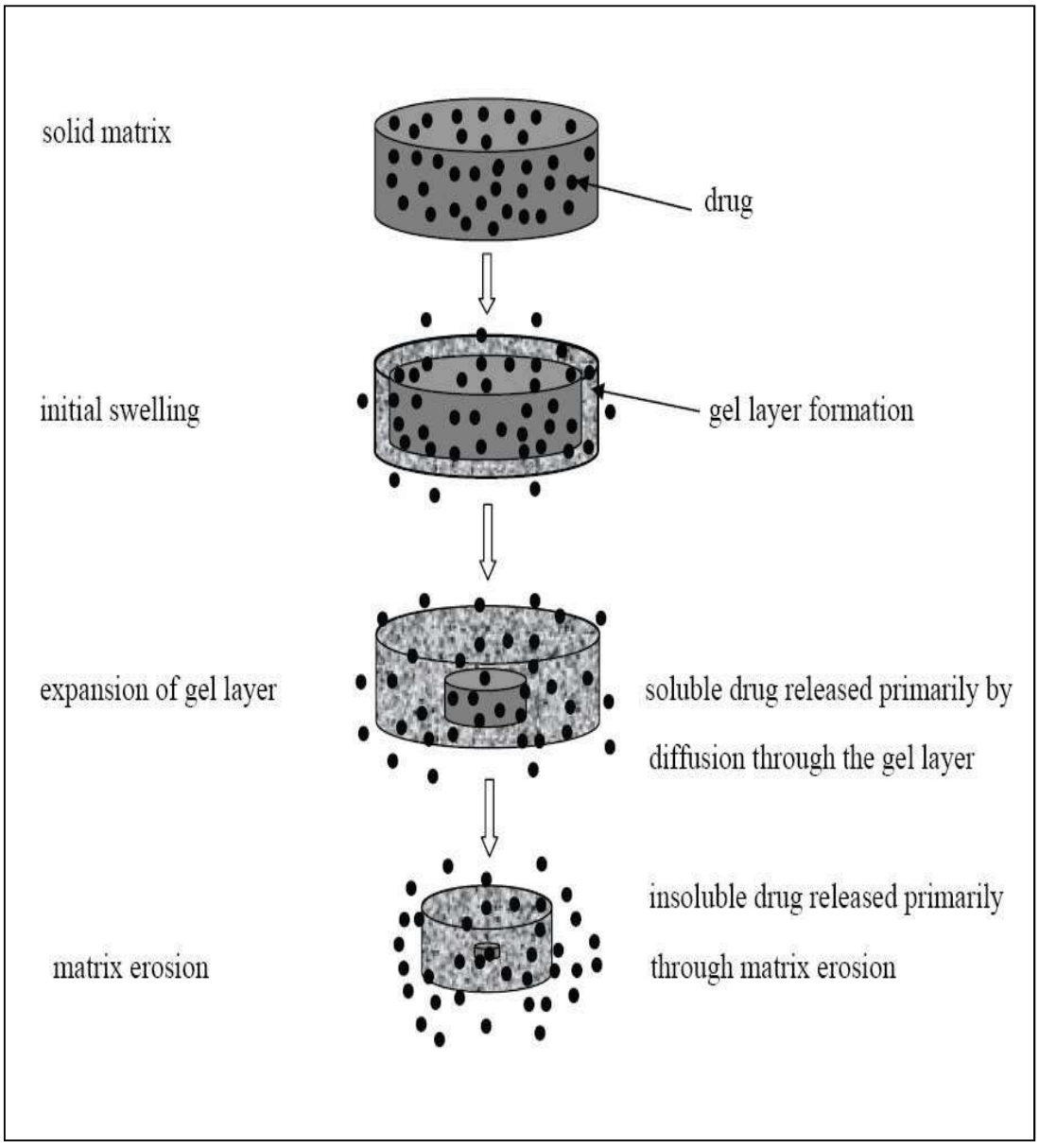


Figure 1.5. Progression of polymer hydration and drug release from a swellable matrix tablet

To further depict the swelling behavior of a hydrophilic polymer in a matrix tablet, the term of "Front Positions" is normally used. This term describes the positions in the matrix core where the dissolving conditions of the polymer sharply differentiate from one another [Colombo et al., 1995]. *Figure 1.6* shows a cylindrical matrix containing the polymer hydroxypropyl methylcellulose (HPMC) and the dye buflomedil pyridoxalphosphate, placed between two transparent discs after one hour of hydration [Colombo et al., 2000]. Being a dye, the aqueous solution of buflomedil pyridoxalphosphate is capable of producing color of various yellow intensities, ranging from light yellow to intense orange depending on its concentration. Three distinct "fronts" are visible from the picture, i.e., "swelling front" that separates the rubbery region from the glassy region, "erosion front" that separates the matrix from the solvent, and "diffusion front" that separates the solid drug from the dissolved drug. Over the course of a hydration-dissolution process, "erosion front" moves outwards at the early stage of polymer swelling but inwards at the late stage of matrix dissolving, while "swelling front" moves inwards until reaching the center of the matrix core. The thickness of the hydrogel layer is dynamically determined by the relative moving positions of the swelling and erosion fronts. Theoretically, drug release could be described as constant, if the polymer were sufficiently soluble and the thickness of hydrogel layer remained constant because of a synchronized movement of the swelling and erosion fronts. Under this condition, drug release kinetics is dependent on the changing dynamics of the hydrogel layer.

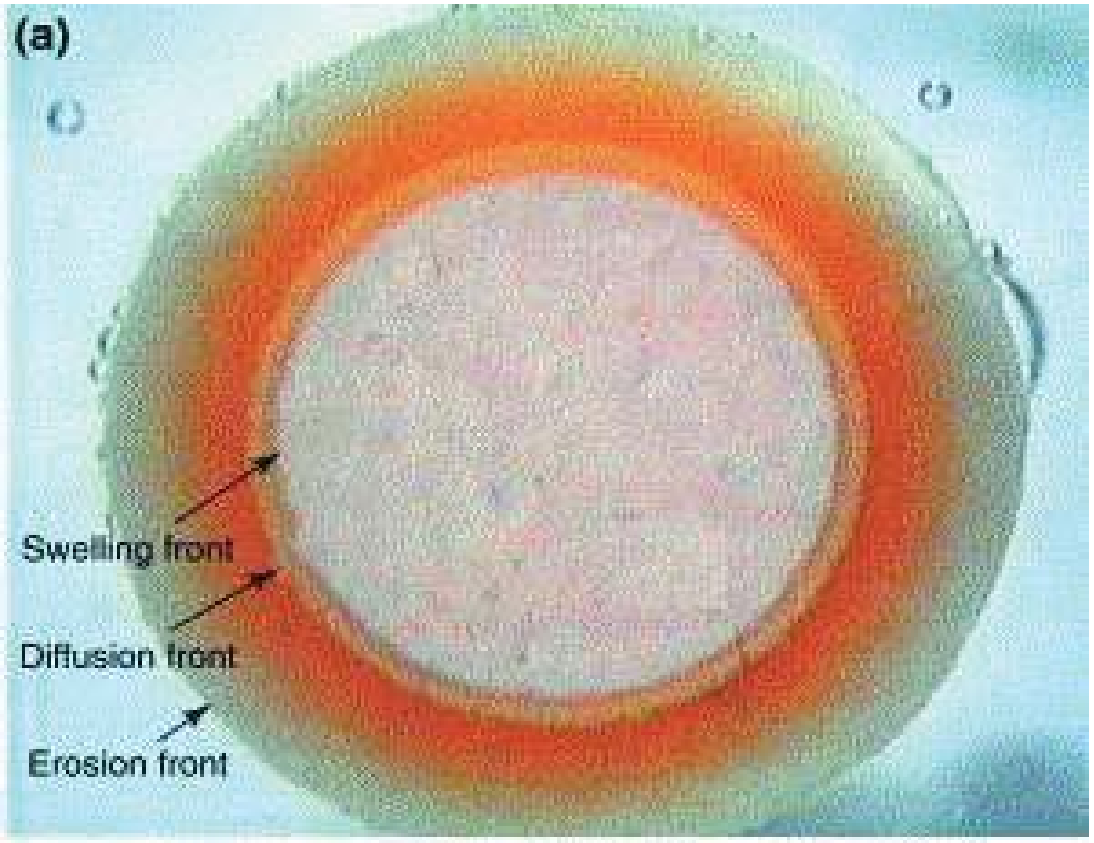


Figure 1.6. Demonstration of "Front Positions" in a swelling HPMC tablet of buflomedil pyridoxalphosphate (Colombo et al., 2000, with permission from Elsevier)

Such a delivery system is sometimes known as a "gel-forming matrix", because the formation of hydrogel layer in a swellable matrix tablet dictates the characteristics of drug release. When the hydration process takes place at a slow rate, the dissolution medium is able to penetrate deep into the matrix, leading to drug dissolution as well as matrix disintegration. The consistency and dynamics of a hydrogel layer are essential in understanding and predicting drug release outcomes, as the hydrogel layer changes continuously in structure and thickness upon exposure to an aqueous medium. At the initial stage of hydration and swelling, polymer chains are highly packed and strongly entangled, so the hydrogel layer is relatively resistant to erosion and dissolution. Once the hydration reaches a certain point, the hydrogel layer will become progressively hydrated, polymer chains will start to disentangle, and complete erosion and dissolution of the matrix will then take place [Lee, 1987, Narasimhan and Peppas, 1997].

1.2.2. Drug Release Kinetics

When drug dissolution from a modified release tablet preparation is predominantly controlled by diffusion mechanism, the rate of drug release is generally described as a function of the square root of dissolution time [Colombo et al., 2000]. As previously indicated, drug release from a swellable matrix tablet is attributed to a combination of matrix swelling, drug diffusion and matrix erosion. Such drug dissolution is interpreted by taking consideration of multiple dynamic parameters, in particular, matrix swelling, drug diffusion and matrix erosion.

Ritger and Peppas proposed an empirical formula (*Equation 1.1*) to describe drug release from a swellable matrix tablet [Ritger and Peppas, 1987a & 1987b]. This equation has been extensively utilized and further derived for drug release analysis from swellable matrix systems. The equation shows a corresponding relationship between drug release fraction and dissolution time raised to an exponent *n*,

$$\frac{M_t}{M_\infty} = Kt^n \qquad \textit{(Equation 1.1)}$$

Where: M_t, amount of drug released at time *t*

M_∞, quantity of drug present in the matrix

K, drug release rate constant

n, diffusional exponent

A similar binomial equation (*Equation 1.2*), in which the contribution of both matrix erosion and drug diffusion is quantified, was later adapted by Peppas and Sahlin for pharmaceutical purposes [Hopfenberg and Hsu, 1978, Peppas and Sahlin, 1989],

$$\frac{M_t}{M_\infty} = k_1\, t^m + k_2\, t^{2m} \qquad \textit{(Equation 1.2)}$$

Where: M_t, amount of drug released at time *t*

M_∞, quantity of drug present in the matrix

k_1, diffusion constant

k_2, erosion constant

m, diffusional exponent

For swellable matrix systems that contain hydroxypropyl methylcellulose (HPMC) or polyethylene oxide (PEO) as a primary matrix component, experimental results have demonstrated a typical diffusional exponent *n* ranging between 0.6-0.8 [Skoug et al., 1993, Kim, 1995]. When another hydrophilic polymer polyvinyl alcohol (PVA) was used, the value of diffusional exponent *n* would approach 1.0, and the resultant drug release was linearly proportional to dissolution time, indicating an erosion-dominant mechanism [Conte et al., 1988]. Studies have also shown that zero-order release could be achieved by using a binary polymer matrix consisting of methoxylated pectin and HPMC. Changing the ratio of pectin to HPMC in the matrix modulated the rate of drug release [Kim and Fassihi, 1996a, 1996b & 1997].

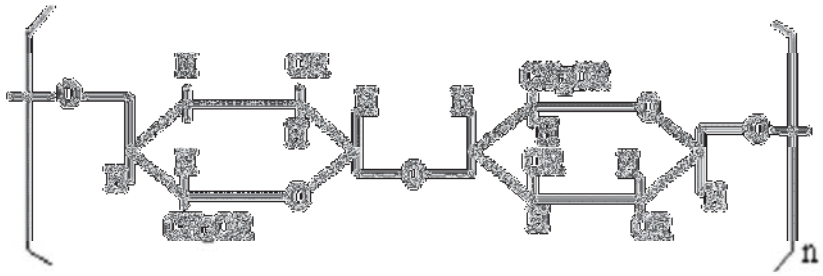
1.2.3. Factors Affecting Drug Release from Swellable Matrix Preparation

1.2.3.1. Effect of Matrix Polymers

As an essential matrix ingredient in swellable delivery systems, hydrophilic polymers play a very important role in regulating matrix hydration and drug dissolution. The type and proportion of polymers not only dictate hydration and erosion of the tablet matrix, but also modify the rate and extent of drug release from the system. Therefore, appropriate selection of hydrophilic polymers for a modified release matrix tablet will allow for desirable characteristics of tablet swelling, drug dissolution, and matrix erosion, cumulating to predictable drug release kinetics. In general, matrix polymers should hydrate and form a hydrogel layer at a reasonably quick rate once in contact with a dissolution medium. Slow polymeric hydration may compromise drug release

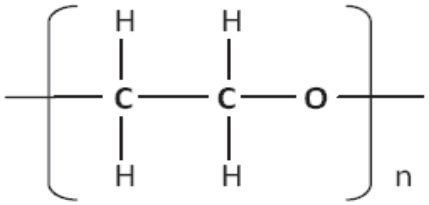
characteristics since it takes time for the medium to penetrate into the matrix and to disintegrate the dosage form.

Hydroxypropyl methylcellulose (HPMC) and polyethylene oxide (PEO) are two typical hydrophilic pharmaceutical polymers that have been frequently utilized to formulate swellable matrix preparations and other modified release delivery systems [Alderman, 1984, Hogan, 1989, Li et al., 2005]. HPMC is a semi-synthetic material derived from cellulose. PEO is an end-product from polymerization of ethylene oxide. *Figure 1.7* show the fundamental chemical configurations of the two polymers, respectively. Different grades of PEOs are obtained by varying the degrees of polymerization during manufacturing. Both HPMC and PEO are white, tasteless, free-flowing, and hydrophilic powders. They are supplied in a wide variety of grades, with different molecular weight, solubility, and aqueous viscosity. Both polymers work extremely well with different active pharmaceutical ingredients (APIs), soluble or insoluble, high or low dosing range. They are compatible with many other non-medicinal ingredients (NMIs) and additives, and easily adaptable to various processing methods. In addition, HPMC and PEO are relatively insensitive to pH changes, meaning that drug release from matrices of HPMC and/or PEO do not vary significantly along the gastrointestinal tract, even though the biological pH changes from ~1 in the stomach to ~8 in the large intestine.



R: H, CH_3 or $[CH_3CH(OH)CH_2]$

HPMC



PEO

Figure 1.7. Chemical structures of HPMC and PEO

Combined use of HPMC or PEO with other polymers and excipients in modified release delivery systems can achieve desirable properties that are clinically beneficial and significant. For example, combined use of HPMC with pectin produced tablets that released drug content as a zero-order rate. A constant drug release can not only maintain

stable drug concentrations in the blood, but also minimize influencing factors of the gastrointestinal tract such as pH and passing time [Kim and Fassihi, 1996a, 1996b & 1997]. Incorporating additional polymers into HPMC or PEO matrix also enhances the physical strength of the formulation, and facilitates processing and tableting of the dosage form. In addition, other excipients may often modify the hydration properties of HPMC or PEO matrix, producing hydrogel barriers of varying consistency that contribute to dissolution characteristics.

While different types of polymer demonstrate distinct characteristics in hydrogel formation and erosion, various grades of the same polymer may also alter drug release profiles based on variations in molecular weight and water permeability [Kim, 1998, Choi et al., 2003]. Polymers with higher molecular weight have shown better hydrogel behaviors appropriate for modified drug release. Increasing polymer molecular weight will suppress drug release rate from a dosage form; this is primarily attributed to a greater polymer entanglement and a lower effective molecular diffusion area. Compared to polymers with lower molecular weight, those with higher molecular weight will form hydrogel layer that possesses greater viscosity, subsequently sustaining polymer erosion and prolonging drug diffusion through the hydrogel layer [Yang et al., 1996].

As with polymer type and grade, ratio of polymer in a swellable matrix tablet also influences drug release property. Research has indicated that the ratio of API versus HPMC in a modified release matrix tablet was the most important factor determining drug release rate, and that higher HPMC proportions suppressed drug dissolution from the preparation [Ford et al., 1985a, 1985b & 1985c, Xu and Sunada, 1995]. Similar

effects were also observed in matrix tablets made of PEO [Choi et al., 2003]. An increase in polymer concentration results in slower penetration of dissolution medium into the matrix core. Formation of the hydrogel layer is delayed, the resultant hydrogel viscosity is increased, and the surface erosion is decreased. Subsequently, the drug diffusional path is extended, and the drug dissolution rate is reduced [Velasco et al., 1999].

1.2.3.2. Effect of Active Pharmaceutical Ingredients (API)

Drug release from a swellable matrix preparation is regulated by polymer swelling, drug diffusion and polymer erosion. Therefore, the properties of an active ingredient present in the formulation, particularly its aqueous solubility, contribute to dissolution rate and extent. Different from other modified release preparations, the concentration gradient to be generated within the hydrogel layer by the solution of an API plays an important role in driving drug molecules from the matrix core. A high dose of soluble API is capable of establishing a favorable concentration gradient within a short period of time than a low dose of API; this will hence produce a relatively faster rate of drug release from the preparation. On the other hand, if the aqueous solubility of an API is small, a high drug dose may not necessarily lead to a quick drug release. Proper matrix polymers and/or other soluble excipients may be required in order to encourage prompt passage of dissolution medium into the solid matrix [Durig et al., 2001]. In this way, it will allow APIs of poor water solubility to create a sufficient concentration gradient and to diffuse through the hydrogel layer that is also eroding at the same time. Formulating APIs of poor solubility into modified release matrix preparations could encounter

numerous challenges; a balance among various physical characteristics of both APIs and matrix components is needed in order to create a desirable environment for predictable and reproducible dissolution profiles.

To produce a steady, prolonged drug release for APIs of high solubility, it is necessary to utilize matrix polymers that possess characters of low to moderate hydration and erosion, so that drug diffusion from the tablet matrix can be sustained for an extended period of time. The initial drug diffusion from such a preparation might be relatively fast due to quick establishment of a drug concentration gradient upon in contact with dissolution medium, but this diffusion rate will gradually decline over the time once the polymer matrix is hydrated and the water penetration is suppressed. Dependent on the erosion properties of the matrix polymers, it is possible to adjust the amount of ingredients in a dosage to generate a reproducible hydrogel thickness and diffusional path for the API molecules. Nevertheless, when drug loading amount exceeds aqueous solubility of an API in the preparation, the tablet matrix tends to produce more erosion than hydration because of suppression in water penetration.

In general, swellable matrix preparations are prepared in large-scale by mixing drug substance with other pharmaceutical excipients followed by direct tablet compression. Appropriate particle size and size distribution of the ingredients are required in order to ensure high-speed processing as well as homogeneity and accuracy of the final preparation. Satisfactory powder characteristics of the mixture, such as uniform blending of the ingredients, free-flowing capability through the tablet press, and minimal physical interaction with the machinery, will not only benefit tableting and batch-to-batch

quality but also warrant reproducible drug release of the preparation. Only under extreme circumstance of a very large drug particles and a relatively small proportion of HPMC was there a significant change in drug dissolution from the prepared matrix formulation [Ford et al., 1985].

1.2.3.3. Effect of Other Excipients

Pharmaceutical dosage forms are composed of API and multiple non-medicinal additives. Each excipient plays its own unique role in the preparation, and the quality and performance of the final product would be compromised without these auxiliary components. There is no exception for swellable matrix tablets in utilizing other tablet excipients. In addition to principal rate-controlling matrix polymers, various additives are incorporated into the matrix system to optimize the physical properties of the powder mixture for improved tableting process and to enhance the quality and stability of the final product. For example, microcrystalline cellulose (MCC) is commonly used in the matrix to improve powder flowability and tableting strength. Acting as a binder in the matrix, high ratio of MCC in the formulation could potentially delay drug release. At low use level (< 10%), MCC may exhibit disintegrating capabilities, which could also alter characteristics of drug dissolution [Peck et al., 1989].

The influence of different tablet diluents on modified drug release from swellable matrix tablets was evaluated by Williams et al. [Williams et al., 2002]. Soluble fillers (lactose, sucrose, and dextrose) and insoluble fillers (dicalcium phosphate dihydrate, dicalcium phosphate anhydrous, and calcium sulphate dehydrate) were incorporated to an

HPMC matrix and their effects on drug dissolution were investigated. Results indicated that drug release from tablets made of soluble fillers was slightly faster than those containing insoluble fillers. Soluble additives are capable of creating a more permeable hydrogel layer by self-dissolution. The increased porosity of the hydrogel structure would facilitate water permeation and drug diffusion, subsequently leading to enhanced drug dissolution and polymer erosion [Hirschorn and Kornblum, 1971, Alderman, 1984].

Lubricants and glidants are incorporated into tablet formulation to promote powder flowability and easy ejection of the tablets from die cavities and to reduce excessive friction between formulation powder and tablet tooling. Magnesium stearate and glyceral behanate are used as lubricants in matrix formulations at a low level (< 2%). They do not generally influence drug release profiles of the active ingredients. However, when present in large quantity, glyceral behanate may bring about a marked impact on drug release characteristics.

1.3. Modeling of Drug Release from Swellable Matrices

Dissolution is one of the primary *in vitro* quality control measurements in estimating how a modified release preparation would behave *in vivo* once administered. Since drug release from a modified release swellable matrix tablet is directly associated with the progression of diffusion and erosion, understanding the relationship between polymer hydration, drug diffusion, matrix geometry and erosion is critical in formulation development and assessment. Numerous mathematical models have been developed to

describe the kinetic relationship among various parameters in the process of drug dissolution from a matrix dosage form. From a perspective of practicability and applicability, it is highly desirable for the formulation scientists to collect relevant experimental data using straightforward protocols and to predict drug release using simplified mathematical approaches. Devising sophisticated mathematical models that are inclusive of all influencing factors would be the ultimate goal in illustrating drug release mechanisms from a dosage. However, their applications in routine operation could be limited due to demands in high-throughput optimization and/or lack of specialized instrumentation and expertise.

1.3.1. Model Derived by Siepmann et al.

Siepmann et al. have used a "sequential layer" model to describe drug release from a cylindrical HPMC matrix tablet [Siepmann et al., 1999, Siepmann and Peppas, 2000 & 2001]. In this model, the tablet matrix is regarded as being structured in sequential layers that can be peeled off one after another (*Figure 1.8*). At the beginning of dissolution process when a dissolution medium penetrates initially into the outermost layer of the matrix core, the first sequential layer is hydrated and starts to swell. Gradually, one after another, the subsequent layers will hydrate and swell.

With this model, it is assumed that the sum of the volumes of water, drug, and polymer within the matrix are always equal to the total volume of the system. A perfect sink condition is maintained to achieve water penetration and polymer swelling on both

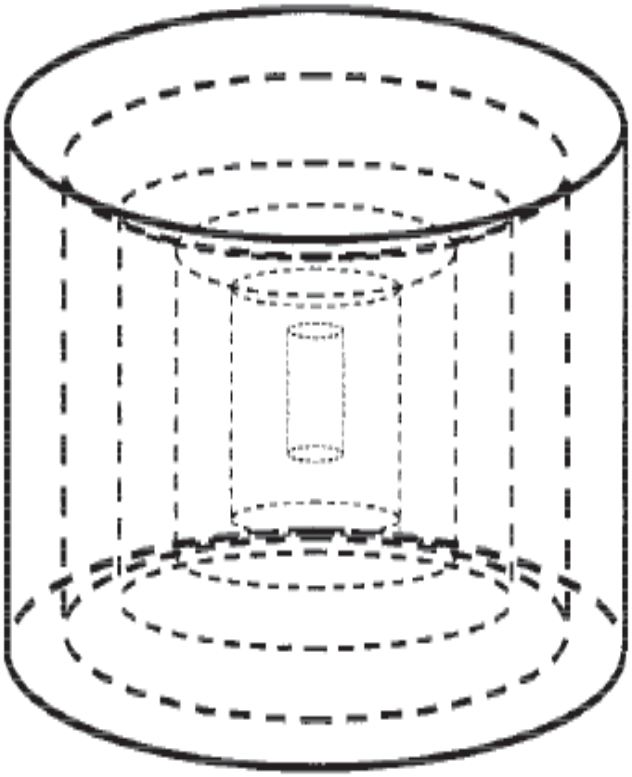


Figure 1.8. "Sequential layer" structure for numerical analysis (Siepmann and Peppas, 2000, with permission from Springer)

axial and radial directions. Water imbibing in the axial/radial direction leads to a volume increase in the axial/radial direction. Drug dissolution within the matrix is faster than drug diffusion out of the matrix. The thermodynamic behavior of the system is ideal. Based on these assumptions the sequential layer model is expressed in the following equations (*Equations 1.3-1.5*),

$$\frac{\partial c_k}{\partial t} = \frac{\partial}{\partial r}\left(D_k \frac{\partial c_k}{\partial r}\right) + \frac{D_k}{r}\frac{\partial c_k}{\partial r} + \frac{\partial}{\partial z}\left(D_k \frac{\partial c_k}{\partial z}\right) \qquad \textit{(Equation 1.3)}$$

$$D_1 = D_{1\mathrm{crit}} \exp\left(-\beta_1\left(1 - \frac{c_1}{c_{1\mathrm{crit}}}\right)\right) \qquad \textit{(Equation 1.4)}$$

$$D_2 = D_{2\mathrm{crit}} \exp\left(-\beta_2\left(1 - \frac{c_1}{c_{1\mathrm{crit}}}\right)\right) \qquad \textit{(Equation 1.5)}$$

Where: c_k and D_k, concentration and diffusion coefficient of the diffusing species (k = 1: water; k = 2: drug), respectively

r, radial coordinate (*Figure 1.9*)

z, axial coordinate (*Figure 1.9*)

t, dissolution time

β_1, dimensionless constant of water

β_2, dimensionless constant of drug

$c_{1\mathrm{crit}}$, water concentration

$D_{1\mathrm{crit}}$, diffusion coefficient of water at matrix/water interface

$D_{2\mathrm{crit}}$, diffusion coefficient of drug at matrix/water interface

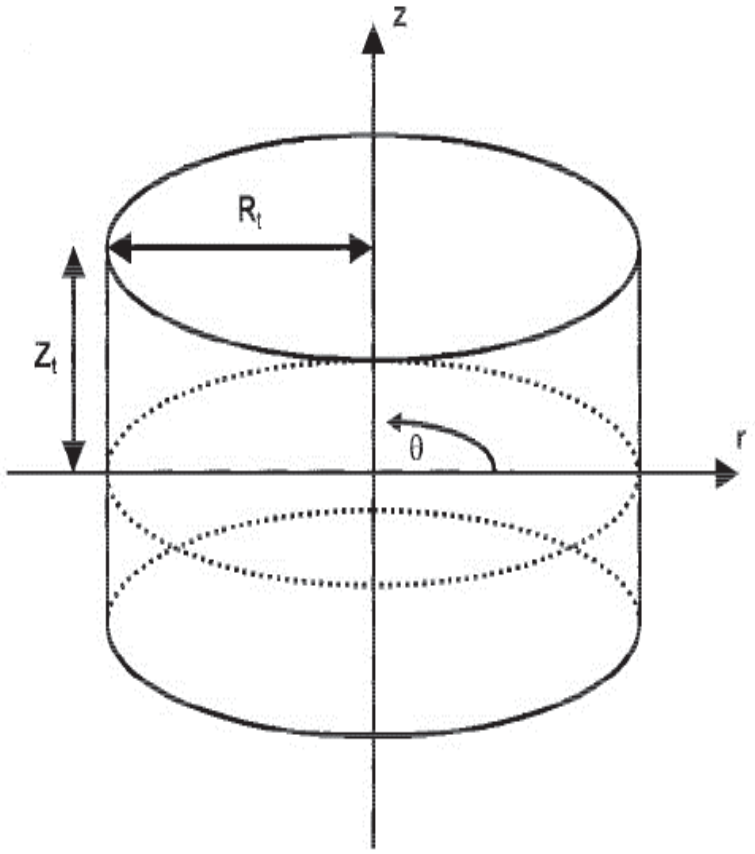


Figure 1.9. Schematic diagram of the matrix for mathematical analysis (Siepmann and Peppas, 2000, with permission from Springer)

1.3.2. Model Derived by Colombo et al.

Colombo et al. also derived a model to depict the relationship between drug release rate and hydrogel layer thickness [Colombo et al., 1999]. This model assumes that a drug volume fraction (concentration) gradient is established in the region between the "swelling front" and the "erosion front" once the dynamic swelling/dissolution has been formed within a swellable matrix. The drug flux, gel layer thickness and drug volume fraction gradient are expressed using following equations (*Equations 1.6-1.7*),

$$J_d = D_d\left(\frac{v_{ds}-v_e}{E-D}\right)\rho_d \qquad \textit{(Equation 1.6)}$$

$$v_{ds} = \frac{c_s v_w}{\rho_d} \qquad \textit{(Equation 1.7)}$$

Where: J_d, flux of drug transport

D_d, drug diffusion coefficient

v_{ds}, drug volume fraction at diffusion front

v_e, drug volume fraction at erosion front

D, diffusion front

E, erosion front

ρ_d, drug density

c_s, drug solubility

v_w, water volume fraction

This model is capable of estimating the relationship between drug flux, drug solubility, drug loading, and hydrogel thickness of an HPMC swellable matrix. Nevertheless, the model involves numerous parameters that are neither directly measurable using routine pharmaceutical instruments, nor necessarily relevant to formulation development. In addition, it does not provide information on how polymer ratio used in a preparation influences the drug release, which is an important determinant in modified drug dissolution.

1.3.3. Model Derived by Kiil and Dam-Johansen

Based on the concept of front movements in swellable matrix preparations, Kiil and Dam-Johansen developed another model for a cylindrically-shaped HPMC matrix, in which drug release kinetics is considered in the radial direction. Three zones of the moving fronts (swelling, diffusion and erosion) within the matrix are divided in a cross-section view during drug release (***Figure 1.10***). This model also assumes that the matrix will start to swell once a threshold in water concentration for hydration is reached, and that the matrix erosion process is negligible. With this approach, the water-induced swelling progress, drug dissolution, and both external and internal resistance to mass transport by the dissolved drug are taken into consideration. The positions of swelling, diffusion and erosion, as well as cumulative fractional drug release over the time, are described by a series of equations [***Equations 1.8-1.11***, Kiil and Dam-Johansen, 2003],

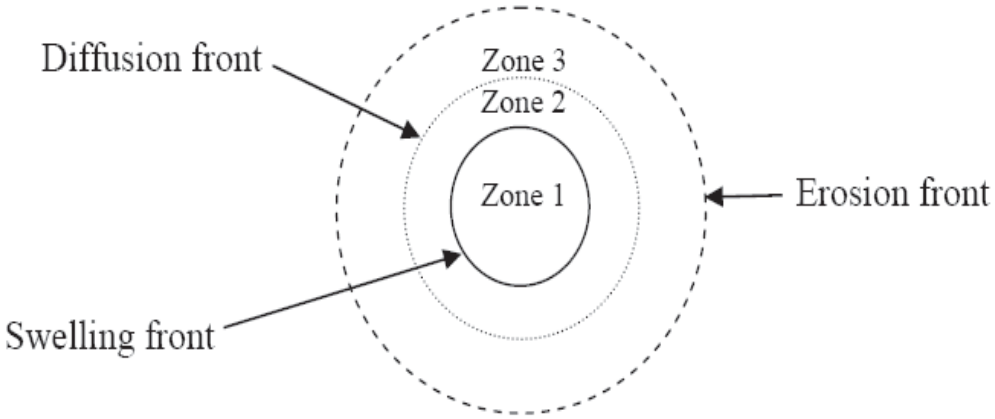


Figure 1.10. Schematic illustration (cross-section view) of radial drug release from a swellable HPMC-based matrix tablet (Kiil and Dam-Johansen, 2003, with permission from Elsevier)

Moving swelling front: $\frac{\mathrm{d}r_s}{\mathrm{d}t} = -K_s\,(\,C_{w2}\mid_{r_s} - C_w^*\,)^n$ *(Equation 1.8)*

with initial condition $r_s(t = 0) = r_o$

Moving erosion front: $r_E = \sqrt{r_s^2 + (r_0^2 - r_s^2) f_s}$ *(Equation 1.9)*

with initial condition $r_E(t = 0) = r_o$

Moving diffusion front: $\frac{\mathrm{d}r_D}{\mathrm{d}t} = \frac{M_D D_{GD} f_s}{V_D \rho_D\,(1-\varepsilon_0)} \frac{\partial C_D}{\partial r}\mid_{r_D} - (f_s - 1)\,\frac{r_s}{r_D}\,\frac{\mathrm{d}r_s}{\mathrm{d}t}$

(Equation 1.10)

with initial condition $r_D(t = 0) = r_o$

Cumulative fractional drug release:

$$F_D(t) = 1 - (\frac{r_s}{r_0})^2 - \frac{r_D^2 - r_s^2}{f_s r_0^2} - \frac{2V_{HPMC}\rho_{HPMC} M_D}{\rho_W f_s V_D \rho_D r_0^2} \int_{r_D}^{r_E} C_D C_{W3}\, r\ \mathrm{d}r \quad \textit{(Equation 1.11)}$$

Where: *Symbols*

r, radial position in matrix

k_s, swelling rate constant in the power-low equation

for the swelling front

C_w^*, swelling threshold concentration of water in matrix

t, time

f_s, equilibrium volume swelling ratio

M, molar mass

D, diffusivity

C, concentration of water or drug

V, initial solid volume fraction

ρ, density

ε_0, initial porosity of matrix

Subscript

G, hydrogel layer

W, water

D, at the position of moving diffusion front or 'drug'

E, at the position of moving erosion front

S, at the position of moving Swelling front

2, zone 2

3, zone 3

Even though a theoretical analysis of drug release from an HPMC matrix can be described using this model, the application of such a calculation would be too complex and overwhelming to become useful in real-life situations. In addition, some of the assumptions of the model, such as that drug release takes place only in the radial direction and that the matrix erosion is negligible, do not generally apply to actual dissolution conditions, and thus may not demonstrate realistic applicability in formulation design and optimization.

1.3.4. Model Derived by Borgquist et al.

The influences of drug diffusion coefficient, drug solubility, and initial drug loading on drug release characteristics from a PEO matrix were studied by Borgquist et al

[Borgquist et al., 2006]. In this model, both radial and axial drug release were considered. The cylindrical polymer tablet was discretized in space *PQ* finite volumes. The axial dimension (index *i*) was discretized in *P* slices and each slice was discretized in *Q* annular rings (index *j*). The axial length of finite volume was denoted *X* and the annular ring thickness was denoted δ. Larger values of *i* and *j* indicated location closer to the bulk phase (*Figure 1.11*).

Borgquist et al. developed more coupled ordinary differential equations to describe drug release and polymer dissolution from cylindrical PEO matrix tablets. It was reported that satisfactory prediction of drug release and polymer dissolution was obtained by using the equations when the matrix was discretized to a 20×20 finite volumes. *Equation 1.12* is one sample of the complicated equation series for describing drug release from a PEO matrix using this model,

$$V_{ij}\left[\frac{\rho^{\mathrm{A}}}{\rho^{\mathrm{A}}-c_{\mathrm{sat}}^{\mathrm{A}}y_{ij}^{\mathrm{AT}}}\right]^{2} y_{ij}^{\mathrm{W}}\,\frac{\mathrm{d}y_{ij}^{\mathrm{AT}}}{\mathrm{d}t}+V_{ij}\frac{\rho^{A}}{\rho^{\mathrm{A}}-c_{sat}^{\mathrm{A}}y_{ij}^{\mathrm{AT}}}\frac{y_{ij}^{\mathrm{AT}}}{y_{ij}^{\mathrm{P}}}\frac{\mathrm{d}y_{ij}^{\mathrm{W}}}{\mathrm{d}t}-\mathrm{A}_{ij}^{es,\mathrm{out}}y_{\mathrm{A},i,j+1}\sum_{k=1}^{j}\frac{\mathrm{d}\delta_{ik}}{\mathrm{d}t}+A_{ij}^{es,\mathrm{in}}$$

$$y_{ij}^{A}\sum_{k=1}^{j-1}\frac{\mathrm{d}\delta_{ik}}{\mathrm{d}t}-A_{ij}^{cs}\,y_{i+1,j}^{\mathrm{A}}\sum_{k=1}^{i}\frac{\mathrm{d}X_{kj}}{\mathrm{d}t}+A_{ij}^{cs}\,y_{ij}^{\mathrm{A}}\sum_{k=1}^{i-1}\frac{\mathrm{d}X_{kj}}{\mathrm{d}t}$$

$$=-\frac{\rho^{\mathrm{A}}}{\rho^{\mathrm{A}}-c_{\mathrm{sat}}^{\mathrm{A}}y_{ij}^{\mathrm{AT}}}\,y_{ij}^{\mathrm{AT}}\,y_{ij}^{\mathrm{W}}\,\Phi_{ij}\,A_{ij}^{B}+A_{ij}^{es,\mathrm{out}}\,N_{i,j+1\to j}^{\mathrm{AD}}-A_{ij}^{es,\mathrm{in}}\,N_{i,j\to j-1}^{\mathrm{AD}}+A_{ij}^{cs}N_{i+1\to i,j}^{\mathrm{AD}}-$$

$$A_{ij}^{cs}N_{i\to i-1,j}^{\mathrm{AD}} \qquad \textit{(Equation 1.12)}$$

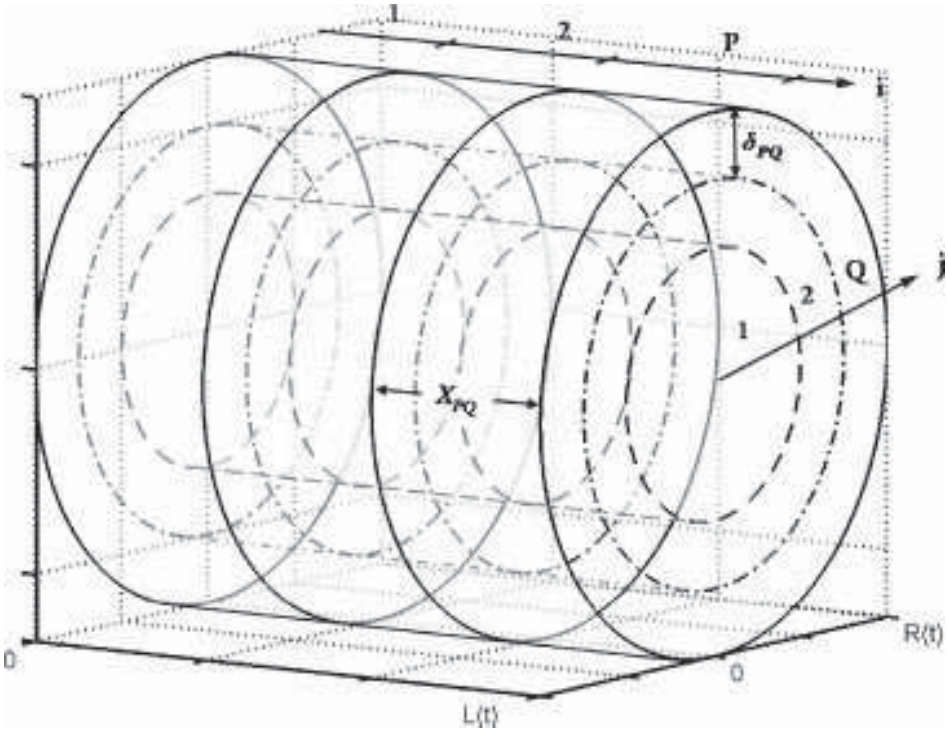


Figure 1.11. Finite volume discretization, exemplified for 9 finite volumes (3 3) (Borgquist et al., 2006, with permission from Elsevier)

The initial and boundary conditions of *Equation 1.12*, for the drug concentration are,

$$\begin{cases} y_{ij}^{\mathrm{A}}(t=0) = y_{ij}^{\mathrm{A}}\,|_0 \\ y_d^{\mathrm{A}} = 0 \\ N_c^{\mathrm{AT}} = 0 \end{cases} \qquad \textit{(Equation 1.13)}$$

The mount of drug released into the bulk,

$$Y^{\mathrm{AB}}(\mathrm{t}) = 1 - \frac{\sum_{i=1}^{\mathrm{P}}\left(\sum_{j=1}^{Q} m_{ij}^{A}(t)\right)}{m^{A}\,|_0} \qquad \textit{(Equation 1.14)}$$

Where: *Symbols*

A, area

ρ, density

c, concentration

m, mass

N, volumetric flux

t, time

V, volume

y, volume fraction or normalized drug concentration

Y, fraction of drug dissolved

δ, annular ring thickness

Φ, dissolution term

Subscripts and Superscripts

0, initial condition (t = 0)

i, index of axial discretization

j, index of radial discretization

P, number of finite volumes in axial direction

Q, number of finite volumes in radial direction

Sat, saturation

A, drug component

B, bulk

cs, cross-section (axial direction)

in, internal

es, envelope surface (radial direction)

out, external

T, total

w, solvent (water)

It is obvious that the above models are all theoretically applicable to a variety of polymers and drug candidates in simulating drug release and polymer swelling from swellable matrix tablets. However, sophisticated instrumentation as well as advanced mathematical skills is also required to determine polymer hydration and to perform data analysis. This has greatly limited the use of these models in routine pharmaceutical research and development where practicality and adaptability are demanded. To simplify the relationship between drug release and formulation factors and to apply useful

mathematical concepts in daily formulation operation, it would be necessary to develop an attainable and practical model.

1.4. Instrumentation for Studying Polymer Hydration

Polymer hydration is critical to drug release characterization from modified release swellable matrices. Formulation scientists have to acquire better understanding of the swelling process within the tablet matrix in order to design novel drug delivery systems and to warrant batch-to-batch reproducibility and accuracy. Numerous analytical methods have been developed and utilized to monitor and determine swelling behaviors of a hydrophilic matrix tablet. Instrumentation involved ranges from simple optical microscope to sophisticated nuclear magnetic resonance (NMR) microscopy. Data collected by each instrument may be useful in illustrating the relationship between drug dissolution and polymer hydration using some of the mathematical modeling previously described.

1.4.1. Optical Microscopy

Optical microscopy has been extensively employed to observe the movement of water at the interface of polymer hydrogel and glassy matrix core. Colombo et al. utilized a photographic method to successfully record and identify the front positions of an HPMC matrix during polymer swelling process. In this study the model dye buflomedil pyridoxalphosphate showed a light yellow color when in a solid state; its aqueous

solutions produced colors ranging from yellow to intense orange depending on the concentration of the dye dissolved. Over the course of polymer hydration, the individual fronts were distinctly visible as concentric circles on the matrix base, corresponding to a sharp change of the colors [*Figure 1.6*, Colombo et al., 2000]. By monitoring the relative position of the swelling and erosion moving fronts, the thickness of hydrogel layers was calculated. It was found that drug release rate was inversely related to dynamics of hydrogel layer thickness.

A similar experiment was performed by using a light scattering imagining (LSI) method [Gao and Meury, 1996], in which an HPMC matrix sample was mounted onto a weighted pin and placed in a beaker filled with distilled water. A light box containing two fluorescent light tubes was positioned at the bottom of the beaker as the light source; visible light that transmitted through the slits on top of the light box was focused to the sample matrix. The entire device was enclosed in a dark setting during the experiment, and a series of images were collected by a camera mounted directly above the matrix tablet. The hydrogel layers that produced over the time were visible as grey circles around the solid matrix core in the images. The light intensity of each grey circle was compared and analyzed. Results indicated that polymer hydration was essentially dependent on the HPMC concentration present in hydrogel layer.

1.4.2. NMR Microscopy

Rajabi-Siahboomi et al. introduced an NMR method to investigate hydrogel formation of an HPMC matrix [Rajabi-Siahboomi et al., 1994 & 1996]. This NMR

microscopy is capable of providing a representation of the spatial variation of self-diffusion coefficients (SDC) and the proton relaxation time (T_2) through the hydrogel layer. Since both SDC and T_2 strongly depend on water mobility, the variations in SDC and T_2 also indicate a gradient of water movement across hydrogel layer of the HPMC matrix. NMR imaging could be utilized to map internal water distribution within a pure HPMC matrix. But it might not reflect actual changes in polymer hydration and drug movement when an HPMC matrix is loaded with an active drug substance. In addition, resolution of the resultant NMR images from this study was not quite satisfactory.

1.4.3. Confocal Laser Scanning Microscopy (CLSM)

To overcome the disadvantage of low resolution from NMR images, a confocal laser scanning microscope (CLSM) method was developed by Cutts et al. [Cutts et al., 1996]. CSLM is capable of producing noninvasive "optical sections" through hydrogel layer at a higher resolution. The changing structure of the hydrogel layer during polymer hydration was recorded by a series of images. In addition, the changing drug distribution in the hydrogel layer could also be characterized by analyzing images collected from CSLM.

While all above-mentioned methods are able to record water mobility across hydrogel layer and drug transport within the polymer matrix, they often require time-consuming sample preparation, and complex, expensive instrumentation. An instrument can only monitor one tablet sample at a time. It is also necessary to select appropriate modeling to correlate the relationship between drug dissolution and polymer hydration.

The applications of these methods have been so far limited in pharmaceutical research and development.

1.4.4. Texture Analysis

Texture analyzer is a versatile instrument of research and development that has been widely applied in food industry. The analyzer is generally equipped with special software that enables the instrument to automatically collect and analyze relevant data in physical strength of an object. *Figure 1.12* shows a complete set of a texture analyzer. By selecting different probes and assessment criteria, food scientists have utilized texture analyzers to monitor or improve the texture quality and palpability of different foods. Numerous scientific articles have been published describing extensive applications of texture analysis in food sciences.

The pharmaceutical applications of a texture analyzer have been significantly explored for the past decade, ranging from studies of pharmaceutical materials to formulation optimization and product quality control. For example, a texture analyzer was used to evaluate the flowability of powder mixtures for tableting process [Nada et al., 2005]. The cohesion flow index of a mixture powder was determinate by recording the energy required to withdraw a rotating spindle for a constant height through the powder bed. The bigger the value of the cohesion flow index, the greater the powder cohesiveness and the smaller the flowability. This new method of texture analysis was able to quantitatively measure the flowability of a powder mixture, of which the traditional powder measurements had failed to provide. Moreover, the methodology

demonstrated a significant advantage in using a texture analyzer for powder materials, because many traditional methods had suffered in measurement accuracy from accumulation and/or blockage of instrument orifices by small powder particles. A similar method was developed by Rao et al. to evaluate the lubrication efficacy of magnesium stearate in different tablet preparations [Rao et al., 2005].

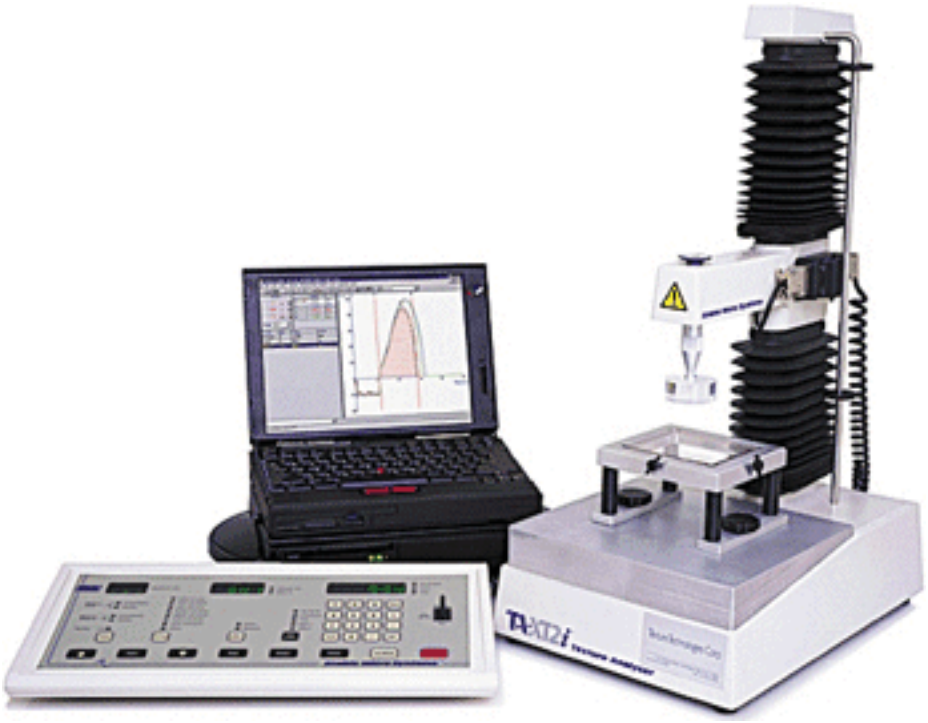


Figure 1.12. A diagram of TA Texture Analyzer

In studies conducted by Lemaitre-Aghazarion et al., a texture analyzer was used to collect data of hardness, cohesiveness, and elasticity from a series of water-in-oil emulsions; formulation optimization was subsequently carried out to modify and improve adhesiveness and cohesiveness of the semisolid preparation [Lemaitre-Aghazarian et al., 2004]. Texture analysis was also involved in measuring disintegration time from a fast-dissolving tablet preparation. Since the normal disintegration time of a fast-dissolving dosage is shorter than a minute, the standard compendial testing protocol is unable to distinguish the differences of tablet disintegration among these specialized formulations. The use of a texture analyzer successfully produced disintegration results that could be accurately quantified [Dor and Fix, 2000, El-Arini and Clas, 2002]. The adhesive properties of polymers incorporated in transmucosal drug delivery systems were also measured using protocols of texture analysis; characterization of mucosal adhesion of the polymers was possible from the data collected [Jimenez-Castellanos et al., 1993, Accili et al., 2004, Cilurzo et al., 2005, Cevher et al., 2008].

Yang et al. investigated the swelling behavior of a polymeric matrix using a texture analyzer [Yang et al., 1998]. In this study a testing probe attached to the arm of the analyzer traveled at a definite speed towards a swelling matrix sample that was positioned on the platform of the texture analyzer. Computer software monitored and recorded the detected force and travel distance from the probe while it was moving inside the swelling hydrogel layer of the matrix until reaching the solid core. The hydrogel thickness of the swelling matrix was then quantitatively correlated to the dissolution time. The operation of a texture analyzer is relatively simple, versatile and cost-effective. One

of the most significant advantages of the instrumentation is its capability to measure multiple samples within a short period of time. In addition, it is also possible to utilize the same instrument for different dosage forms by changing either the testing probes or the measurement parameters.

1.5. Objectives and Scope of the Thesis

In this thesis, a new approach of correlating the behavior of polymer hydration and drug dissolution from modified release swellable matrix tablets by using a texture analyzer was further investigated and refined. It was hypothesized that drug release from a swellable matrix tablet was influenced by drug solubility, polymer hydration, and proportion of matrix polymer in the preparation, and that a relationship between drug dissolution, polymer ratio, and polymer hydration could be formulated based on data collected from the texture analysis and dissolution testing. Therefore, matrixes of PEO and HPMC were prepared by incorporating four drugs of variable aqueous solubility, and their hydration characteristics were measured and compared. The primary objective of the investigation was to explore and validate a practical and attainable protocol that could aid in formulation development and optimization, by utilizing directly measurable parameters of swellable matrix preparations, such as polymer/drug ratio, drug solubility, drug dissolution, and polymer hydration. In addition, various simplified modeling was also attempted to analyze the data and to refine the experimental protocol.

Chapter 2

Effect of Drug Solubility on Polymer Hydration and Drug Dissolution from Polyethylene Oxide (PEO) Matrix Tablets

2.1. Introduction

The water-soluble polymer polyethylene oxide (PEO) has been extensively used to regulate drug release and dissolution from hydrophilic matrix preparations. This is mainly attributed to the desirable hydration and modified release properties of PEO with variable grades and molecular weights [Apicella et al., 1993, Zhang and McGinity, 1999, Razaghi and Schwartz, 2002, Choi et al., 2003]. Once in contact with a liquid, PEO will start to hydrate and swell, forming a hydrogel layer that regulates further penetration of the liquid into the matrix and diffusion of the drug molecules from the dosage form [Colombo et al., 2000]. As a result of hydrogel formation, the rate of water intake is slowed down, and drug dissolution is reduced and prolonged. The formation of a hydrogel layer on the surface of a modified release matrix tablet is generally categorized into three stages, i.e., initial hydrogel increase due to polymer swelling, maintenance of constant hydrogel thickness between swelling front and dissolution front, and reduction of gel thickness due to depletion of the glassy core [Colombo et al., 1995, Bussemer et al., 2006]. It has been hypothesized that drug release at a zero-order mechanism would be achieved as long as a constant thickness of the hydrogel layer were maintained [Lee and Peppas, 1987, Narasimhan and Peppas, 1997].

The mechanism of drug release from a PEO matrix is attributed to a combination of polymer swelling, drug diffusion and matrix erosion under most conditions; the behavior of the hydrogel layer hence plays a key role in modulating drug release characteristics. The swelling behavior of a PEO matrix core can be described by three front positions: swelling front, diffusion front, and erosion front. The hydrogel layer is

constituted by the swelling front and erosion front, and its thickness is determined by the relative position of these two fronts [Colombo et al., 2000].

In this study, we utilized a texture analyzer to evaluate the formation of hydrogel layer from a series of modified release PEO matrix tablets during a simulated dissolution process. Data on polymer hydration and drug dissolution was collected and analyzed using a multiple regression model. Three drug substances, pseudoephedrine hydrochloride (PSE), acetaminophen (ACE) and ibuprofen (IBU) were used as model compounds in the tablet preparations. A fourth drug substance, chlorpheniramine (CHL) was also utilized to further validate the model, by comparing the actual drug release collected from dissolution experiment to that obtained from modeling prediction.

2.2. Materials and Methods

2.2.1. Materials

The following chemicals and pharmaceutical excipients were used in the study:

Acetonitrile (HPLC Grade): Fisher Scientific, Fair Lawn, NJ, USA

Acetaminophen USP (ACE): Medisca Pharmaceutique Inc., Montreal, QC, Canada

Chloroacetic Acid: Fisher Scientific, Fair Lawn, NJ, USA

Chlorpheniramine (CHL): Sigma Chemical Co., St. Louis, MO, USA

Compritol® 888ATO (GB, glyceryl behenate NF): Gattefossé s.a., Lyon, France

Glacial Acetic Acid (Analytical Grade): Fisher Scientific, Fair Lawn, NJ, USA

Ibuprofen Sodium (IBU): Sigma Chemical Co., St. Louis, MO, USA

Methanol (HPLC Grade): Fisher Scientific, Fair Lawn, NJ, USA

Phosphoric Acid, 85% (HPLC): Fisher Scientific, Fair Lawn, NJ, USA

Polyox® WSR301 (PEO, polyethelene oxide): Union Carbride Corporation, Danbury, CT, USA

Prosolv® HD90 (SMC, silicified microcrystalline cellulose): The Dow Chemical Company, Midland, MI, USA

Pseudoephedrine Hydrochloride USP: Medisca Pharmaceutique Inc., Montreal, QC, Canada

PVP K30 USP (polyvinylpyrrolidone): Spectrum Chemical Manufacturing Corp., Gardena, CA, USA

Sodium Acetate Trihydrate (Analytical Grade): Fisher Scientific, Fair Lawn, NJ, USA

Sodium Perchlorate (AC Grade): Sigma Chemical Co., St. Louis, MO, USA

Triethylamine (AC Grade): Fisher Scientific, Fair Lawn, NJ, USA

2.2.2. Instruments/Software

The following instruments were used:

Denver Instrument PI-114 Analytical Balance (Bohemia, NY, USA)

Waters® High Performance Liquid Chromatograph System (Milford, MA, USA)

VenKel® 600 Dissolution Apparatus (Palo Alto, CA, USA)

Manesty® Single-punch Tablet Press (Liverpool, UK)

Erweka® Tablet Hardness Tester (Düsseldorf, Germany)

TA. XT. plus Texture Analyzer (Scardale, NY, USA)

SAS statistical application Version 9.1 (SAS Institute Inc., Cary, NC)

2.2.3 Tableting

Twenty eight test formulations were designed and prepared according to *Table 2.1*; the active ingredient was kept identical at 40% of the total tablet weight in all formulations, while the content of PEO varied between 10% and 50% of the total tablet weight. Several other tablet excipients were also incorporated to achieve a consistent tablet weight of 300 mg. A validation formulation of chlorpheniramine was prepared according to Formula 5 of *Table 2.1*. In this preparation the amount of chlorpheniramine comprised 40% of the total tablet weight, and the ratio of PEO was chosen at 30% of the tablet weight.

For each formulation batch, approximately 100 matrix tablets were prepared by direct compression of the powder mixtures using a Manesty® Single-punch Tablet Press (Liverpool, UK). A set of 7/16 punches and die was used for the tableting, and the compression pressure was maintained at 50 kg/cm^2 for all tablet formulations. Resulting tablets showed a cylinder shape: 1.1 cm in diameter and 0.3 cm in thickness. The tablet hardness was also monitored during tableting with an Erweka® Tablet Hardness Tester (Düsseldorf, Germany). The hardness strength ranged from 9.0 to 13.5 kg depending on the composition of the tablets.

Table 2.1. Compositions of modified release matrix tablets of ACE, CHL, IBU and PSE

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Study Drug*	120	120	120	120	120	120	120	120	120
PEO	30	45	60	75	90	105	120	135	150
GB	9	9	9	9	9	9	9	9	9
PVP	15	15	15	15	15	15	15	15	15
SMC	126	111	96	81	66	51	36	21	6
Total Weight	300	300	300	300	300	300	300	300	300
PEO Ratio (%)	10	15	20	25	30	35	40	45	50

* ACE, IBU or PSE: F1-F9, CHL: F5

2.2.4. Drug Dissolution Test

A dissolution test was carried out on a VanKel® 600 Dissolution Apparatus (Palo Alto, CA, USA) using USP Apparatus II. The dissolution medium was 900 ml of deionized water. The dissolution temperature was maintained at 37 ± 0.5 °C, and the paddle rotation speed was set at 50 rpm. 1 mL sample was collected from the dissolution medium in each vessel at 0.5, 1, 1.5, 2, 4, 6, 8 and 12 hr. Each sample volume removed was replenished with an equal volume of fresh, pre-heated dissolution medium. Six replicates were tested for each batch of the tablet formulations. Dissolution samples were filtered through a 0.2 μm membrane filter, and diluted to appropriate concentrations

using deionized water for drug analysis. The exact total active drug amount of each tablet was calculated based on the tablet weight and the content of the active ingredient.

2.2.5. Determination of Drug Solubility

Over amount of drug substance was added into a test tube containing about 2 mL distilled water, solution was stirred overnight and temperature of the solution was kept at 25°C with a water bath. Saturated solution was filtered through a 0.2 μm membrane filter, and diluted to suitable concentration for HPLC analysis to determine the water solubility.

2.2.6. Drug Analysis

Concentrations of ACE, CHL, IBU and PSE in the collected dissolution samples were analyzed using either official USP chromatographic assay [USP 24/NF 19, 2000] or a method developed in our laboratory [Gu et al., 2005] by a Waters® HPLC system. In brief, a Waters® HPLC system (Milford, MA, USA) comprised of a 600S Controller, a 616 Solvent Delivery Pump, a 717 Autosampler, and a 996 Photodiode Array Detector was utilized together with a C_{18} Nova-Pak® column (4 μm, 3.9 mm × 150 mm). *Table 2.2* shows the details of HPLC conditions for the four test compounds. Prior to drug analysis, the samples were filtered through a 0.2 μm membrane filter and diluted to an appropriate concentration within the established calibration curves using deionized water. The detection limit was 10 ng for all study drugs, and the calibration concentration of the assays ranged between 50-1000 ng. No interference was found from other tablet excipients or additives.

Table 2.2. HPLC conditions for ACE, CHL, IBU and PSE

Analyte	Mobile Phase Composition (v/v)	Flow Rate (ml/min)	Retention Time (min)	Detection Wavelength (nm)
ACE	HPLC water:methanol (3:1)	1.2	1.8	243
CHL	5.7‰ sodium perchlorate: methanol:triethylamine (350:648:2)	1.0	5.5	261
IBU	1% chloroacetic acid (pH3.0):acetonitrile (2:3)	1.4	2.5	220
PSE	Acetate buffer (pH4.0): acetonitrile:methanol (45:47:8)	0.8	2.0	214

2.2.7. Polymer Swelling Testing

To prepare samples for texture analysis, each modified release matrix tablet was inserted into a cylindrical polyethylene cap that had an internal diameter (1.1 cm) equal to the diameter of the prepared tablets. Samples prepared in this manner would allow water penetration from only one surface of the tablet matrix and produce hydrogel swelling in one direction, which facilitated the characterization using a texture analyzer. These tablet samples were then placed in 900 ml of deionized water, and subjected to the same dissolution testing as previously described. Samples were collected at 0.5, 1, 1.5, 2, 4, and 6 h for texture analysis. Six replicates were tested for each time interval.

The hydrogel layer thickness (GelThick) was determined on a TA.XT.Plus Texture Analyzer (Texture Technologies Corp., Scardale, NY, USA). A flat-end, round cylindrical stainless steel probe (Ø 2 mm × *L* 30 mm) was utilized to measure the distance that the probe traveled within the hydrogel layer. The probe initially traveled at a speed of 2.0 mm/s until the surface of the tablet was detected at 0.7 g of the force, at which point the probe penetrated the swollen hydrogel layer at a speed of 0.2 mm/s, and the computer started to record the travel distance of the probe until the probe detected 500 g of the force, which was determined as the un-swollen, solid matrix core. The probe would hence withdraw automatically out of the gel layer at a rate of 0.2 mm/s [Yang et al., 1998]. Data were collected and processed by Texture Expert software.

2.2.8. Data Analysis

The empirical Peppas-Ritger dissolution equation [Ritger and Peppas, 1987a & 1987b] was used to characterize drug release from the prepared matrix tablet formulations. The relationship between drug diffusion from the matrix tablet and dissolution time was analyzed through the following equations,

$$M_t / M_\infty = K \cdot t^n \qquad \textit{(Equation 2.1)}$$

$$\log [M_t / M_\infty] = \log k + n \log t \qquad \textit{(Equation 2.2)}$$

where M_t/M_∞ is the fraction of drug release, k is a release rate constant, n is the diffusional release exponent indicative of drug release mechanism, and t is the dissolution

time. The values of k and n were obtained using simple linear regression analysis of $log\ [M_t / M_\infty]$ and $log\ t$ according to *Equation 2.2*.

The time required for 50% of the drug content to be released ($DT_{50\%}$, hours) of the formulations were also obtained to compare differences in drug release rate and extent among the prepared formulas [Khan, 1975, Efentakis and Koutlis, 2001]. $DT_{50\%}$ was estimated according to the collected drug dissolution results and the Peppas-Ritger equation.

The swellable matrix tablet is a complex drug delivery system; the drug dissolution profile is affected by the mixture of different formulation parameters such as polymer selection, active drug property and excipients used. Among those formulation parameters the type and the ratio of polymer incorporated, and the solubility of the active ingredient embedded are the most critical factors that can modify the drug dissolution profile. Upon exposure to dissolution medium, swellable polymer hydrates, swells, and forms a gel barrier layer, which retards the diffusion of drug out of the matrix. The solubility of the active ingredient may also modify the polymer swelling process. In the study the behavior of the gel barrier/gel layer was monitored during the polymer swelling test on all 27 test formulations by Texture Analyzer, which recorded several pre-determined parameters of the tablet matrix, including the force (F) that the probe experienced and the distance (D) that the probe traveled within the hydrogel layer. D was also considered as the thickness of the hydrogel layer. A typical curve of the measurement is shown in *Figure 2.1*. The area under the curve (AUC_{TA}) was automatically calculated and record by the TA Texture analyzer system. The relationship

between drug dissolution or polymer hydration and dissolution time, drug solubility, and PEO proportion in the formulation was analyzed by multiple regression (*Equation 2.3*) (SAS Version 9.1, SAS Institute Inc., Cary, NC). It was hypothesized that by using ordinary least square regression techniques the effect of the major formulation factors (e.g., polymer ratio and drug solubility) of the matrix tablet on the polymer swelling and drug dissolution could be evaluated. Multiple regression model can be developed between drug dissolution as dependent variable and dissolution time, polymer ratio, and drug solubility as independent variables. The model would be adaptable to similar formulations. Based on the model, the drug dissolution will be predictable if the formulation factors are known in advance, or alternatively, if a specific drug dissolution profile were expected during the development of new formulation, the formulation factors could be estimated in a simplified manner. For polymer swelling evaluation, similar regression models can be developed between gel layer thickness/AUC_{TA} as dependent variables and dissolution time, polymer ratio, and drug solubility as independent variables.

Multiple regression:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots \beta_n X_n + \varepsilon \qquad \textit{(Equation 2.3)}$$

where β is the regression coefficients;

ε is the error term or noise.

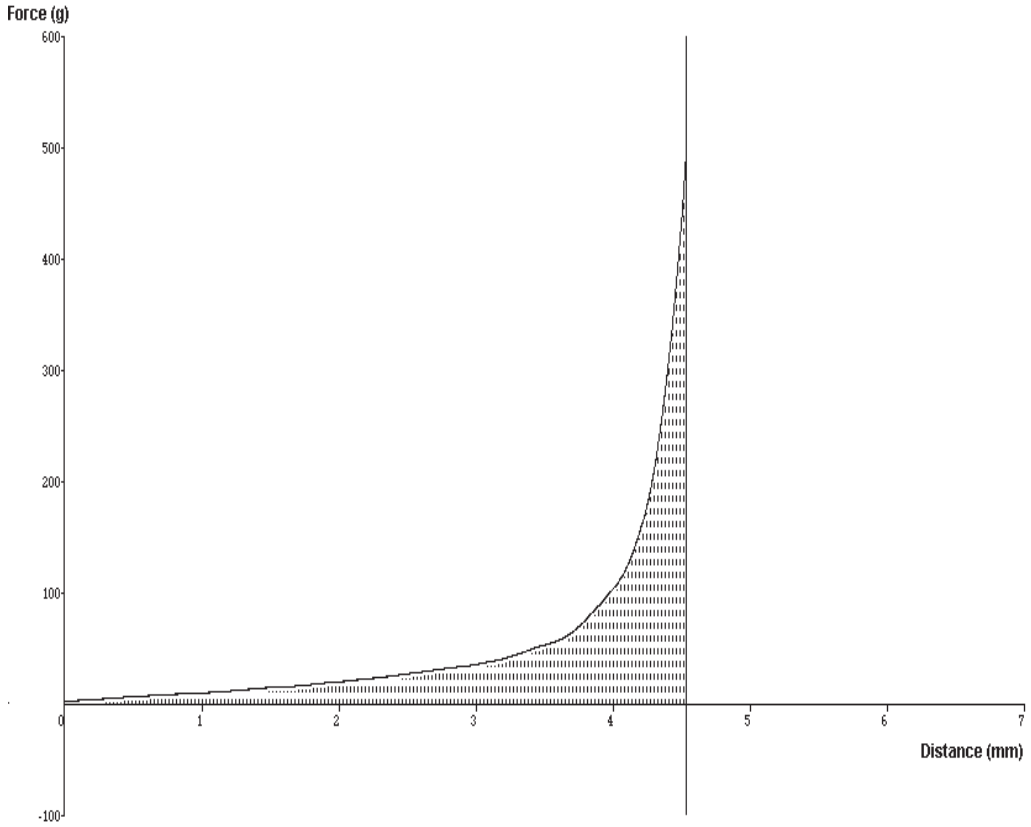


Figure 2.1. A typical graph of the texture analyzer (force vs. probe travel distance)

Data was collected from 6 replicates at each sampling point (0.5, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, 12.0 hr) during dissolution process and was split into two sets according to the sampling order of the replicates: data from the first 3 replicates were assigned to set#1 (training set), and data from the remaining 3 replicates were assigned to set#2 (validation set). Set#1 data was used to develop the model and set#2 data was used to evaluate the reasonableness and predictability of the developed model from Set#1. After the model was validated, the two data sets were merged together and a final regression model was further established. In addition, drug dissolution of a chlorpheniramine formulation containing 30% PEO polymer was estimated based on the validated model. The predicted drug dissolution profile was compared to the observed drug dissolution result from the dissolution test to verify the predictability of the model.

Multiple regression was employed for the model development. In order to develop a model that is capable of projecting an optimized predictability, following procedures were performed: 1). Multiple regression was performed between drug dissolution (DISSOL) as the dependent variable and polymer ratio (PRATIO), dissolution time (TIME), and drug solubility (SOLU) as the independent variables. The residual analysis was performed to check for the fit of the model. 2). Assuming that there was a cross-level interaction between the independent variables, the regression was expanded by adding the cross-products of the variables. The significance of the impact of the cross-products on the DISSOL was evaluated. 3). To optimize the fit of the multiple regression model, the quadratics of the variables were introduced into the regression model. The significance of the impact of the quadratics on the DISSOL was evaluated.

Based on the above procedures each preceding model was nested in the following, so model comparison was facilitated using an F test. The F statistic was calculated as per *Equation 2.4*:

$$F = \frac{\left(\frac{RSS_1 - RSS_2}{p_2 - p_1}\right)}{\left(\frac{RSS_2}{n - p_2}\right)} \qquad (Equation\ 2.4)$$

where RSS_i is the residual sum of squares of model i, n is the sample size, p_i is the number of variables in model i. Under the null hypothesis that model 2 did not provide a significantly improved fit than model 1, F would have an F distribution, with (p_2 - p_1, n - p_2) degrees of freedom. The null hypothesis would be rejected if the F calculated from the data were greater than the critical value of the F distribution ($p < 0.05$).

Data transformation was performed as necessary for dependent variable or independent variable, or both. The significance criterion was decided as $P<0.05$ throughout the analysis. Residual analysis was employed to evaluate the model fit. If the regression model fits the data the points in the residual plot should then be randomly dispersed around the horizontal axis ($y = 0$), displaying no systematic tendencies to be positive or negative.

2.3. Results and Discussion

Polyethylene oxide polymers have been widely used in the development of various tablet formulations. When in contact with water, hydrophilic polyethylene oxide polymers allow gradual hydration of the tablet matrix, leading to modified dissolution and diffusion of the active ingredient from within the swelling matrix. Lipid-based excipients are water-insoluble materials. When incorporated appropriately in a tablet preparation, they not only supplement essential tableting properties, but also aid in modified drug release through slow matrix erosion (Gu et al., 2004). The use of a small amount of GB in this study enabled the preparation of modified release matrix tablets with satisfactory flowing properties and direct compressibility of the mixtures. Among the formulas tested in the study, PEO ranged between 10% and 50% of the total tablet weight and GB was incorporated at a constant rate of 3% of the total tablet weight. The other two excipients present in all study samples, PVP and SMC, were believed to contribute minimally to hydrogel formation and drug release regulation. They were used primarily as tablet fillers to achieve required tablet weight for all formulations.

Drug solubility is one of the primary parameters that dictate drug release rate and dissolution from solid dosage forms such as tablets and capsules. As a result, solubility also influences *in vivo* performance of the preparation, specifically bioavailability and therapeutic efficacy, since an active ingredient must be in the form of a solution before being systemically absorbed and distributed. Many solid controlled release delivery systems rely on aqueous solubility of the active ingredients to achieve modified drug release characteristics. In this study model drugs ACE, IBU and PSE have different

aqueous solubility. PSE is readily soluble in the water. Its aqueous solubility was measured at 56.5 ± 0.3 g/100ml (25 °C, mean ± SEM, $n = 6$) in our laboratory. The aqueous solubility of ACE and IBU was found to be 1.9 ± 0.3 g/100ml (mean ± SEM, $n = 6$) and 13.4 ± 0.4 g/100ml, respectively. There was a range of approximately 30-fold in aqueous solubility between ACE (the least soluble) and PSE (the most soluble). It was anticipated that this solubility range would produce differences in drug release characterization from swellable matrix tablets.

Not only did drug solubility dictate the rate and extent of drug dissolution from the prepared tablets, but it influenced polymer hydration and swelling of hydrophilic PEO matrix as well. PEO polymer gradually hydrates and swells once in contact with a dissolution medium. While physical properties play a primary role in hydration and swelling of PEO, drug solubility does facilitate the progression of hydration by allowing continuous water penetration through diffusion and dissolution. *Figure 2.2* shows the representative dissolution curves from the three test drug compounds. As demonstrated in the curves, drug dissolution was reduced with the decrease in aqueous solubility of the active ingredients. Both ACE and IBU were able to sustain drug release for 10 to 12 hours, while PSE completed drug dissolution within 6 hours owing to a higher aqueous solubility. It appeared that initial PSE release was not influenced by the proportion of PEO in the tablet formulations. Neither was total drug release percentage affected by PEO amount in the tablets, as its hydrophilicity enabled complete diffusion of PSE after a 6 hr period. In addition, modification of the drug release was influenced by the PEO proportion present in the tablet preparation. Increase in the PEO proportion retarded the

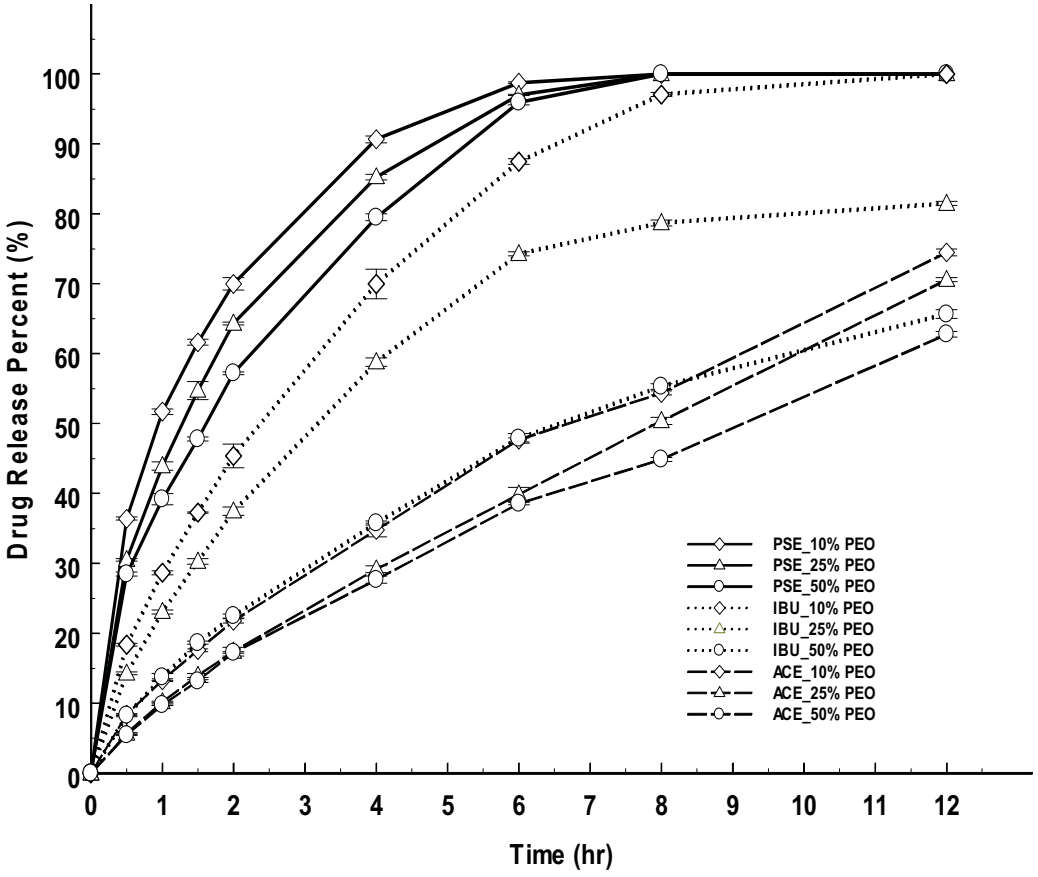


Figure 2.2. Representative dissolution-time plots of modified release matrix tablets of PSE, IBU and ACE (Mean ± SE, n=6)

uptake of water by the matrix core, consequently prolonging the drug diffusion and dissolution from the preparation.

Dissolution kinetics are good indicators of drug release characteristics, and thus are commonly used as determinants in formulation design and optimization. There are numerous empirical equations depicting the rate and extent of drug dissolution from a modified release tablet or capsule; The Peppas-Ritger dissolution equation (*Equation 2.1*) is one such example. Derived from this equation, the logarithmized drug dissolution is described as a function of the logarithmized dissolution time (*Equation 2.2*). This relationship has been widely recognized and used by formulation researchers because of its simple and practical application. *Tables 2.3-2.5* list dissolution kinetics obtained from Peppas-Ritger dissolution equation for three model drugs, respectively. The dissolution half-life ($DT_{50\%}$), which stands for the time required for a 50% drug release, was also included in the tables. The effects of drug solubility on drug release modification were evident among the three study formulations. $DT_{50\%}$ decreased with an increase in drug solubility. For an incorporated polymer ratio range of 10%-50%, $DT_{50\%}$ for ACV, IBU, and PSE formulations ranged from 6.6 - 8.5, 2.5 - 6.4, and 0.9 - 1.7 hr, respectively. The release rate constant and dissolution half-life were inversely related to the solubility properties. Nevertheless, no distinction was observed for drug release mechanism among all tablet preparations. The diffusional exponents (n) were within the range of 0.45-0.89, indicating a non-Fickian drug release mechanism for all matrix formulas. This further confirmed that drug dissolution was mainly controlled by the diffusion of drug molecules from the tablet matrix, and that erosion of the hydrophilic polymer during the dissolution

Table 2.3. In vitro drug release and dissolution of ACE preparations

Formulation Code	PEO Ratio (%)	Diffusional Exponent (*n*)	Release Rate Constant (*k*)	$DT_{50\%}$ (hr)
F1	10	0.698	0.134	6.6
F2	15	0.783	0.108	7.1
F3	20	0.856	0.089	7.5
F4	25	0.778	0.100	7.9
F5	30	0.785	0.097	8.4
F6	35	0.746	0.100	8.5
F7	40	0.785	0.097	8.1
F8	45	0.802	0.093	8.1
F9	50	0.774	0.097	8.5

Table 2.4. In vitro drug release and dissolution of IBU preparations

Formulation Code	PEO Ratio (%)	Diffusional Exponent (*n*)	Release Rate Constant (*k*)	$DT_{50\%}$ (hr)
F1	10	0.632	0.282	2.5
F2	15	0.629	0.269	2.7
F3	20	0.641	0.247	3.0
F4	25	0.667	0.231	3.2
F5	30	0.623	0.179	5.2
F6	35	0.674	0.158	5.5
F7	40	0.698	0.148	5.7
F8	45	0.697	0.142	6.1
F9	50	0.700	0.137	6.4

Table 2.5. In vitro drug release and dissolution of PSE preparations

Formulation Code	PEO Ratio(%)	Diffusional Exponent (*n*)	Release Rate Constant (*k*)	$DT_{50\%}$ (hr)
F1	10	0.471	0.509	0.9
F2	15	0.501	0.499	1.0
F3	20	0.530	0.480	1.1
F4	25	0.537	0.442	1.3
F5	30	0.563	0.425	1.4
F6	35	0.500	0.410	1.5
F7	40	0.492	0.408	1.6
F8	45	0.494	0.400	1.6
F9	50	0.496	0.398	1.7

occurred at a much slower rate than drug diffusion.

The presence of hydrophilic polymer PEO in a matrix tablet would result in dynamic formation and change of a hydrogel layer on the surface of the tablet upon in contact with water. Solid drug-polymer matrix core will transform from its initial dry (glassy) stage to a wet (rubbery) stage while a dissolution medium is permeating through the tablet surface. This is another critical parameter in addition to drug solubility that would modify drug release characteristics. Drug release rate and extent are inversely proportional to the thickness of this hydrogel layer, because it takes time for the drug molecules to travel across the hydrogel layer and reach the dissolution medium [Colombo et al., 1995, Williams et al., 2002]. Moreover, a higher proportion of polymer in the tablet enables the formation of a thicker hydrogel layer and subsequently slower erosion of the gel shell, further retarding drug dissolution from the preparation.

Dependent on the type and amount of the polymers used in the tablet core, transition from the glassy state to the rubbery state might be variable. The interval that is required of the transition is also associated with the aqueous solubility of the active ingredient, since polymer hydration will take place only after penetrating water has dissolved the solid drug substance. For PSE matrices, the phase transition was achieved within 30 minutes of the drug dissolution, as the compound has a very high aqueous solubility. The hydrogel thickness was not influenced by the amount of PEO present in the study formulations (*Figure 2.3*). Nevertheless, the formation of hydrogel layer was dependent on the solubility of ACE and IBU in this study. In particular, the thickness of hydrogel measured at 30 minutes demonstrated differences among the nine formulas for

both compounds (*Figure 2.4* and *Figure 2.5*). This was primarily attributed to the ability of water penetrating into the tablet core and drug diffusion out of the preparation. While the hydrogel layer thickness in both ACE and IBU tablets at 6 hours was approximately 50% of the value of the pseudoephedrine tablet, the two formulas that contained 50% of PEO produced identical hydrogel layer, suggesting that PEO contributed more to hydrogel swelling at a higher proportion.

To develop the multiple regression model, a total 972 samples were collected from 27 different formulations at predetermined time intervals. Samples were divided into two sets according to the sampling order of the replicates, i.e., a training set and a validation set. A standard multiple regression was performed on the training set (section 2.2.7) data with DISSOL as the response variable and TIME, PRATIO, and SOLU as explanatory variables:

$$\text{DISSOL} = \beta_0 + \beta_1 \times \text{TIME} + \beta_2 \times \text{PRATIO} + \beta_3 \times \text{SOLU}$$

Model #1 *(Equation 2.5)*

Table 2.6 shows the regression results. All three variables were significant ($P < 0.05$), but the residual plot (*Figure 2.6*) showed curvature and nonconstant variance, which indicating poor model fit. Variable transformation or high-order term might be required to improve the normality of the residuals.

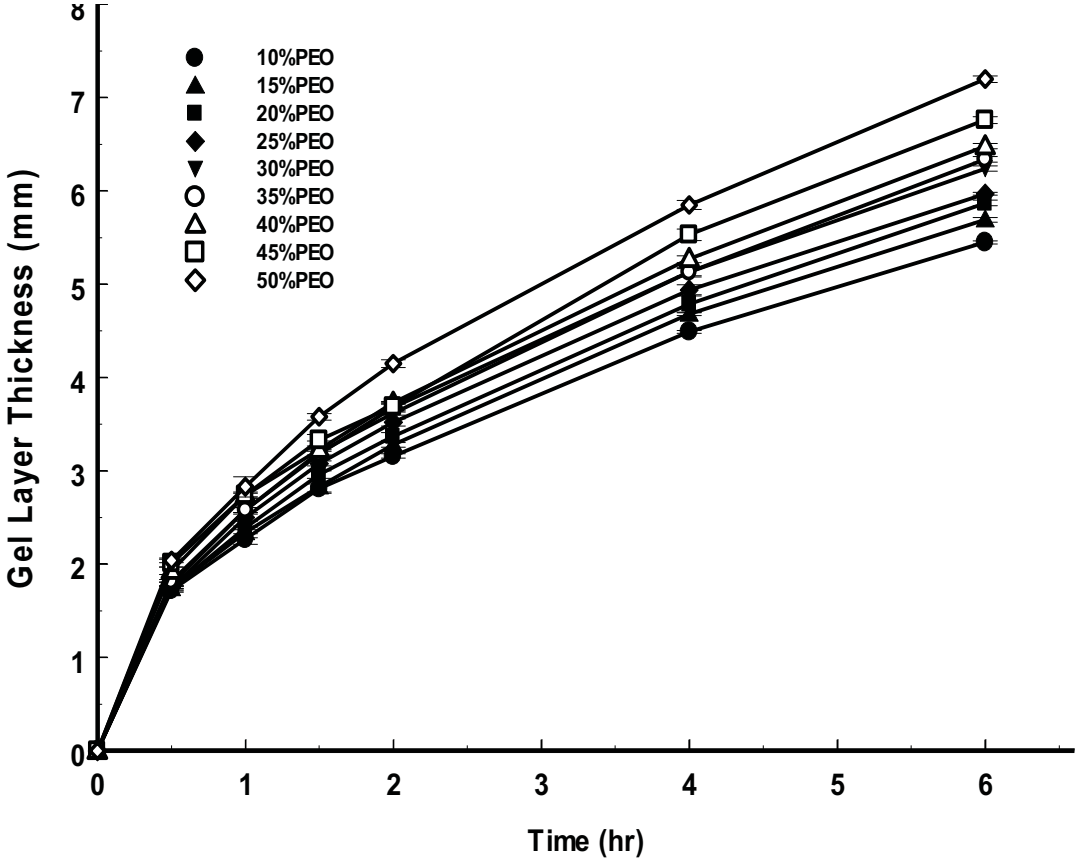


Figure 2.3. Hydrogel thickness-time plots of PSE preparations (Mean ± SE, n=6)

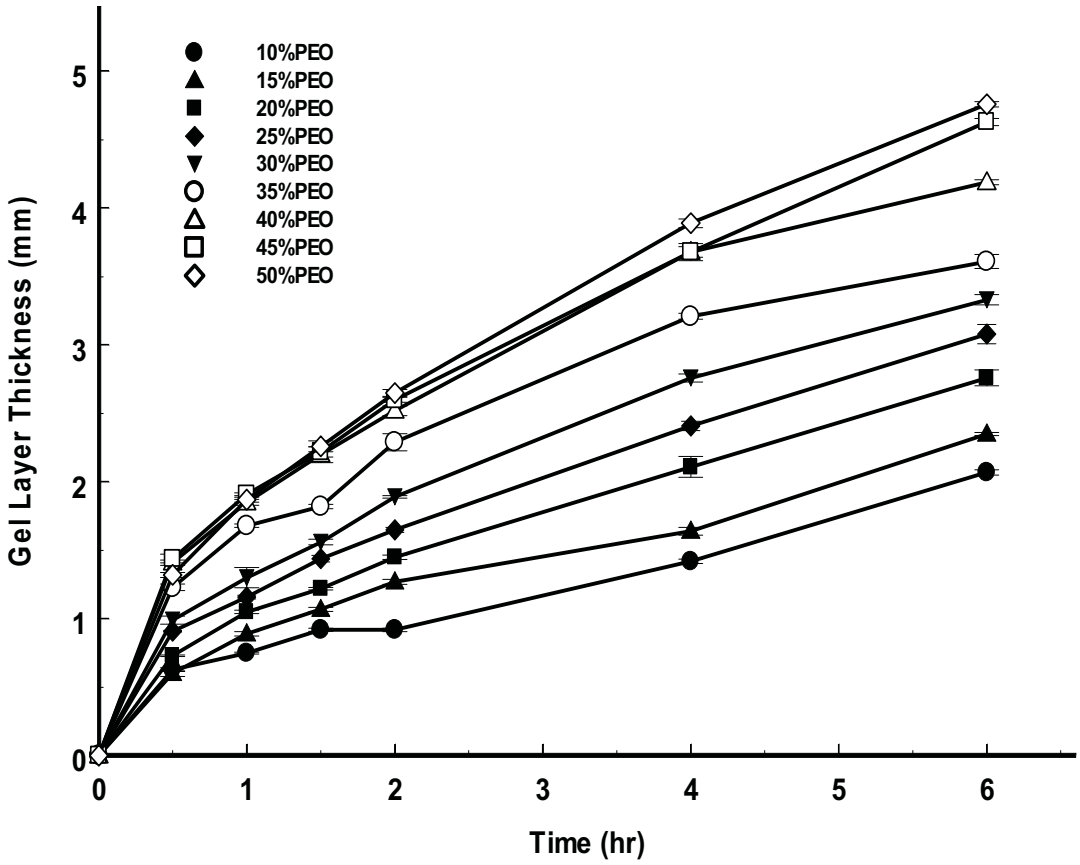


Figure 2.4. Hydrogel thickness-time plots of ACE preparations (Mean ± SE, n=6)

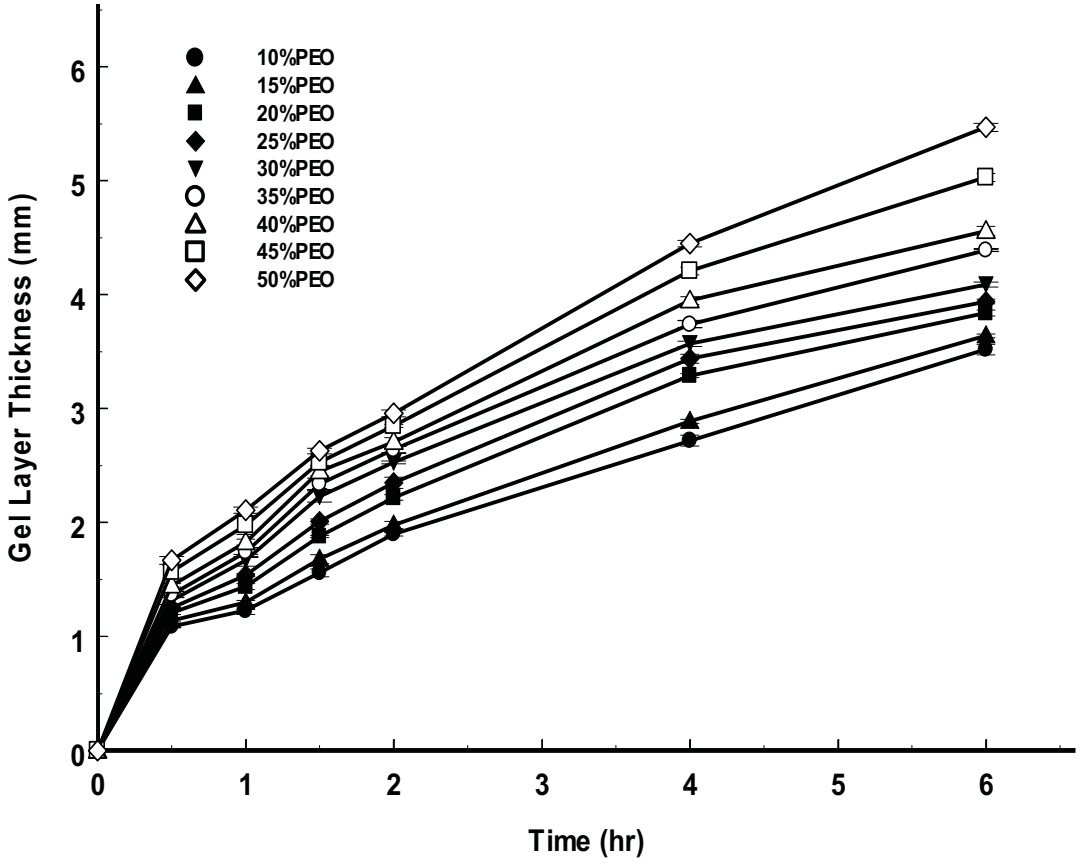


Figure 2.5. Hydrogel thickness-time plots of IBU preparations (Mean ± SE, n=6)

Table 2.6. Summary statistics of Model #1

a) Analysis of Variance

Source	DF	Sum of Squares	Mean Square	*F*-value	Prob > *F*
Model	3	3.01E+01	1.00E+01	1861.01	0.0001
Error	482	2.60E+00	5.40E-03		
Total	485	3.28E+01			

b) Parameter Estimates

Variable	Label	Estimate	Std Error	*t*-value	Prob > $\lvert t \rvert$
Intercept	Intercept	8.23E-02	1.01E-02	8.17	< 0.0001
TIME	Dissolution Time	8.93E-02	1.74E-03	51.29	< 0.0001
PRATIO	PEO Ratio	-3.41E-01	2.58E-02	-13.21	< 0.0001
SOLU	Drug Solubility	7.47E-03	1.42E-04	52.70	< 0.0001

According to Peppas-Ritger empirical dissolution equations (***Equation 2.1&2.2***) the logarithmized drug dissolution (LDISSOL) is a function of the logarithmized dissolution time (LTIME). Based on the concept natural log transformation was performed on both response variable "DISSOL" and explanatory variable "TIME". ***Figure 2.7-2.8*** shows the histogram of DISSOL and the histogram of LDISSOL respectively. After the transformation the normality of the response variable was improved.

A regression was undertaken with LDISSOL as the response variable, LTIME, PRATIO, and SOLU as the explanatory variables (see Table 2.7):

$$\text{LDISSOL} = \beta_0 + \beta_1 \times \text{LTIME} + \beta_2 \times \text{PRATIO} + \beta_3 \times \text{SOLU}$$

Model #2 *(Equation 2.6)*

The impact of all three independent variables (LTIME, PRATIO, and SOLU) on the dependent variable (LDISSOL) was significant ($p<0.05$). Compared to Model #1 the distribution of residual points of Model #2 (***Figure 2.9***) was improved; however, the residual plot still shows some curvature, indicating poor linear fit.

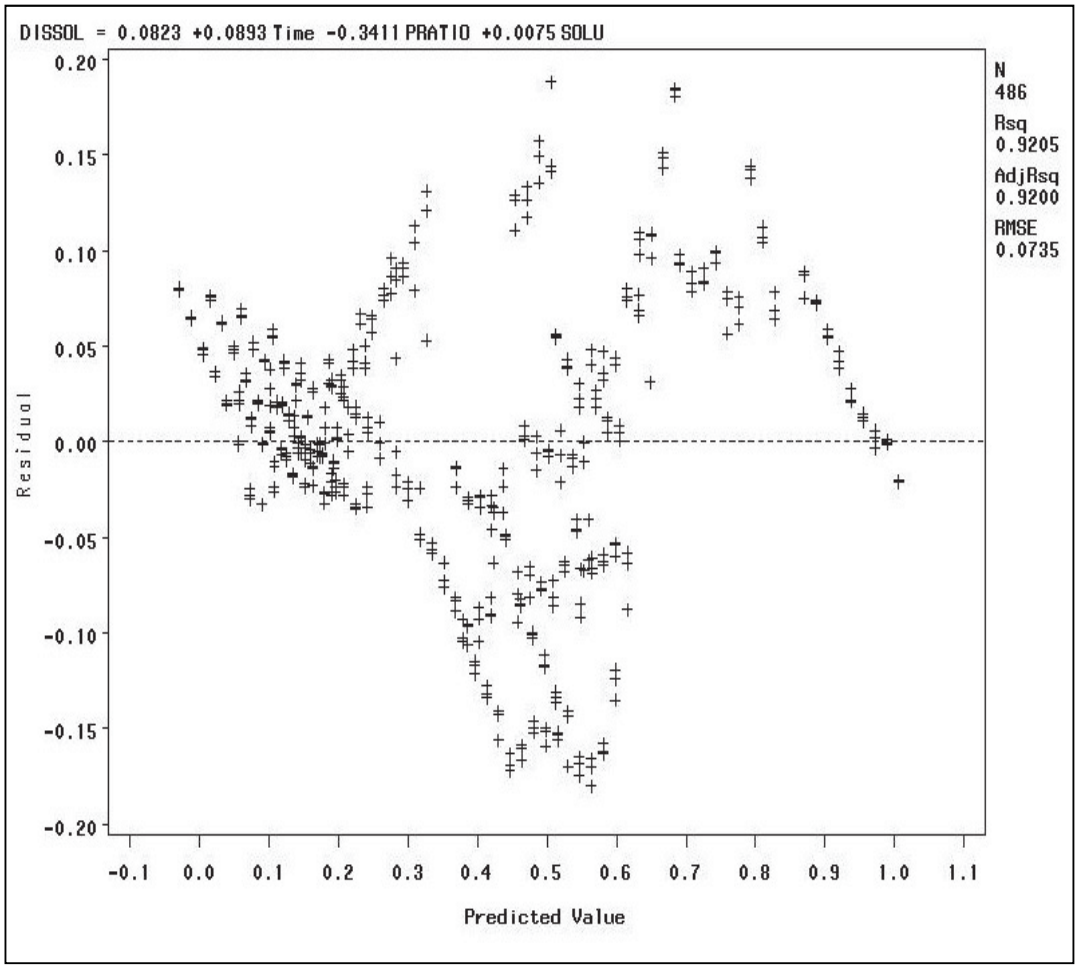


Figure 2.6. Residual plot of regression Model #1

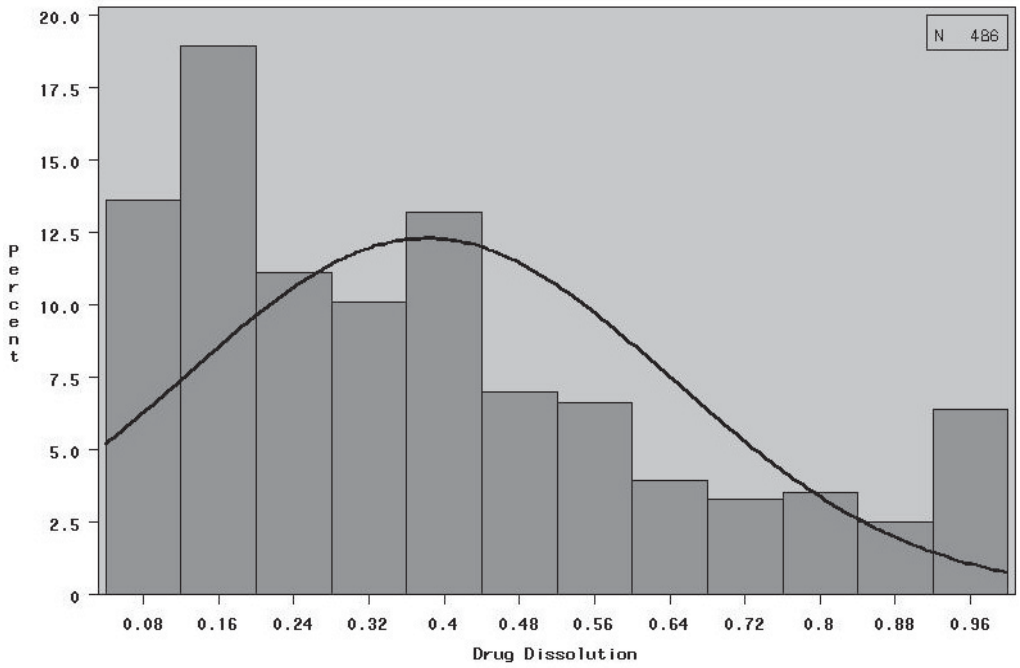


Figure 2.7. Histogram with Normal Curve of variable "DISSOL"

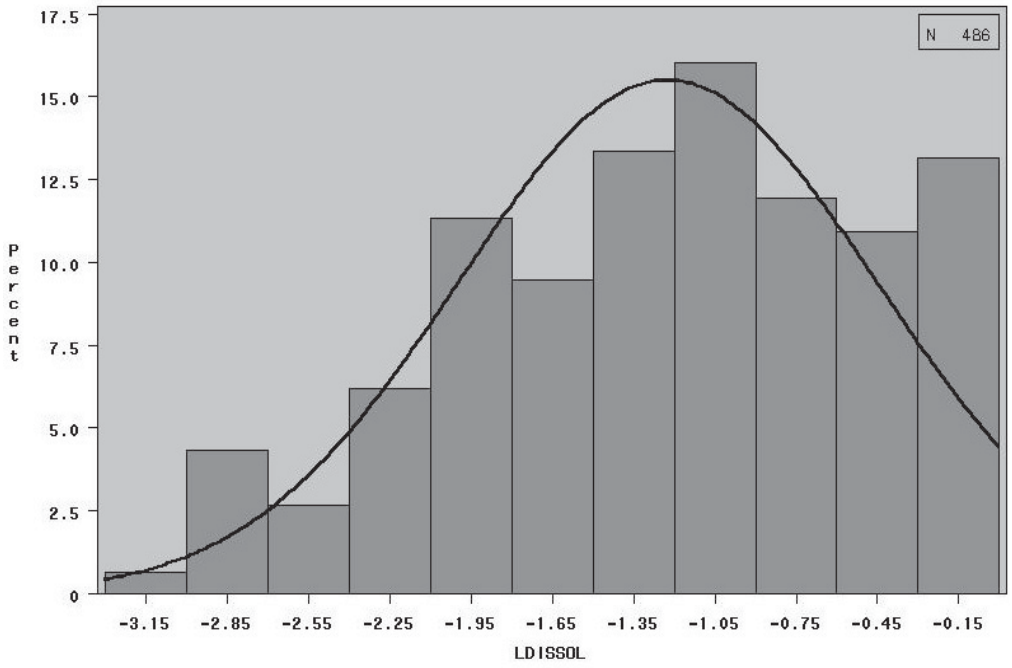


Figure 2.8. Histogram with Normal Curve of transformed variable "LDISSOL"

Table 2.7. Summary statistics of Model #2

a) Analysis of Variance

Source	DF	Sum of Squares	Mean Square	*F*-value	Prob > *F*
Model	3	2.70E+02	9.00E+01	2307.85	< 0.0001
Error	482	1.88E+01	3.90E-02		
Total	485	2.89E+02			

b) Parameter Estimates

Variable	Label	Estimate	Std Error	*t*-value	Prob > $\lvert t \rvert$
Intercept	Intercept	-1.81E+00	2.53E-02	-71.74	< 0.0001
LTIME	Log(Time)	6.39E-01	1.08E-02	59.07	< 0.0001
PRATIO	PEO Ratio	-1.03E+00	6.94E-02	-14.89	< 0.0001
SOLU	Drug Solubility	2.16E-02	3.81E-04	56.68	< 0.0001

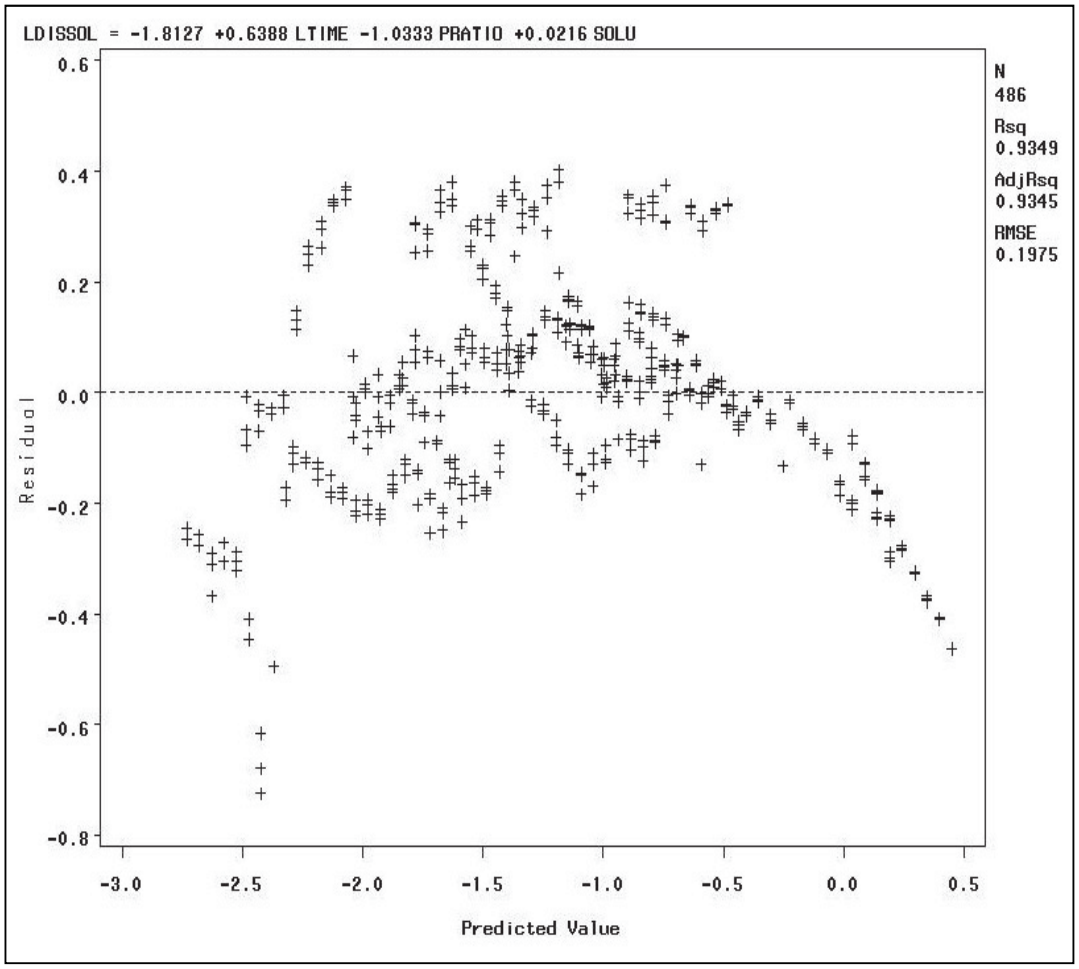


Figure 2.9. Residual plot of regression Model #2

The ultimate goal of the study was to develop a model that was capable of providing accurate prediction of the drug dissolution from the swellable matrix. Although over 93% of the variability of the training date could be explained by Model *#2,* there still was room for improvement regarding data predictability and application of the linear model remained questionable. This is evident in the *Plot of LDISSOL against predicted value from regression Model #2 (Figure 2.10)*. The plots were not distributed tightly around $Y = X$, which suggested that the developed model might not be able to provide a precise prediction. The model could be further optimized.

Model #2 demonstrates that LDISSOL from the PEO swellable matrix was significantly affected by LTIME, PRATO and SOLU. During the drug dissolution process the PEO polymer keeps absorbing water and hydrating afterwards, its physical condition changes along the dissolution time. This change can also affect the drug dissolution. There might be interactive effect between the dependent variables. Or in other words that with the continuous progression of drug dissolution (PRATO or SOLU) might affect drug dissolution at various levels along LTIME. To assess the effect from the interactive parameters on LDISSOL the cross products (*Table 2.8*) of each two of the three variables were added to the model, and another regression was attempted following Model *#3*:

$$\text{LDISSOL} = \beta_0 + \beta_1 \times \text{LTIME} + \beta_2 \times \text{PRATIO} + \beta_3 \times \text{SOLU} + \beta_4 \times \text{LTCPR} + \beta_5 \times \text{LTCSOLU} + \beta_6 \times \text{SOLUCPR}$$

Model #3 *(Equation 2.7)*

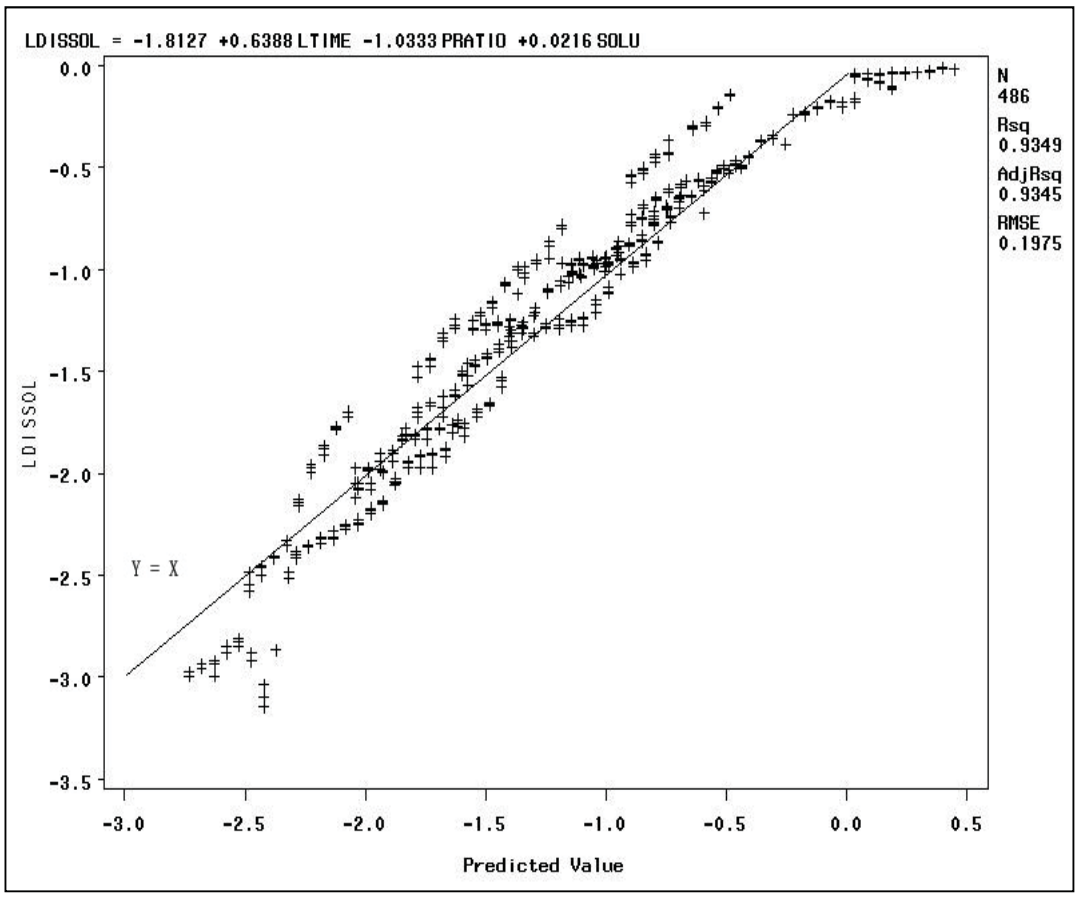


Figure 2.10. Plot of LDISSOL against predicted value from regression Model #2

Table 2.8. Crossprodut Variables for Regression Analysis

	Parameter/Variable	Label
Cross Product	LTCSOLU	Log(Time) × Drug Solubility
	LTCPR	Log(Time) × PEORatio
	SOLUCPR	Drug Solubility × PEORatio

A summary of the statistics for Model *#3* is listed in *Table 2.9*. All three cross-products demonstrate significant impact on LDISOL. Because of the addition of the cross products R^2 increased to 0.9541 from 0.9349, and the RSME decreased from 0.1975 to 0.1664. Model *#3* explained more variability of the training data set, and some improvement was observed on the residual plot (*Figure 2.11*). It was clear that a majority of the residual plots were randomly distributed around y = 0 with the exception of several outliers when time approaches 0.5 hr, which could be attributed to a "burst dissolution" at the very early stage of the dissolution process.

Table 2.9. Summary statistics of Model #3

a) Analysis of Variance

Source	DF	Sum of Squares	Mean Square	*F*-value	Prob > *F*
Model	6	2.76E+02	4.59E+01	1657.59	< 0.0001
Error	479	1.33E+01	2.77E-02		
Total	485	2.89E+02			

b) Parameter Estimates

Variable	Label	Estimate	Std Error	*t*-value	Prob > $\lvert t \rvert$
Intercept	Intercept	-1.78E+00	3.10E-02	-57.42	< 0.0001
LTIME	Log(Time)	7.03E-01	2.49E-02	28.27	< 0.0001
PRATIO	PEO Ratio	-1.38E+00	9.35E-02	-14.76	< 0.0001
SOLU	Drug Solubility	2.18E-02	8.45E-04	25.82	< 0.0001
LTCPR	Log(Time) × PEO Ratio	1.99E-01	7.06E-02	2.82	< 0.005
LTCSOLU	Log(Time) × Drug Solubility	-5.16E-03	3.88E-04	-13.30	< 0.0001
SOLUCPR	Drug Solubility × PEO Ratio	9.54E-03	2.49E-03	3.83	< 0.0001

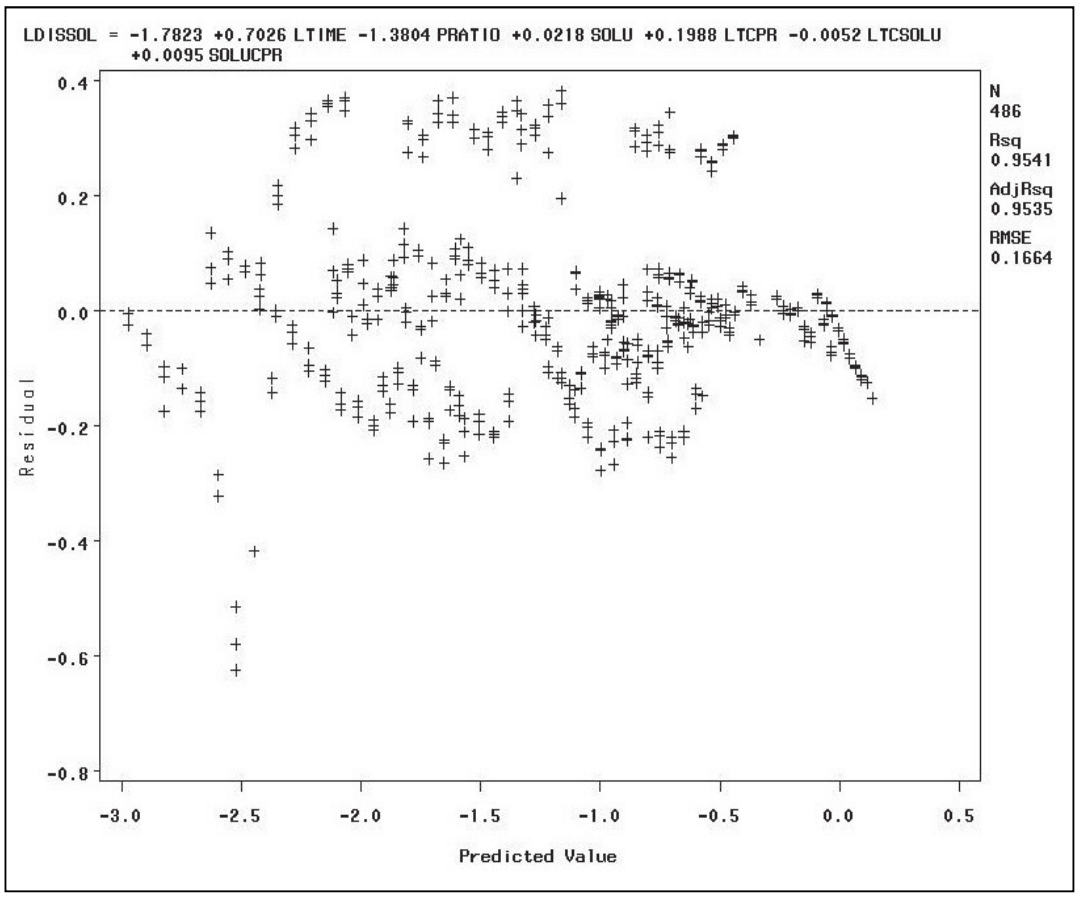


Figure 2.11. Residual plot of regression Model #3

To further improve the predictability of the regression model the quadratic (*Table 2.10*) of each of the three major variables, LTIME, PRATIO, and SOLU, were added to the model. The impact of the quadratics variable was evaluated in the following model:

$$\begin{aligned} \text{LDISSOL} = {} & \beta_0 + \beta_1 \times \text{LTIME} + \beta_2 \times \text{PRATIO} + \beta_3 \times \text{SOLU} + \beta_4 \times \text{LTCPR} \\ & + \beta_5 \times \text{LTCSOLU} + \beta_6 \times \text{SOLUCPR} + \beta_7 \times \text{SQLT} + \beta_8 \times \text{SQPRATIO} \\ & + \beta_9 \times \text{SQSOLU} \end{aligned}$$

Model #4 *(Equation 2.8)*

Table 2.10. Quadratic Variables for Regression Analysis

	Variable	Label
Quadratic	SQSOLU	Drug Solubility × Drug Solubility
	SQPRATIO	PEORatio × PEORatio
	SQLT	Log(Time) × Log(Time)

Regression statistics (*Table 2.11*) demonstrate incorporation of the quadratic variables into the model, R-square was improved from 0.9541 to 0.9831, more variability of the training data set was explained by Model #4. RMSE was also reduced to 0.1014 from 0.1664. Further improvement was obtained on the residual plot (*Figure 2.12*) too. *Figure 2.13* showed the plots of LDISSOL against predicted LDISSOL. Compared this model to Model #2 the LDISSOL against predicted LDISSOL plots of Model #4 were distributed closer to $Y = X$, which suggested a better or more accurate prediction from this model than the previous models.

On the residual plot of Model *#4*, there are several outliers, associated with the observation of the early stage of the dissolution process (0.5 hr). The cause for this might be due to the "burst dissolution event" at the beginning. This can also be confirmed by the residual plot (*Figure 2.14*) of the regression by fitting the model with the same training data set but excluding the observations at 0.5 hr. Removing observation at 0.5 hr eliminated these residuals as seen in the residual plot. The latter regression showed similar regression coefficients (*Table 2.12*). Although the latter approach demonstrated a better residual distribution around zero line than the previous one, there was no clear improvement on *Root SME* (0.1014 to 0.0932) and R^2 (0.9831 to 0.9806), and the latter regression lost 81 observations. Therefore, the regression coefficients of the Model #4 were selected to cover the entire training data set. Burst dissolution usually occurs at the beginning of the dissolution process of swellable matrix tablets because of the absence of a hydrogel layer. For the swellable matrix the hydrogel layer can act as a barrier to delay drug release [Peppas, 1987, Colombo et al., 2000]. On the other hand after a sufficient

Table 2.11. Summary statistics of Model #4

a) Analysis of Variance

Source	DF	Sum of Squares	Mean Square	*F*-value	Prob > *F*
Model	9	2.84E+02	3.15E+01	3067.62	< 0.0001
Error	476	4.89E+00	1.03E-02		
Total	485	2.89E+02			

b) Parameter Estimates

Variable	Label	Estimate	Std Error	*t*-value	Prob > | *t* |
Intercept	Intercept	-1.86E+00	3.08E-02	-60.37	< 0.0001
LTIME	Log(Time)	7.32E-01	1.72E-02	42.46	< 0.0001
PRATIO	PEO Ratio	-2.33E+00	1.97E-01	-11.80	< 0.0001
SOLU	Drug Solubility	5.74E-02	1.38E-03	41.69	< 0.0001
LTCPR	Log(Time) × PEO Ratio	1.99E-01	4.30E-02	4.62	< 0.0001
LTCSOLU	Log(Time) × Drug Solubility	-5.16E-03	2.36E-04	-21.83	< 0.0001
SOLUCPR	Drug Solubility × PEO Ratio	9.54E-03	1.52E-03	6.29	< 0.0001
SQLT	Square of Log(Time)	-2.54E-02	7.14E-03	-3.55	< 0.0001
SQPRATIO	Square of PEO Ratio	1.58E+00	3.15E-01	5.01	< 0.0001
SQSOLU	Square of Drug Solubility	-5.79E-04	2.10E-05	-27.87	< 0.0001

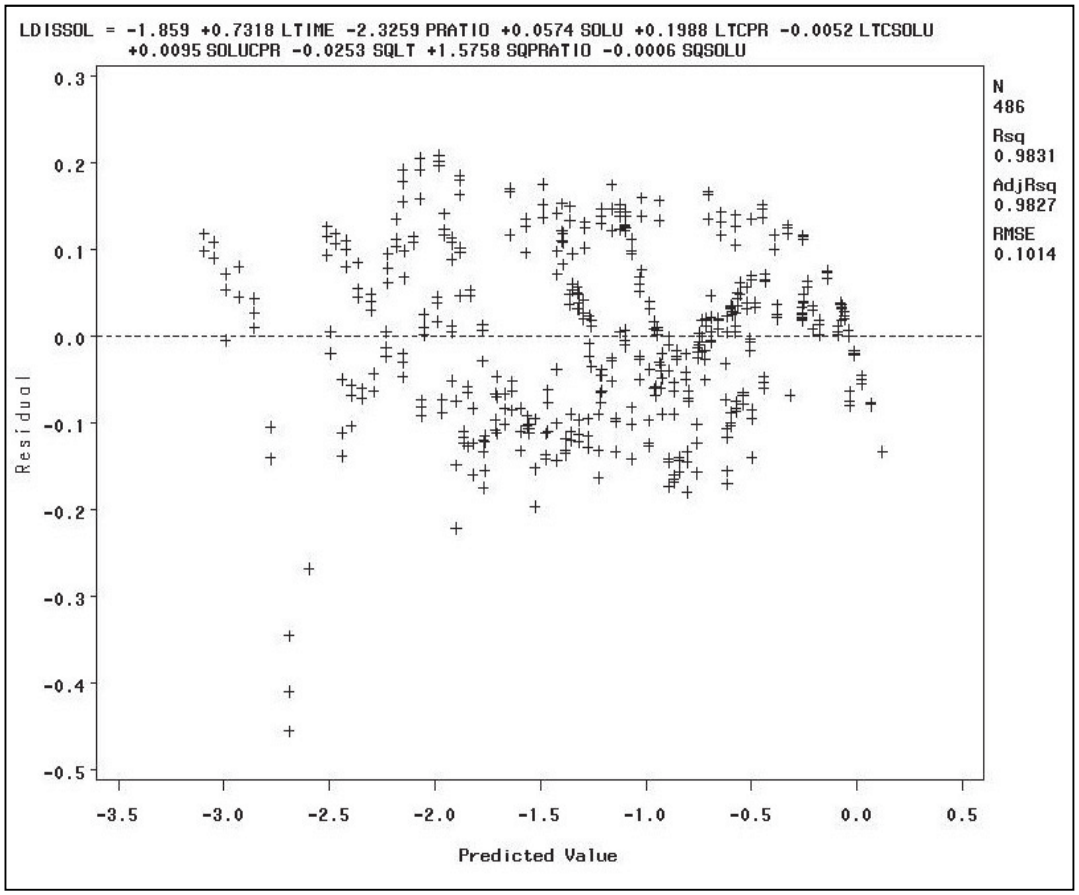


Figure 2.12. Residual plot of regression Model #4

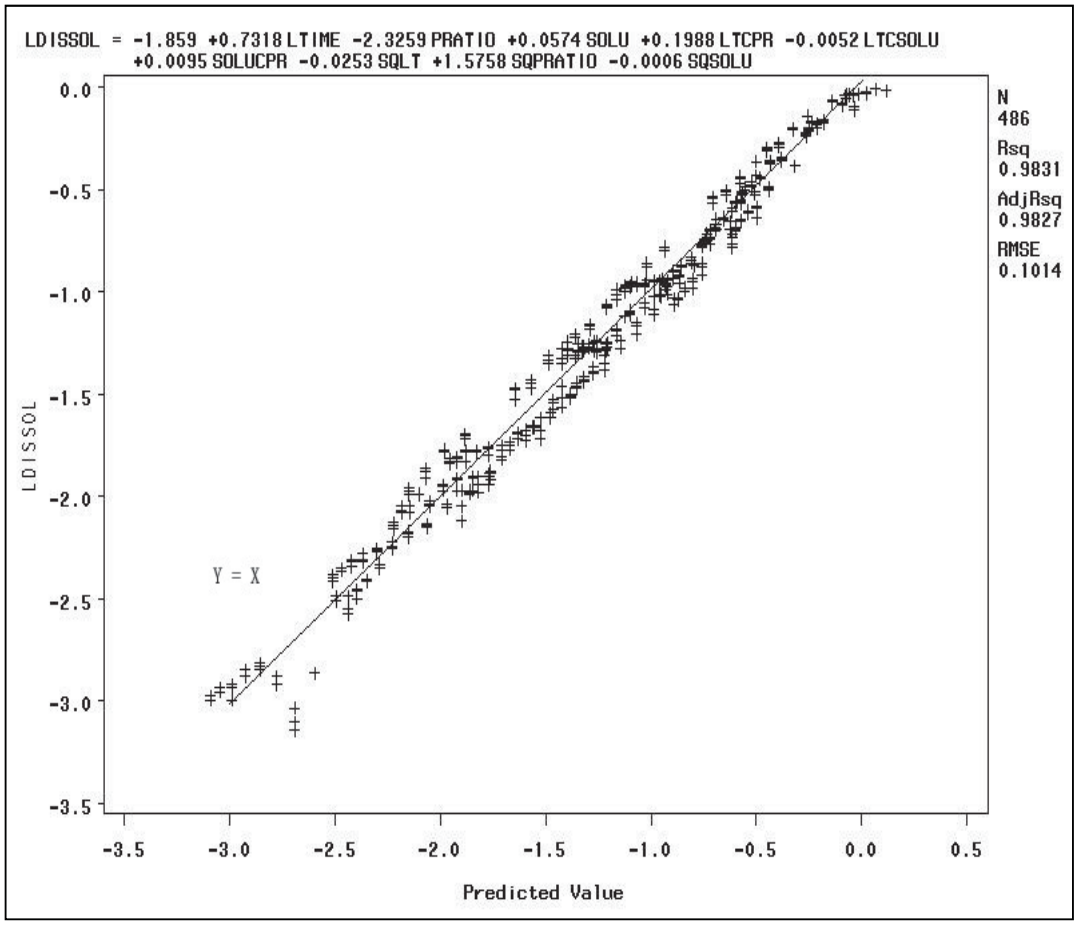


Figure 2.13. Plot of LDISSOL against predicted value from regression Model #4

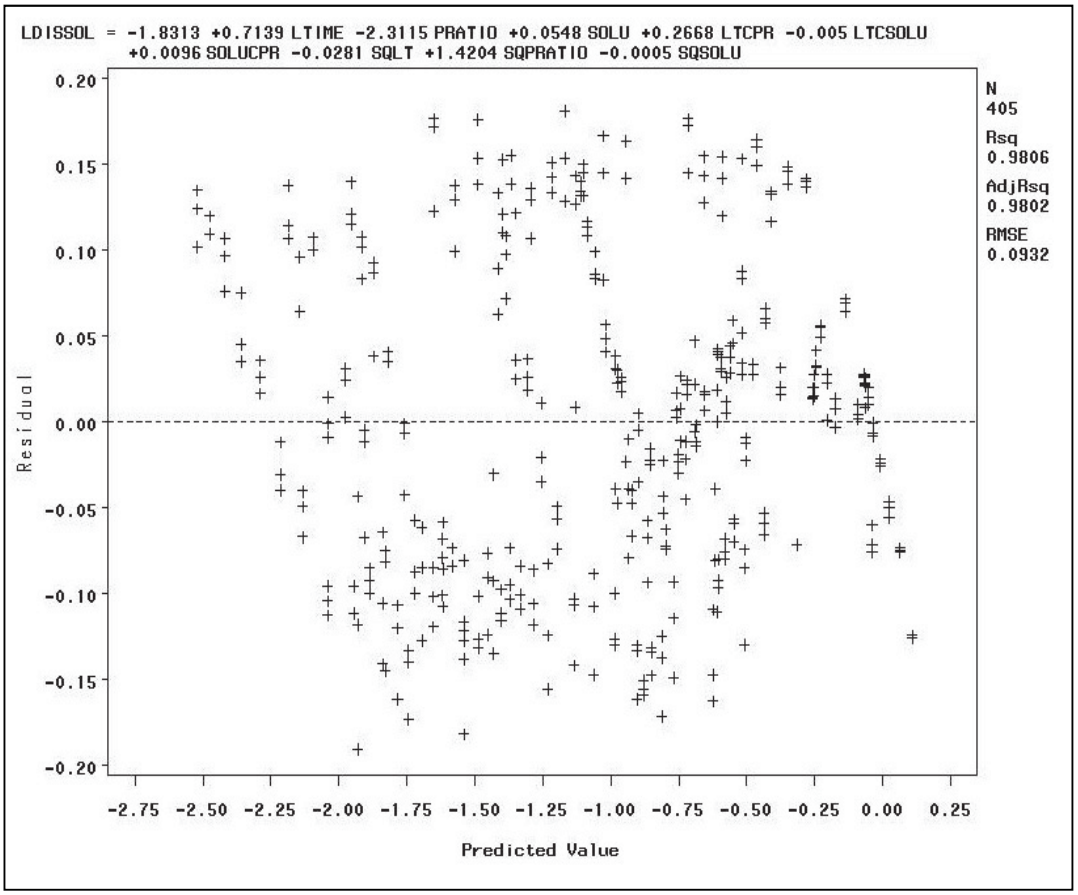


Figure 2.14. Residual plot of regression Model #4 excluding 0.5 hr observations

Table 2.12. Summary statistics of Model #4 on training set including and excluding 0.5 hr observations

Variable	Model #2 on Training Set Including 0.5 hr observations		Model #2 on Training Set Excluding 0.5 hr observations	
	Parameter Estimate	Standard Error	Parameter Estimate	Standard Error
Intercept	-1.86E+00	3.08E-02	-1.83E+00	3.44E-02
LTIME	7.32E-01	1.72E-02	7.14E-01	3.31E-02
PRATIO	-2.33E+00	1.97E-01	-2.31E+00	2.02E-01
SOLU	5.74E-02	1.38E-03	5.48E-02	1.40E-03
LTCPR	1.99E-01	4.30E-02	2.67E-01	5.51E-02
LTCSOLU	-5.16E-03	2.36E-04	-5.04E-03	3.03E-04
SOLUCPR	9.54E-03	1.52E-03	9.62E-03	1.58E-03
SQLT	-2.54E-02	7.14E-03	-2.81E-02	1.47E-02
SQPRATIO	1.58E+00	3.15E-01	1.42E+00	3.17E-01
SQSOLU	-5.79E-04	2.08E-05	-5.39E-04	2.09E-05

hydration time the gel layer on the outside of the tablet matrix will over-hydrate and slowly dissolve. Drug dissolution will behave slightly different compared to the main stage. That might explain the abnormal error variation at the high end of the residual plot.

From the statistical summary of models #2, #3, and #4, improvement of the fit on the data was observed with the additional parameters in the modeling. The significance of the improvement between the models was evaluated by *Equation 2.4* and summarized in *Table 2.13*. Results supported rejection of the null hypothesis. The models with more explanatory parameters would fit the data significantly better than models with fewer parameters. It was concluded that Model #4 provided the best fit and was hence selected as the final model for the training set data.

As a further validity check, the researcher fitted the model to the validation data set. The estimated regression coefficients, standard error, root MSE, and R^2 were compared to those from the training set data and summarized in *Table 2.14*. Good agreement between the two sets of estimated regression coefficient and two sets of regression coefficient standard error was observed. The Root MSE and R^2 were almost identical. These agreements suggested that the model was valid.

Table 2.13. Model comparison

Model Comparison	*F*	*DF*	**P > *F***
Model #3 *versus* Model #2	66.50	(3, 479)	0.0001
Model #4 *versus* Model #3	272.09	(3, 476)	0.0001

Table 2.14. Summary statistics of Model #4 on training and validation Data set

Variable	Model #4 on Training Set		Model #4 on Validation Set	
	Parameter Estimate	Standard Error	Parameter Estimate	Standard Error
Intercept	-1.86E+00	3.08E-02	-1.81E+00	3.01E-02
LTIME	7.32E-01	1.72E-02	7.42E-01	1.69E-02
PRATIO	-2.33E+00	1.97E-01	-2.26E+00	1.93E-01
SOLU	5.74E-02	1.38E-03	5.77E-02	1.35E-03
SQSOLU	-5.79E-04	2.08E-05	-5.92E-04	2.03E-05
SQPRATIO	1.58E+00	3.15E-01	1.47E+00	3.08E-01
SQLT	-2.54E-02	7.14E-03	-3.26E-02	6.98E-03
LTCPR	1.99E-01	4.30E-02	1.65E-01	4.21E-02
SOLUCPR	9.54E-03	1.52E-03	1.02E-02	1.48E-03
LTCSOLU	-5.16E-03	2.36E-04	-5.24E-03	2.31E-04
Root MSE	0.1014		0.0991	
R^2	0.983		0.983	

A final regression model was estimated using the entire data set, see *Table 2.15* and *Equation 2.9*:

$$\begin{aligned} LDISSOL = {} & -1.8351 + 0.7370\times LTIME - 2.292\times PRATIO + 0.05756\times SOLU \\ & + 0.1821\times LTCPR - 0.005200\times LTCSOLU + 0.009850\times SOLUCPR \\ & - 0.02898\times SQLT + 1.525\times SQPRATIO - 0.0005855\times SQSOLU \end{aligned}$$

(*Equation 2.9*)

For a given swellable PEO matrix tablet in which the tablet composition (PEO Ratio) and active drug solubility information are available, LDD may be estimated using the above equation. And the LDD could then be back transformed to provide corresponding drug dissolution value.

To verify the model on a different active drug in the PEO swellable matrix, the drug dissolution of a chlorpheniramine (CHL) swellable formulation at 0.5, 1, 1.5, 2, 4, and 6 hr was estimated based on *Equation 2.9*, and the composition of the formulation. The CHL formulation contains 30% of the PEO polymer, the aqueous solubility of CHL was measured at 11.8 ± 0.5 g/100ml in our lab. The estimated results were compared to the observed dissolution results (*Table 2.16*) from the dissolution test and plotted in *Figure 2.15*. Close simulation was observed from the plot. It suggested that the developed modeling was adaptable to CHL swellable tablets too.

Table 2.15. Summary of statistics of regression Model #4 on entire data set

a) Analysis of Variance

Source	DF	Sum of Squares	Mean Square	*F*-value	Prob > *F*
Model	9	5.59E+02	6.21E+01	5914.44	< 0.0001
Error	962	1.01E+01	1.05E-02		
Total	971	5.69E+02			

b) Parameter Estimates

Variable	Label	Estimate	Std Error	*t*-value	Prob > $\lvert t \rvert$
Intercept	Intercept	-1.84E+00	2.20E-02	-83.42	< 0.0001
LTIME	Log(Time)	7.37E-01	1.23E-02	59.86	< 0.0001
PRATIO	PEO Ratio	-2.29E+00	1.41E-01	-16.28	< 0.0001
SOLU	Drug Solubility	5.76E-02	9.84E-04	58.49	< 0.0001
LTCPR	Log(Time) × PEO Ratio	1.82E-01	3.07E-02	5.93	< 0.0001
LTCSOLU	Log(Time) × Drug Solubility	-5.20E-03	1.69E-04	-30.82	< 0.0001
SOLUCPR	Drug Solubility × PEO Ratio	9.85E-03	1.08E-03	9.09	< 0.0001
SQLT	Square of Log(Time)	-2.90E-02	5.10E-03	-5.68	< 0.0001
SQPRATIO	Square of PEO Ratio	1.53E+00	2.25E-01	6.79	< 0.0001
SQSOLU	Square of Drug Solubility	-5.86E-04	1.48E-05	-39.49	< 0.0001

Table 2.16. Estimated and observed drug dissolution of CHL matrix tablet containing 30% PEO

Time (hr)	Estimated Drug Dissolution	Observed Drug Dissolution
0.5	0.103	0.115
1.0	0.173	0.145
1.5	0.232	0.210
2.0	0.283	0.275
4.0	0.451	0.410
6.0	0.584	0.540

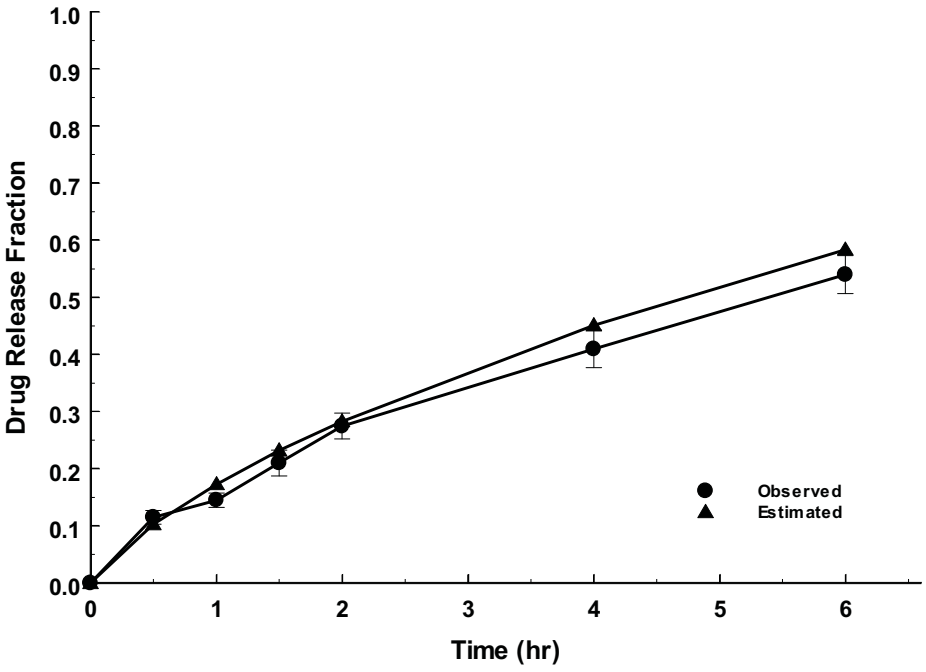


Figure 2.15. Estimated and observed drug dissolution-time Plots of CHL matrix tablet containing 30% PEO (Observed value is the mean of 6 measurements)

The same methodology described above was used for the matrix swelling study during the dissolution process. Satisfactory fit was found for a multiple regression model with gel layer thickness (GELTHICK) as response variable and dissolution time (TIME), PEO Ratio (PRATIO), Drug Solubility (SOLU), and their cross-products (TCPR, TCSOLU, SOLUCPR) and quadratics (SQT SQPRATIO SQSOLU) as independent variables (*Table 2.17*). All variables showed significant impact on GELTHICK. The residual plot demonstrated a random distribution of residuals (*Figure 2.16*), which suggests an appropriate modeling. And the model provided satisfactory prediction of the data set as demonstrated in *Figure 2.17,* which is the plots of experimental GELTHICK and predicted GELTHICK by the model. The plots were distributed closely to the $Y = x$. Impacts of TIME, PRATIO, and SOLU on the gel layer thickness of the matrix can be explained by the following regression model:

$$\begin{aligned}GELTHICK = {} & -0.8015 + 0.7133\times TIME + 2.817\times PRATIO + 0.09780\times SOLU + \\ & 0.4863\times TCPR - 0.005170\times TCSOLU - 0.05317\times SOLUCPR - 0.05432\times SQT + \\ & 2.075\times SQPRATIO - 0.001090\times SQSOLU\end{aligned}$$

Model #5 *(Equation 2.10)*

Table 2.17. Summary of statistics of regression Model #5

a) Analysis of Variance

Source	DF	Sum of Squares	Mean Square	*F*-value	Prob > *F*
Model	9	2.24E+03	2.49E+02	3563.50	< 0.0001
Error	962	6.66E+01	6.92E-02		
Total	971	2.31E+03			

b) Parameter Estimates

Variable	Label	Estimate	Std Error	*t*-value	Prob > | *t* |
Intercept	Intercept	-8.02E-01	6.47E-02	-12.38	< 0.0001
TIME	Time	7.13E-01	2.35E-02	30.37	< 0.0001
PRATIO	PEO Ratio	2.82E+00	3.69E-01	7.64	< 0.0001
SOLU	Drug Solubility	9.78E-02	2.56E-03	38.24	< 0.0001
TCPR	Time × PEO Ratio	4.86E-01	3.41E-02	14.24	< 0.0001
TCSOLU	Time × Drug Solubility	5.17E-03	1.88E-04	27.56	< 0.0001
SOLUCPR	Drug Solubility × PEO Ratio	-5.32E-02	2.78E-03	-19.11	< 0.0001
SQT	Square of Time	-5.43E-02	3.09E-03	-17.59	< 0.0001
SQPRATIO	Square of PEO Ratio	2.07E+00	5.77E-01	3.59	< 0.0003
SQDS	Square of Drug Solubility	-1.09E-03	3.81E-05	-28.74	< 0.0001

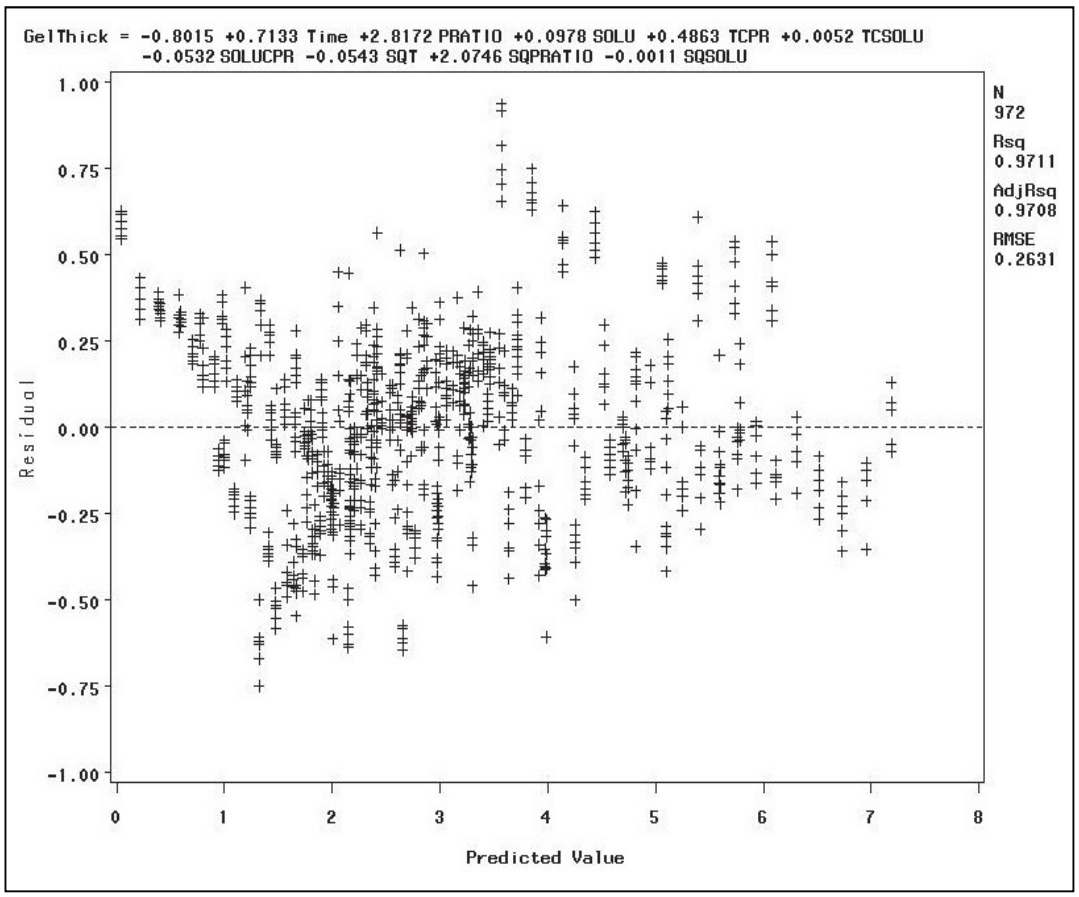


Figure 2.16. Residual plot of regression Model #5

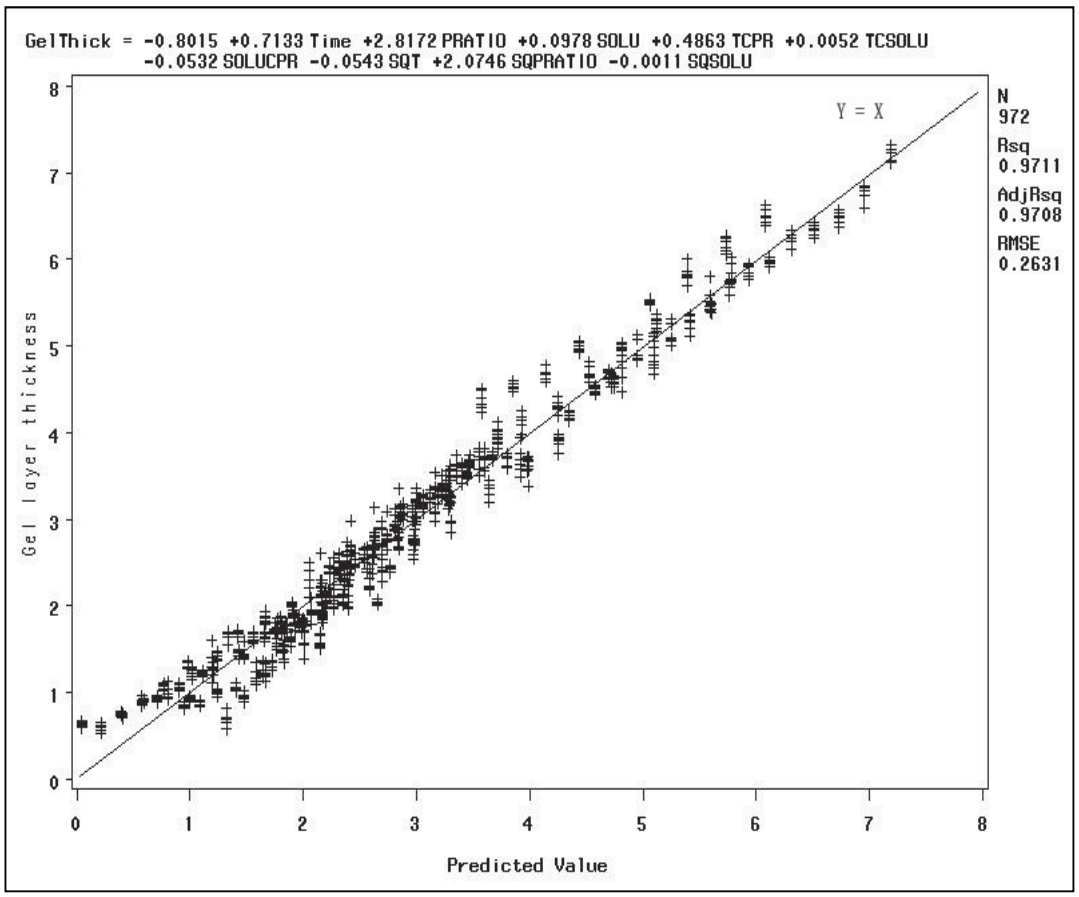


Figure 2.17. Plot of Hydro Gel Thickness versus predicted value from Model #5

But when AUC_{TA}, as a dependent variable, was incorporated into fitting a similarly multiple regression model, no appropriate fit was found. The AUC_{TA} was a measurement that stands for the area under the curve "*force vs. probe travel distance curve" (Figure 2.1)* from TA Texture analysis. It takes into account both the probe force and the probe travel distance. A linear regression model cannot accurately describe the relationship between AUC_{TA} and dissolution time, PEO Ratio, Drug Solubility.

Both drug solubility and polymer hydration play important roles in drug diffusion and dissolution from a modified release matrix tablet. These two parameters are closely related to each other and contribute to drug release modification. High drug solubility facilitates faster water penetration into the polymer matrix and diffusion of soluble drug molecules across the hydrogel layer. Polymer hydration enables swelling of the hydrophilic PEO, subsequently leading to more water penetration and drug dissolution. Using three test compounds that possess a wide range of aqueous solubility, this study obtained satisfactory results demonstrating that the models provided a practical and simple approach for formulation design and optimization.

Since the models were built based on specific PEO matrix with certain excipients (PVP, SMC), it may be possible that deviation from the model would occur for some matrix containing different excipients, especially for those excipients with completely different aqueous solubility compared to PVP or SMC. Drug dissolution or polymer hydration could be modified by those excipients. When different excipients were to be used, test on the solubility of the excipients is recommended to be performed before the modeling approach could be applied. In addition, polymer swelling test in this study was

conducted under a specific protocol, i.e., the tablet contacted with water and swelled from a single dimension. This deviated from the actual tablet swelling process during drug dissolution test. The model for the PEO swelling behaviour in this study would only be applicable to estimation of a single-dimension tablet swelling. This methodology should be further expanded to test matrix formulations of other hydrophilic polymers, so that its applicability in expediting development routines could be realized with accuracy and reliability.

There are numerous methods available for the determination of polymer hydration and swelling from modified release matrix tablets. Each method employs variable criteria and collects different parameters. Texture analysis appears to be an inexpensive and straightforward instrumentation that has demonstrated unique applicability in pharmaceutical development and assessment. In comparison to other sophisticated instruments utilized in polymer characterization, this method is considered to be more adaptable and acceptable to formulation optimization due to its operation simplicity and versatility. It would provide additional and beneficial tools to formulators in designing and optimizing novel modified release tablet preparations.

2.4. Conclusion

Texture analysis is a new and simple methodology added to the pharmaceutical research and development; under a simple protocol, as demonstrated in this study, the dynamical swelling behaviors of the polymer in the swellable polymer tablets can be

monitored during the dissolution process. The multiple regression model presented (with gel layer as dependent variable and polymer ratio, dissolution time, and drug solubility as independent variables) provided a clear understanding of the continuous texture change of the polymer during the dissolution process and the effects from the formulation composition. This study demonstrated a unique and versatile aspect of texture analysis for pharmaceutical applications.

Drug dissolution from modified release PEO matrix tablets is controlled by two mechanisms: drug diffusion through the gel layer and drug release along polymer erosion. Multiple factors can affect the drug diffusion and polymer erosion and further modify the final drug dissolution profiles. It is impossible to have a model to cover all the factors and describe exactly the drug dissolution process for this tablet. Delayed drug release from PEO swellable tablets was mainly attributed to the rate and degree of hydrogel formation on the surface of the tablet and of water penetration into the matrix core. Polymer ratio and drug solubility contribute the major effects on both the hydrogel formation and water penetration. The model developed in this study is an empirical model based on model drugs PSE, IBU, and ACE, which describes the relationship between the drug dissolution and major formulation factors (polymer ration and drug solubility) by a multiple regression modeling. It was further verified against the drug dissolution data from a chlorpheniramine formulation, showing good agreements. Using the empirical model, drug dissolution from modified release PEO matrix tablets can be reliably estimated. It is beneficial to the formulation scientist on the new formulation design.

Chapter 3

Modeling of Drug Dissolution and Matrix Swelling from Hydroxypropyl Methylcellulose (HPMC) Matrix

3.1. Introduction

Hydroxypropyl methylcellulose (HPMC) is another hydrophilic polymer that is commonly utilized to formulate modified release swellable matrix delivery systems. The use of HPMC in pharmaceutical preparations dates back to the early 1960s, and this polymer has become one of the most versatile and inexpensive excipients for pharmaceutical purposes [Pham and Lee, 1994]. Physically, HPMC possesses satisfactory compressibility and swelling properties, and hydrogels formed by HPMC display high viscosity and stability capable of regulating water permeation into the dosage and prolonging drug release from the matrix. Chemically, HPMC is non-toxic, biocompatible, and tolerant to high drug loading [Tahara et al., 1995, Rodriguez et al., 2000]. Numerous studies have investigated mechanisms of drug release from various HPMC matrices. Mathematical models were also established to quantitatively simulate drug dissolution kinetics [Colombo et al., 1999, Siepmann et al., 1999, Grassi et al. 2000, Siepmann et al., 2002, Kiil and Dam-Johansen, 2003, Borgquist et al. 2006]. These mathematical simulations are able to model drug diffusion, polymer hydration, and matrix erosion, by establishing and involving advanced mathematical parameters and expressions. However, the models might not be practical or applicable to routine formulation development and optimization, since simplicity and easy utility are appropriate traits for those working in pharmaceutics and formulation.

In Chapter 2, several models were established and validated for matrix tablets made of hydrophilic polymer PEO. These models described either the relationship between the drug dissolution and polymer ratio, drug solubility; or the relationship

between gel layer thickness and polymer ratio, drug solubility during the dissolution process. The models facilitate prediction of drug dissolution based on primary formulation factors such as polymer proportion used in the preparation and aqueous solubility of the active ingredient, and optimization of drug release could then be performed with reliable simulation over the course of formulation. This modeling approach provided a simple tool to routine pharmaceutical development and demonstrated high applicability as well as scientific benefits for PEO matrix design.

In this study, the adaptability and suitability of such regression modeling approach were further evaluated using HPMC matrices. For the purpose, a series of modified release matrix tablets were prepared by using the same active ingredients (e.g., PSE, IBU and ACE) and identical proportions of HPMC in the formulation. Similar experimental protocols were then applied to test drug dissolution and polymer hydration. The data obtained was then analyzed by multiple regression as described for PEO matrix tablets in Chapter 2.

3.2. Materials and Methods

3.2.1. Materials

Acetaminophen USP (ACE): Medisca Pharmaceutique Inc., Montreal, QC, Canada

Acetonitrile (HPLC Grade): Fisher Scientific, Fair Lawn, NJ, USA

Compritol® 888ATO (GB, glyceryl behenate NF): Gattefossé s.a., Lyon, France

Glacial Acetic Acid (Analytical Grade): Fisher Scientific, Fair Lawn, NJ, USA

Hydrochloric Acid (Analytical Grade): Fisher Scientific, Fair Lawn, NJ, USA

Ibuprofen (IBU): Sigma Chemical Co., St. Louis, MO, USA

Methanol (HPLC Grade): Fisher Scientific, Fair Lawn, NJ, USA

Methocel® K100M (HPMC, hydroxypropyl methylcellulose): Union Carbride Corporation, Danbury, CT, USA

Prosolv® HD90 (MC, silicified microcrystalline cellulose): The Dow Chemical Company, Midland, MI, USA

Pseudoephedrine Hydrochloride USP (PSE): Medisca Pharmaceutique Inc., Montreal, QC, Canada

PVP K30 USP (polyvinylpyrrolidone): Spectrum Chemical Manufacturing Corp., Gardena, CA, USA

Sodium Acetate Trihydrate (Analytical Grade): Fisher Scientific, Fair Lawn, NJ, USA

Sodium Perchlorate (Analytical Grade): Fisher Scientific, Fair Lawn, NJ, USA

3.2.2. Instruments/Software

Denver Instrument PI-114 Analytical Balance (Bohemia, NY, USA)

Waters® High Performance Liquid Chromatograph System (Milford, MA, USA)

VenKel® 600 Dissolution Apparatus (Palo Alto, CA, USA)

Manesty® Single-punch Tablet Press (Liverpool, UK)

Erweka® Tablet Hardness Tester (Düsseldorf, Germany)

TA. XT. plus Texture Analyzer (Scardale, NY, USA)

SAS statistical application Version 9.1 (SAS Institute Inc., Cary, NC)

3.2.3. Tableting

Fifteen test tablet formulas were designed and prepared according to *Table 3.1*. The proportion of each active ingredient was kept identical at 40% of the total tablet weight in all formulas, while HPMC ratio varied between 10% and 50%, with a 10% increment among the five tablet preparations for each active ingredient. Compritol® 888 ATO (3%) was incorporated as a tablet lubricant, and PVP K30 (5%) was embedded to increase the tablet strength. In order to produce a consistent tablet weight of 300 mg, Prosolv® HD90 (MC) was added to the tablet matrix as a filler; MC also enhanced the flowability and compressibility of the mixture for desirable tablet compression.

Table 3. 1. Compositions of modified release HPMC formulations

Components	F1	F2	F3	F4	F5
Study Drug *	120	120	120	120	120
HPMC	30	60	90	120	150
GB	9	9	9	9	9
PVP	15	15	15	15	15
MC	126	96	66	36	6
Weight (mg)	300	300	300	300	300
HPMC Ratio (%)	10	20	30	40	50

* ACE, IBU or PSE

The HPMC matrix tablets (approximately 100 tablets for each formulation batch) were prepared by direct compression using a Manesty® Single-Punch Tablet Press. A set of 7/16 punches and die was utilized for the tableting, and the compression force was maintained consistently at 50 kg/cm^2 for all 15 tablet formulations. The hardness of the tablets prepared was monitored during tableting, using an Erweka® Tablet Hardness Tester. The tablet hardness was remained within the range of 9.0-12.0 kg for all tablet batches.

3.2.4. Drug Dissolution

Dissolution of the prepared HPMC matrix tablets was evaluated using a USP Apparatus II Method. The dissolution medium was 900 ml of deionized water, the temperature of the apparatus was maintained at 37.5 °C, and the paddle speed was set at 50 rpm. Dissolution samples were collected at 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours, respectively. Six replicates were tested for each preparation of the 15 formulas.

Concentrations of ACE, IBU, and PSE in the collected dissolution samples were analyzed using the official USP chromatographic assays [USP 24/NF 19, 2000]. A Waters® HPLC system comprised of a 600S Controller, a 616 Solvent Delivery Pump, a 717 Autosampler, a 996 Photodiode Array Detector, and a C_{18} Nova-Pak® column (4 μm, 3.9 mm × 150 mm) was utilized. Prior to drug analysis, the samples were filtered through a 0.2 μm filter membrane and diluted to appropriate concentration within the established range of the calibration curves. The detection limit was 10 ng for all test analytes, and the

linear calibration range of the assays ranged between 50-1000 ng. No interference was found from other tablet excipients or additives with these assay methods.

3.2.5. Polymer Swelling Testing

Polymeric hydration and swelling characterization from the prepared HPMC matrix were measured using a TA Texture Analyzer as previously reported [Yang et al., 1998, Li and Gu, 2007]. The instrument was equipped with a flat-end, round cylindrical stainless steel probe (∅2 × L30 mm) to measure the distance with which the probe traveled within the hydrogel formed from HPMC hydration. The probe traveled initially at a speed of 2.0 mm/s into the hydrogel layer until a force of 0.7 g was sensed by the probe on the surface of the tablet, at which point it reduced the penetrating speed to 0.2 mm/s. Once the probe detected a force of 500 g upon the un-swollen, solid matrix core, the probe would then withdraw automatically out of the hydrogel layer, at a speed of 0.2 mm/s. All testing data were collected and processed by Texture Expert software.

To prepare samples for texture analysis, each matrix tablet was inserted into a cylindrical polyethylene cap that had an internal diameter equivalent to that of the tablets. Samples prepared in this matter would allow for water penetration and polymer hydration only in one direction, subsequently facilitating standardization of the texture analysis. The tablet samples were then placed in 900 ml of deionized water, and subjected to the same dissolution conditions as previously described. Samples were collected at 0.5, 1, 1.5, 2, 4, 6 and 8 h for texture analysis. Six replicates were tested for each time interval.

3.2.6. Data Analysis

The empirical Peppas-Ritger dissolution equation (*Equation 2.1*) was used to characterize drug release from the prepared HPMC tablets. Diffusional exponent (*n*), release rate constant (*k*) were calculated according to equation, and the results were compared among the 15 preparations [Ritger and Peppas, 1987a & 1987b]. Based on the equation a diffusional exponent (n) value < 0.45 suggests a Fickian release, and 0.45 < n < 0.89 suggests a non-Fickian release. The time required for 50% of the drug dose to be released ($DT_{50\%}$) was also estimated according to the collected drug dissolution results and the Peppas-Ritger equation.

Regression models were developed and tested in Chapter 2 for matrix tablets made of hydrophilic polymer PEO. The developed models described the relationship between drug dissolution and several primary formulation factors from PEO matrix tablets, which demonstrated highly practical benefit and applicable relevance to design and optimization of modified release preparations. As a substitute polymer in swellable matrix preparations, HPMC was further assessed using a similar protocol to determine whether or not the established methodology would still be applicable to a different matrix polymer. These confirmatory experiments were also intended for refining and improving data analysis using multiple regression, because it was observed from previous study that there were various mathematical interpretations that could be employed to prescribe drug dissolution from PEO tablet preparations. If similar patterns of regression were valid in both HPMC and PEO matrix preparations, the same methodology could become potentially adaptable to other hydrophilic pharmaceutical polymers, which would

certainly simplify formulation development and assessment of modified release tablet preparations.

Similar to the developed model for PEO matrix tablets, multiple regression (*Equation 3.1*) was used to model the drug dissolution from HPMC tablets. A backward elimination method was employed to check and optimize the model. The significance of all independent variables (Table 3.2) in the model was evaluated with a significance criterion $P < 0.05$. The most Non-significant variable was eliminated first from the model and the modified model was re-evaluated till all the variables showed to be significant. Residual analysis was also employed to evaluate the model fit.

$$\text{LDISSOL} = \beta_0 + \beta_1 \times \text{LTIME} + \beta_2 \times \text{HRATIO} + \beta_3 \times \text{SOLU} + \beta_4 \times \text{LTCHR} - \beta_5 \times \text{LTCSOLU} + \beta_6 \times \text{SOLUCHR} + \beta_7 \times \text{SQLT} + \beta_8 \times \text{SQHRATIO} + \beta_9 \times \text{SQSOLU} \quad \textit{(Equation 3.1)}$$

The previous study for PEO matrix has demonstrated a multiple regression model for describing the relationship of Gel layer thickness (GELTHICK) and polymer ratio, drug solubility, and dissolution time (Chapter 2). In this study the similar model *(Equation 3.2)* was analyzed on the HPMC matrix. The adaptability of the model from PEO matrix table was evaluated too.

$$\text{GELTHICK} = \beta_0 + \beta_1 \times \text{TIME} + \beta_2 \times \text{HRATIO} + \beta_3 \times \text{SOLU} + \beta_4 \times \text{TCHR} + \beta_5 \times \text{TCSOLU} + \beta_6 \times \text{SOLUCHR} + \beta_7 \times \text{SQT} + \beta_8 \times \text{SQHRATIO} + \beta_9 \times \text{SQSOLU} \quad \textit{(Equation 3.2)}$$

Table 3. 2. Variables for Regression Analysis

	Variable	Label
Dependent Variable	LDISSOL	Log(Drug Dissolution)
Independent Variable	LTIME	Log(Time)
	HRATIO	HPMC Ratio
	SOLU	Drug Solubility
	LTCSOLU	Log(Time) × Drug Solubility
	LTCHR	Log(Time) × HPMC Ratio
	SOLUCHR	Drug Solubility × HPMC Ratio
	SQSOLU	Drug Solubility × Drug Solubility
	SQHRATIO	HPMC Ratio × HPMC Ratio
	SQLT	Log(Time) × Log(Time)

3.3. Results and Discussion

As one of the most commonly-used hydrophilic polymers in pharmaceutical preparations, HPMC offers desirable characteristics of polymeric hydration and gelation that are critical to modified drug release. Upon in contact with a liquid, HPMC hydrates quickly to form a protective hydrogel layer surrounding the matrix, subsequently preventing the tablet from immediate disintegration and regulating water penetration and drug dissolution. As a result, prolonged drug dissolution with steady drug release rate and matrix erosion is achieved.

Results of polymer hydration from texture analysis indicated that increase in HPMC proportion in tablet matrix led to increase in hydrogel thickness, which subsequently suppressed drug release rate from the preparation. This pattern was similar to what had been observed in PEO matrix, and was primarily attributed to a prolonged diffusion of the drug molecules across the hydrogel layer of HPMC. *Figure 3.1* shows the hydrogel thickness-time plots of HPMC matrix that contained ACE and a varied proportion (10% – 50%) of HPMC. The hydration degree of HPMC matrix was much faster in the first 30 minutes than that of later stages of swelling process, which could be explained by a faster water penetration at the initial dissolution stage. After the gel layer had formed around the matrix core, water penetration into the tablet was regulated. Although the gel layer continuously grew with the water penetration, the growth of gel layer became relatively slow and steady. Figure 3.2 demonstrate the drug dissolution profiles of 5 ACE formulations containing various proportions of HPMC. Drug dissolution decreased with increase in HPMC usage. After 12 hours of dissolution

approximately 63% of ACE was released from tablet containing 10% HPMC while about 48% of ACE was release from tablet containing 50% HPMC.

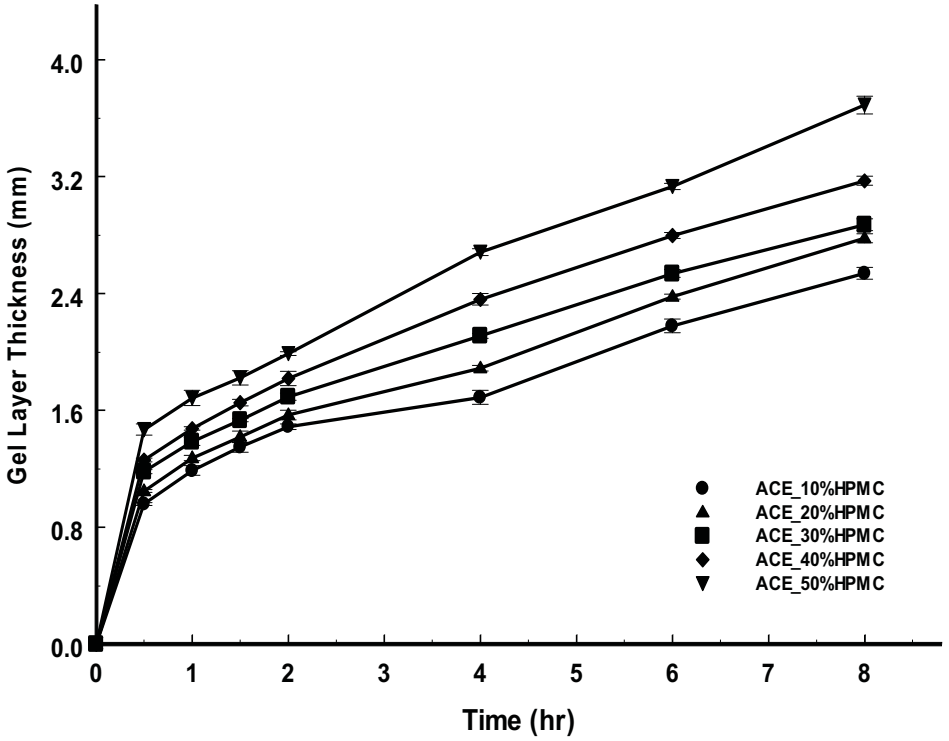


Figure 3.1. Hydrogel thickness-time plots of ACE-HPMC matrix tablets (Mean ± SE, n=6).

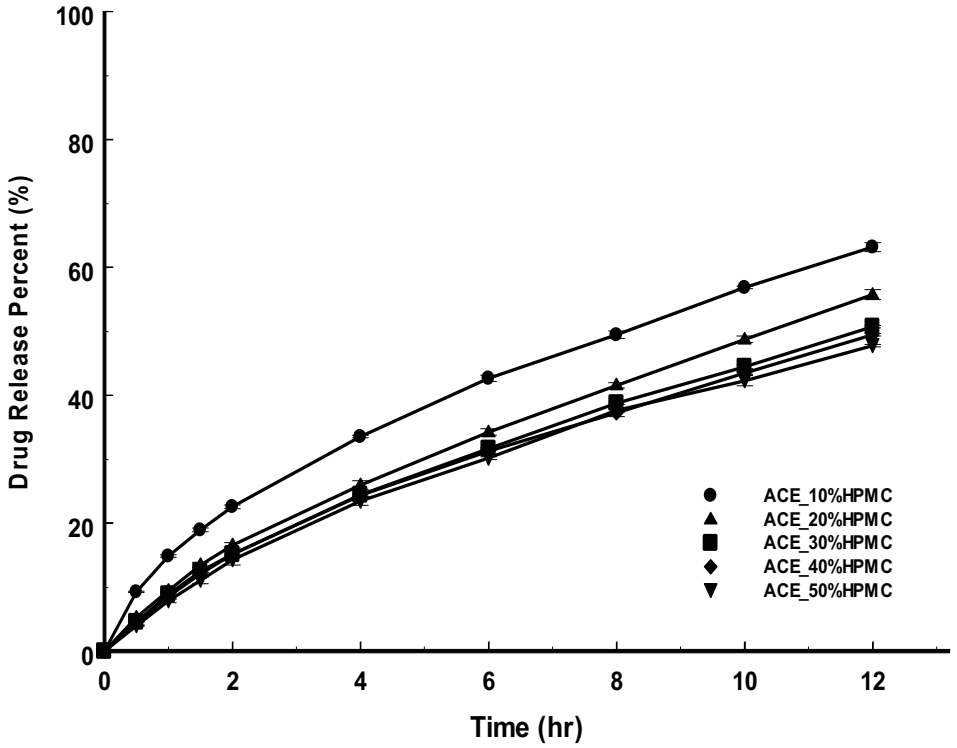


Figure 3.2. Drug dissolution-time plots of ACE-HPMC matrix tablets (Mean ± SE, n=6)

Similar dissolution patterns were observed on IBU and PSE tablets (Figure 3.3 - 3.6). For all three model compounds increasing HPMC amount in the formulation led to a thicker hydrogel layer surrounding the tablet matrix and subsequently slower drug dissolution. Compared to matrix tablets made of PEO, hydration of HPMC in the tablets was larger than that of PEO, indicating some differences in matrix hydration and erosion between the two polymers. HPMC and PEO are water-soluble polymers; both polymers will hydrate and generate hydrogel layer once in contact with water. However, they demonstrate different viscosities, which might attribute to variable strength and dissolving characters of the gel layer formed. The viscosity of an HPMC solution (2%) ranges between 80,000-120,000 cP while that of a PEO solution (1%) is only 1,650-5,500 cP [www.dow.com]. As a result, HPMC matrix would theoretically erode at a slower rate than PEO matrix. *Table 3.3* lists the comparative data in hydrogel thickness between HPMC and PEO preparations. It was observed that HPMC demonstrated a larger hydrogel layer than PEO at both beginning and later stages when IBU was incorporated in the tablet matrix, which demonstrated that the HPMC matrix hydrated faster and eroded relatively slower than PEO matrix. When the active ingredient was changed to ACE or PSE, the HPMC matrix did not show a bigger gel layer than PEO matrix throughout the dissolution process. This could be due to the extreme aqueous solubility of the two ingredients: ACE is slightly soluble (1.9 g/100mL) and PSE is very soluble (56.5 g/100mL).

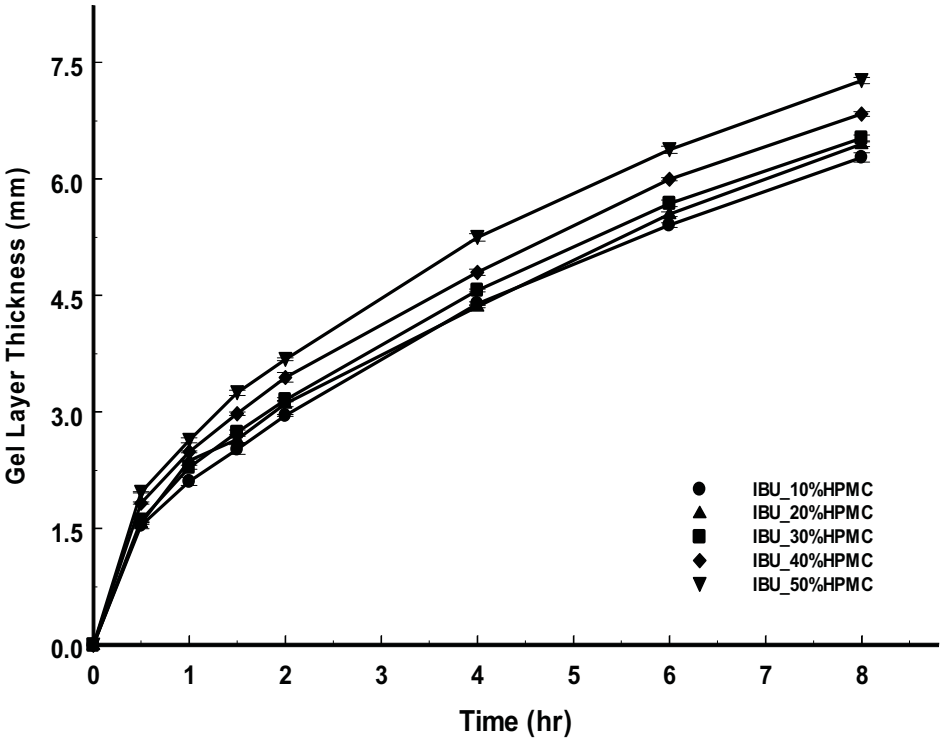


Figure 3.3. Hydrogel thickness-time plots of IBU-HPMC matrix tablets (Mean ± SE, n=6)

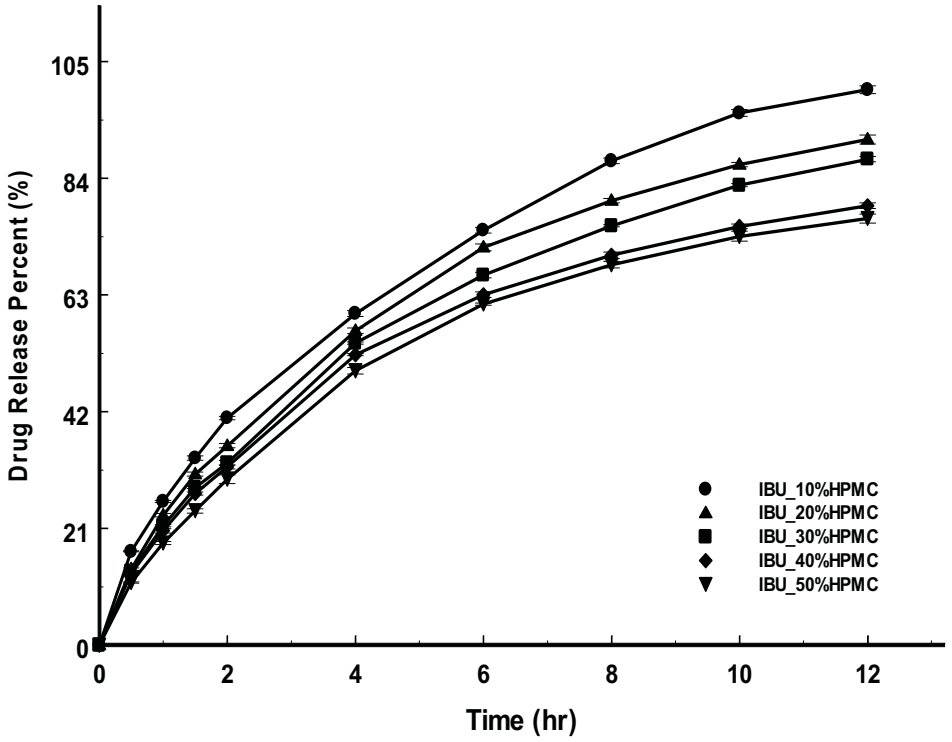


Figure 3.4. Drug dissolution-time plots of IBU-HPMC matrix tablets (Mean ± SE, n=6)

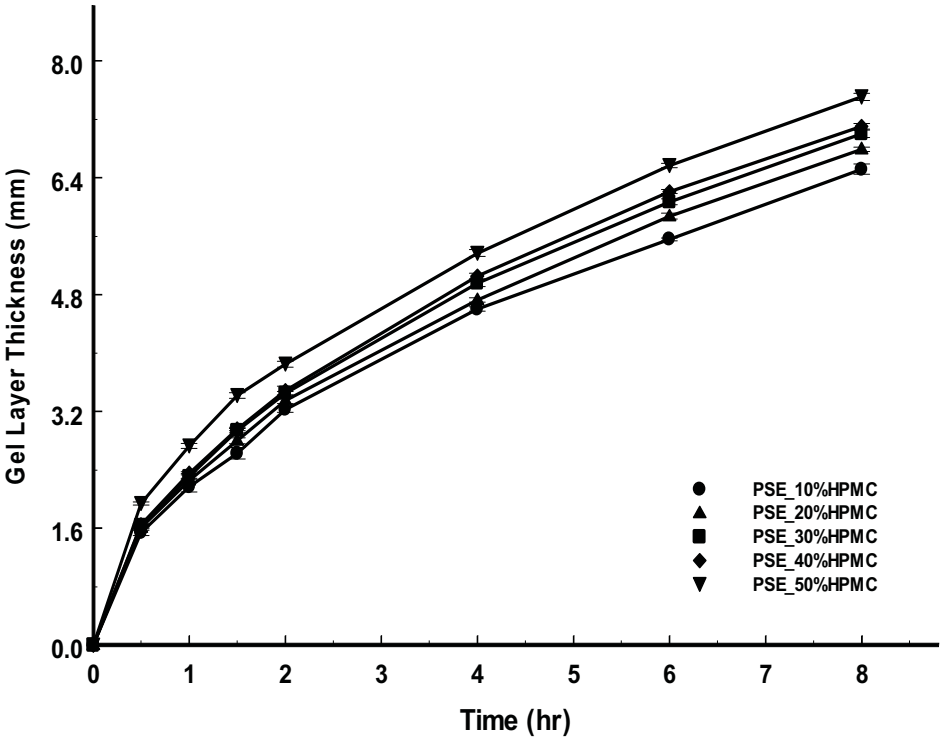


Figure 3.5. Hydrogel thickness-time plots of IBU-HPMC matrix tablets (Mean ± SE, n=6)

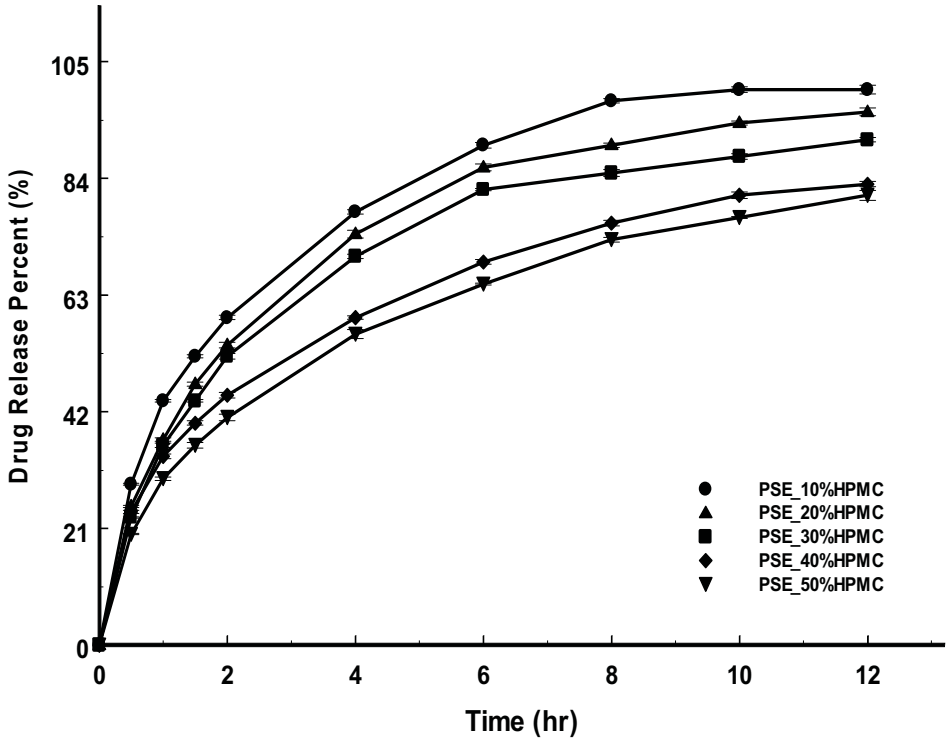


Figure 3.6. Drug dissolution-time plots of PSE-HPMC matrix tablets (Mean ± SE, n=6)

Table 3.3. Comparison of hydrogel thickness between PEO and HPMC formulations

Polymer	Hydrogel Thickness (mm)					
	ACE Tablets		IBU Tablets		PSE Tablets	
	0.5 hr	6 hr	0.5 hr	6 hr	0.5 hr	6 hr
10% PEO	0.63	2.07	1.09	3.50	1.71	5.45
10% HPMC	0.96	2.18	1.54	5.40	1.54	5.56
20% PEO	0.73	2.76	1.21	3.84	1.74	5.87
20% HPMC	1.05	2.38	1.57	5.55	1.61	5.88
30% PEO	0.99	3.33	1.32	4.09	1.79	6.24
30% HPMC	1.18	2.54	1.61	5.69	1.64	6.07
40% PEO	1.41	4.19	1.45	4.56	1.93	6.48
40% HPMC	1.26	2.8	1.83	6.00	1.65	6.21
50% PEO	1.32	4.76	1.55	5.47	2.01	7.20
50% HPMC	1.47	3.30	1.97	6.38	1.94	6.57

Similar to PEO preparations, solubility of the active ingredients also affected the permeation of water into the HPMC matrix and subsequently drug dissolution from the preparations. The order of dissolution amount was PSE > IBU > ACE, which was corresponding to the order of their aqueous solubility. *Figures 3.7-3.8* show the representative plots of hydrogel thickness and drug dissolution for ACE, IBU, and PSE tablets, respectively. It was evident from the results that increase in HPMC ratio reduced the drug release rate from the tablets. The reduction in drug dissolution became more pronounced when the solubility of active ingredient was decreased.

Tables 3.4-3.6 list the dissolution parameters of 15 prepared HPMC formulations in accordance to empirical Peppas-Ritgers equation. The diffusional exponent (n) of the HPMC matrix ranged between 0.35-0.81, suggesting a non-Fickian drug release mechanism for all three test compounds. Nevertheless, the n values in HPMC tablets were smaller than those in PEO tablets. Drug release rate constant (k) in HPMC tablets were also smaller than that in PEO tablets. This would indicate that HPMC did possess a slower hydration and erosion character than PEO.

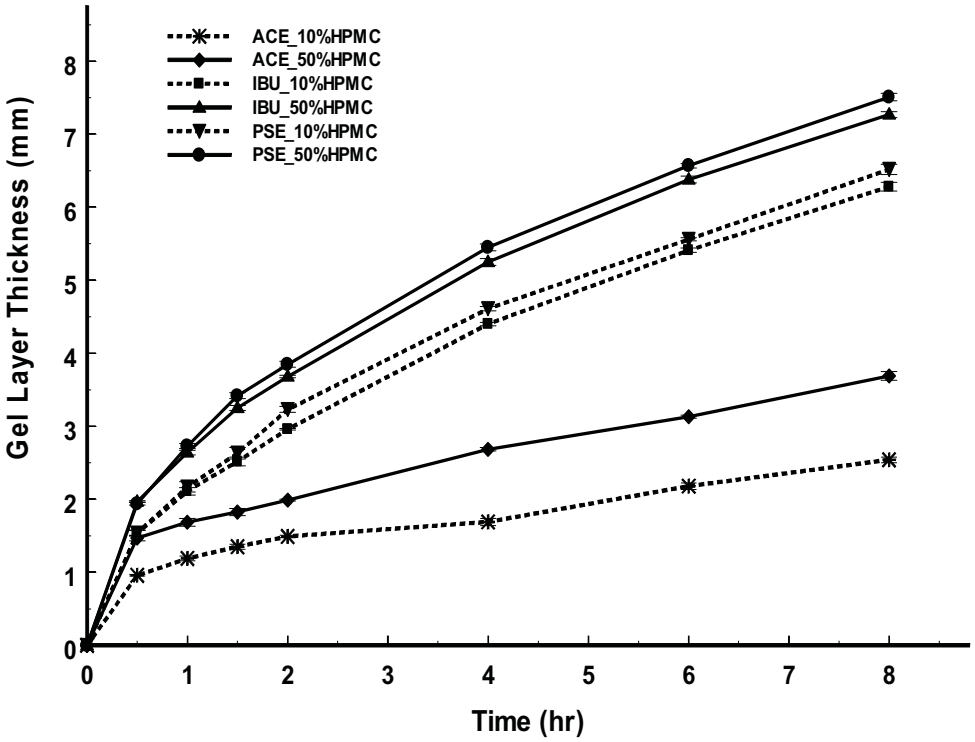


Figure 3.7. Representative hydrogel thickness-time plots of ACE, IBU, and PSE from tablets containing 10% and 50% HPMC (Mean ± SE, n=6)

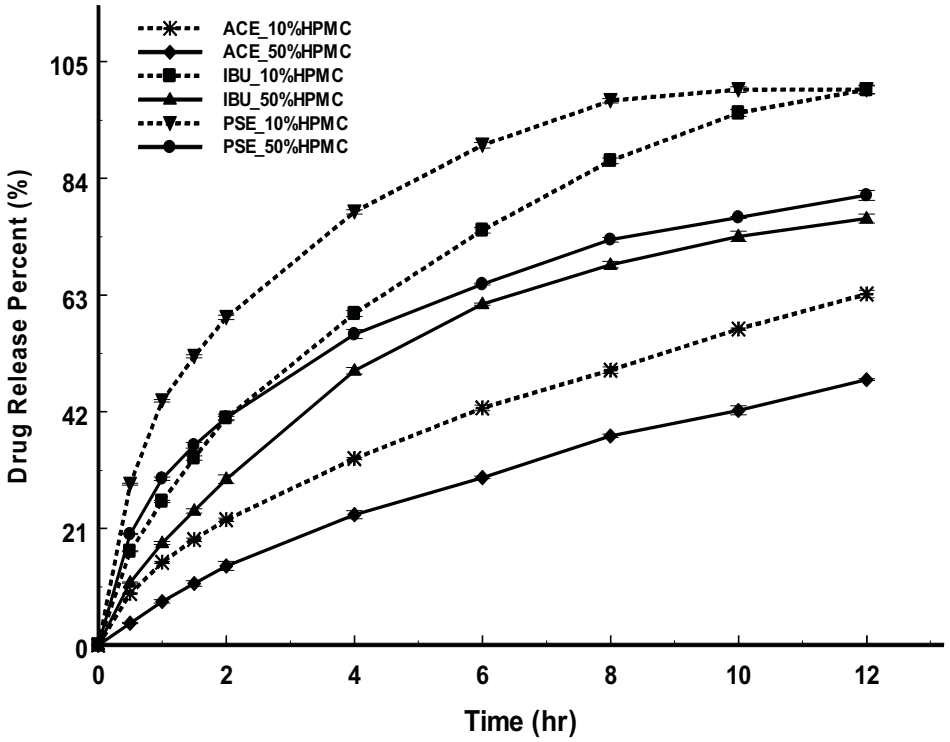


Figure 3.8. Representative drug dissolution-time plots of ACE, IBU, and PSE from tablets containing 10% and 50% HPMC (Mean ± SE, n=6)

Table 3.4. In vitro drug release and dissolution parameters of ACE formulations

Formulation Code	HPMC Ratio (%)	Diffusional Exponent (*n*)	Release Rate Constant (*k*)	$DT_{50\%}$ (hr)
F1	10	0.606	0.146	8.0
F2	20	0.744	0.094	10.5
F3	30	0.763	0.086	12.0
F4	40	0.785	0.083	12.2
F5	50	0.809	0.076	12.5

Table 3.5. In vitro drug release and dissolution parameters of IBU formulations

Formulation Code	HPMC Ratio (%)	Diffusional Exponent (*n*)	Release Rate Constant (*k*)	$DT_{50\%}$ (hr)
F1	10	0.612	0.261	2.9
F2	20	0.671	0.213	3.6
F3	30	0.660	0.212	3.7
F4	40	0.670	0.206	3.8
F5	50	0.665	0.200	4.0

Table 3.6. In vitro drug release and dissolution parameters of PSE formulations

Formulation Code	HPMC Ratio (%)	Diffusional Exponent (*n*)	Release Rate Constant (*k*)	$DT_{50\%}$ (hr)
F1	10	0.442	0.424	1.5
F2	20	0.496	0.369	1.8
F3	30	0.351	0.499	2.0
F4	40	0.422	0.331	2.7
F5	50	0.462	0.294	3.2

Compared to the PEO matrix tablets, HPMC tablets showed similar swelling behavior and drug dissolution profiles. The developed regression model based on the PEO matrix was fitted with data from HPMC tablets. The regression was performed with LDISSOL as the response variable and LTIME, HRATIO, SOLU, LTCHR, LTCSOLU, SOLUCHR, SQLT, SQHRATIO, and SQSOLU as explanatory variables (Table 3.2). Regression results (*Table 3.7*) show that all variables are statistically significant. Similar to the PEO matrix tablets, several outliers were observed on the left side of the residual plots graph (*Figure 3.9)*. Those outliers are associated with the "burst dissolution event" at the early stage of the dissolution process. Most residual plots of the regression were randomly distributed around y = 0, which suggests a good fit of the linear model.

Table 3.7. Summary statistics of regression Model #1

a) Analysis of Variance

Source	DF	Sum of Squares	Mean Square	*F*-value	Prob > *F*
Model	9	3.42E+02	3.80E+01	6868.58	< 0.0001
Error	619	3.42E+00	5.53E-03		
Total	628	3.45E+02			

b) Parameter Estimates

Variable	Label	Estimate	Std Error	*t*-value	Prob > | *t* |
Intercept	Intercept	-2.06E+00	1.80E-02	-114.5	< 0.0001
LTIME	Log(Time)	7.50E-01	1.02E-02	73.82	< 0.0001
HRATIO	HPMC Ratio	-1.99E+00	1.12E-01	-17.75	< 0.0001
SOLU	Drug Solubility	8.51E-02	8.83E-04	96.38	< 0.0001
LTCHR	Log(Time)×HPMC Ratio	1.62E-01	2.27E-02	7.13	< 0.0001
LTCSOLU	Log(Time)×Drug Solubility	-4.80E-03	1.36E-04	-35.37	< 0.0001
SOLUCHR	Drug Solubility×HPMC Ratio	2.51E-03	8.93E-04	2.81	0.0051
SQLT	Square of Log(Time)	-5.54E-02	3.95E-03	-14.01	< 0.0001
SQPRATIO	Square of HPMC Ratio	1.56E+00	1.77E-01	8.79	< 0.0001
SQSOLU	Square of Drug Solubility	-1.10E-03	1.30E-05	-79.42	< 0.0001

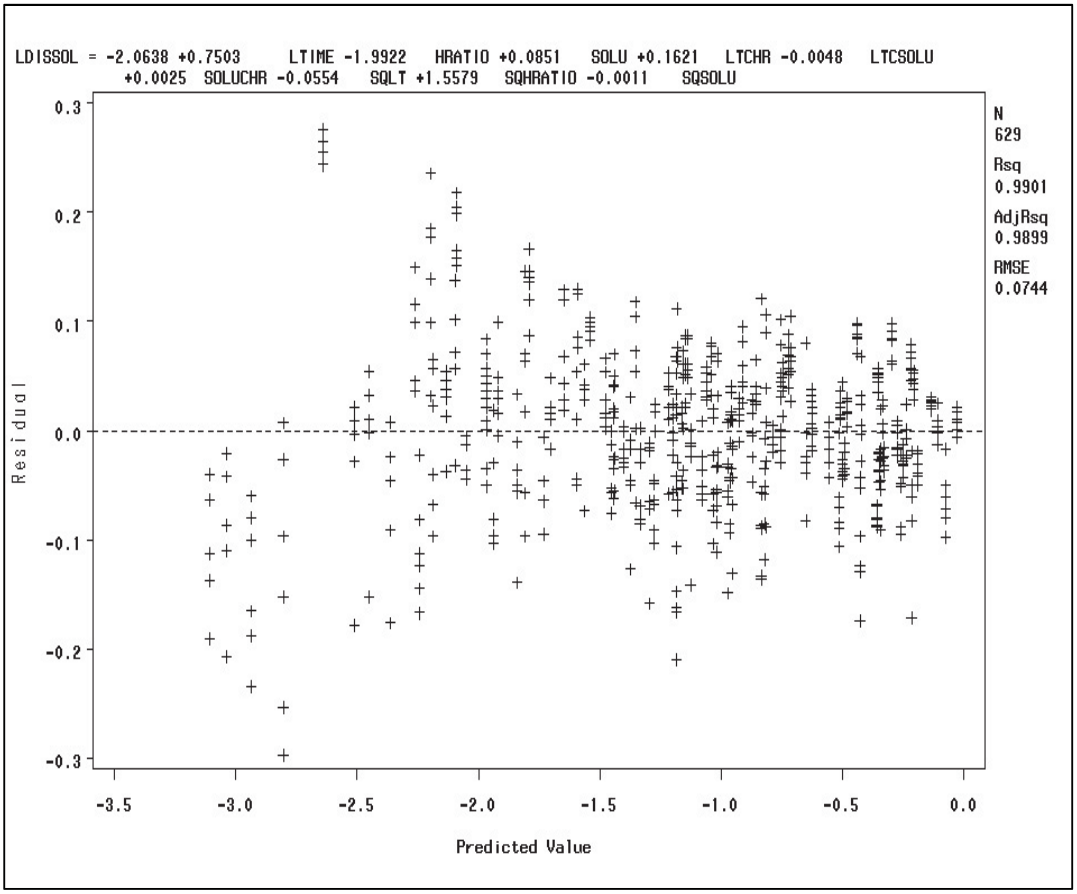


Figure 3.9. Residual plot of regression Model #1

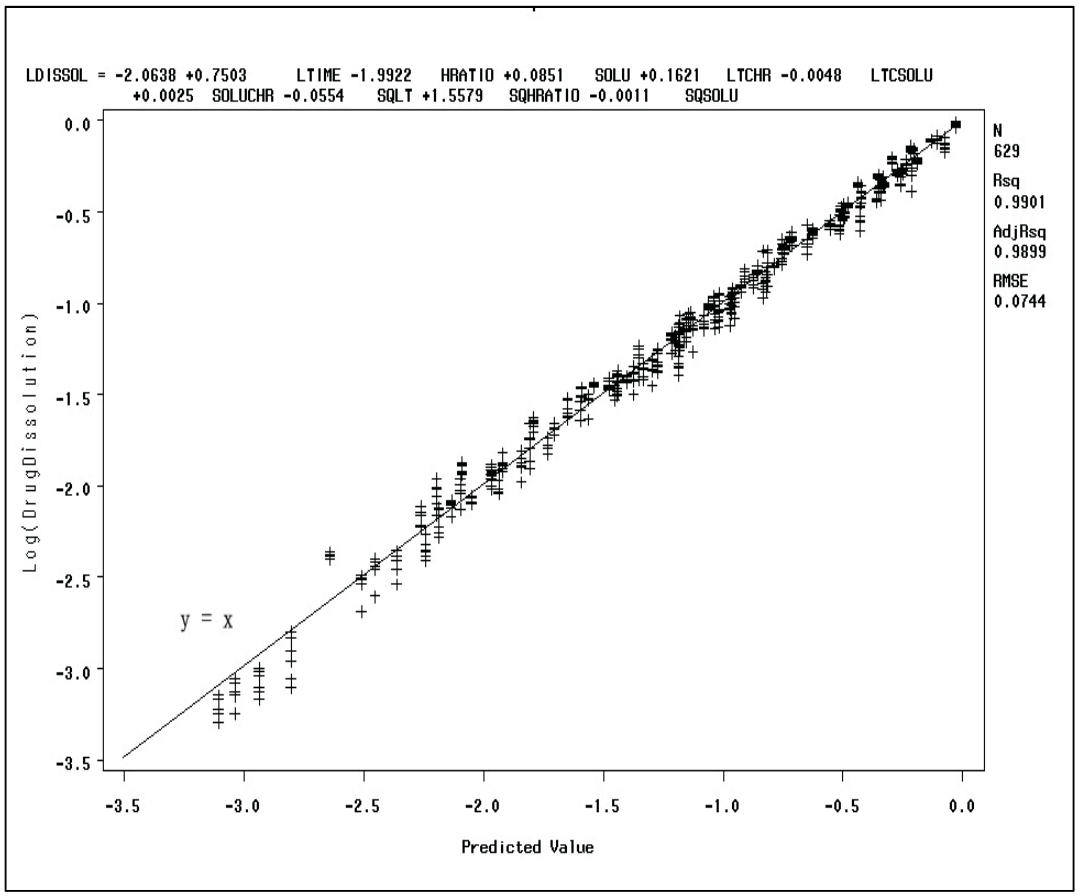


Figure 3.10. Plot of LDISSOL against predicted value from regression Model #1

$$LDISSOL = -2.064 + 0.7503 \times LTIME - 1.992 \times HRATIO + 0.08514 \times SOLU + 0.1621 \times LTCHR - 0.004820 \times LTCSOLU + 0.002510 \times SOLUCHR - 0.05540 \times SQLT + 1.558 \times SQHRATIO - 0.001060 \times SQSOLU$$

(*Model #1*)

Figure 3.10 is the plots of LDISSOL against predicted value from the regression model. The plots are distributed around y = x tightly, which also suggests a good prediction of the model on the observations. Dissolution data from the HPMC tablets fit the similar regression model as previously found for PEO matrix tablets.

The same methodology was employed to test the adaptability of the developed regression model based on polymer swelling of PEO matrix tablets on HPMC tablets. Data from HPMC swelling study was fitted to the model with gel layer thickness (GELTHICK) as response variable and dissolution time (TIME), HPMC Ratio (HRATIO), Drug Solubility (SOLU), and their cross-products (TCHR, TCSOLU, SOLUCHR) and quadratics (SQT SQHRATIO SQSOLU) as independent variables. Regression analysis showed that independent variable HRATIO was not significant; therefore, it was eliminated from the model. Regression analysis was re-performed with GELTHICK as response variable and TIME, SOLU, TCHR, TCSOLU, SOLUCHR, SQY, SQHRATIO, and SQSOLU as independent variables. All the independent variables were found significant. Statistical analysis of the final model is summarized in *Table 3.8*.

Table 3.8. Summary of statistics of regression Model #2

a) Analysis of Variance

Source	DF	Sum of Squares	Mean Square	*F*-value	Prob > *F*
Model	8	1.91E+03	2.38E+02	1358.28	< 0.0001
Error	62	1.09E+02	1.76E-01		
Total	628	2.02E+03			

b) Parameter Estimates

Variable	Label	Estimate	Std Error	*t*-value	Prob > | *t* |
Intercept	Intercept	-2.67E-01	6.90E-02	-3.88	< 0.0001
TIME	Time	6.10E-01	3.22E-02	18.96	< 0.0001
SOLU	Drug Solubility	2.01E-01	5.01E-03	40.12	< 0.0001
TCHR	Time×HPMC Ratio	2.08E-01	4.39E-02	4.73	< 0.0001
TCSOLU	Time×Drug Solubility	6.23E-03	2.70E-04	22.92	< 0.0001
SOLUCHR	Drug Solubility HPMC Ratio	-1.58E-02	4.94E-03	-3.19	0.0015
SQT	Square of Time	-3.56E-02	3.35E-03	-10.62	< 0.0001
SQHRATIO	Square of HPMC Ratio	2.06E+00	3.51E-01	5.86	< 0.0001
SQSOLU	Square of Drug Solubility	-3.10E-03	8.00E-05	-40.51	< 0.0001

$$GELTHICK = -0.2673 + 0.6104 \times TIME + 0.2009 \times SOLU + 0.2078 \times TCHR - 0.006230 \times TCSOLU - 0.01575 \times SOLUCHR - 0.03557 \times SQT + 2.059 \times SQPRATIO - 0.003050 \times SQSOLU \quad \text{(Model \#2)}$$

Although all independent variables are shown to be significant in the model, the residual plots *(Figure 3.11)* of the regression Model #2 shows clear curvature, which suggests that the linear model is not appropriate. The model from PEO matrix tablet is not adaptable to HPMC tablets. The swelling characters of PEO and HPMC tablets can not be described with the same model. Generally, water penetration/uptake is faster in PEO matrix, the fully hydrated gel layer from PEO matrix is formed rapidly, at the same time the gel layer erodes from the outside surface faster too, which was observed from the dissolution medium during the dissolution process. HPMC matrix shows relatively slow erosion during the dissolution process. The solubility of the other ingredients in the tablets also affects the polymer swelling too. The effect from those ingredients was found different between the two polymers. All these factors may contribute to the difference on the polymer swelling behaviors and thus the modeling results.

Both HPMC and PEO are hydrophilic and commonly used in the swellable matrix formulations as major dissolution control ingredients. Relationship of drug dissolution and polymer ratio, drug solubility, and dissolution time can be described using a regression model. The empirical model can provide the formulation scientist another tool to expedite the process of new formulation design and optimization. At the same time,

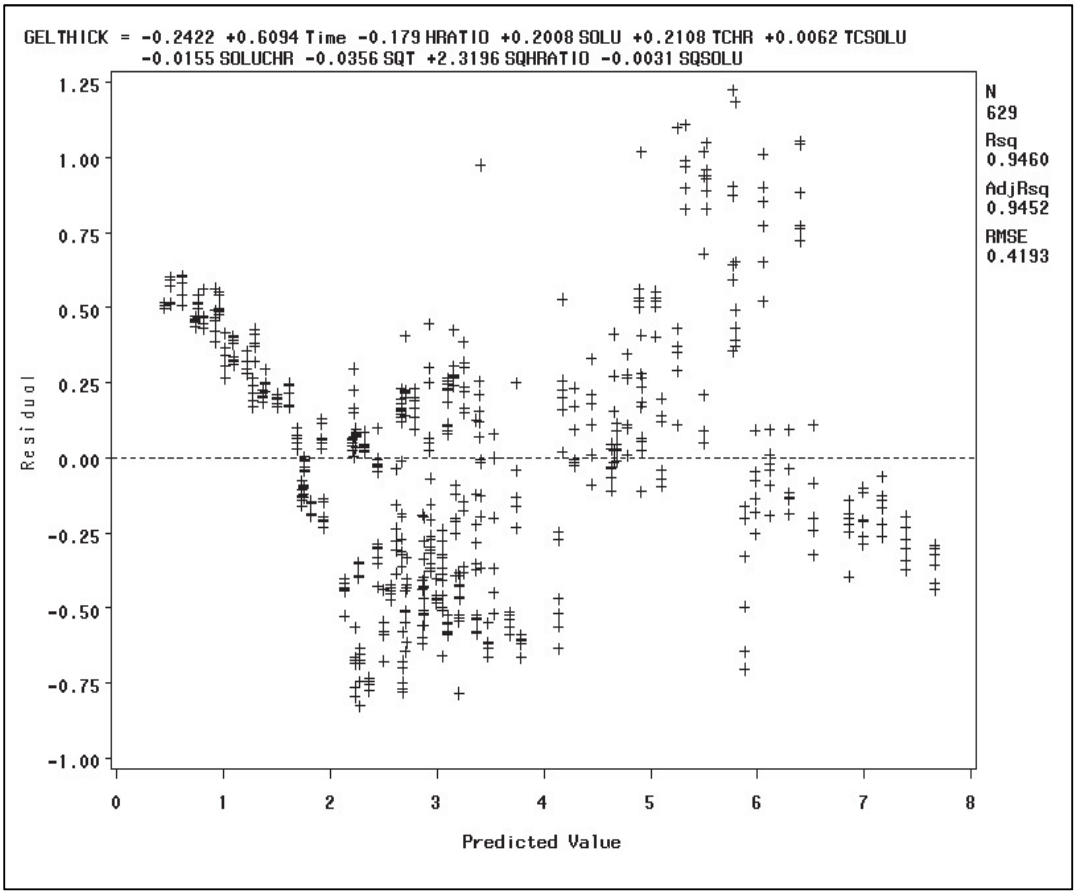


Figure 3.11. Residual plot of regression Model #2

due to the physical and chemical differences between the two polymers the swelling behavior of HPMC and PEO cannot be characterized using the same regression model.

3.4. Conclusion

Drug dissolution from modified release HPMC matrix tablets was dependent upon drug solubility, polymer hydration, and polymer proportion in the preparations. Drug release from the hydrophilic HPMC matrix was mainly regulated by the rate and extent of HPMC hydrogel formation on the surface of the tablet and of water penetration into the matrix core. The multiple regression modeling that was developed and validated in PEO matrix tablets was still applicable to HPMC matrix in describing the relationship between drug dissolution, polymer ratio, dissolution time, and drug solubility.

For polymer swelling HPMC matrix exhibited fast hydration, the continuously growth of the gel layer was affected by polymer ratio and the aqueous solubility of other ingredients embedded. Hydrogel from HPMC matrix was relatively more stable than from PEO matrix, the regression model for the PEO matrix swelling behaviors was not adaptable to HPMC tablets.

Texture analysis is a simplified and versatile methodology added to the pharmaceutical research and development. The practical application of texture analysis together with the simple regression modeling would certainly be beneficial to formulation development and optimization with reduced experimental requirements and enhanced productivity.

Chapter 4

Conclusion

Efficacy and safety are essential for drug delivery; at the same time, application convenience and patient compliance are also very important. Today's drug delivery technologies can modify drug release profile and achieve enhanced therapeutic outcomes, as well as improved patient compliance. Modified release matrix preparations are some of the most successful and reliable novel drug delivery systems. By selecting appropriate pharmaceutical polymers and excipients and formulating the active ingredient in appropriate dosages, it is possible for pharmaceutical scientists to design and produce modified release matrix formulations that possess reproducible and well-controlled drug release characteristics. The resulting modified release preparations provide advantages in formulation, large-scale industrial production, and unit cost effectiveness, which are favourable to both manufactures and end-users. It is expected that modified release matrix tablets will remain as one of the primary drug delivery systems in clinical practice for years to come.

Drug release from modified release preparation is governed by mechanisms that may be simulated using mathematical and/or statistical models. Dependent upon their formulation configurations and excipient types, modified release dosage forms may demonstrate different drug release characteristics, which involve in different release mechanisms. Understanding these drug release mechanisms and using the simulating models would benefit formulation scientists in designing modified release dosage preparations with precision and expediting the formulation development and optimization process.

The major drug release mechanism for most modified release swellable matrix tablets involves a combination of drug diffusion and matrix erosion. The collective contribution of hydration of the hydrophilic matrix polymers and the water solubility of the active ingredient produces a modified drug release mechanism that is independent of environmental pH conditions and transition time *in vivo*. However, drug diffusion or matrix erosion may take a primary role in determining how the drug release mechanism is projected from a specific swellable matrix preparation. For example, when the active ingredient possesses sufficient aqueous solubility in the formulation, water penetrates inside the matrix quickly at the initial stage of the dissolution process, and that results in polymer hydration and the generation of a hydrogel layer; the active drug will be released by diffusing through this hydrogel layer. If the hydrogel is stable enough, the diffusion mechanism is the major determinant of drug release from the matrix. On the other hand, if the active ingredient has very poor water solubility, no stable hydrogel layer is generated because of the lack of water penetration; in this case drug release would be controlled by matrix relaxation and erosion processes. Owing to the variability in polymer hydration behaviours and solubility of the active ingredients embedded in the matrix, drug release simulation and prediction becomes more complex. There have been numerous mathematical or deterministic modeling approaches reported in the literature (Chapter 1 Section 1.3). Some of these models can simulate drug release and polymer swelling from a variety of polymers. In reality, those models are either unattainable due to their complexity or contain parameters that are not readily available from published experiments, which limits the use of the models in routine formulation development and

optimisation. In this thesis a more practical statistical model (least-squared multiple regression) was attempted. Using multiple regression model effects from the major matrix formulation factors, such as polymer ratio and drug solubility (independent variables) on drug dissolution (dependent variable) were well simulated, the estimates of unknown parameters was also optimized. The developed models are easily-interpretable for drug release predictions based on the formulation factors.

Several methods, such as optical microscopy, NMR microscopy, confocal laser scanning microscopy (section 1.4), have also been developed by other scientists for monitoring polymer hydration and water mobility across the hydrogel during the dissolution process of swellable matrix tablets. Those methods often require either time-consuming sample preparation, or complex, expensive instruments. In this study polymer hydration was monitored using a TA Texture Analyzer, which recorded the gel layer thickness and strength information for the complete dynamic polymer hydration process. The operation procedure was practical and data collected by the method was reliable.

Hydrophilic pharmaceutical polymers polyethylene oxide (PEO) and hydroxypropyl methylcellulose (HPMC) were selected for the study. Four drug compounds with various solubility characteristics were incorporated in the preparations, and drug release and polymer hydration from these tablets were characterized and compared by dissolution testing and texture analysis. It was found from a series of experiments that drug dissolution from prepared PEO and HPMC swellable matrix tablets was dependent on drug solubility, hydrogel formation, and polymer proportion used in the tablets. Drug candidates with higher aqueous solubility demonstrated faster water

penetration into the matrix core, and subsequently faster drug diffusion across the hydrogel layer. Polymer hydration from the matrix containing drugs with high solubility was also accelerated. Increasing the polymer proportion in the tablet matrix prolonged drug release from the tablets. As expected, matrix tablets of PEO and HPMC released their drug content primarily by diffusion mechanism.

To develop a multiple regression model, data collected from PEO matrix tablets was split into two sets. For both dissolution and polymer swelling tests, six replicate results from each individual sample/tablet were taken at each sampling point. The first three results of six replicates at each sampling point were signed to set #1; the rest three results at each sampling point were signed to set #2. The first set of data was used to develop the model while the second set of data was used to validate the model developed afterwards. Multiple regression was performed between drug dissolution as dependent variable and polymer ratio, dissolution time, and drug dissolution as independent variables. For a better predictive capability of the model, the cross-products and quadratics of the independent variables were also introduced in the model. The significance of the impact of all the variables on dependent variable was evaluated and confirmed. Residual analysis was employed to evaluate the model fit. The developed model demonstrated good fit for most part of the data for PEO matrix. By applying the model to a CHL formula containing 30% of the PEO polymer the applicability of the model was further validated. The predicted dissolution profile was consistent with the observed real-time dissolution results. The model was also shown its adaptability on

HPMC matrix. Drug dissolution could be quantitatively simulated based on the polymer ration and drug solubility by the application of the model.

As a statistical modeling approach, multiple regression model generally has its limitation. First, the unexplained error always exist, which can certainly affect the predictability of the final model. Second, the extrapolation properties of the model could be possibly poor due to the limited sample size or range. When applying the developed model the measurement of the independent variables is recommended to be within certain range for a reliable prediction on the dependent variable. Third, the model is very sensitive to outliers. The outliers can easily bias the regression coefficients. Extra care is required for those outliers during the model development stage.

It was also observed that the prediction of the model showed some deviation from the real-time data in early stage (first 15-30 min) of the dissolution. This could be attributed to a different drug release mechanism for this special period of dissolution time. Because of a lack of the gel layer at the early dissolution stage, drug release from the matrix was more likely to dissolve directly along with the matrix erosion. A multiple regression model was not sufficient to describe this particular drug release mechanism. Though the model did not show desirable accuracy on the drug release prediction for the early stage of the dissolution process, the prediction on drug release for the major stage from PEO and HPMC matrix was satisfactory. Compared to other existing mathematic simulations that required complicated and advanced mathematical skills, the regression approach offered an improved alternative in practicability and applicability of using common formulation parameters of the modified release matrix tablets for the prediction

of drug release. This could facilitate formulation design and optimization with reduced resource requirements and increased throughputs.

Polymer hydration and tablet swelling from the prepared PEO and HPMC matrix preparations were monitored by a TA Texture Analyzer in this study. As a result, this work also explored and expanded the application of texture analysis in pharmaceutical research and development. As a relatively new methodology in formulation assessment, texture analysis demonstrated a unique and feasible aspect in measuring polymer hydration and matrix erosion. In particular, operation of a texture analyzer was simple, inexpensive, versatile, and reproducible. Gel layer thickness during the hydration process of the tablets was directly measureable, and meaningful in preparation optimization. It was anticipated that the applications of texture analysis in pharmaceutical sciences would be further refined and enhanced to benefit formulation development in the future.

Hydrophilic polymers PEO and HPMC demonstrated their hydration and swelling properties that made them appropriate for modified drug release observed in the swellable matrix delivery systems. This study also detected differences in swelling kinetics for the two polymers tested. A multiple regression model was able to describe the dynamic relationship between drug dissolution, gel layer thickness, drug solubility, dissolution time, and polymer ratio for the PEO matrix formulations. A similar multiple regression approach was only capable of describing the relationship between drug dissolution, drug solubility, dissolution time, and polymer ratio for the HPMC matrix formulations. The discrepancy was attributed to difference of polymer hydration between the two polymers, specifically, a stronger and longer-lasting hydrogel of HPMC in

comparison to that of PEO. Therefore, it would be beneficial to test several other hydrophilic polymers that are commonly used in modified release matrix formulations in future studies, which could further assess the applicability and versatility of the developed multiple regression modeling in swellable matrix tablets, with the hope of refining important tablet parameters that would become applicable to all modified release matrix formulations. Models developed in this study were based on the cylindrical tablet preparations using 7/16 inch I.D., the effect of the geometric factor (size and shape) of the tablets was not considered, which might also affect its application in the practice. Tablets with different shape possess different surface areas, which are directly related to the diffusion rate. Future studies could also be carried out to evaluate the effect of geometric configuration of the tablet matrix on regression modelling of the modified release matrix tablets.

Modified release drug delivery systems provide a vast and diverse field of applications that demonstrate the potential for various research interests and knowledge. It still is a great challenge for formulation scientists to efficiently develop desired drug formulations for accurate drug delivery results. This thesis demonstrated its practical merit in pharmaceutical sciences by exploring the use of texture analysis and establishing a simplified regression modeling for drug dissolution and other important preparation parameters. The multiple regression modeling approach will provide additional tool and benefit to formulation scientists in developing novel modified release technologies. Subsequently, more innovative and efficient medications could be manufactured by the

pharmaceutical industry to enhance the therapeutic outcomes in clinical practice and to improve the quality of life for the general public in the future.

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