Comparison of Polymeric Drug Delivery Models

A thesis submitted in partial fulfilment of the requirements for the degree of Bachelor

By

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Declaration

We, confirm that the work presented in this thesis is our own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Although there have been significant advances in the fields of theoretical condensed matter and computational physics, when confronted with the complexity and diversity of nanoparticles available in conventional laboratories a number of modeling challenges remain. These challenges are generally shared among application domains, but the impacts of the limitations and approximations we make to overcome them (or circumvent them) can be more significant one area than another. In the case of nanoparticles for drug delivery applications some immediate challenges include the incompatibility of length-scales, our ability to model weak interactions and solvation, the complexity of the thermochemical environment surrounding the nanoparticles, and the role of polydispersivity in determining properties and performance. Some of these challenges can be met with existing technologies, others with emerging technologies including the data-driven sciences; some others require new methods to be developed. In this thesis we will briefly review some simple methods and techniques that can be applied to these (and other) challenges, and demonstrate some results using nanoparticle polymeric based drug delivery platforms as an exemplar.

A mathematical model is developed for the simultaneous treatment of polymeric nanoparticles and drug release with autocatalytic effects and nonconstant effective diffusivity of the drug. A mechanistic reaction-diffusion model with pore evolution coupled to hydrolysis and related to the effective diffusivity through hindered diffusion theory is proposed. Experimental background motivating the attention to the size-dependent effects of autocatalysis on drug release and a brief review of related mathematical models are presented. The model equations are derived, solved numerically with a computational [MATLAB] code developed for this work and described in detail, and compared to the analytical solutions to the model in limiting cases. The model performance for the case of drug release from microspheres of different sizes is presented to highlight the capability of the model for predicting size-dependent, autocatalytic effects on the polymer and the release of drug.

Lastly, we examined which release model of the nanoparticles gave the best fit to the experimental results. The released profile was fitted to several release models (the Higuchi, zero-order, Hixson Crowell, first order, and KorsmeyerPeppas) and the best fit determined based on coefficient of determination (R^2) value.

المستخلص:

تعتبر الهندسة الطبية الحيوية من التخصصات التي تعنى بالكثير من النواحي الحياتية حيث تجمع التطبيقات الرياضية والهندسية مع العلوم الطبية وتعتبر تقنية النانو هي التقنية الاحدث في مختلف المجالات وتم تطويرها بهدف تسهيل التصميم ورفع كفاءة الانتاج في شتى الأغراض لذلك تم دمجها مع تقنيات ال**drug delivery systems** للحصول على افضل أداء.

نسبة للتطور الذي حدث في تقنية **(drug delivery)**حيث كانت عملية ال **release**تحدث تلقائيا حتى أصبح بالامكان التحكم بها في الوقت الحاضر,وبدأت الدراسات تتجه نحو استنتاج معادلات لوصف اليات ال **release**المختلفه والتحكم فيه عن طريق تغيير قيم متغيرات وثوابت المعادلات.

وفي هذا البحث تم اختيار مجموعة من المعادلات الاكثر استخداما في مجال أنظمة ال **controlled drug delivery**ومقارنتها اعتمادا على معامل التحديد R^2 باستخدام برنامج ال**MATLAB** لرسم منحنيات توضح كيفية تأثير تغير معاملات كل معادلة على عملية ال**release**واعتمادا على ماسبق ذكره تم تحديد المعادلة الافضل في هذا البحث.

Dedication

For your infinite love…. For all the support

The friend and love you have given us

For all time we never said thank you because we thought you knew

we thank you more than ever

To our pear mothers

For all your protected and guiding us in the right direction

For your listening and caring

Thank you for being our princes

To the greatest men in the world

our Dear Fathers

To Our Dear Teacher

We really appreciate all what you made for us…….

You taught us amazing coarsest……

And helped us find out what kind of life We want... Thank you

For your efforts to teach us every thing

You didn't learn us just lessons but also the morals

We are so grateful to have been supervised by such Doctor

Thanks a lot ……

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Chapter 1 Introduction and Background

1.1 Background

Controlled-release drug delivery systems are being developed as alternatives to conventional medical drug therapy regimens for pharmaceuticals that require frequent administrations. Many mathematical models have been developed for polymeric drug delivery systems, and a lot of modeling e□orts have been published.There are three main strategies for drug encapsulation represented in the figure below:

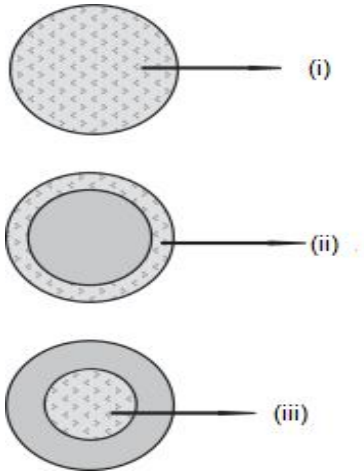


Figure 1: Drug encapsulation; (i) Homogeneous matrix. (ii) Drug component enriched shell. (iii) Drug component enriched core.

These models can be distributed among three categories based on the mechanisms of drug release:

1.1.1 Di□usion-controlled systems

The transport mechanism of diffusion-controlled release systems is modelled by Fick's second law of diffusion. In diffusion controlled system the drug is dissolved or dispersed in a polymer matrix and allowed to diffuse from the monolith[1].

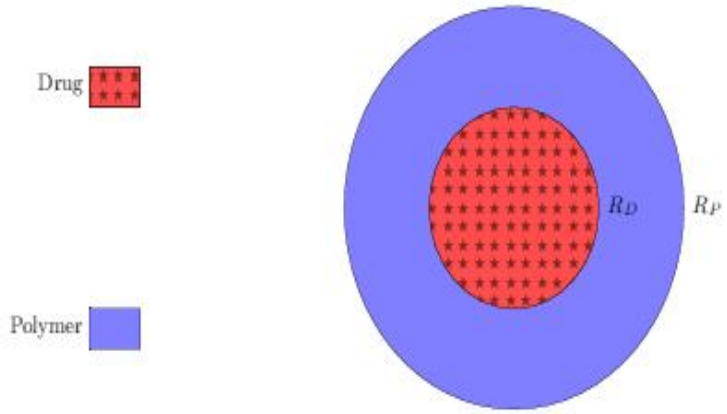


Figure 2:A glassy polymer ball.

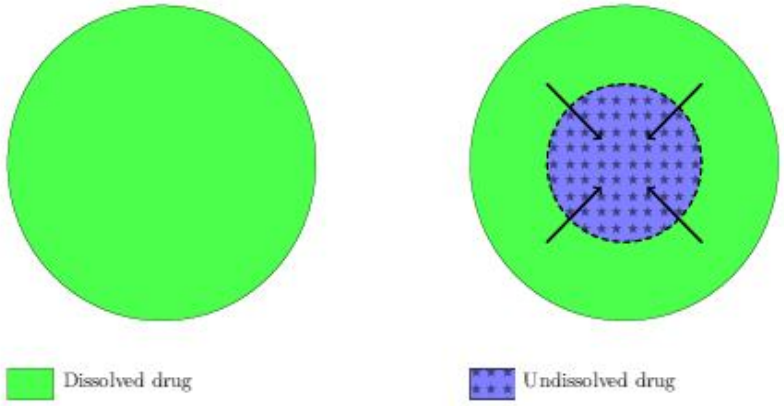


Figure 3: a swollen polymer ball after the solvent permeates into the polymer.

1.1.2 Swelling-controlled systems.

Swelling-controlled release systems can provide enhanced drug diffusion from hydrophilic polymer networks into the external medium.

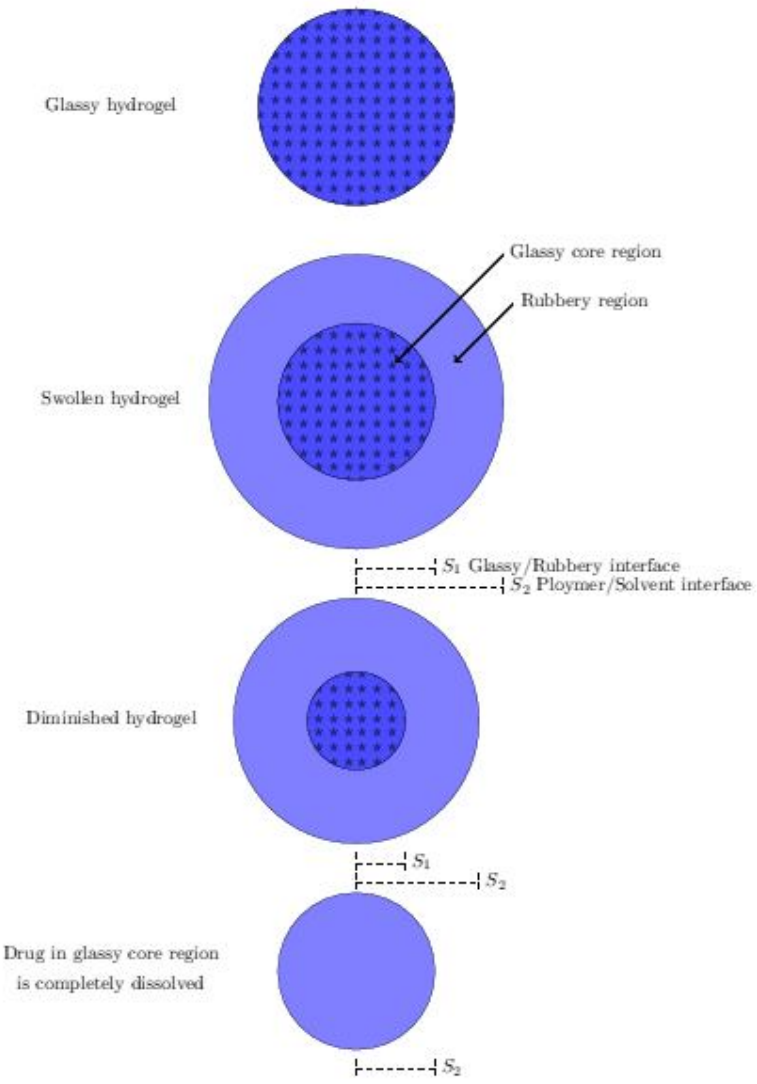


Figure 4: There are two interfaces, S1 and S2, in the swelling-controlled release system. The interface S1 separates the glassy and rubbery parts, and moves inwards after the hydrogel is embedded in an aqueous environment. The interface S2 separates hydrogel and external solvent and it is also a moving front, moving outwards as hydrogel swells, before moving inwards when the hydrogel starts to dissolve.

The cause of enhanced drug diffusion is theswellingcharacteristicofhydrophilicpolymernetworkwhichoccursoncontactwith an external solvent (water or biological fluid). The drug carriers formed by hydrophilic polymerssuchasmethylcelluloseandhydroxypropylmethylcellulose(HPMC)arecalled hydrogels. When water starts to penetrate into the hydrogel, polymer disentanglement or polymer chain relaxation occurs, resulting in an increase in volume of the hydrogel. Theswellinghydrogelimpliesthesimultaneoustransitionfromaglassystatetorubbery state at the outermost region of hydrogel. The drug in the glassy region is yet to be dissolved, but the drug in the rubbery region dissolves with enhanced diffusivity. The diffusioncoefficientofthedrugisgreatlyincreasedwhenmoresolventisintherubbery region.Thehydrogelwilleventuallystopswellingandstarttodissolvewhenthepolymer entanglement is adequatelyweak[2, 3].

1.1.3 Erosion-controlled systems

Erosion-controlled release systems have complex drug release behavior, disparting polymer chains from the polymer network either by chemical or physical processes. The chemical process refers to the polymer chain, bond cleavage or scission reaction with a solvent. There are two general scenarios of polymer erosion; surface (heterogeneous) and bulk (homogeneous) erosions.

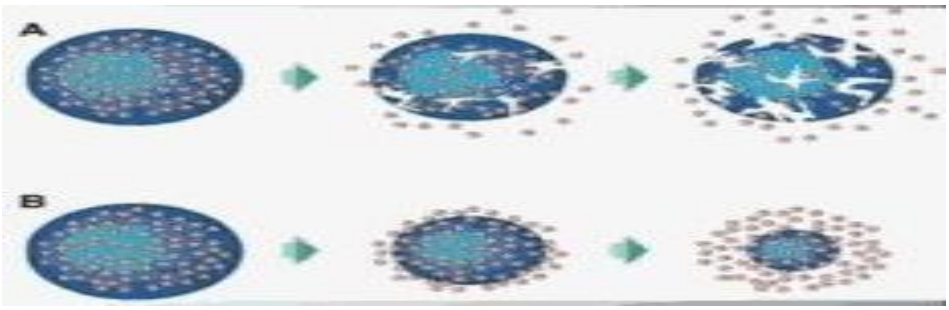


Figure 5: (A) homogeneous erosion, (b) heterogeneous erosion: when water penetration is restricted to surface.

In surface erosion, the spherical polymer has a shrinking diameter as the erosion of the polymer taking place from the surface of the polymer net- work. In bulk erosion, a spherical polymer has a constant diameter size and external fluid is allowed to penetrate into the polymer, so that the erosion process occurs within the polymer network[2, 4]

1.2 How to choose the best model:

But what are the criteria to choose the ‘‘best model’’ tostudy drug dissolution/release phenomena? Onecommonmethod uses the coefficient of determination, R^2 , to assessthe ‘‘fit’’ of a model equation. However, usually, this valuetends to get greater with the addition of more modelparameters,irrespective of the significance of the variableadded to the model. For the same number of parameters,however, the coefficient of determination can be used todetermine the best of this subset of model equations.

In other words, the ‘‘best’’ model would be the one with the highest coefficient of determination.

1.3 Problem statement:

Comparison between release models in order to choose the applicable model for control systems using polymer nanoparticle

1.4 Objectives of the research

The research objectives for this dissertation concern the modeling of drug release:

- ☐ Study and analysis of drug delivery models using MATLAB.
- ☐ Compare between models under study.
- ☐ Decide the best models depend on comparison.

1.5 The structure of the thesis

In this thesis Chapter 1 provides the Introduction and background to the work and summaries the contributions made by the research. In Chapter 2 literature review also highlights existing challenges encountered in nanoparticles and some of the latest developments targeting these problems. Chapter 3Methodology and result. In Chapter 4 the Discussion obtained from the experiments are presented and discussed in conjunction with those from the literature. Chapter 5 covers the Conclusion and future work.

Chapter 2 Literature review

2.1 Modelling researches

2.1.1 Linear diffusion of drug from a sphere:

The simplest case of drug release from spherical polymer only considers the diffusion of the drug and neglects other mechanisms. Hence the transport mechanism of the drug within the spherical polymer is modelled by a linear diffusion equation and does not involve moving boundaries. The model of drug release from the spherical drug carrier is:

$$\frac{\partial V}{\partial T} = Dd \frac{1}{R} \frac{\partial^2}{\partial}$$

V=0 at r=S2 (2.2)

$$\frac{\partial V}{\partial R} =$$

V=Vi at T=0 (2.4)

Where:

Dd: is diffusion coefficient of drug concentration

V : is drug concentration in the spherical drug carrier

The model (1.2) - (1.4) based on the linear diffusion is scaled by the following non-dimensional variables

Where:

Da : is diffusion coefficient of drug or some other material

S2: is the fixed radius of the spherical drug carrier

Vi: initial coefficient of drug within spherical drug carrier

The model (2.1)-(2.4) is also called the matrix system in the diffusion-controlled release system with the initial amount of drug concentration less than the solubility of the drug in the polymer matrix.

The other matrix system in the diffusion -controlled release system has the initial amount of drug concentration higher than the solubility of the drug in the polymer matrix and is also called dispersed matrix system. Thedispersed drug system has a core (non-diffusing) region and the dissolved (diffusing) region after commencement of drug release. In the core region, the drug is undissolved and the drug concentration of the core region is the same as the initial drug concentration. In the dissolved region, the drug is dissolved and diffusion takes place. The core region continuously diminishes and more drug dissolves into the dissolved region. This is ongoing process implies theoccurrence of a moving front at the interface that separates the core and the dissolved region. Higuchi(1963)[5] is the first one to propose the idea of modelling the dispersed matrix system as a moving boundary problem and drives the amount of drug release from a planar sheet.Cohen and Erneux(1988b)[6] studied Higuchi's model for a matrix controlled release system which uses nonswellable polymer, and obtained the same result as Higuchi's.Another matrix controlled release system investigated by Cohen and Erneux(1998)[6]they use pseudo-steady – state approximation to solve the problem for the case of the initial drug loading which is much larger than the solubility of drug. They also investigate the difference between the initial drug loading Vi and the maximum solubility of the drug in the polymer Vs, approaching zero on the drug release. They find that the drug concentration within the polymer is approximately equal to Vsexcept near the boundary that separates the polymer and solvent. Therefore they employ a singular perturbation technique and the method of matched asymptotic expansions to handle the boundary layer.

2.1.2 Swelling controlled release system

Polymer materials are important to the pharmaceutical industry and are used as drug carriers in controlled drug release devices. Polymers are often stored in a glassy state before contacting with thermodynamically compatible solvent. Figure (1) depict a glassy polymer ball and Figure(2) depicts a swollen polymer ball after the solvent permeates into the polymer , parts of polymer that are near the surface will firstly undergo structural relaxation and then transform from the glassy state to the rubbery state . Consequently, there is a volume expansion of the polymer ball. Therefore an interface forms to dentify the concentration difference of solvent between the glassy and rubbery parts of polymer and this interface will move inward as the rubbery part expands. This interface is often called the swelling interface or solvent preface and S1 (T) is denoted as the distance from the centre of polymer ball to this interface.

The other interface is named as the polymer solvent interface or the volume expansion interface and it will moved out word due to the volume expansion of swelling process. S2 (T) is denoted as the distance from the centre of polymer pill to the polymer solvent interface and B is denoted as the thickness of boundary layer. However not all polymer will swell upon contacting with solvent. The swelling ability is dependent on the physiochemical properties of polymer and the thermal compatibility between polymers and solvent.

Good(1976)[2] experimented with the release of HCL from an insoluble and lightly cross-linked polymer sheet , PHEMA, to water and noted that there is virtually no thickness change of the slab. He ascribed this non-swelling to the balance between drug diffusion and solvent absorption.

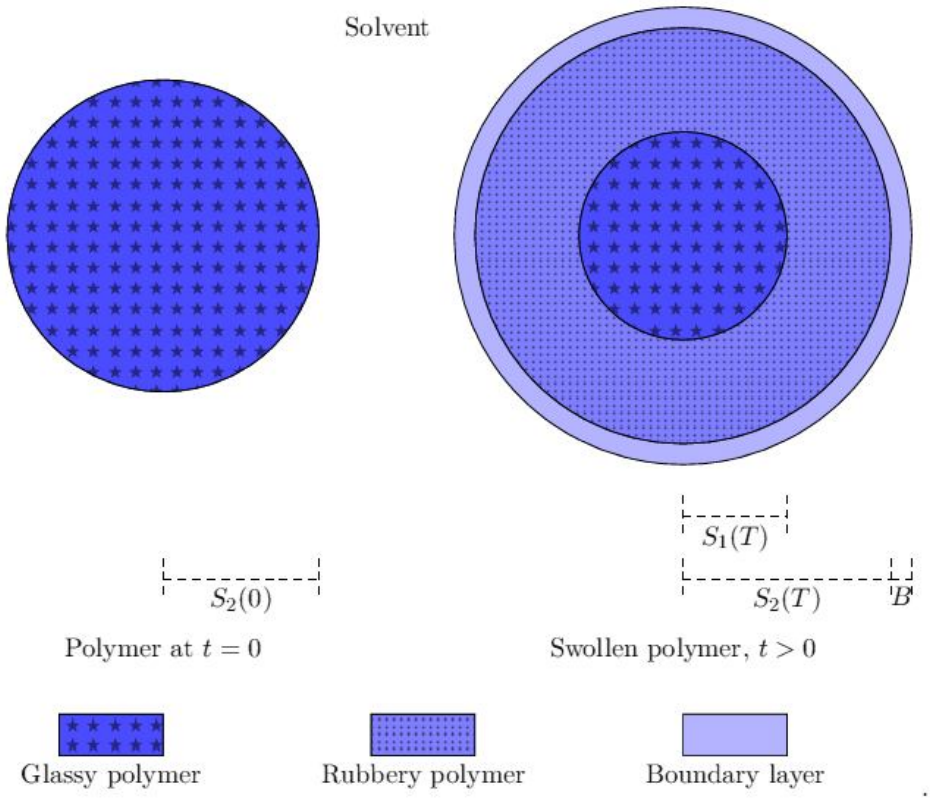


Figure 6:Polymer swelling

Astarita and Sarti(1978)[7]summarise experimental evidences of solvent penetrating intoa glassy polymer from other researchers in the following:

a) There is a morphological discontinuity in the polymer which partitions the glassy regionandrubberyregionofpolymer.

b) Thevelocityofglassy-rubberyinterfaceisinitiallyconstantintime.

c) Theamountofsolventinthepolymerinitiallyincreaseslinearlywithtime.

d) The activation energy for the initial velocity of glassy-rubbery interface is close to the crazeformation.

e) Atintermediatetimes,thecurveoftheglassy-rubberyinterfacepositionversustime canbefittedbyapowerlawwithanexponentrangingbetween0.5and1.Feature (c) will stop before feature(b).

They point out features (b) and (c) are “case-two-transport”, which implies the glassy-rubberyinterfacepositionisinitiallyalinearfunctionoftime.Aftersomefinitetime,the glassy-rubbery interface position is proportional to the square root of time which they referas“pseudo-Fickiantransport”.

AstaritaandSarti[7]proposeamathematicalmodelforapolymerslabexposingtosolvent without volume change which fixes the position of the polymer-solvent interface ($S2$ is constant)orignorethevolumeexpansionduetoswelling.Theyassumethephasetran- sition is a kinetic one and the concentration of solvent is zero in the glassy polymer. Themovingboundarybetweentheswollen(rubbery)regionandtheglassyregionobeys an empirical penetration law which relates the velocity of the moving boundary with a empiricalfunctionofthesolventconcentration.Theyuseasimple$n$-ordertypefunction to describe the kinetics of phase transition at $X = S1(T)$.

There is another condition at the moving boundary and it isthe mass balance equation at the moving boundary which equates the mass density current to the product of the solvent concentration and the velocity of the moving boundaryCohenandErneux(1988a)[8]:investigatetwoproblemsofpolymer-penetrantsystems.These problemsoriginatefromtheswelling-controlledreleasesystemswithoutconsideringvolumechange,asstudiedbyKorsmeyerandPeppas(1983)[2].The first problem is a polymeric film exposed to a solvent which is consisted by smaller molecule and capable to diffuse into the film. The model, based on the work byAstaritaand Sarti(1978)[7].

The second problem considered by Cohen and Erneux is a polymeric film which is exposed initially to a finite amount of solvent and then the polymer boundary is insulated afterward. This problem is different from the first problem by the boundary conditionand initial conditions.Cohen and Erneux(1988b)[6] investigated two problems of the controlled drug release systems. Cohen and Erneux first study Higuchi's model for a matrix-controlled release system which uses non-swellable polymer. Cohen et al. investigate this problem asymptotically for an asymptotic limit which is approaching zero. The leading order term of their asymptotic solution is actually the same as the solution proposed by Higuchi who uses the steady state approximation approach. The second problem investigated by Cohen and Erneux(b)[6] is the drug release from a swelling controlled release system. In this problem, the model proposed by Higuchi(1961) and Higuchi(1963)[5]is used to describe the drug transport and the model proposed by Astarita and Sarti(1978)[7] is used to describe the solvent transport.This model is similar to the model proposed by Peppas(1980).[9]And the differences between these two models are the boundary conditions at moving boundaries and drug diffusion in the glassy part of the polymer. Cohen et al. assume no kinetics of drug in the glassy part of the polymer. Peppas(1980) [9]used the Dirichlet boundary condition and the idea of continuity at the glassy- rubbery interface for drug and insulate boundary condition at glassy-rubbery interface for solvent.Hu(1991)[10]studied the asymptotic solution of a diffusive solvent penetrating into a glassy polymer and the model is obtained from the first problem ofCohen and Erneux (1988a).[8].Hu explored the short and long time behavior of the model and his results confirm the results derived byCohen and Erneux (1988a) [8] by using auxiliary problems which are similar to the model and may have analytic solutions.

Lin and peng(2001)[11]investigated a model of the solvent penetration in a spherical polymer but the model is really the spherical version of the model proposed by (Cohenand Erneux)[8]Lin and Peng(2005)[12]investigated a swelling-controlled release model from a spherical drug carrier however the model is actually the spherical version of the model proposed byCohen and Erneux(b).[6]

2.1.2.1 Diffusionmodelsinswellingcontrolledreleasesystem

Peppas(1980)[9]proposed a model of the swelling controlled release system which takes the glassy and rubbery parts of the polymer into account. The main release mechanism of their model is the diffusion but the idea of a moving boundary due to the swelling is also used in the model. Peppas et al. used KCI as a drug, hydroxypropyl methyl cellulose (HPMC) as polymer matrices and water as a solvent for the drug release experiment as a comparison with their model. The diffusion coefficient of a drug in the rubbery part of the polymer is a function of solvent concentration in the polymer. However, due to the high solvent content in the rubbery part of the polymer they assumed a constant average diffusion coefficient in the rubbery polymer. They also assumed the solvent only exists in the rubbery part of the polymer and in the external environment.

Peppas model is similar to the model proposed by Cohen and Erneux (1988b)[6] except for the drug diffusion in the glassy part of the polymer. After non-dimensionalisation, Peppas. Obtained the steady state solutions of the model. They claim their model can accurately predict the drug and solvent concentrations in the polymer for most of the time except the initial time of release when they compare their model to the experiment result.

Peppas- Korsmeyer(1986)[13] proposed a model for the swelling controlled release system and utilised concentration dependence of diffusion coefficients. The model does not make the distinction between the glassy and rubbery parts of the polymer.

Korsmeyer model is simpler than Peppas model(1980)[9]but has the solvent dependent diffusivities which is also used in Siepmann(1999) [14].They solved the model numerically using finite difference methods and studied the model for different scenarios.

Lee and Peppas(1987)[15] investigated the solvent penetration of the swelling controlled release system based on the Fickian equation with very small initial film thickness. This viewpoint is also supported by Hopfenberg(1978) who considered the polymer dissolution in the model. After non- dimensionalisation, Lee and Peppas used a pseudo-steady state assumption to obtain the approximate analytical solutions which implies the volume fraction of solvent is a linear function of space variable after a certain period of time. And compared the resulted model with experimental results.

The above two sections review and discuss different mechanistic models of the swelling controlled drug release system. In contrast to mechanistic models, the other popular modelling approach is the empirical model which quantifies the drug release without using the exact description of the involved chemical and physical phenomena. In practice empirical models are generally less accurate than the mechanistic models but easier to use. Generally empirical models describe the normalised amount of drug released from the polymeric network.

Some empirical models exhibit the zero order release which is dmt/dt is constant and is favored by the pharmaceutical industry due to the control on the dose. The empirical models are also developed in the erosion controlled release system. Besides the power law of time, the exponential function of time is also used to describe the normalised amount of drug released from the polymeric network in the erosion controlled release system.

2.1.3 Erosion controlled release system

Erosion is the main feature for degradable polymers in the biomedical applications. Upon contact with thermo-compatible solvent, the backbone of the polymer is mostly broken by hydrolysis or other chemical reactions that depend on the type of solvent and polymer constituents. The polymer then gradually degrades and eventually disappears into its surroundings via the diffusion of the monomers which are the products of the erosion reaction. The two types of polymer erosion are bulk erosion and surface erosion. Bulk erosion means the polymer undergoes the erosion homogeneously because the rate of solvent diffusion in the polymer is faster than the rate of polymer degradation in the polymer. On the other hand, surface erosion is heterogeneous. The polymer undergoing the surface erosion is less hydrophilic than the polymer undergoing bulk erosion. The rate of polymer degradation in surface erosion is faster than the rate of solvent diffusion in the polymer. Hence, the erosion starts from the surface of the polymer and the solvent only penetrates into the polymer exterior.

In terms of hydrogel, the hydrophilic polymer swells and forms a gel layer when the thermodynamically compatible solvent diffuses into the polymer. The polymer chains disentangle in the gel layer and start to diffuse after an induction time at the surface of the polymer where the polymer chains are diluted enough. Therefore hydrogel has the feature of swelling and surface erosion. The following reviews document models of the erosion controlled release system that involve bulk erosion and surface erosion. Again we hope to determine the important phenomena of the erosion controlled release systems mathematically after reviewing these models.

2.1.3.1 The surface erosion

Devotta et al. (1994)[16] proposed a model of polymer dissolution from a polymeric sphere and the model is categorised as surface erosion because the radius of the polymeric sphere reduces with time. The model does not involve the drug. The model does not make the distinction between the glassy and rubbery parts in the polymer because Devotta et al. (1994) assumed the transition process from the glassy state to the rubbery state is rapid. Devotta et al. (1994) proposed a reptationtime Trept which is the minimum time that a polymer chain requires to reptateout of the entangled swollen network and diffuse itself.

Narasimhan and Peppas (1996a)[17] proposed a model of polymer dissolution that only involves and polymer molecules. The model is classified as surface erosion. Narasimhan and Peppas solved the model numerically and found the dissolution mechanism is affected by the polymer molecular weight. However, Narasimhan and Peppas did not present the parameter value in the model.[2]

Narasimhan and Peppas (1997a) proposed a one-dimensional model of drug release that include the effect of polymer dissolution. They use a water soluble, crystalline drug in their model and the drug is loaded into an amorphous, uncross linked and linear polymer film. The model includes the solvent, polymer and drug.[2]

Siepmann et al.(1999)[14]proposed a two-dimensional model of drug release that includes theeffectofpolymerdissolution.Themodelincludesthesolvent,drugandpolymer.[14]

Siepmann and Peppas(2000)[18]improved the model proposed by Siepmann et al.(1999)by adoptinginhomogeneousswellingofpolymernetworks(thesequentiallayermodel)and includedpoorlywater-solubledrugsandhighinitialdrugloadings.Thenewassumption usedbySiepmannandPeppasistherateofdrugdissolutionwithinthepolymerisfaster than the rate of the drug diffusion. The polymer swelling now occurs layer by layer fromthesurfaceofpolymernetworktowardsthecentreandthisisdonenumericallyby modifyingthestructureofthegrid.

Wuetal.(2005)[19]proposedatwo-dimensionalmodelofdrugreleasethatincludestheeffect of polymer dissolution and the model is similar to the model inSiepmann et al.(1999) [14]Wuetal.(2005)usedtheconcentration-dependentdiffusivitiesandderivedanequation forthecontinuouslyvariedvolume.

2.1.3.2 Thebulkerosion

Charlieretal.(2000)[20]proposedadrugreleasemodelforadegradableslabandthemodelis bulkerosionwithoutamovingboundary. Charlieretal. (2000)usedpseudosteady-state approximationtomodelthedrugreleaseandmodelledthelossofpolymermass. Theyalsopostulatedthatthediffusioncoefficientofdrugdependsonthepolymermolecularweight.T he idea of linking the diffusion coefficient of drug and the polymer molecular weight together is also supported byFaisantet al. (2006)[21] who proposed an equation of drug release fromsphericaldevicethat undergoesbulkerosion.Inaddition,severalresearchers have modelled the bulk erosion by reaction-diffusion and they are Lyu et al. (2005)[22],Rothstein et al.(2009)[23]etc.

2.2 Comparative researches:

Further researches tend to comparison between different drug release models, as in this research.Ramteke K.H[24], compared between Higuchi, First order, Hixson-Crowell cube root law, Gompertz model, Hopfenberg model, Korsmeyer-Peppas, Weibull model, Hixon-crowell and Baker Lonsdale.G.S.N.Koteswara Rao, who compared between first and zero-order models.Costa, P. and J.M. Sousa Lobo,(2001)[25], compared between Zero order, First order, Second order, Hixson–Crowell, Weibull, Higuchi, Baker–Lonsdale, Korsmeyer–Peppas, Quadratic, Logistic and GompertzHopfenberg, and concluded that The release models with major appliance and bestdescribing drug release phenomena are, in general, the Higuchi model, zero order model, Weibull model andKorsmeyer–Peppas model. The Higuchi and zero ordermodels represent two limit cases in the transport and drugrelease phenomena, and the Korsmeyer–Peppas model canbe a decisionparameter between these two models. Whilethe Higuchi model has a large application in polymericmatrix systems, the zero order model becomes ideal todescribe coated dosage forms or membrane controlleddosage forms.

HussainLokhandwala(2013)[3], compared between Zero order, First order, Higuchi model, Hixon-crowell, Korsmeyer-Peppas model, Baker-Lonsdale model and Weibull model. They concluded that the reviews of the kinetic modeling on drug releaseillustrate that these models have beenrecognized to describe the relationship betweendrug dissolution and geometry on drug releasepatterns mathematically. It is evident from thepharmaceutical literature that no singleapproach is widely accepted to determine ifdissolution profiles are similar. The applicationand evaluation of model dependent methodsand statistical methods are more complicated,whereas the model independent methodspresent satisfactory model approach to the truerelationship between the dependent andindependent variables of the dissolution data.

Chapter 3 Methodology

3.1 Introduction:

In the past; drug delivery systems was used in many applications, e.g. for food, cosmetics and medical applications. Traditional drug regimens include oral, inhalation, topical and injection dosage forms. Controlled-release drug delivery systems are being developed as alternatives to conventional medical drug therapy regimens for pharmaceuticals that require frequent administrations. Many mathematical models have been developed for polymeric drug delivery systems, and a lot of modeling e□orts have been published. The activation energy for the initial velocity of glassy-rubbery interface is close to the crazeformation.

3.2 Methodology

3.2.1 Operating Parameters

Optimization of the operating parameters and formulation with regard to their influence on nanoparticle physical properties and drug release rate was carried out prior to this work (Eltayeb et al., 2013)[26] and the operating parameters for this study (i.e. polymer concentration, drug concentration (

Table 1)

Table 1: operating parameters and formulation[27].

	Drug (weight %**)**	**Polymer (**weight %**)**	D**iameters of the nanoparticles** size
S1	1	1	52
S2	1	2	56
S3	1	3	59
S4	1	4	65
S5	2	4	63
S6	3	4	61
S7	4	4	58

Using the parameters represented in the (

Table 1), we examined which release model gave the best fit to the experimental results[27].

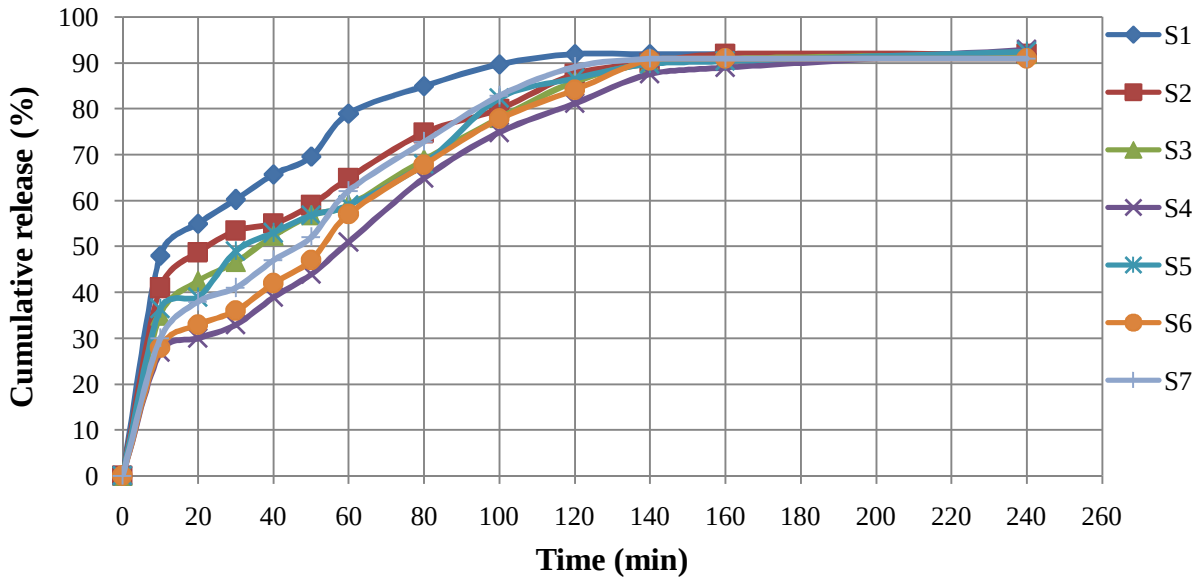


Figure 7: Drug release profile for nanoparticles with different sizes[27].

3.3 Mathematical Model for Release Models:

Next MATLAB was used to analyse the commonly used equations in modelling drug delivery systems. M.file was used to display release curves for each equation with aid of (plot) instruction. Where X-axis represents time (t) and Y-axis represents rate of release (q). Next step was measuring (R^2) value for each curve using excel program. Comparing different (R^2) values help to determine which curve is the best. Equation which have corresponding properties were compared to choose the best equation for different cases. Represents the effects of different models on release rates, where drug release (Q) = (y-axis), and time (t) = (x-axis).

3.3.1 Zero-Order Model:

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Q(t) = Q(0) + Kt$$

where Q t is the proportion of drug released in time t, and K 0 is the zero order release constant with units of inverse time.

Figure 8 shows the relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low solubility drugs in coated forms, osmotic systems, etc.[25]

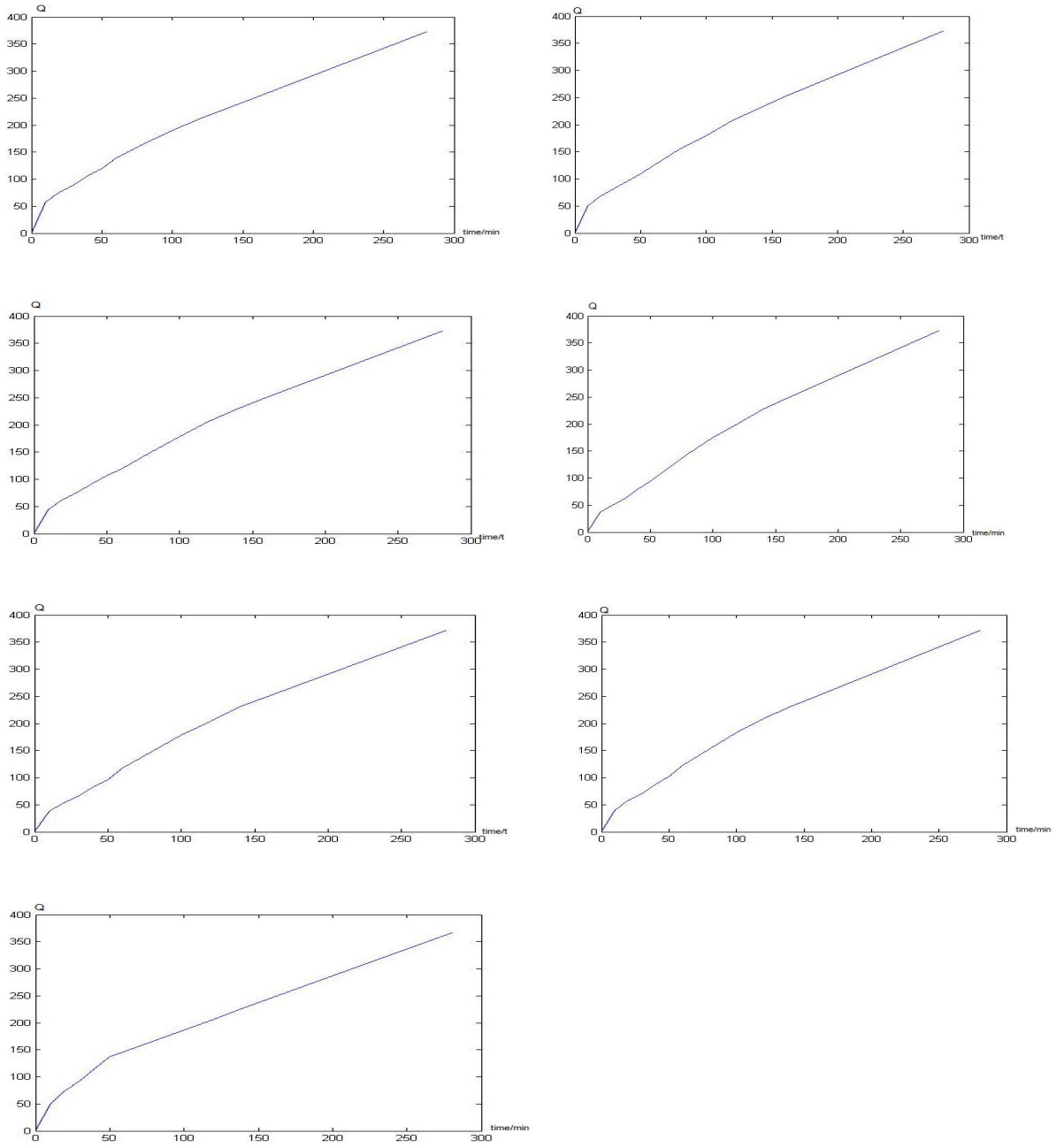


Figure 8: Release kinetics zero order model form nanoparticles with drug; S1, S2, S3, S4, S5, S6, and S7 in order.

3.3.2 First Order Model

This model also known as the homogeneous model has also been used to describeabsorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis.

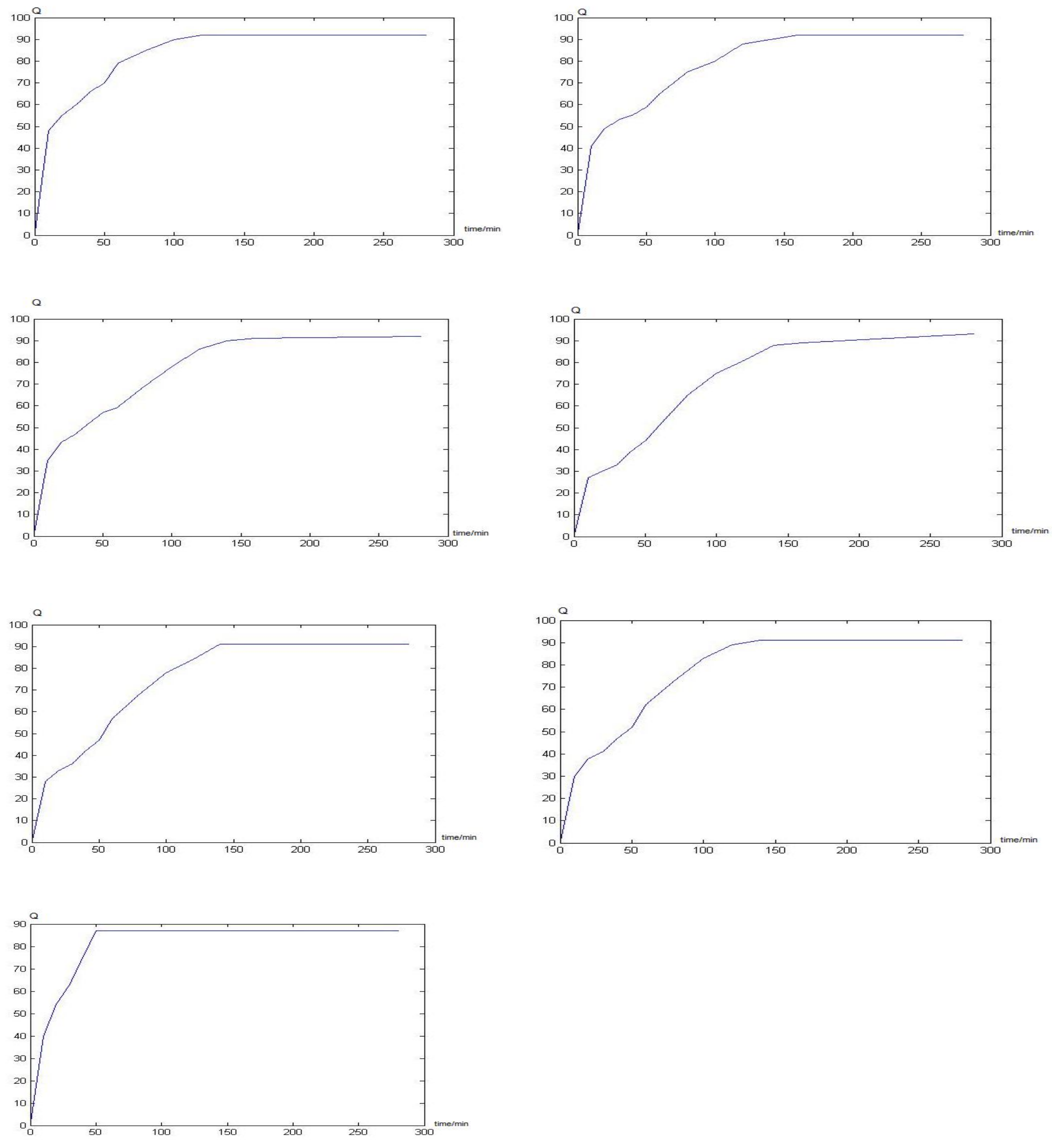


Figure 9: Release kinetics first order model form nanoparticles with drug; S1, S2, S3, S4, S5, S6, and S7 in order.

The release of the drug which followed first order kinetics can be expressed by the equation:

$$Q_t = Q_\infty (1 - e^{-K_1 t})$$

where Q∞ is the total fraction of drug released from the nanoparticles, Qt is the proportion released in time t and K1 is the release constant

Figure 9 show the relationship can be used todescribe the drug dissolution in pharmaceuticaldosage forms such as those containing water-solubledrugs in porous matrices[28].

3.3.3 Higuchi Model

This model is used to study the release of water soluble and poorly soluble drugs incorporated in semi-solid and/or solid matrices. Mathematical expressions are obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. To study the dissolution from a planar system having a homogeneous matrix, the relation obtained is as following:

Where *Q* is the amount of drug released in time *t* per unit area, *C* is the drug initial concentration or the drug solubility in the matrix media and *D* is the diffusivity of the drug molecules (diffusion constant) in the matrix substance. This relation was first proposed by Higuchi to describe the dissolution of drugs in suspension from ointments bases, but is clearly in accordance with other types of dissolution from other pharmaceutical dosage forms.

where Q t is the proportion of drug released in time t, and K is the Higuchi dissolution constant.[3]

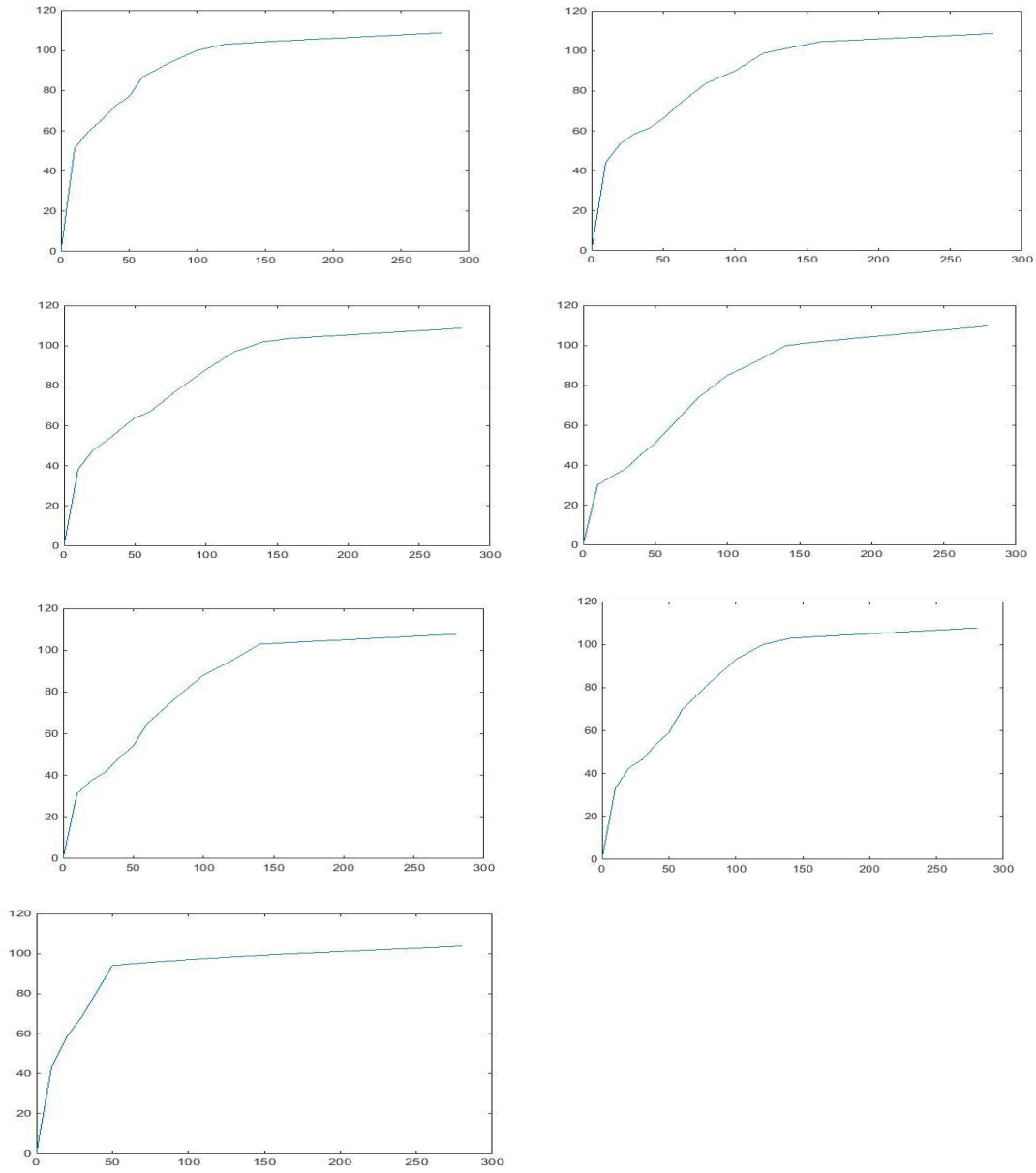


Figure 10: Release kinetics Higuchi model form nanoparticles with drug; S1, S2, S3, S4, S5, S6, and S7 in order.

To these dosage forms a concentration profile, which may exist after application of the pharmaceutical system, can be represented. This relation is valid during all the time, except when the total depletion of the drug in the therapeutic system is achieved. To study the dissolution from a planar heterogeneous matrix system, where the drug concentration in the matrix is lower than its solubility and the release occurs through pores in the matrix, the expression is given by equation: Where D is the diffusion coefficient of the drug molecule in the solvent, d is the porosity of the matrix, t is the tortuosity of the matrix and Q, A, Cs and t have the meaning assigned above. In a general way it is possible to simplify the Higuchi model as (generally known as the simplified Higuchi model):

3.3.4 Hixson-Crowell

This model is based on a physical model of dissolution of a solid particle: dissolution takes place at the surface and as the material dissolves the size of the particle reduces.

$$Q_t = Q_\infty \left(1 - (1 - \alpha t)^3\right)$$

where Q∞ is the total fraction of the drug released from the nanoparticles, Qt is the fraction of drug released in time t and α=9KHC/r0 depends on the release constant for Hixson-Crowell release.

Figure 11 show the relationship can be used to describe the drug dissolution from several types of modified releasepharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with watersoluble drugs [24].

This expression is applied to Pharmaceutical dosage form such as tablet; where the dissolution occurs in planes which is parallel to drug surface if dimensions of the tabletdiminish proportionality, in such a manner that the initial geometry form keep constant all the time[29].

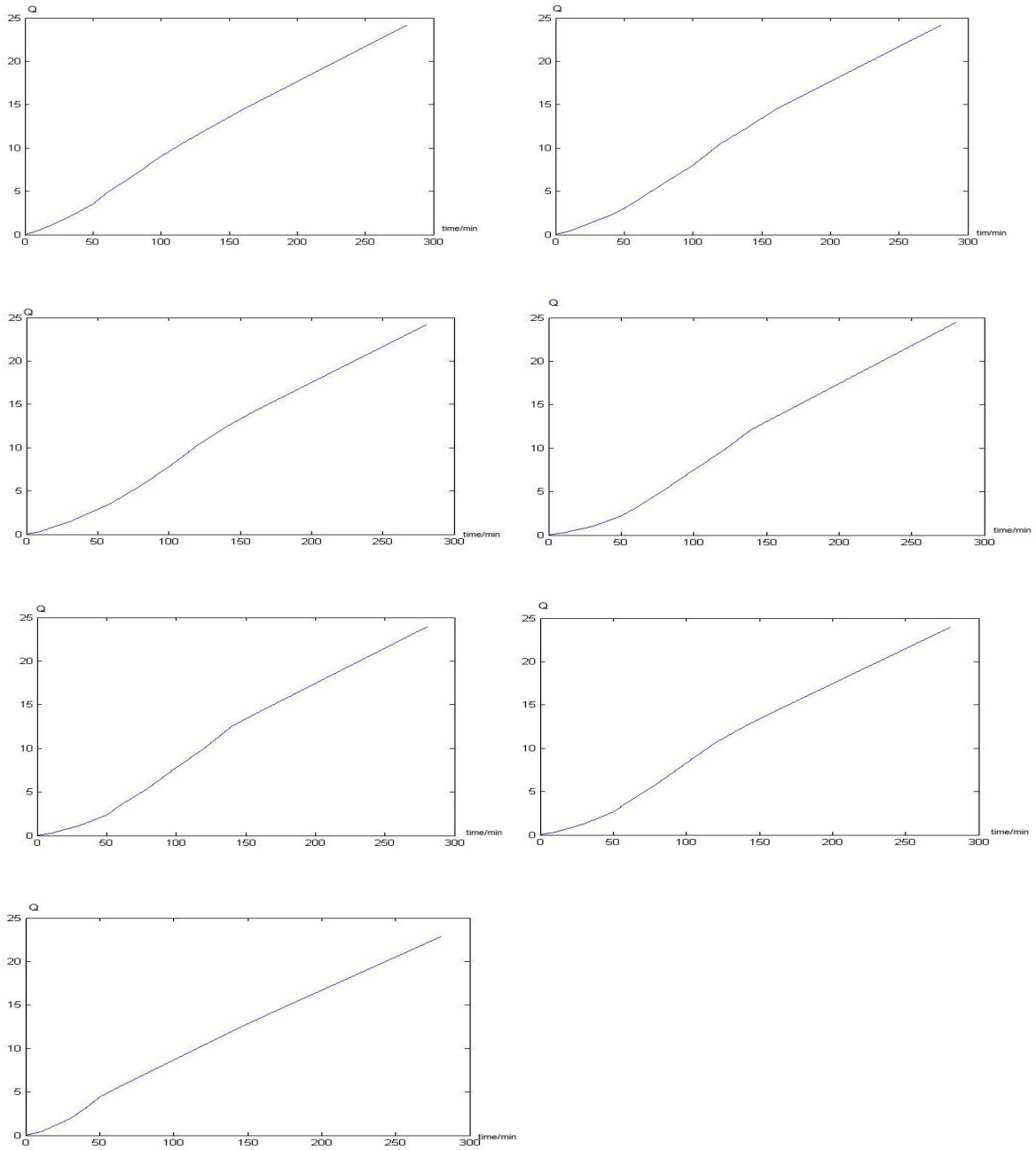


Figure 11: Release kinetics Hixon-Crowell model form nanoparticles with drug; S1, S2, S3, S4, S5, S6, and S7 in order.

3.3.5 General Power Law Model

One could lump together the zeroth-order, first-order and Hixson-Crowell models as generalised power-law models, of the form

with the zeroth-order model corresponding to n = 0, the first-order model(with a logarithmic rather than powersolution) n = 1 and the Hixson-Crowell model n = 2/3, following clearly from the assumption of dissolution
from the surface of a shrinking volume. One could imagine situationsin which dissolution produces an irregular surface, with a power lawn > 2/3, but this is unlikely for nanoparticles.

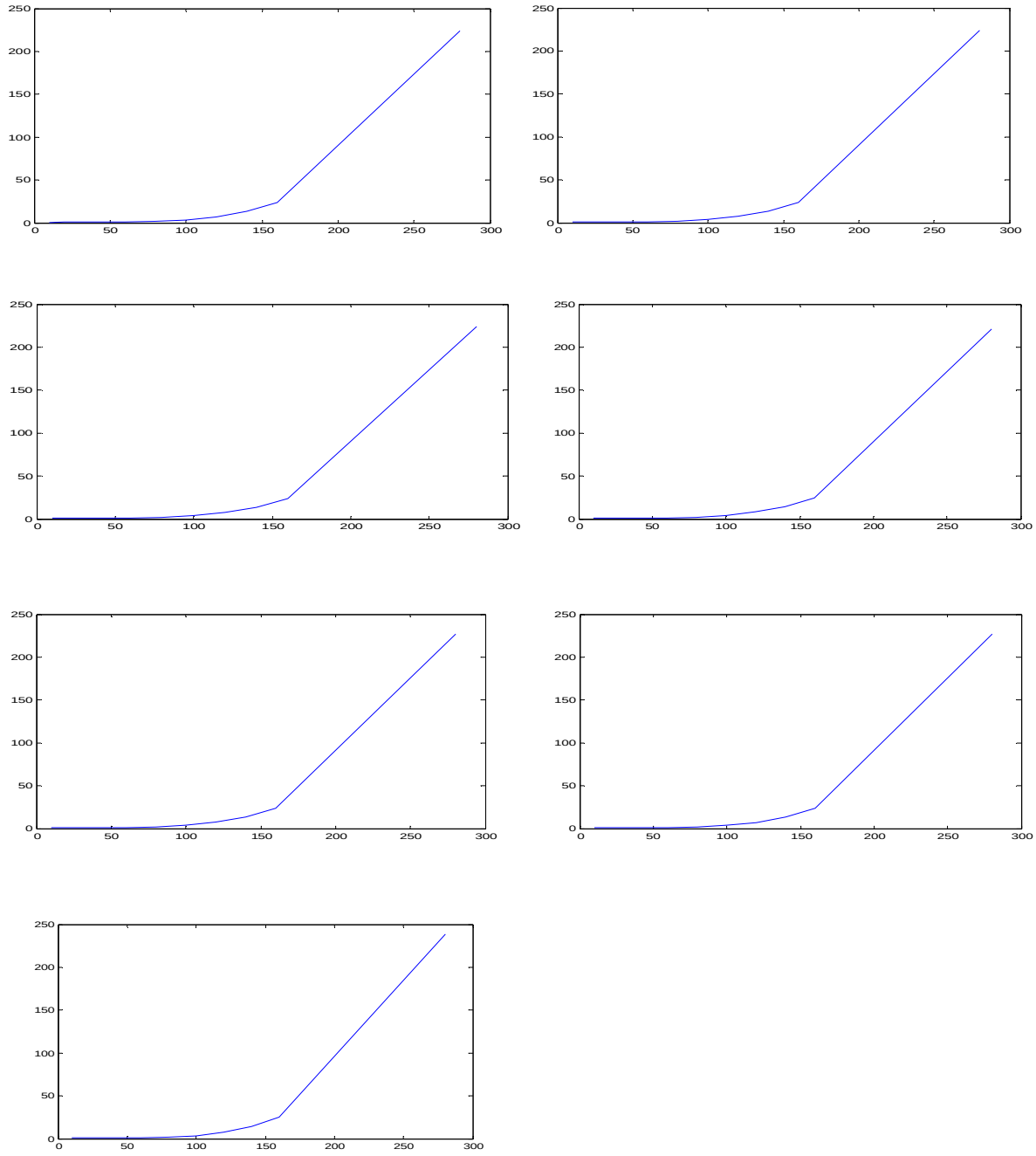
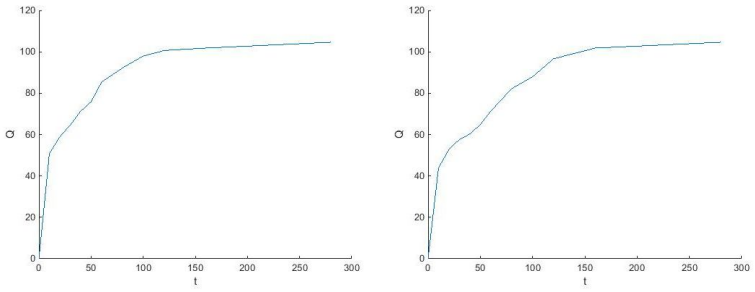


Figure 12: Release kinetics power law model form nanoparticles with drug; S1, S2, S3, S4, S5, S6, and S7 in order.

3.3.6 Ritger-Peppas or Korsmeyer-Peppas Model

In a series of papers, Peppas and collaborators solved the equations for diffusive release of solute from a particle: it was assumed that solute was removed rapidly from the surface of the particle, so that the rate is determined by diffusion through the particle. As with Higuchi's model, for short times the fractional release depends on the square root of the time. Ritger and Peppas then fitted a power law to the portion of the release up to 60% to a power law

where n is typically slightly less than 0.5 They claim that the value of n can be used to determine the geometry of the system (they compared cylindrical and spherical particles) and to detect non-Fickian and more complex release mechanisms. For spherical particles at short times they find



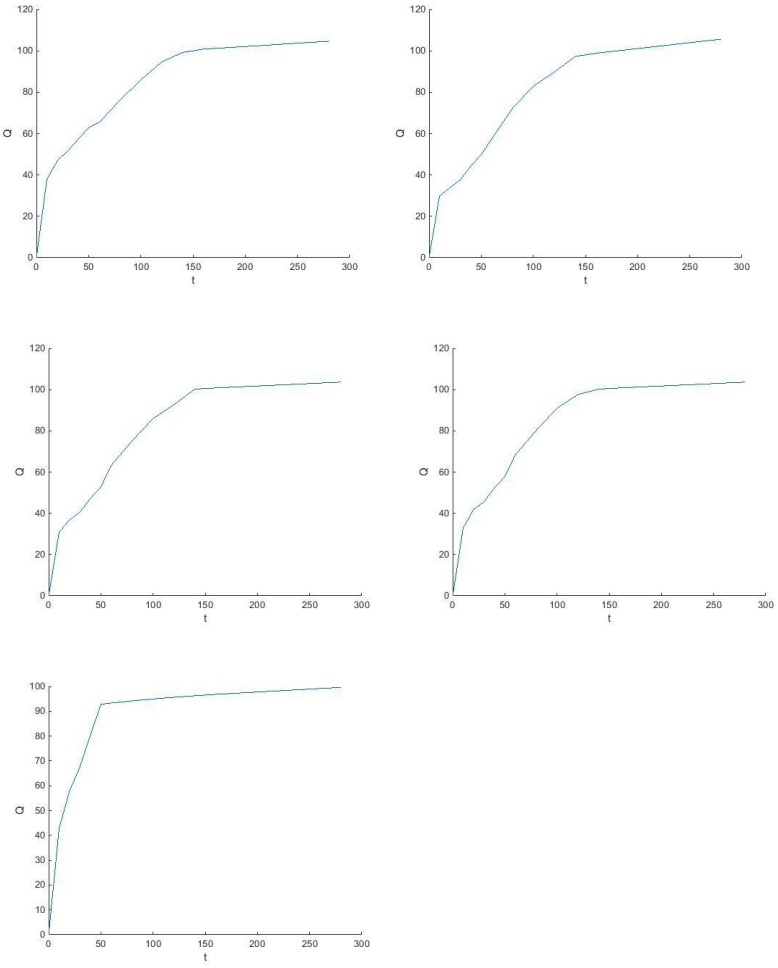


Figure 13: Release kinetics Korsmeyer-Peppas model form nanoparticles with drug; S1, S2, S3, S4, S5, S6, and S7 in order.

This model isdescribe the drug release from several modified release dosage forms[24].

3.3.7 Weibull Model

This model has been described for different dissolution processes as the equation

$$Qt = Q\infty(1 - e^{-at^b})$$

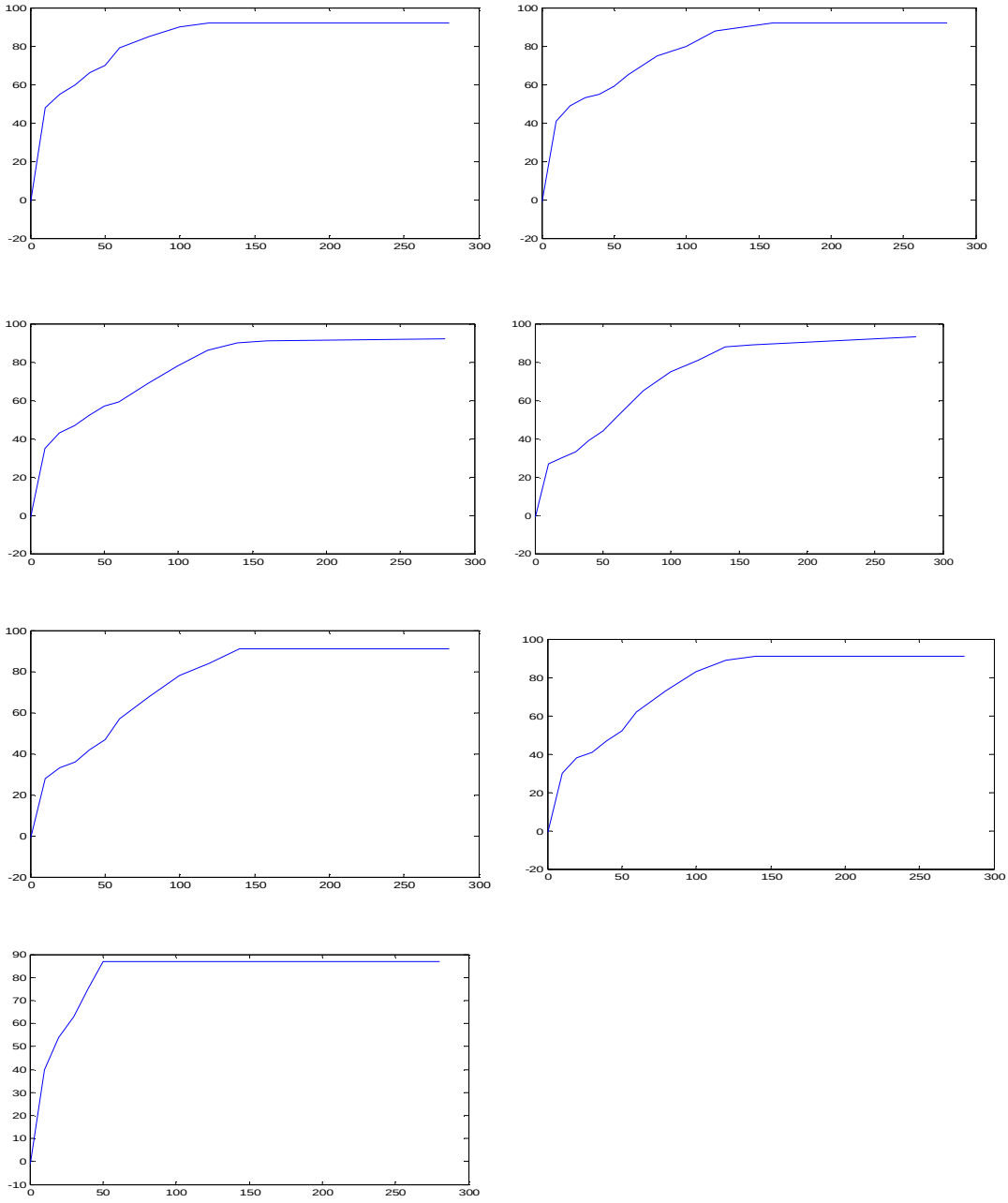


Figure 14: Release kinetics weibull model form nanoparticles with drug; S1, S2, S3, S4, S5, S6, and S7 in order.

And is characterised by a shape parameter b and a scale parameter a. For b = 1 this coincides with the first-order model. It is more use full for comparing release profiles of matrix type drug release.[28]

3.3.8 tanh model:

Because of need for a model for diffusive release from a homogeneous particle which could be applied across the whole release process not one which not limited to a part of the process or which had to be artificially truncated to limit the release to 100%. We therefore developed an expression based on the same diffusive release model as used by Peppas and collaborators but applicable to the whole of the release process:

where $Q\infty$is the total fraction released from the nanoparticles, Qt is the fractionreleased in time t and is a constant which may berelated to the particle size and diffusion constant.[27]

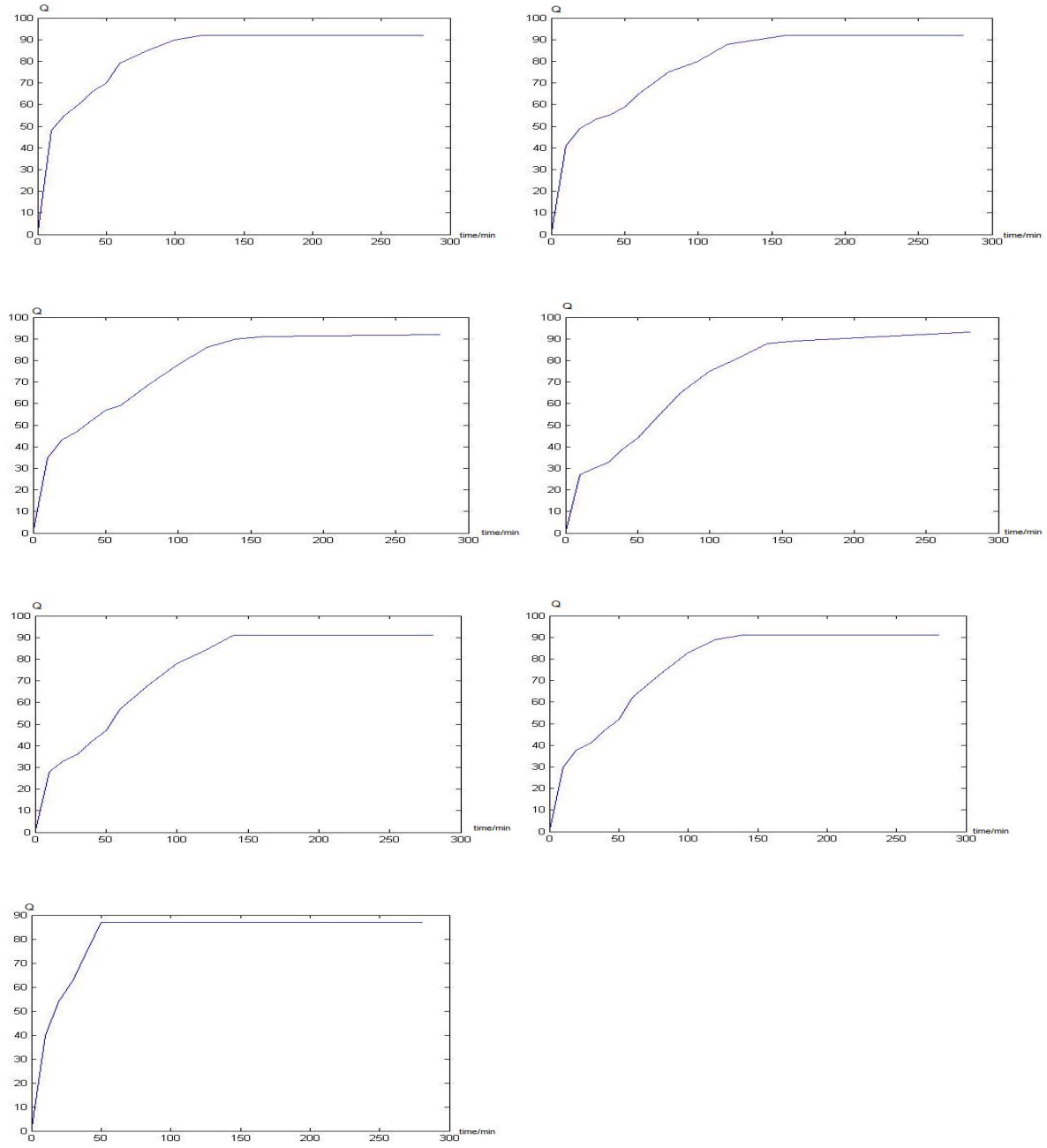


Figure 32: Release kinetics tanh model form nanoparticles with drug; S1, S2, S3, S4, S5, S6, and S7 in order.

Chapter 4 Discussionand Result

As represented in table1, the value of the drug was constant in S1, S2, S3 and S4 with increased value of the polymer for the same particles.

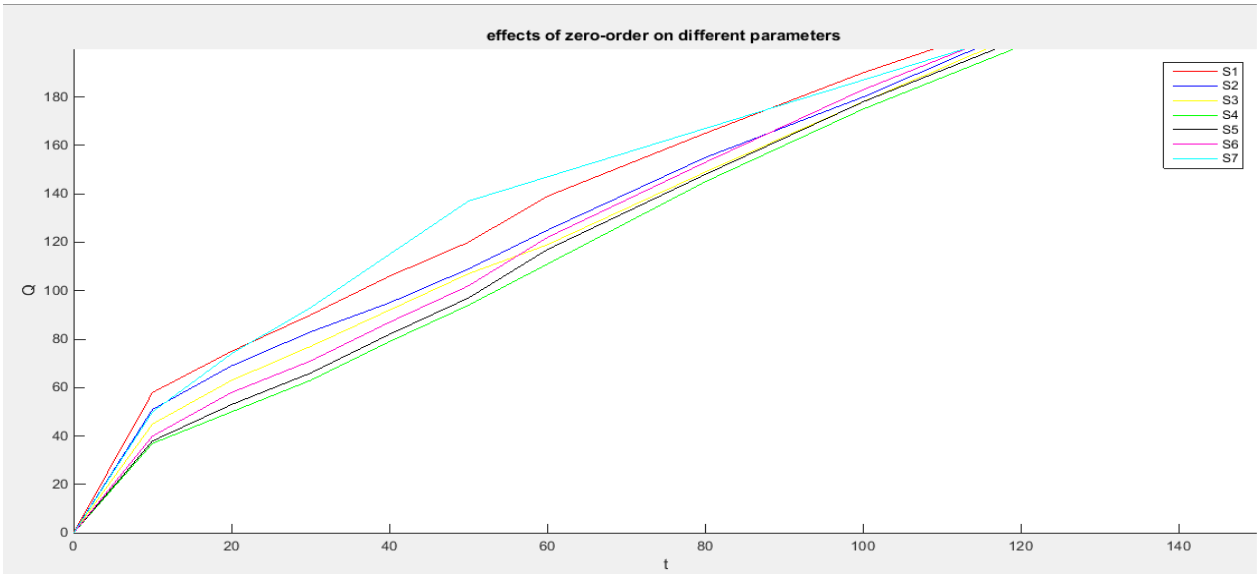


Figure 15: zero-order mechanism using different parameters.

This results in increased thickness-of capsule-which in turn slowed the rate of release. This mechanism is clear in the above curve, where S2 (blue) lies under S1 (red) and so on.

In S4, S5, S6 and S7 values of the polymer was constant with increasing values of the drug. This results in decreased thickness-of capsule-and enhanced release rate. The previous curve indicates that S7 has the highest rate of release.

Zero-order process takes place at constant rate, so at some time it comes to an end.

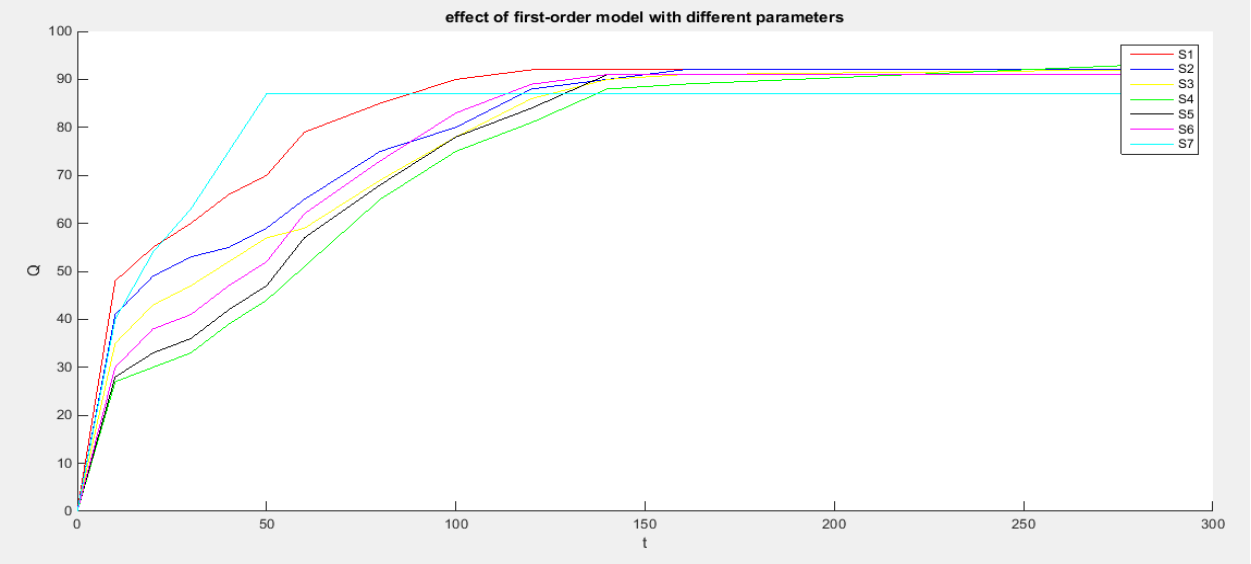


Figure 16: first-order mechanism using different parameters.

The previous model (first order) differs from zero-order in that it is linear kinetic process and it is directly proportional to the drug concentration involved. Also first-order never comes to an end, since it takes place at certain proportion of the concentration existing at that time.

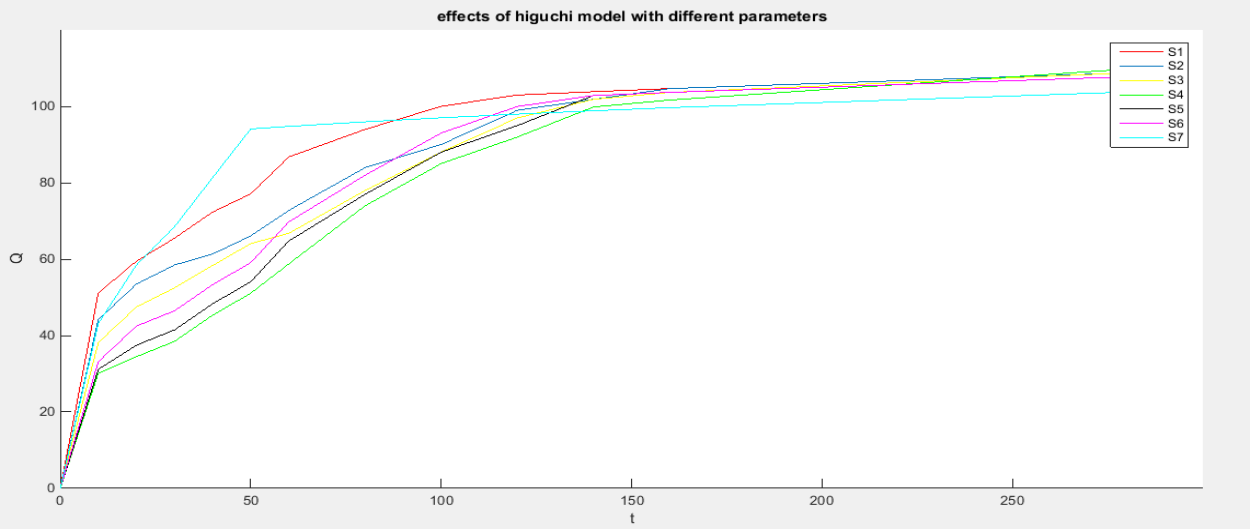


Figure 17:higuchi mechanism using different parameters.

From the previous two figures, it is clear that the first-order model behavior and Higuchi's are approximately the same because both of them were derived from Fick's law.

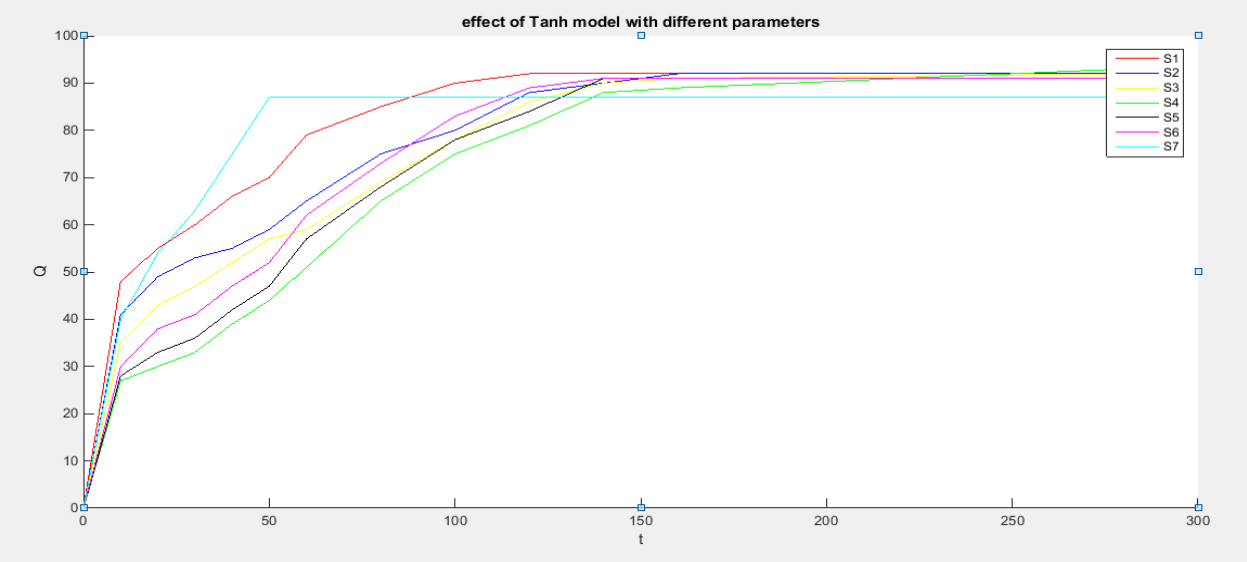


Figure 18: tanh mechanism using different parameters.

As represented in figure 56, tanh model effects was approximately similar to first -order model. This observation was documented in table 2 as values of R^2.

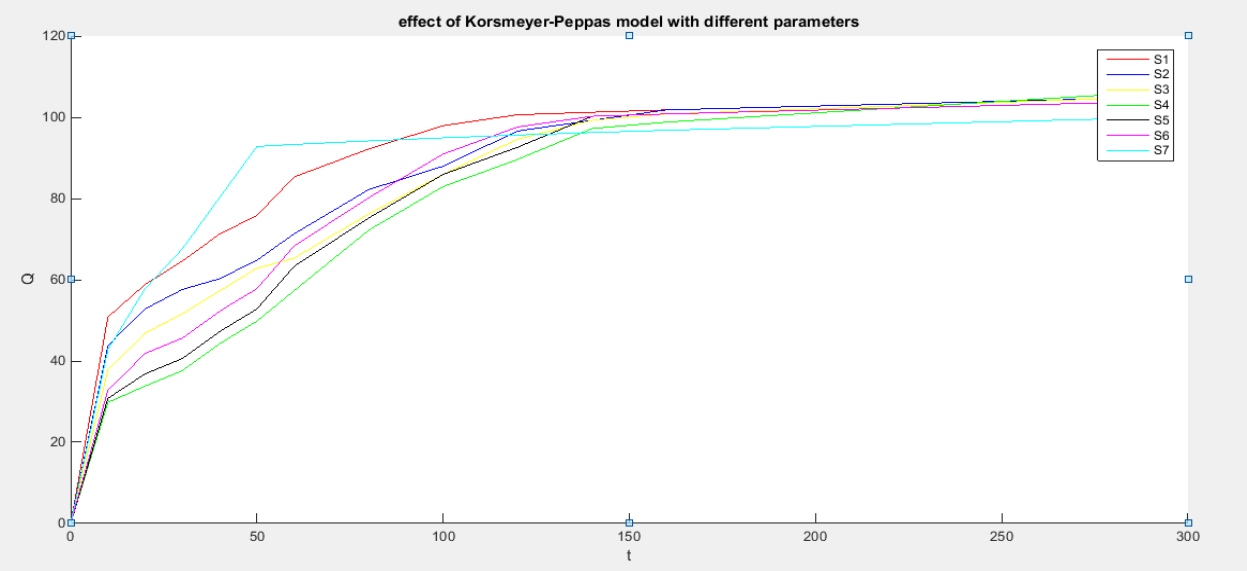


Figure 19: Korsmeyer-Peppas mechanism using different parameters.

Peppas model effects depends on values of (n) which is the release exponent[6]. For the case of cylindrical tablets, if n= 0.45 the curves corresponds to a Fickian diffusion mechanism, and represents approximately same behavior as first-order (figure57).

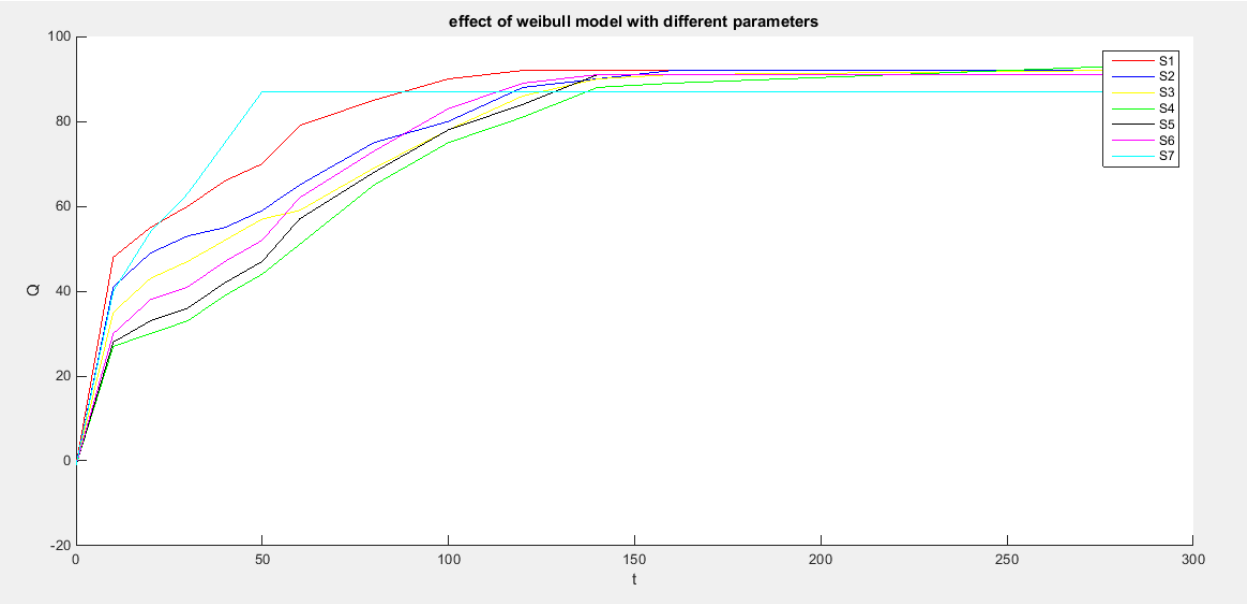


Figure 20: weibull mechanism using different parameters.

The effect of empirical equation of Weibull ,depend on b value [29]. In case of(b>=1), curves behave like the first –order model which is derived from Fick's law. According to the experimental results, this comparison represents that the first –order and tanh models generated the closest values. The other models generated different values with great variance from the experimental results.

In comparison between first-order and tanh, it had been found that tanh models generates values of R^2 approximately equal 1(table 2). So tan models is the best.

Table 2: represents the values of R^2 for the fist-order and tanh models:

	First order	**Tanh**
S1	0.99983	0.9999

S2	0.99985	0.99999
S3	0.99987	0.9999
S4	0.99990	0.9999
S5	0.99999	0.9999
S6	0.99989	0.9999
S7	0.99986	0.9999

Chapter 5 Conclusions and future work

5.1 Conclusion

Model with pore evolution coupled to hydrolysis and related to the effective diffusivity through hindered diffusion theory was proposed to fill the gap in the modelling literature for the simultaneous treatment of polymer properties and drug release with autocatalytic effects and nonconstant effective diffusivity of the drug. The system of partial differential equations comprising the model was solved numerically using the method of MATLAB. The numerical methods and the computational implementation of the model were described in detail. Three limiting cases for the model were presented with the derivations of the analytical solutions and comparison between the solutions and the model predictions.

The model performance for the case of drug release from microspheres of different sizes was presented to highlight the capability of the model for predicting size-dependent, autocatalytic effects on the polymer and the drug release. Limitations of the model were also discussed. The model presented in this dissertation can be used to investigate the dynamic behavior of the polymer and drug system under different physical conditions. The model may also be extended to apply to other drug delivery systems for similar types of polymers and other device geometries such as nanoparticles composed of layers of different microspheres. Drug characteristics like hydrophobicity and pH sensitivity also can be incorporated with knowledge of effects of the drug-polymer interactions on the physical parameters of the model. Further utilization of the model developed in this work could aid in the development of a database that could include the predictions of the effects of many possible polymer nanoparticle fabrication designs under a range of conditions. The optimum design for producing a desired drug release profile could be determined, which would be important for manufacturers making nanoparticles for medical therapeutic use in patients. The nanoparticles were found to have a core-shell structure, with the thickness of the outer polymer layer being dependent upon the concentration of polymer. The encapsulation efficiency and loading capacity were similarly found to be dependent on the polymer to drug concentration ratio; although there was found to be a limit above which both started to decrease. It was shown that the release of the drug was consistent with diffusion through a polymer membrane. A new release model incorporating a tanh function provided the best overall fit to the time dependence of the release of drug from the nanoparticles.

5.2 Future work

- Enhancing drug encapsulation yield
- Polymeric materials characteristics satisfying the requirements for the pharmaceutical industry
- Polymeric materials value, satisfaction and demands in the pharmaceutical industry
- Controlling nanoparticles monodisperse size
- Investigate (NPs) morphology under various governing parameters
- Investigate production of consumable nanoparticles of different materials to improve pharmaceutical industries
- Improve drugs delivery quality
- Enhancing drug encapsulation efficiency
- Enhancing drug encapsulation yield

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