CHAPTER 9

IN VITRO DRUG RELEASE STUDY

IN VITRO DRUG RELEASE STUDIES OF FRUSEMIDE LOADED CALCIUM ALGINATE MICROPELLETS

9.1 Introduction

In recent years, much attention has been focused on the problem of drug availability and usually is determined by the rate of release from the physical system commonly referred to as the dosage form. The release of the drug from the system is in turn governed by such processes as the absorption of the drug in the system, the dissolution rate of the drug and other factors. As early as 1948, it was recognized that while the efficiency of a compressed tablet is to some degree related to the rate of disintegration, the dissolution of the drug is of prime importance.[1]

The development and use of *in vitro* models to stimulate and describe dissolution and absorption *in vivo* serves three useful purposes. Firstly, when a successful model that adequately mimics the *in vivo* situation, has been developed it is likely that the physico-chemical properties existing in the model may also be of significance in the *in vivo* process. Second, is the use of these model systems to screen potential drugs and their associated formulations for their dissolution and absorption characteristics? If an *in vivo* and *in vitro* correlation has been established, meaningful quantitative screening can readily be undertaken by the use of the model system. Even in the absence of *in vivo* data or *in vitro* and *in vivo* correlation, it is possible to predict, on the basis of *in vitro* data alone, which form of the drug or dosage form will result in optimization of a particular designed effect. Third, *in vitro* model systems, especially those concerned with the dissolution process, can serve as quality control procedures once the form of the drug and its formulation has been established. Parrot *et al*[2] clearly indicated the importance of dissolution kinetics. Subsequently, Nelson and coworkers[3,4,5] reported that the dissolution rate does indeed control the rate of build up of certain drugs in the blood stream. In a review article dealing with drug absorption, Wagner[6] discussed the dissolution rate in some details and indicated its importance in the absorption process.

The dissolution test can be a good index of bioavailability if it meets two conditions, namely,

1. The dissolved drug remains free and intact and does not decompose or form a drug complex with food in the gastrointestinal tract, and,

2. Dissolution and not absorption, is the rate-limiting step in the availability of the drug in the systemic circulation.

9.2 Theories of Dissolution

Higuchi [7] described three processes, which either alone or in combination describe dissolution rate mechanisms, the diffusion layer model, the interfacial barrier model and Danckwert's model. Dissolution by diffusion layer model is diffusion limited and consists of two stages:

1. Interaction between the solvent with surface of the drug, resulting in the hydration and solvation of the drug to form a saturated layer around the drug particles.
2. The diffusion of drug molecules into the bulk of the system.

The diffusion of drug away from the saturated layer is regarded as the rate-determining step. Therefore, this model regards the rate of dissolution as being diffusion-limited. Once the molecules of the solute pass the liquid film/bulk interface, rapid mixing will destroy the concentration gradient. In the interfacial barrier model, it is proposed that all collisions of solvent molecules with the solid surface do not result in release of solute molecules because of high free energy of activation requirements. Danckwert's model postulated that removal of solute from the solid is achieved by microscopic pockets of solvents being carried right up to the solid - liquid interface by eddy currents. Goyan[8] used Danckwert's model to study the dissolution of spherical particles.

9.2.1 Factors affecting the rate of dissolution of drugs from solid dosage form[9]

Important factors that affect the rate of dissolution of drugs from solid dosage forms are summarized below:

1) **Environmental factors during dissolution:**
    i) Intensity of agitation, rate and type of flow of fluids and geometrical factors of dissolution apparatus.
    ii) Concentration gradient, i.e. the differences in concentration between the solubility of the drug in the dissolution medium and the average concentration in the bulk field.

iii) Composition of the dissolution medium, the pH, ionic strength, viscosity, surface activity, enzymes, etc. are all important and the rate of dissolution is determined by the composition of the medium.

2) Factors related to the physicochemical properties of the drug:

A. Factors affecting solubility:-

1. Polymorphism.
2. Amorphous state and salvation.
3. Free acid, free base or salt form.
4. Complexation, solid solutions and eutectics.
5. Particle size.
6. Surfactants.

B. Factors affecting surface area available for dissolution:-

1. Particle size.
2. Manufacturing variables.

3) Factors related to the composition of dosage form and method of manufacture:

These factors vary widely depending on the particular solid dosage form, the excipients and the manufacturing processes.

4) Environmental factors involved with dosage forms:

1. Humidity during manufacture.
2. Storage conditions of dosage forms.
3. Age of dosage forms.

Drug release rate or dissolution rate is the amount of the active ingredient of a solid pharmaceutical preparation, which is dissolved within a unit of time, under strictly controlled conditions in a fluid medium surrounding the sample.[10]

Restricting this discussion to orally administered solid dosage forms containing drug, the dissolution process must be rate-limiting with respect to the absorption process if the former is going to exert an effect on the rate and the amount of drug appearing in the body. This, in turn, will control the onset, duration and intensity of the pharmacologic response of the drug. This dependence on dissolution rate for biological availability is generally only

significant with relatively water insoluble drugs. The physicochemical factors that control the rate of dissolution may be detected from the previous discussion on the theories of dissolution. These include temperature, degree of agitation, pH, solubility, concentration gradient, composition and viscosity of dissolution medium and its potential for micellar solubilization, the presence of active or inactive additives, drug polymorphism, crystal mass and effective surface.

It is evident that dissolution rate is subject to a large number of physicochemical influences. It is of great practical value of studying these effects in biological systems.

5) Factors influencing dissolution related to Apparatus and Test parameters:

A. Volume of dissolution fluid:-

Volume of the dissolution fluid should conform to the volume of the physiological secretion, which is illustrated in Table 9.1.1

Table 9.1.1 Secretion in GI tract (ml/day)[11]

Saliva	500-1500
Stomach	2000-3000
Duodenum and Pancreas	300-1500
Gall Bladder	250-1100
Jejunum	3000

Though USP XX prescribed 1 litre of volume for satisfactory maintenance of sink condition, which is also dependent on the saturation, 3, 4 or 5 litres of volume have also been reported[12,13,14,15]. In the present study, 900 ml of volume was used to maintain the perfect sink condition.

B. Effect of pH:-

The effect of pH on the dissolution rate of drug from an oral dosage form depends on:

1. The pH of the gastrointestinal fluids, a patient variable.
2. The acid or base strength of the drug, a pharmaceutical variable.
3. The physicochemical properties of the dosage form, another pharmaceutical variable.

An orally administered solid dosage form will be subject to a gradient of pH change ranging from acidic in the stomach (the average pH of gastric fluid in men is about 1.9 while it is reported to be approximately 2.6 for women[16]), to neutral medium in the intestine (the pH of the duodenal secretion for both men and women varies from 5.8 to 7.6[17]). This change in pH will affect the solubility and degree of ionization of acidic or basic drugs, and consequently the dissolution rate and the rate of absorption. The pH of the dissolution fluids simulating the 'in-vivo' pH conditions should be as follows (Table 9.1.2):

Table 9.1.2 Dissolution mediums in respect of pH [18]

Medium	pH
Simulated Gastric fluid	1.0 – 4.5
Simulated Intestinal fluid	4.5 – 8.0
Simulated Jejunal fluid	4.5 – 7.5
Simulated Ileum fluid	7.5 – 8.0
Rectum	7.2 – 7.5

The salt form of the drug dissolves much faster than the non-ionized forms or zwitterions in all media and more of the salt forms of the drugs are absorbed and subsequently excreted in each time period. For a dissociable drug, either an acid or base, the pH of the gastrointestinal fluids will determine whether the drug is ionized and/or non-ionized. It has been derived that as the pH increases, the dissolution rate of a weak acid increases and the dissolution rate of a weak base decreases.

In recent years, the FDA has been gathering *in vivo* and *in vitro* data on controlled release dosage forms that strongly suggest that the pH specificity of the drug or the formulation may often affect the controlled release profile. A formulation with pH dependent *in vitro* dissolution profile may behave poorly *in vivo* because it is subjected to pH variation along the gastrointestinal tract and it is at the mercy of gastrointestinal motility, in particular, gastric emptying. Furthermore, there is the possibility that the prevailing gastric physiology, e.g., achlorhydria may also impact adversely on such dosage forms. Similarly, one should be aware of poorly soluble drugs that undergo rapid metabolic or renal clearance. Such drugs will often require clinical trials to establish safety and efficacy.

Ever newer aspect in dissolution testing is the continuous change of pH of dissolution fluid. Takenaka *et. al*[9] have reported the continuous change of pH in a flow cell, simulating

continuous change of pH *in vivo*. Another method for continuously changing pH of dissolution fluids has been reported by B.K.Gupta *et. al.*[20]

C. Effect of Temperature:-

From the reports of the investigations of several workers[21,22,23], it is shown that if a heterogeneous reaction is diffusion-controlled, the 10° temperature coefficient should be in the neighbourhood of 1.3, while an interfacial-controlled reaction possesses a coefficient of about 2.0. The temperature of dissolution medium has been maintained in most of the articles at $\pm$ 1°C, which is also prescribed by USP XXV.

D. Effect of Agitation:-

The agitation intensity affects the process controlling the heterogeneous reactions. Investigations [24,25] involving agitation have led to the following empirical relationship.

$$K = a\,(N)^{b} \qquad (9.1)$$

Where **N** is the agitation or stirring rate, **K** is the reaction rate and **'a'** signifies agitation rate constant and **'b'** as coefficient of agitation. If the reaction is diffusion-controlled, then the value of **'b'** should be 1 or near 1. This is, in accordance with the Nernst-Brunner Film Theory, which stated that the thickness of the film was inversely proportional to the stirring speed. For the reactions controlled by the rate of the interfacial reactions, it would be expected that the agitation intensity would not influence the reaction rate, and **'b'** should approach zero. If both processes are influential in the control of the rate, **'b'** should vary between zero and one, if sufficiently wide ranges of agitation intensities are employed.

Under conditions of natural convection or very mild agitation, the mass transfer coefficient may be obtained from a correlation of the form:

$$S_h = 2 + 0.56(G_r . S_c)^{0.25} \qquad (9.2)$$

where, the left hand side of the equation, the Sherwood number, S_h = **KL/D** ; groups the mass transfer coefficient **K** with a characteristic linear dimension of the system **L**, in this case, the dissolving particle size, and the diffusivity **D** of the solid in the solvent. The right hand side contains two dimensionless groups, the Grashof and Schmidt numbers. The Grashof number takes the form,

$$G_r = L^3 \rho \Delta \rho g / \eta^2 \qquad (9.3)$$

ρ = solution density,

$\Delta \rho$ = density difference between bulk solution and interface solution,

η = viscosity, and **g** = gravitational acceleration.

Schmidt number is given by[26]

$$S_c = \eta / \rho D \qquad (9.4)$$

Both groups are raised to the same power for correlation purposes. The numerical factor 2, on the right hand side, represents the minimum value that the Sherwood number can take when the other groups are zero.

When the agitation is more pronounced, the recommended correlation equation includes the Reynolds number instead of the Grashof number, this being appropriate group to choose in situations where there is relative motion between the solid and the fluid. Quite a slight forced motion is usually enough to swamp the gentle convection currents.

The equation $S_h = 2 + 0.56\ Re^{0.55}\ S_c^{\ 0.33}$. (9.5)

is given by Freessling[27]. At values of $S_h > 100$, it is normal to ignore the factor 2 due to natural convection, since an accuracy of 2% is much better than can be hoped for, from predicted equations of this type.

The reports[28,29] clearly establish that even for controlled release preparations containing a drug whose solubility is pH dependent, it is the degree of agitation which has the greatest influence on the *in vitro* drug release. An appropriately four-fold change in stirring rate thus produces a greater change than an approximately 65-fold change in solubility.

E. Effect of Viscosity:-

Diffusion-controlled reactions should decrease in rate with an increase in viscosity, whereas viscosity has little effect on interfacial controlled reactions. Several equations have been derived which show the dissolution rate to be a function of viscosity raised to some power where the exponent varies from 0.25 to 0.8[30].

F. Effect of Surface active agents:-

Wurster[31] showed that the surface-active agents in the dissolution medium increased the effective surface area available for dissolution. It is possible that with certain substances solubilization will occur at concentrations significantly below the CMC (Critical Micelle Concentration). This can be solubilizate if oriented between ionized surfactant molecules, the repulsive forces of the surface active agent will be reduced, thus facilitating micelle formation at lower concentration[32,33]. Other investigators feel that limited association or aggregation between the solubilizate and surfactant at concentrations considerably below the CMC is responsible for the increase in solubility[34,35].

G. Effect of Gastric mucin and enzymes:-

Abbott *et al*[36], have reported that the mucoid content of human gastric fluid could notably change the *in vitro* dissolution time observable as compared to simulated gastric fluid. Wood[37] suggested the omission of pepsin and mucin, and continued further formulative dissolution studies with straight inorganic systems.

H. Effect of Drug solubility:-

According to Noyes and Whitney equation, the dissolution rate shows a first-order dependence on the difference in solubility (C_s - C) where Cs is the concentration of the drug at saturation and C is the concentration of the drug. By any means whereby C_s increased and/or C reduced will cause a corresponding increase in dissolution rate. The point has been made earlier that if dissolution is to be biopharmaceutically significant, it must be the rate-limiting step in the *in vivo* dissolution absorption process. This being so, the connection of free drug in solution in the lumen of the gut, C, will be low on account of the relatively high absorption rate. Sink conditions, therefore, likely to prevail *in vivo*. For meaningful data to be obtained from an *in vivo* system, it is necessary to ensure that these too, operate under similar sink conditions. According to Gibaldi and Feldman[38], sink conditions can be assumed if the total amount of drug in solution does not exceed 10 to 20% of the saturated concentration. Unfortunately, with drugs having only a very low solubility in dissolution medium, this can result in the use of very large volumes of fluid. The saturation solubility of a weak acid or base is not an invariant property of that compound, but will vary with the pH of the dissolution medium.

9.3 Development of Dissolution Rate Testing Methodology

Taking into consideration the appreciable amount of work done to date on dissolution of controlled release dosage forms, it is not surprising that more than 100 different apparatuses have been proposed for the measurement of *in vitro* drug release from solid dosage forms. Lattir[39], Hersey[40], Baun and Walker[41], Koch[11]and Lerk[42] described the technology in detail. It is not the author's intention to review the apparatus and method in detail, rather to highlight the official methods together with other that gained importance for the *in vitro* dissolution testing of controlled release dosage forms.

Swarbrick[5] classified the various techniques of dissolution from a consideration of their associated hydrodynamics. Striker[43] divided the dissolution methods into three groups: i)

Closed-compartment Systems ii) Open flow through Chambers iii) Dialysis and iv) Diffusion Models. Closed compartment systems usually employ large volumes of dissolution solvent. Open flow through Chambers also use large volumes of solvent, but only a small amount similar to the volume present in the gastrointestinal tract, is actually active in the dissolution process at any point of time. In Diffusion Models, dissolved substance passes through a membrane or dividing layer into a second compartment.

The types of apparatus, as indicated by Barr[44] differ in a number of respects. These differences involve the type of agitation, the intensity of agitation, the dispersion of the particle, the abrasion of the intact tablet or particles, the volume and rate of exchange of the dissolving medium, the flexibility of the system to vary with volumes or agitation intensities, the reproducibility of the system from run to run. The reproducibility of the system in different laboratories, which depends on the availability of standardized components, the container, the stirrer, the volume and rate of exchange of the dissolving fluid relating to the solubility of the drug tested and experience and documentation available for the method.

Considerable interest has been focused to develop reliable *in vivo* dissolution rate controlled absorption of drugs administered in solid dosage forms. One basic requirement to achieve this goal, seems to be the availability of a reliable and flexible dissolution test apparatus which is not only suitable for characterizing *in vivo* dissolution behaviour of essentially all types of solid dosage forms but it is also convenient to use for research, development and quality control. Wagner [45] and Shah *et al* [46] have summarized the criteria which should be met by the *in vitro* dissolution testing apparatus for both research and quality control purposes.

9.4 Dissolution Testing of Controlled Release Dosage Forms

In vitro dissolution rate testing is an important tool in the design, evaluation and control of controlled release dosage forms. There is no 'Standard' dissolution rate testing method for these kinds of preparations. The methods described in the literatures[50] vary according to the drug, release sustaining materials and dosage forms tested. The methods are dependent on the principle of the use of simulated gastric and intestinal fluids at a temperature of 37°C, the use of mechanical device to agitate the dissolving fluid and the product at a fixed stirring rate, and the use of sieve to retain the disintegrated particles of the dosage form. The rate of disappearance of the drug from the product, or appearance in the dissolution fluid, is

measured as a function of time[47,48]. The usual variations in these methods are the sampling intervals, the fluid composition, the agitator and the size of the sieve utilized. Among the most commonly used techniques are that of Souder and Ellenbogen[49,50] , Levy and Heyes[51] and that of Stall Gerschberg[52]. All the devices have been shown to produce data satisfactorily related to *in vivo* effects[48]. Another modified USP XX method[51] has been reported which correlates well with the *in vivo* data[21].

9.5 Interpretation of *in-vitro* drug release kinetics

The principle of dissolution kinetics is summarized below:-

The release of drugs from different solid dosage forms is time-dependent and this could be shown with the help of various equations. In this chapter, the most important dissolution rules are summarized and their significance is discussed. The equations are represented only in the integral forms that are suitable for practical purposes. In these forms, they could be used as algorithms for the development of appropriate computer programs. Mathematical models used to describe the kinetics of drug release from microcapsules or micro particles are usually based on drug release from microcapsules or micro matrix devices, respectively. Because of the size difference, drug release from the macro dosage forms tends more quickly to attain steady state that is of shorter duration. These dosage forms are often irregular in shape so that conventional models based on spherical, cylindrical or other regular geometry often show a poor fit for release data. Also, many micro capsules, particularly those produced by various coacervation procedures, are multinuclear or are composed of aggregates of smaller micro capsules so that their release kinetics do follow that expected of a reservoir type device but rather than that of a monolithic device. Because of the diversity of inclusion and lack of homogeneity of many polymeric coatings, the following mathematical approaches that have been used to quantify drug release *in vitro* from micro capsules and micro particles are of interest primarily for indicating those factors that influence drug release.

9.5.1 Noyes – Whitney Rule

The fundamental for evaluation of the kinetics of drug release is offered by the equation of Noyes and Whitney in 1897[54]

$$dM/dt = KS (C_s - C_t) \qquad (9.6)$$

The left hand side here is the rate at which mass, **M**, is transferred with respect to time, **t**, by dissolution from the solid particle of instantaneous surface, **S**, under the effect of the prevailing concentration driving force (C_s - C_t), where C_t is the concentration at time **t** and C_s is the equilibrium solubility of solute at the experimental temperature. The rate of dissolution **dM/dt** is the amount dissolved per unit area per unit time and for most solids can be expressed in units of $g.cm^{-2}$ sec^{-1}.

When C_t is less than 15% of the saturated solubility C_s, C_t has a negligible influence on the dissolution rate of the solid. Under such circumstances the dissolution of the solid is said to be occurring under 'sink' conditions[55]. In general, the surface area, **S** is not constant except when the quantity of material present exceeds the saturation solubility, or initially when only small quantities of drug have dissolved.

9.5.2 Nernst and Brunner Film Theory

Brunner and Nernst[56] used Fick's law of diffusion to establish a relationship between the constant in the equation (9.1) and the diffusion coefficient of the solute,

$$K = DS/hv \qquad (9.7)$$

Where **D** is the diffusion coefficient, **S** is the area of dissolving surface or area of the diffusion layer, **v** is the solution volume and **h** is the diffusion layer thickness. In formulating their theories, Nernst and Brunner assumed that the process at the surface proceeds much faster than the transport process and that a linear concentration gradient is confined to the layer of solution adhering to the solid surface.

The ideal condition can never be achieved as the actual surface is changed permanently with the progress of dissolution processes during the usual determination of drug release.

In the Noyes-Whitney equation, the dissolution process corresponds to a first-order reaction. In fact, the ideal case is only seldom practically realized. In this rule, there occur more or less strong deviations from the ideal situations and one is forced to apply one or more correction terms to the function equation[57].

$$M = M_0 (1 - e^{-kt}) \qquad (9.8)$$

Where M_0 = limiting concentration and **M** = actual concentration at time **t**, the proportional factor **k** is known as dissolution constant.

Micro capsules with constant activity cores usually exhibit an initial delay or lag time[58] before achieving the steady state value if tested very shortly after preparation because the concentration gradient within the coating will not yet have been fully achieved. In that case, the functional equation must be corrected as:

$$M = M_0 [1 - e^{-k(t-to)}] \qquad (9.9)$$

On the other hand, for a delayed dissolution [59,60] in the beginning, the curve can be described as

$$M = M_0 [A_0 e^{-\beta t} - B_0 e^{-\alpha t}] \qquad (9.10)$$

Where, A_0 and B_0 are constants. Alternatively, if the micro capsules have been stored for a considerable period of time before testing, which is more commonly the case, they will exhibit as initial release rate higher than the steady state value. This so called 'burst effect' can be troublesome in practice, as it leads to initial over dosage. It arises from saturation of the coating by drug during storage with rapid release of drug from the outer regions of the coating[61, 62]. A similar effect is observed when the drug particles are embedded in the outer surface of the coating. In this case of a rapid initial dissolution, the dissolution curve can be reproduced through a composite exponential function made up of two terms:

$$M = A_0 (1 - e^{-\alpha t}) + B_0 (1 - e^{-\beta t}) \qquad (9.11)$$

9.5.3 Weibull Equation

The dissolution curves frequently assume more or less clearly a sigmoid form. These and also other forms of curves could be described by a formula of general validity, as far as the basic part of the equation is of first order, the equation being[63-64].

$$M = M_0 [1 - e^{-\{(t-to)\, b\}/a}] \qquad (9.12)$$

In this equation, t_0 is a local parameter, same as before, equivalent to the beginning of the curve or the lag time of the dissolution, **'a'** is a scalar parameter, which signifies the time dependence of the total process (theoretically **'a'** = reciprocal of the rate constant), **'b'** is a shape parameter which express whether the curve is purely exponential (b = 1); rising sigmoid with a turning point (b > 1); or a steep rising branch which will correspond to the purely exponential form (b<1). It is obvious that the Weibull equation only then has any significance, when $t\text{-}t_0 \geq 0$. This equation is almost universally applicable[64]; it is optimally suitable for most of the dissolution curves.

Langenbucher[65] defined the dissolution time, T_d by a term, **a (1/b)**, where, "**a**" is a scale parameter and "**b**" is a shape parameter of the Weibull function. T_d represents the time interval necessary to dissolve 63.2% of the material. T_d coincides with Mean Dissolution Time (MDT) if the dissolution rate time curve can be approximated by a mono-exponential equation.

9.5.4 Dissolution Efficiency:

Khan [66], who introduced the idea of Dissolution Efficiency, suggested a parameter suitable for the evaluation of '*in-vitro*' dissolution. This is defined as the area under dissolution curve up to a certain limit, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

This can be represented as:

$$\textbf{Dissolution Efficiency (D.E.)} = \int_0^t (Y.dt/Y.\ 100.t) \times 100 \qquad (9.13)$$

where, Y denotes concentration of the drug at any time t. The concept of dissolution efficiency has certain advantages. The first is that summation of drug release data into a large number of formulations, the second advantage and probably the most important is that it can be theoretically related to '*in-vitro*' data.

9.5.5 Mean Dissolution Time (MDT):

Statistical moment, which is model independent characteristics, can be defined for all statistical distribution curves. Cutler[67] and Yamaska *et al* [68] applied the moments to analyze *in vivo* time course curve and urinary excretion rate time curve. Riegelman and Collier proposed the mean *in vivo* dissolution time (*in vivo* MDT) for bioavailability evaluation.

Dissolution phenomenon includes a stochastic feature; a drug molecule in a tablet or a capsule transfer with a certain probability from the solid state to the dissolved state. We observe the total behavior of numerous drug molecules, each of which has its own transit probability. Thus the dissolution time curve represents a statistical cumulative distribution. Therefore, moment analysis can also be applied for the characterization of the *in vitro* dissolution time curve. Mean *in vitro* dissolution time (*in vitro* MDT) is defined as follows[69]

$$\textbf{MDT} = {}^{\alpha}\int_0 \textbf{t. (dm/dt).dt} \,/\, {}^{\alpha}\int_0 \textbf{(dM/dt). Dt} \qquad (9.14)$$

$$\textbf{or, MDT} = {}^{\alpha}\int_0 \textbf{t. dM/M}_{\alpha} \qquad (9.15)$$

where, **M** is the amount, concentration or fraction of drug dissolved in solution at time **t**, **dm/dt** is the dissolution rate and **D** is the total amount dissolved or final concentration at infinite time. The *in vitro* **MDT** is calculated in the same way as the Mean *in vivo* Residence Time (MRT) of the trapezoidal integration.[68]

9.5.6 Logarithmic Logistic Equation:

This equation can be used for reducing the dissolution data to linear form, the correlation coefficients being close to unity[70]. The equation being,

$$M = K\,[1 - e^{(a+bt)}]^{-1} \qquad (9.16)$$

K is the rate constant and **'a'** and **'b'** are constants.

9.5.7 Hixon – Crowell's Cube-root Model:

As a solid dissolves, the surface area S changes with time. The Hixon and Crowell Cube-root Equation is based on the assumption that

1. Dissolution occur normal to the surface of the solute particle.
2. Agitation is uniform on overall exposed surfaces and there is no stagnation.
3. The particle of solute retains its geometric shape.

This equation postulates that during the dissolution process, the decrease in weight of the undissolved solid at certain time is proportional to the cube-root of the mass of the solid body[70], thus

$$W_0^{1/3} - W^{1/3} = Kt \qquad (9.17)$$

Since $W_0 = M_0$ = **initial mass** and $W = M_0 - M$, where **M = mass dissolved at time't'.**

This cube-root equation can not be used in its original form, because the characteristic dimensions of the solid bodies change strongly during dissolution process. Specially in case of the anisotropic crystals the dissolution from different crystal surfaces take place at different rates, also in case of powders, which exist in an irregular crystal size, hence cannot be normally or log-normally divided.[71]

9.5.8 Zero-order Kinetic Model:

The general functional equations for reactions of zero-order, for example, refer to the liberation of active ingredients from the surface, which remains constant with time. The determination of the intrinsic dissolution rate of drugs is one of its applications. Moreover, this equation obeys the drug release phenomenon from 'Osmotic Pumps'[72]. The equation is given by[73]

$$M = K^0 t \qquad (9.18)$$

Equation (9.18) signifies that the rate of dissolution remains constant with time (K^0 = **dissolution constant of zero-order**) and independent of absolute ambient of substances. Indeed, this will be valid only for very dilute solutions, hence under sink conditions. If the

concentration comes close to the saturation limit, then the dissolution will proceed in a pseudo-first order process.

9.5.9 First-order Kinetic Model:

In the case of drug release from reservoir devices as well as multiparticulate systems the first-order kinetics is followed. There are two approaches of using the first-order rate equation in the case of '*in-vitro*' dissolution kinetics under sink conditions[74].

1. For the case when there are sink conditions and surface area varies with time, one may assume that during some parts of the dissolution process the surface area available for dissolution decreases exponentially with time.

$$\log (W^{\infty}-W) = \log M = \{k_s/2.303\}(t-t_0) \text{ for } t> 0 \qquad (9.19)$$

where, $(W^{\infty} - W)$ is the amount of drug not released from the dosage form.

2. For the case when the effective surface area available for dissolution at any time is proportional to the amount of undissolved drug, the equation is given by[73]

$$\log (W^{\infty} - W) = \log W^{\infty} - \{k/2.303\}t \qquad (9.20)$$

where, W^{∞} represents the amount in solution at infinite time.

Gibaldi and Feldman[73] have reported that a drug, which may be absorbed or dissolved under sink condition in a zero-order fashion, may demonstrate first-order dissolution kinetics under non-sink conditions. An organic solvent reservoir that functions to maintain approximate sink condition is also applicable to the determination of first-order dissolution rates. The rate of appearance of drug in the organic phase may be related to the first-order dissolution rate in the aqueous phase by means of the following kinetic model.

$$A \xrightarrow{K_l} B \xrightarrow{K_p} C \qquad (9.21)$$

If the choice of organic solvent and other experimental conditions are such that $K_p/K_l \geq 10$, then with a short period of time after initiation of dissolution, the appearance of drug in the organic solvent phase may be approximated by equation (9.21).

9.5.10 Second – order Kinetic Model:

For few slow release formulations, produced by embedding technique, the release of drugs proceeds via the second order kinetic process. The corresponding functional equation runs as follows:

$$M = M_0 (M_0 - M) K_2 t \qquad (9.22)$$

where, K_2 is the rate constant for second-order. Both Gibaldi and Feldman[73] and Raghunathan and Becker[75] showed how, under special non-sink conditions, one can obtain second order *in vitro* dissolution kinetics.

9.5.11 Wiesman Exponential Release Model:

Wieseman and Federce[76] published plots of per cent aspirin release on the logarithmic scale of semilogarithmic graph paper versus time in hours for the release of aspirin from various matrices in tablet form. This indicates exponential release of the growth type with equation describing such data being of the form of equation (9.23).

$$M = M_{0e}^{\,k(t-t_0)} \qquad (9.23)$$

Where **M** is the per cent released, M_0 is the amount which has been released at the time t_0 when the exponential release began, **k** is a constant and **t** is the time.

9.5.12 Higuchi Model:

Diffusion controlled drug release, when the drug is dispersed as a solid in a matrix, has been studied by T. Higuchi[77] and W. I.Higuchi[78]. If the matrix is homogeneous, planar diffusion to a perfect sink leads to equation (19).

$$Q = \sqrt{[D\,(2A - C_s)\,C_s\,t]} \qquad (9.24)$$

Where **Q** is the amount of drug released per unit surface area, **D** is the drug molecule's diffusion coefficient in the matrix, **A** is the total amount of drug in the matrix per unit volume, C_s is the solubility of the drug in the matrix substance and **t** is the time.

If the matrix is heterogeneous and diffusion takes place in the inter granular pores, one obtains

$$Q = \sqrt{[(D\varepsilon/\tau)\,(2A - \varepsilon\,C_s)C_s\,t]} \qquad (9.25)$$

Where **D** is the diffusion coefficient of the drug molecule in the solvent, ε is the porosity of the matrix, τ is the tortuisity of the matrix and **Q**, **A**, C_s and **t** have the meanings assigned above. This equation holds good for release of drugs from an insoluble porous matrix. Tortuisity is defined as the dimension of radius and branching of the pores and canals in the matrix.

For both of these cases, a plot of **Q** versus the square-root of time will be linear. Desai *et al*[79,80] have shown such matrices yield linear square-root of time plots. Numerous modifications of the square-root law were established for all possible types of indecomposable dosage forms[77-84].

9.5.13 Other Models:

Further equations must be mentioned here for the release of drugs from an indecomposable matrix through progressive erosion of the upper surface[85] and the diffusion of drugs from hydrogels.

When the liberation of drugs proceeds through erosion of the drug containing slabs, cylinders and spheres, then this process represents at most a kinetic process of zero-order. According to Hoffenberg[85], the liberation profile in this case can be described by the following relation:

$$M/M_0 = 1 - [1 - (K^0 t)/(Aa)]^n \qquad (9.26)$$

Here, **M**, M_0 and **t** have their usual meanings, K^0 is the rate constant of zero-order, **A** is the initial drug concentration in the matrix, **a** is the distance factor (half of the thickness in case of flat surface, radius in case of spheres and cylinders), and **n** is a type factor (**n = 1** for planar surface, **n = 2** for cylinders and **n = 3** for spheres).

Davis[86] has reported empirical relation for the release of drug from polymers in water-soaked gels. The equation is given by

$$D_p = D_0 \exp(-0.05 + 10^{-6} m) P \qquad (9.27)$$

where, D_p is the diffusion coefficient of solute polymer. D_0 is the diffusion coefficient in water, both have the dimension (cm^2.sec), **m** stands for the molecular weight of the drug and **P** stands for the portion in per cent of the polymer in gel.

For the liberation of drug from hydrogels, another cubic dissolution factors have been given recently. By a series of experiments with water-soaked gel producing retard preparations, Bamba[87] *et al*, found that the liberation curve could be matched test according to an equation (9.28) of the third degree with the experimental data.

$$M = at^3 + bt^2 + ct \qquad (9.28)$$

The coefficients **a, b** and **c** are based on theory and include in themselves one permeation coefficient, which describes the diffusion of drug through the gel barrier and one permeation coefficient which reproduces the incoming rate of the fluid in the gel producing matrix.

Finally there are some more experiments, which describe dissolution equations with the kinetic process in polydispersed systems and variable test conditions.

Which of these diverse dissolution equations would be really applicable is not a priori known. It depends upon the characteristics of the dosage forms and the conditions under which the experiment of dissolution was carried out.

The inference, which could be put forward, is that, the experimental data should be solved in the linearization procedure, which would be described in the treatments on computerized interpretations of dissolution data. This would yield the best possible adoption of the dissolution curve and the experimental points.

9.5.14 Korsmeyer-Peppas Model:

Korsmeyer[88] *et al.* (1983) developed a simple, semi-empirical model, relating exponentially the drug release to the elapsed time (**t**):

$$Mt/M\infty = Mo/M\infty + K_{KP}\, t^{n} \qquad (9.29)$$

where, K_{KP} is a constant incorporating structural and geometric characteristic of the drug dosage form, **n** is the release exponent, indicative of the drug release mechanism, and the function of **t** is **Mt /M∞** (fractional release of drug). **Mo /M∞** signify the initial burst release fraction.

Peppas used this **n** value in order to characterize different release mechanisms, concluding for values for a slab, of **n**=0.5 for Fick diffusion and higher values of **n**, between 0.5 and 1.0, or **n**=1.0, for mass transfer following a non-Fickian model (Table 9.2). In the case of a cylinder, **n**=0.45 instead of 0.5, and 0.89 instead of 1.0 can only be used in systems with a drug diffusion coefficient fairly concentration independent. To the determination of the exponent **n** the portion of the release curve where Mt /M∞ <0.6 should only be used.

Table 9.2 Value of n and its implications on Diffusional mechanism from polymeric film

Release Exponent (n)	Drug Transport Mechanism	Rate as a function of Time
0.5	**Fickian diffusion**	$t^{-0.5}$
0.5 < n < 1.0	**Anomalous Transport**	t^{n-1}
1.0	**Case II Transport**	**Zero Order Release**
Higher than 1.0	***Super Case II Transport***	t^{n-1}

9.5.15 Baker-Lonsdale Model:

This model was developed by Baker and Lonsdale[89] (1974) from the Higuchi model and describes the controlled release of the drug from a spherical matrix, being represented by the following expression:

$$f_t = \frac{3}{2}\left[1-\left(1-\frac{M_t}{M_\infty}\right)^{2/3}\right]-\frac{M_t}{M_\infty} = kt \qquad (9.30)$$

where, **Mt /M∞** is a function of time (f_t) which signifies fractional release of the drug. The release constant, **k**, corresponds to the slope of the curve between **Mt /M∞** versus **time (t)**. This equation has been used to the linearization of release data from several formulations of microcapsules or microspheres.

9.6 *In Vitro* Dissolution Study of Frusemide Loaded Micropellets

The Frusemide micropellets of different batches were subjected to *in vitro* dissolution study as per following protocol (Table 9.3).

Table 9.3 Protocol for Dissolution Study of Frusemide

Sl.#	Parameters	Specifications
1.	Dissolution medium	Phosphate Buffer of pH 6.8
2.	Volume of the medium	900 ml
3.	Dissolution apparatus	USP XXIV Apparatus I (Paddle type)
4.	RPM	50
5.	Temperature of the water bath	37 ± 2°C
6.	Time of sampling (hours)	0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9 hrs.

At these specified time intervals, a fixed volume of sample (10 ml) was withdrawn from the dissolution medium and substituted by equal volume of fresh medium. The withdrawn samples were diluted suitably and the drug contents in the samples were determined by using Shimadzu UV-VIS 2400 spectrophotometer at 277.5 nm.

9.6.1 Release profile of Frusemide from micropellets at low (-1) level of Sodium alginate and at low, medium and high level of Acrycoat E30D

Frusemide micropellets prepared with low level of alginate (1% w/v) and Acrycoat E30D at 0% w/v, 2% w/v and 4% w/v level i.e. Batch F1, F2 and F3 were subjected to dissolution study as per the protocol given in the Table 9.3. The release data of these batches is given in the Table 9.4. The cumulative release data and the other derived data of Frusemide from these batches is plotted in different release kinetic models, namely, zero order kinetics, first order kinetics, Higuchi kinetics and Hixon Crowell model and the graphical representations of each kinetic model are shown in the Fig 9.1.1 – 9.1.4.

The correlation coefficients (R^2) and the release rates (K_0, K_1, K_H and K_{HC}) of these batches are shown in the Table 9.7 and 9.8 respectively. The release rates (K) of each model have been calculated by linear regression with the Microsoft Excel 2003 software. Coefficients of correlation (R^2) were used to evaluate the accuracy of fit. Since the number of dissolution parameters were kept constant, correlation coefficients (R^2) was used as indicators of best fitting model equations. To further confirm the release kinetic model the dissolution data were analyzed with Korsmeyer-Peppas Model as shown in Table 9.12.

Table 9.4 Cumulative percent release of Frusemide from micropellets when the alginate level is low (-1) (n = 3)

Time (hr)	Cumulative % Release ± S.D		
	F 1	F 2	F 3
0.5	0.22 ± 0.25	0.22 ± 0.39	0.62 ± 0.13
1.0	17.7 ± 0.31	16.34 ± 0.28	23.29 ± 0.26
2.0	36.43 ± 0.33	37.71 ± 0.64	37.54 ± 0.28
3.0	68.89 ± 0.45	59.69 ± 0.37	65.45 ± 0.36
4.0	89.5 ± 0.17	77.64 ± 0.19	73.48 ± 0.19
5.0	95.12 ± 0.06	86.73 ± 0.34	79.91 ± 0.18
6.0	97.42 ± 0.09	89.75 ± 0.16	90.95 ± 0.11
7.0	98.46 ± 0.56	92.17 ± 0.53	95.97 ± 0.24
8.0	99.09 ± 0.21	96.40 ± 0.48	97.37 ± 0.36
9.0	99.51 ± 0.33	98.42 ± 0.68	99.78 ± 0.41

9.6.2 Release profile of Frusemide from micropellets at medium (0) level of Sodium alginate and at low, medium and high level of Acrycoat E30D

Frusemide micropellets prepared with medium level of alginate (2 % w/v) and Acrycoat E30D at 0% w/v, 2% w/v and 4% w/v level i.e. Batch F4, F5 and F6 were subjected to dissolution study as per the protocol given in the Table 9.3. The release data of these batches is given in the Table 9.5. The cumulative release data and the other derived data of Frusemide from these batches is plotted in different release kinetic models, namely, zero order kinetics, first order kinetics, Higuchi kinetics and Hixon Crowell models and the graphical representations of each kinetic model are shown in the Fig 9.2.1 – 9.2.4.

The correlation coefficients (R^2) and the release rates (K_0, K_I, K_H and K_{HC}) of these batches are shown in the Table 9.7 and 9.8 respectively. The release rates (K) of each model have been calculated by linear regression with the Microsoft Excel 2003 software. Coefficients of correlation (R^2) were used to evaluate the accuracy of fit. Since the number of dissolution parameters were kept constant, correlation coefficients (R^2) was used as indicators of best fitting model equations. To further confirm the release kinetic model the dissolution data were analyzed with Korsmeyer-Peppas Model as shown in Table 9.12.

Table 9.5 Cumulative percent release of Frusemide from micropellets when the alginate level is medium (0) (n = 3)

Time (hr)	Cumulative % Release ± S.D		
	F 4	F 5	F 6
0.5	0.23 ± 1.02	0.02 ± 0.59	0.24 ± 0.68
1.0	7.41 ± 1.08	6.98 ± 0.29	6.92 ± 0.61
2.0	17.98 ± 0.96	17.32 ± 0.36	8.77 ± 0.55
3.0	28.76 ± 0.86	27.80 ± 0.57	10.53 ± 0.59
4.0	36.99 ± 0.76	35.70 ± 0.19	19.49 ± 0.49
5.0	53.90 ± 0.91	51.30 ± 0.38	36.34 ± 0.67
6.0	69.96 ± 0.84	67.96 ± 0.27	59.32 ± 0.72
7.0	77.99 ± 1.03	75.88 ± 0.18	71.36 ± 0.73
8.0	90.90 ± 0.97	85.06 ± 0.22	83.83 ± 0.69
9.0	96.59 ± 0.63	96.82 ± 0.39	91.94 ± 0.70

9.6.3 Release profile of Frusemide from micropellets at high level (+1) of Sodium alginate and at low, medium and high level of Acrycoat E30D

Frusemide micropellets prepared with high level of alginate (4 % w/v) and Acrycoat E30D at 0% w/v, 2% w/v and 4% w/v level i.e. Batch F7, F8 and F9 were subjected to dissolution study as per the protocol given in the Table 9.3. The release data of these batches is given in the Table 9.6. The cumulative release data and the other derived data of Frusemide from these batches is plotted in different release kinetic models, namely, zero order kinetics, first order kinetics, Higuchi kinetics and Hixon Crowell models and the graphical representations of each kinetic model are shown in the Fig 9.3.1 – 9.3.4.

The correlation coefficients (R^2) and the release rates (K_0, K_1, K_H and K_{HC}) of these batches are shown in the Table 9.7 and 9.8 respectively. The release rates (K) of each model have been calculated by linear regression with the Microsoft Excel 2003 software. Coefficients of correlation (R^2) were used to evaluate the accuracy of fit. Since the number of dissolution parameters were kept constant, correlation coefficients (R^2) was used as indicators of best fitting model equations. To further confirm the release kinetic model the dissolution data were analyzed with Korsmeyer-Peppas Model as shown in Table 9.12.

Table 9.6 Cumulative percent release of Frusemide from micro pellets when the alginate level is high (+1) (n = 3)

Time (hr)	Cumulative % Release ± S.D		
	F 7	F 8	F 9
0.5	0.44 ± 1.02	0.44 ± 0.39	0.63 ± 0.61
1.0	6.86 ± 0.95	6.55 ± 0.25	4.68 ± 0.39
2.0	24.09 ± 0.86	17.78 ± 0.48	11.38 ± 0.44
3.0	31.97 ± 0.93	27.78 ± 0.66	22.74 ± 0.49
4.0	38.83 ± 1.11	34.93 ± 0.84	30.66 ± 0.27
5.0	52.31 ± 0.87	45.75 ± 0.19	40.61 ± 0.17
6.0	56.89 ± 1.04	51.89 ± 0.76	49.34 ± 0.27
7.0	75.56 ± 1.12	67.61 ± 0.54	60.09 ± 0.43
8.0	79.93 ± 0.93	74.76 ± 0.29	70.25 ± 0.52
9.0	92.38 ± 0.42	88.23 ± 0.37	78.36 ± 0.38

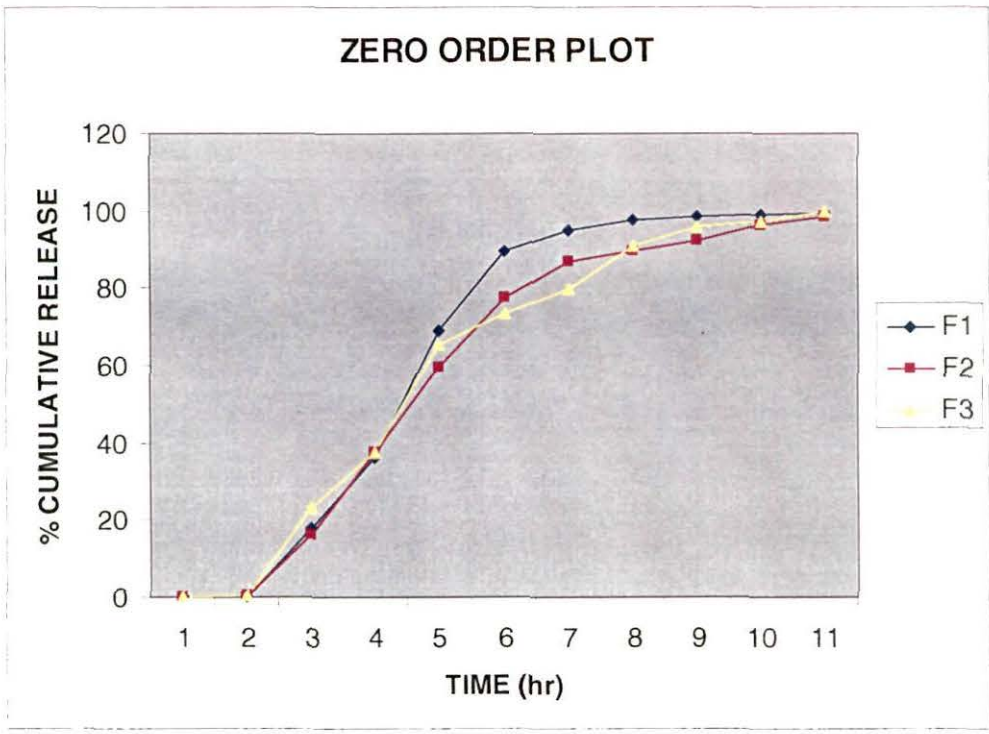

Figure 9.1.1 Zero order kinetic model for formulations F1, F2 and F3

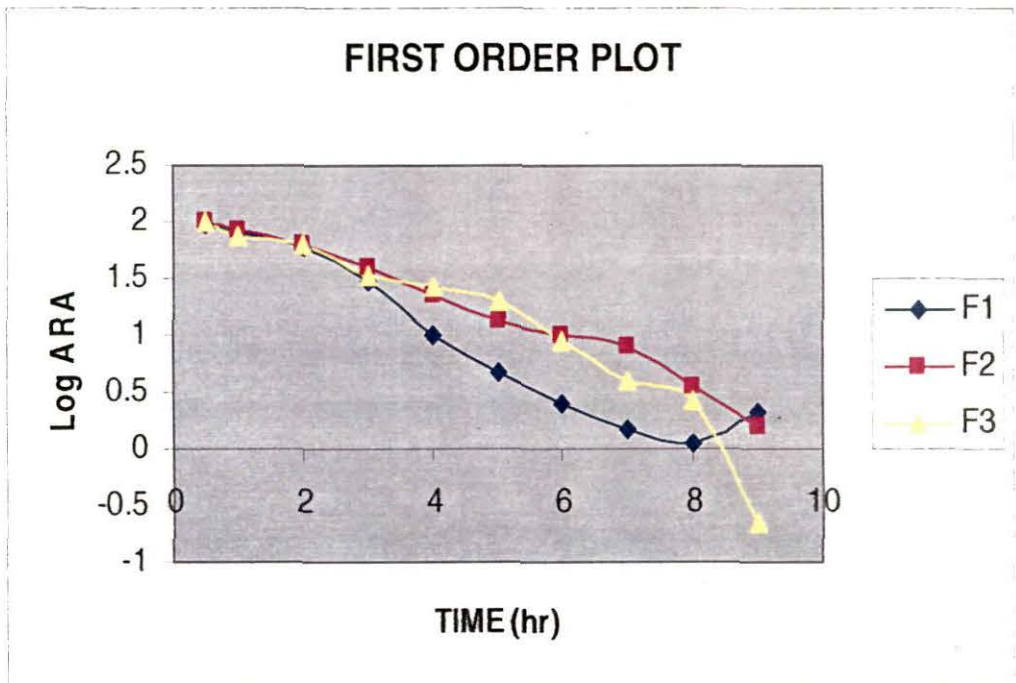

Figure 9.1.2 First order kinetic model for formulations F1, F2 and F3

Where, **ARA** – **A**mount **R**emaining to be **A**bsorbed

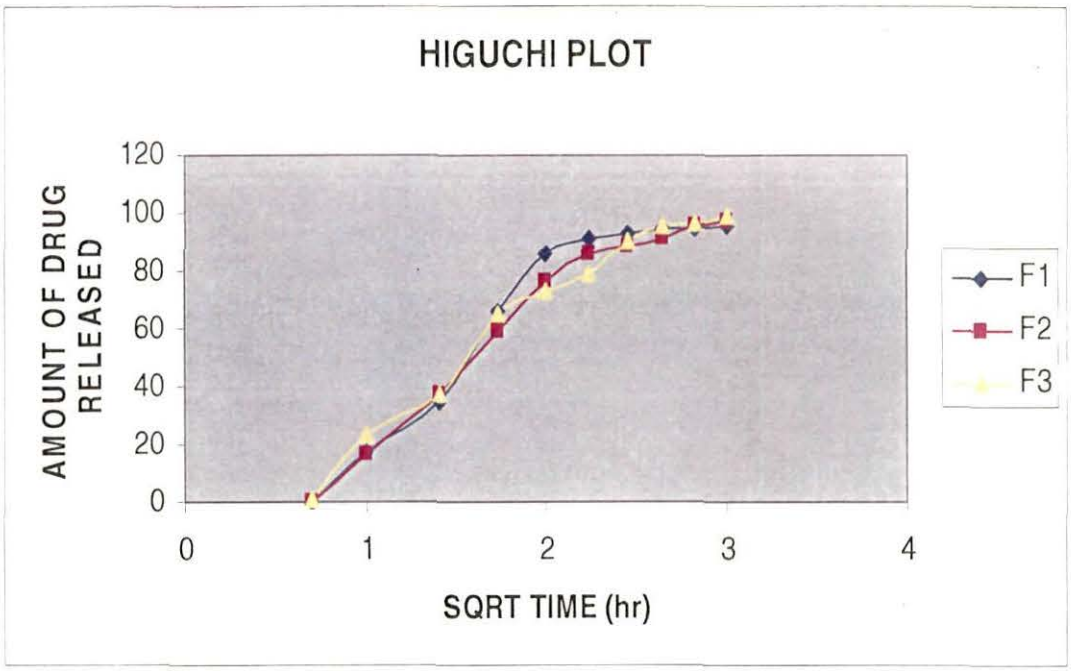

Figure 9.1.3 Higuchi kinetic model for formulations F1, F2 and F3

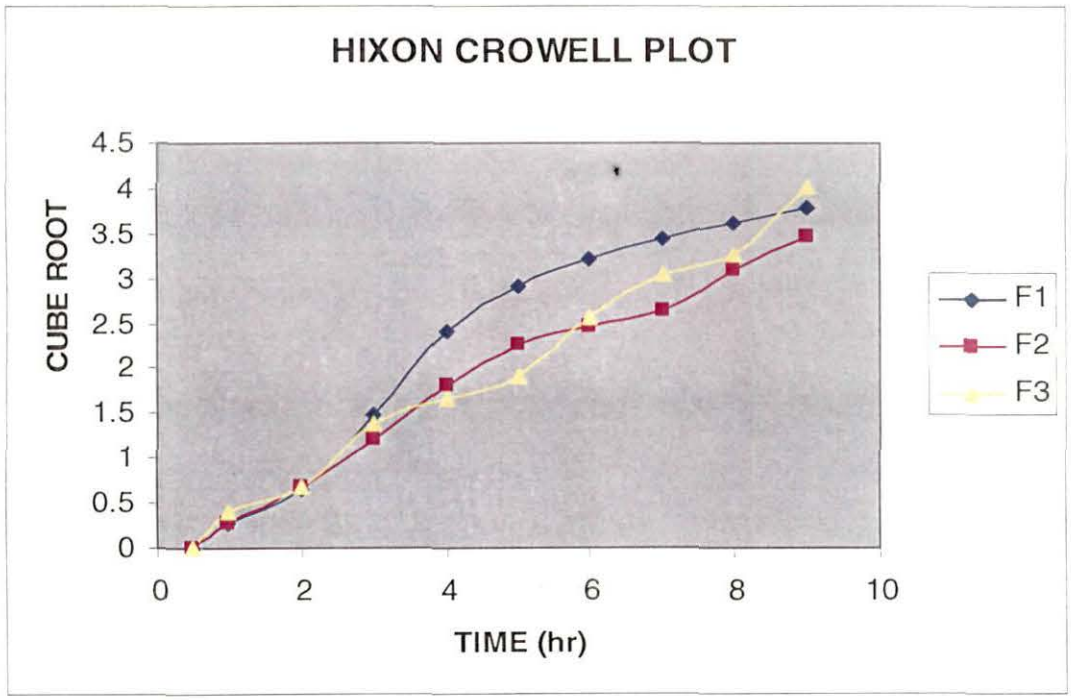

Figure 9.1.4 Hixon Crowell kinetic model for formulations F1, F2 and F3

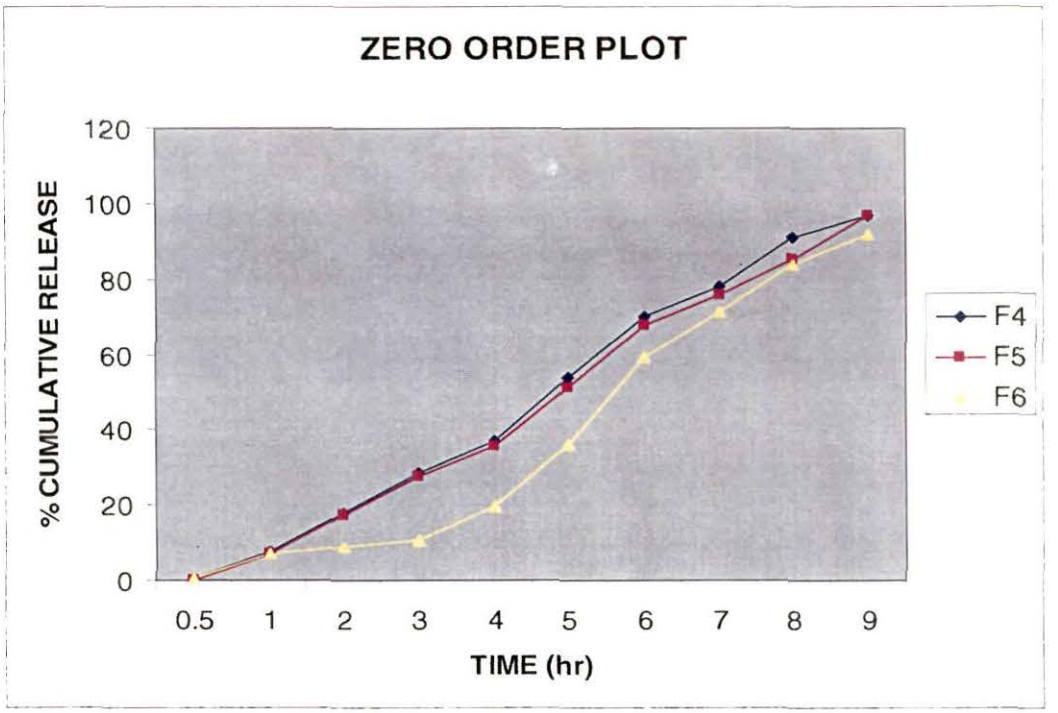

Figure 9.2.1 Zero order kinetic model for formulations F4, F5 and F6

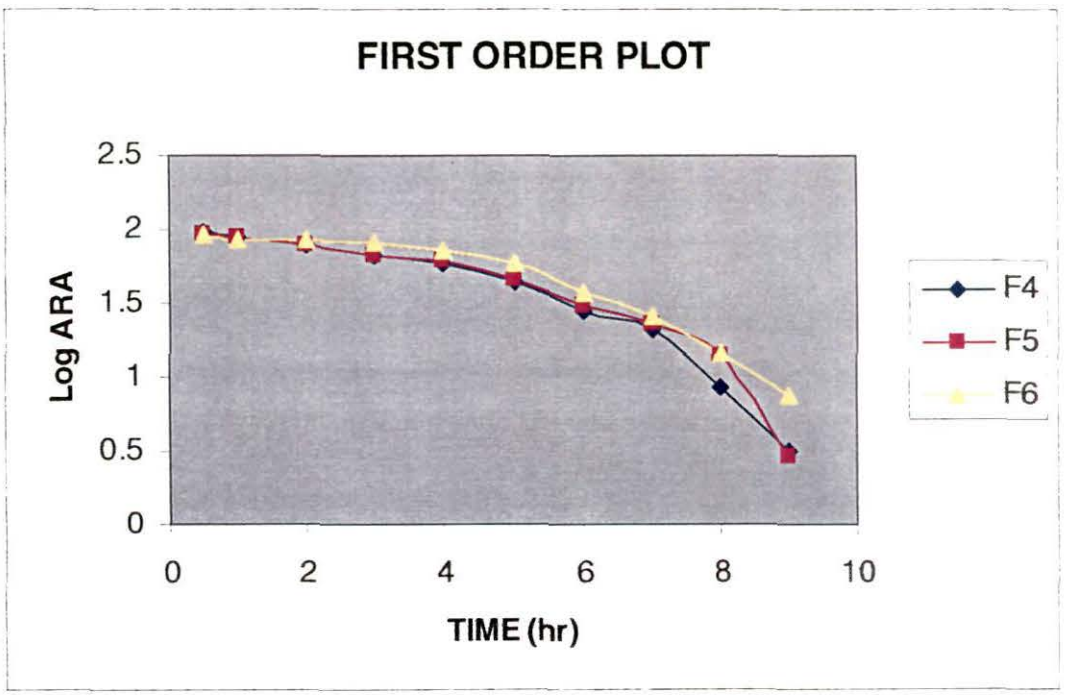

Figure 9.2.2 First order kinetic model for formulations F4, F5 and F6

Where, **ARA** – **A**mount **R**emaining to be **A**bsorbed

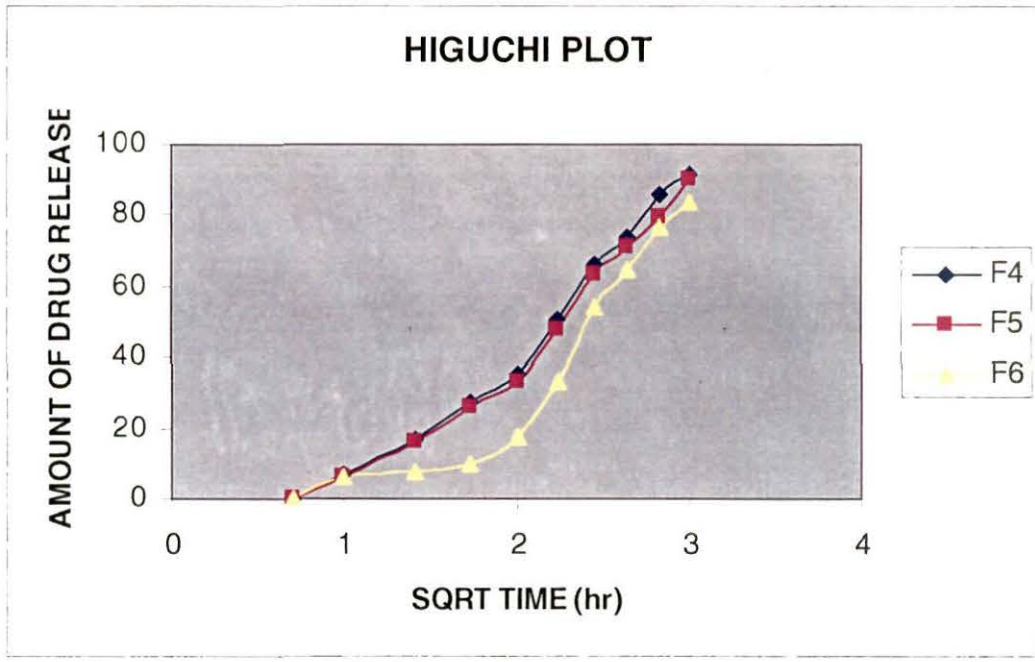

Figure 9.2.3 Higuchi kinetic model for formulations F4, F5 and F6

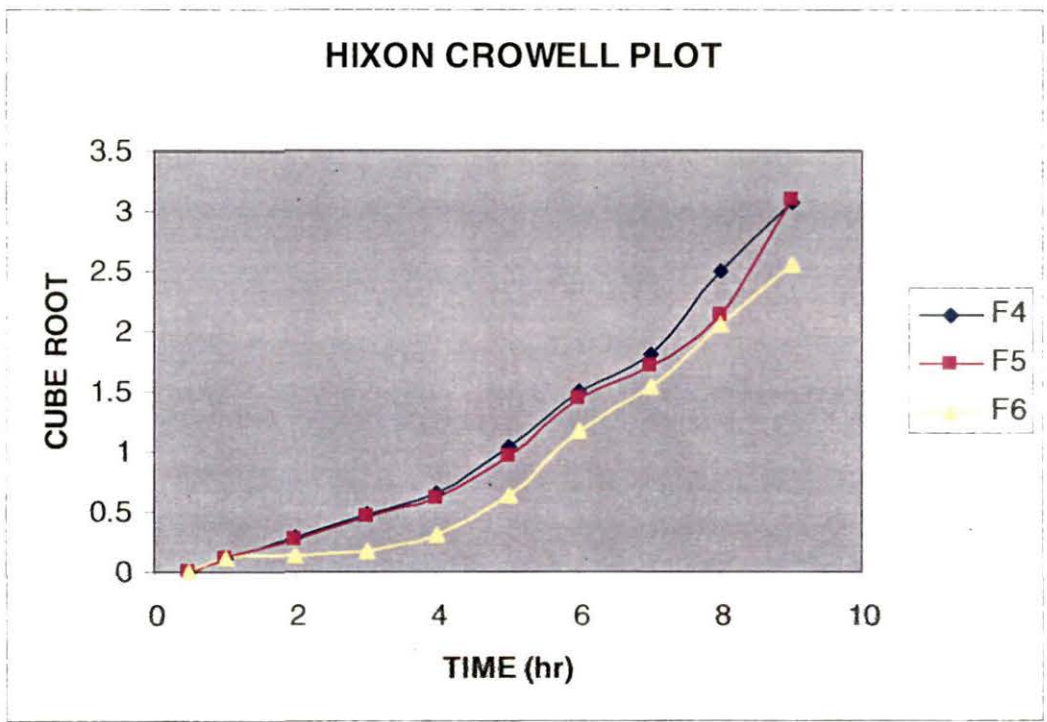

Figure 9.2.4 Hixon Crowell kinetic model for formulations F4, F5 and F6

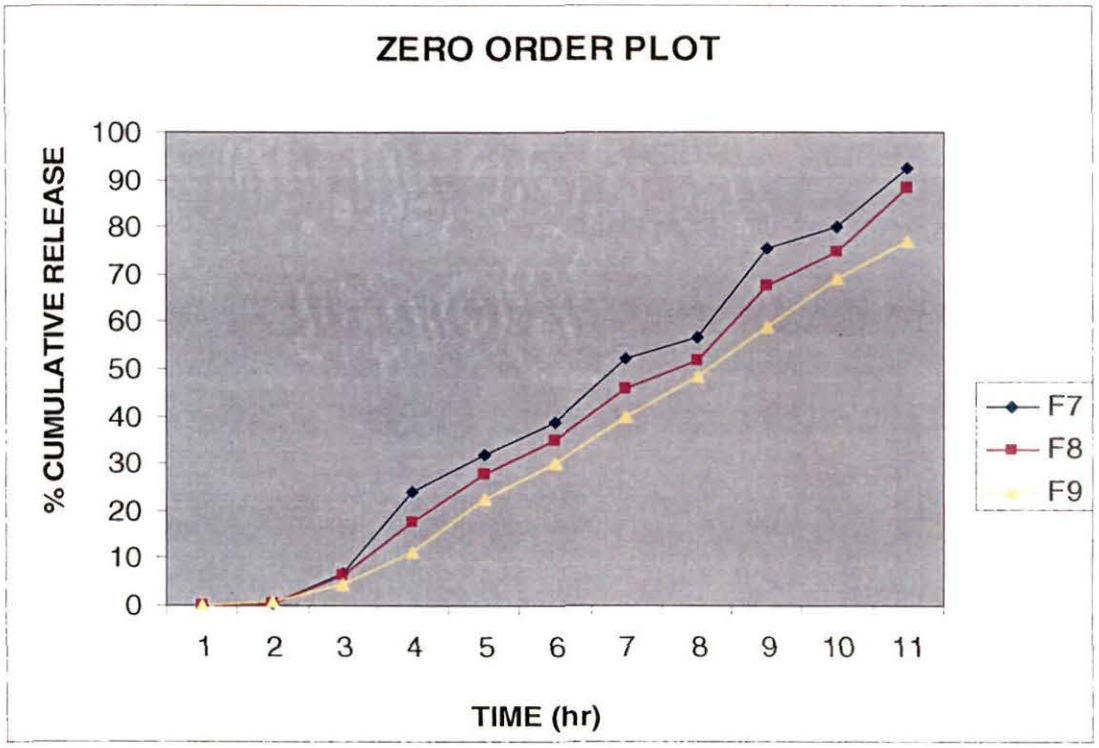

Figure 9.3.1 Zero order kinetic model for formulations F7, F8 and F9

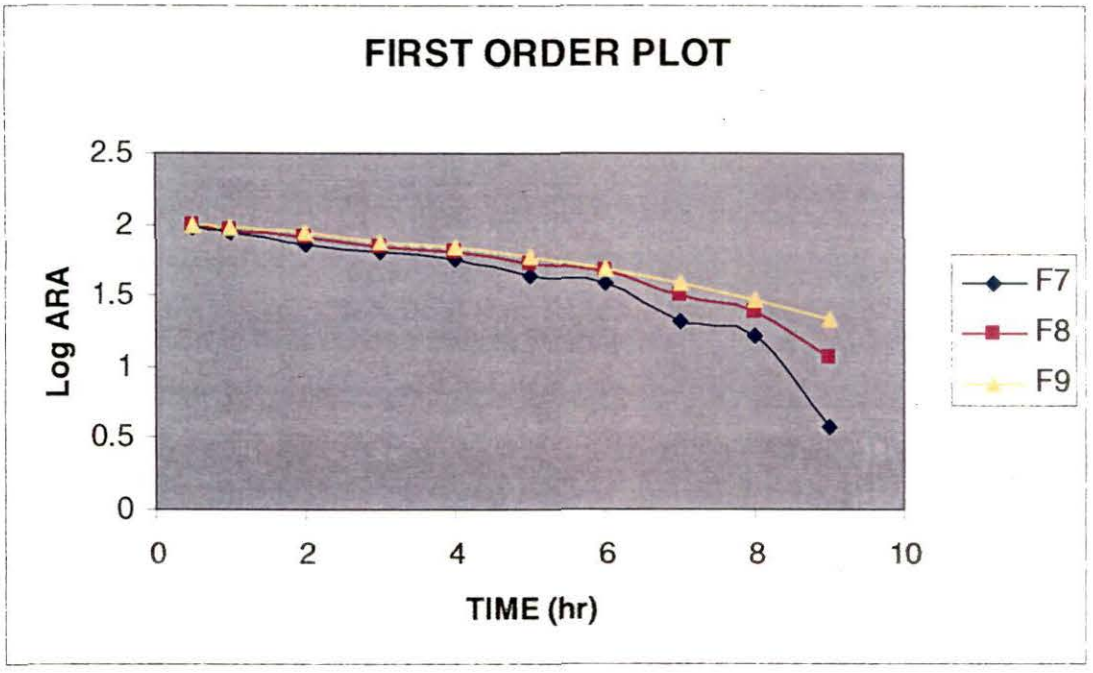

Figure 9.3.2 First order kinetic model for formulations F7, F8 and F9

Where, **ARA** – Amount Remaining to be Absorbed

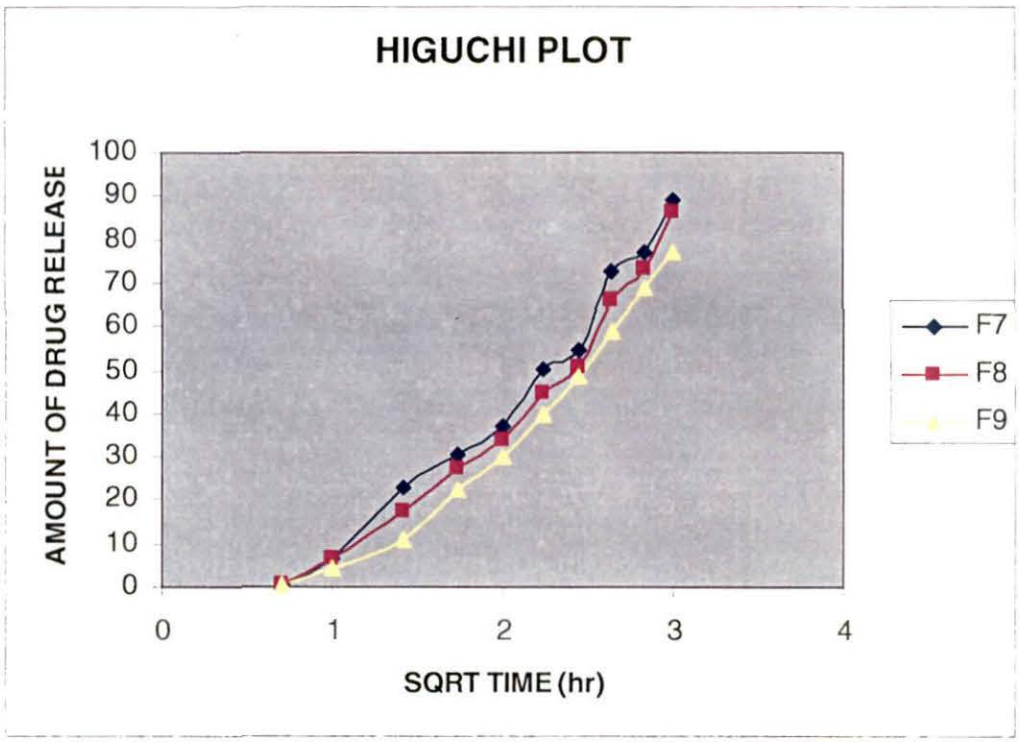

Figure 9.3.3 Higuchi kinetic model for formulations F7, F8 and F9

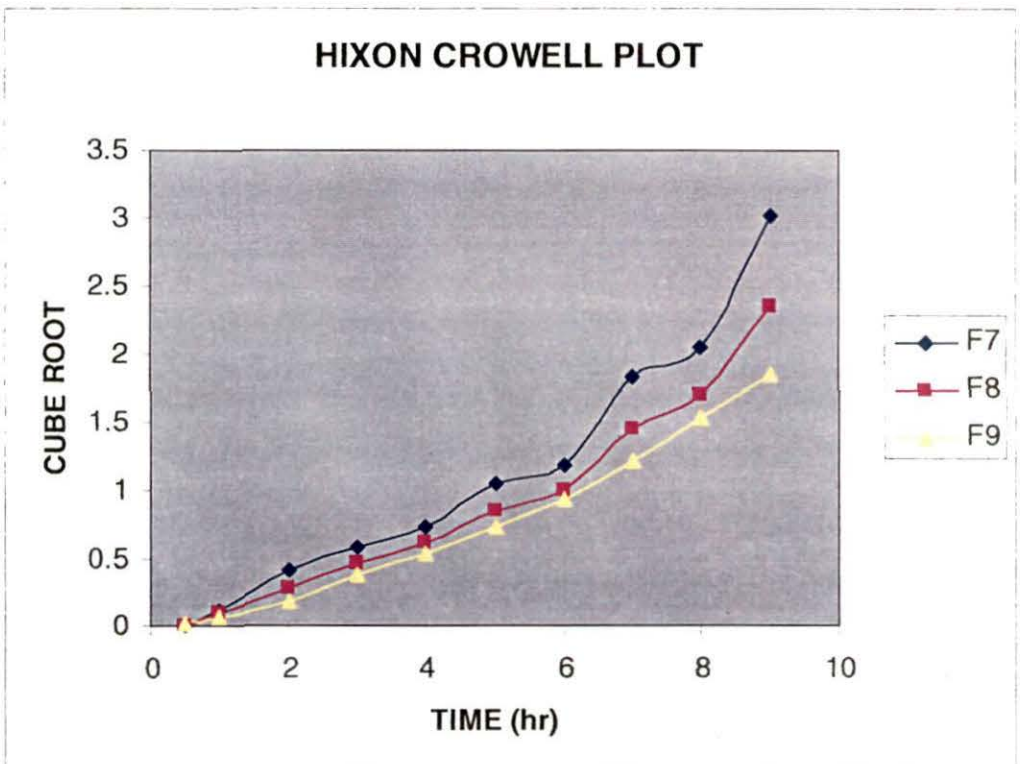

Figure 9.3.4 Hixon Crowell kinetic model for formulations F7, F8 and F9

Table 9.7 Correlation coefficients (R^2) of different plots for overall (0-9hr) release kinetics of Frusemide from prepared micro pellets.

KINETIC MODELS	Correlation coefficients (R^2 values)								
	Level (-1)			Level (0)			Level (+1)		
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero order	0.8091	0.8749	0.8949	0.9918	0.9931	0.9397	0.9918	0.9945	0.9945
First order	0.9240	0.9824	0.8916	0.8678	0.8265	0.8531	0.8328	0.8933	0.9498
Higuchi	0.9003	0.9495	0.9599	0.9653	0.9638	0.8666	0.9750	0.9644	0.9606
Hixon-Crowell	0.9400	0.9819	0.9911	0.9473	0.9314	0.9025	0.9303	0.9485	0.9756

Table 9.8 Release Rate constants (K values) of Frusemide from micro pellets with different level of alginate level (-1, 0, +1)

KINETIC MODELS	Release Rate constants (K values)								
	Level (-1)			Level (0)			Level (+1)		
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero Order (K_0)	11.301	11.004	10.825	11.468	11.192	11.151	10.209	9.6962	8.8885
First Order (K_1)	0.2459	0.2014	0.2627	0.1529	0.1437	0.1181	0.1332	0.0937	0.0742
Higuchi (K_H)	44.508	44.179	43.398	41.599	40.091	38.018	37.893	36.327	34.017
Hixon-Crowell (K_{HC})	0.4795	0.4043	0.4474	0.3469	0.3285	0.2942	0.3120	0.2488	0.2133

Table 9.9 Zero order Model - Release Rate constants (K_0) and correlation coefficient (R^2) of Frusemide from micro pellets with different level of alginate level (-1, 0, +1)

Zero order Model	Independent Variables (% w/w)		Overall Release		Phase I (0-2 hr)		Phase II (2-9 hr)	
Formulation Code	Alginate	Acrycoat E30D	K_0	R^2	K_0 I	R^2	K_0 II	R^2
F1	1	0	10.865	0.8503	23.367	0.9713	7.4017	0.6606
F2	1	2	10.209	0.8961	24.47	0.9881	7.7992	0.8233
F3	1	4	10.299	0.9145	23.133	0.9004	8.0213	0.8648
F4	2	0	9.3247	0.9477	11.653	0.9936	11.905	0.989
F5	2	2	9.0388	0.9463	11.363	0.994	11.667	0.9921
F6	2	4	7.9428	0.8407	5.1386	0.765	13.42	0.9723
F7	4	0	7.5642	0.9234	15.976	0.9954	9.9119	0.9868
F8	4	2	6.9212	0.9101	11.513	0.9995	9.9075	0.992
F9	4	4	6.1069	0.8929	6.9871	0.9976	9.4018	0.999

Table 9.10 Higuchi Matrix Model - Release Rate constants (K_H) and correlation coefficient (R^2) of Frusemide from micro pellets with different level of alginate level (-1, 0, +1)

Higuchi Model	Independent Variables (% w/w)		Overall Release		Phase II (2-9 hr)	
Formulation Code	Alginate	Acrycoat E30D	K_H	R^2	K_H II	R^2
F1	1	0	44.508	0.9003	33.781	0.7515
F2	1	2	44.179	0.9495	35.87	0.8929
F3	1	4	43.398	0.9599	36.76	0.9227
F4	2	0	41.599	0.9653	50.042	0.9841
F5	2	2	40.091	0.9638	48.407	0.9833
F6	2	4	38.018	0.8666	53.91	0.9477
F7	4	0	37.893	0.9750	42.076	0.9661
F8	4	2	36.327	0.9644	42.726	0.9704
F9	4	4	34.017	0.9606	53.91	0.9477

Table 9.11 First order Model - Release Rate constants (K_1) and correlation coefficient (R^2) of Frusemide from micro pellets with different level of alginate level (-1, 0, +1)

First order Model	Independent Variables (% w/w)		Overall Release		Phase I (0-2 hr)	
Formulation Code	Alginate	Acrycoat E30D	K_1	R^2	K_1 I	R^2
F1	1	0	-0.2459	0.9240	-0.1279	0.9887
F2	1	2	-0.2014	0.9824	-0.1332	0.9985
F3	1	4	-0.2627	0.8916	-0.128	0.9357
F4	2	0	-0.1529	0.8678	-0.0561	0.9971
F5	2	2	-0.1437	0.8265	-0.0545	0.9973
F6	2	4	-0.1181	0.8531	-0.0234	0.7715
F7	4	0	-0.1332	0.8328	-0.0837	0.9907
F8	4	2	-0.0937	0.8933	-0.0554	1
F9	4	4	-0.0742	0.9498	-0.0329	0.9988

Table 9.12 Korsmeyer-Peppas Model fitting - Release Rate constants (K_{KP}), correlation coefficient (R^2) and release exponent (n) of Frusemide from micro pellets with different level of alginate level (-1, 0, +1)

Korsmeyer-Peppas Model	OVERALL RELEASE (0-9 hr)					PHASE I (0-2 hr)			PHASE II (2-9 hr)
Formulation code	K_{KP}	R^2	n	K_{KP} I	R^2 I	n I	K_{KP} II	R^2 II	n II
F1	0.6731	0.7589	1.7429	0.7173	0.8535	3.6857	1.4996	0.7718	0.5952
F2	0.6529	0.7663	1.7309	0.7107	0.8682	3.7106	1.4664	0.8925	0.6015
F3	0.8685	0.7749	1.4378	0.9114	0.8359	2.96	1.4686	0.9026	0.6005
F4	0.4384	0.8909	1.8142	0.4954	0.895	3.1443	0.9029	0.9924	1.1637
F5	0.0197	0.7984	2.3807	0.1278	0.8487	4.8791	0.8831	0.9935	1.1705
F6	0.3049	0.9127	1.8064	0.3878	0.7992	2.5957	0.3002	0.9606	1.7854
F7	0.567	0.9004	1.6173	0.6205	0.9558	2.8874	1.0778	0.9844	0.9125
F8	0.5268	0.9177	1.6074	0.5699	0.9341	2.6683	0.9295	0.995	1.0477
F9	0.4982	0.969	1.5608	0.5086	0.9527	2.0875	0.7198	0.9928	1.2522

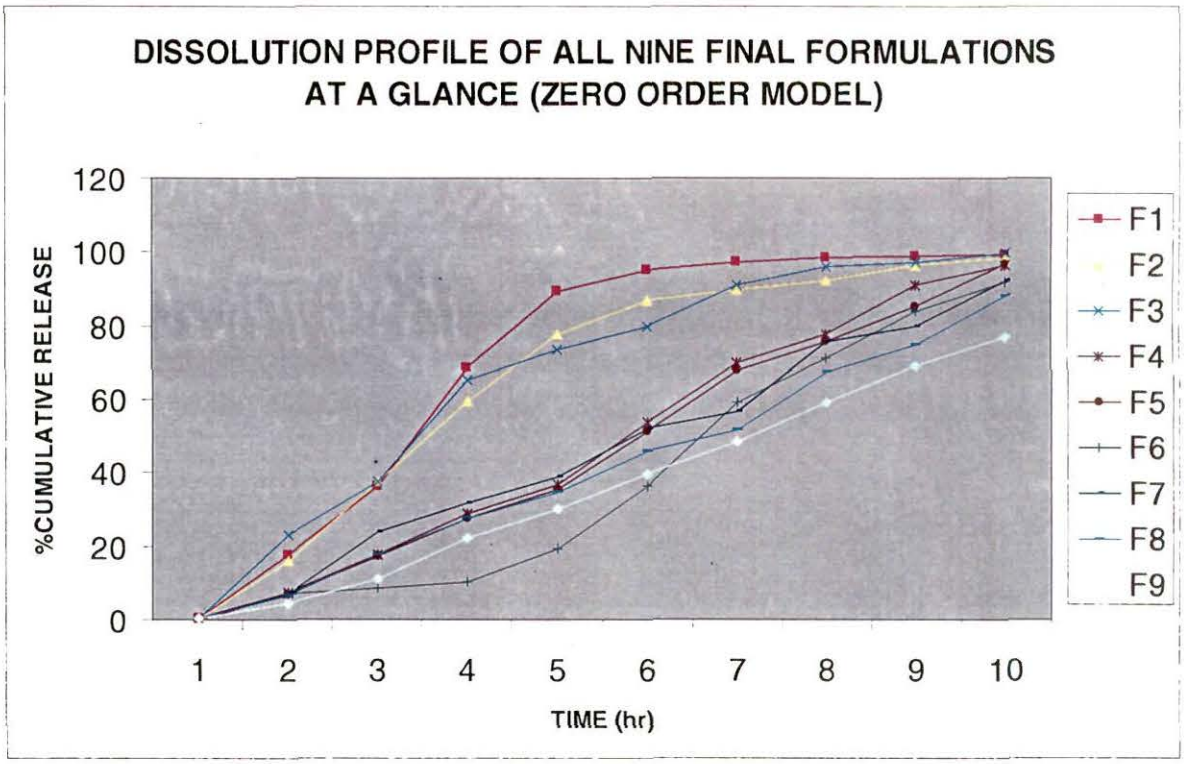

Figure 9.4 Release profile of Frusemide from micropellets at different level of sodium alginate (-1, 0, +1) following zero order model

9.7 Discussion

The *in vitro* release study unfolds quite an interesting result. Prior to the *in vitro* studies it was expected that at a particular concentration of sodium alginate, with the increase in concentration of Acrycoat E30D there would be a decrease in the release rate with the extension of the sustaining release of Frusemide from micropellets. In order to analyze the drug release mechanism from the micropellets the following mathematical models were studied, namely, Zero order model, First order model, Higuchi model and Hixon-Crowell model. The correlation coefficient (R^2) was used to compare the model equations and to determine the 'best fit' model that explains the release kinetics of the drug from the prepared micropellets. It was found that six (F4 to F9) out of nine batches of formulation followed Zero order kinetics and the rest (F1 to F3) followed Hixon Crowell kinetics for overall release (0 – 9 hrs) as depicted in the Figure 9.4. Among the three batches (F1, F2 and F3) F2 was found to be best fit with first order kinetics and for F1 and F3 the R^2 value of both Hixon-Crowell and First order kinetics were in close proximity. Hence it can be inferred that at low concentration of sodium alginate, the surface area of micropellets

decreased exponentially with the time during the dissolution process. During the agitation of the dissolution process there was no stagnation of dissolved drug and thus proper sink conditions were maintained. In these three formulations the drug released at any time remained proportional to the residual drug inside the dosage form. Further, when the release profile was divided into two phases to get a more specific release mechanism it was seen from the R^2 value (Table 9.11) that in the phase-I the drug release was predominantly following the first order kinetics. Thus, it can be concluded that at low concentration of sodium alginate the micropellets acted as reservoir devices of frusemide which released its content depending on the concentration gradient. In spite of incorporation of Acrycoat E30D as copolymer, there could not form any drug-polymer matrix.

In the rest six batches (F4 – F9), the phase-I release again followed first order (Table 9.11), except the formulations F3 and F6 which followed the Zero order release (Table 9.8) with a constant release rate (Table 9.9) over the time, independent of drug concentration in the system. On the basis of the results obtained, it could be concluded that release of Frusemide from the micropellets followed a mixed kinetics *i.e.* initially first order kinetics followed by zero order kinetics. The effect of Acrycoat E30D as release rate controlling polymer was evident (Table 9.9) from the fact with increase in the Acrycoat concentration value of Ko decreased in every case. At the high level of alginate this fact was more pronounced where the micropellets were found to release the active ingredients at a rate ranging from 8 – 10 mg/hr.

Since the release mechanism involved more than one type of release kinetics, the investigator used the semi-empirical formula of Korsmeyer-Peppas[88] equation to justify the primary outcome of the analysis of release mechanism. For all the batches of formulation the release exponent (n) (Table 9.12) in an overall span of 0-9 hr was > 1 signifying super Case-II non-Fickian anomalous diffusion transport mechanism. The dehydrated hydrogels generally involves the simultaneous absorption of water and desorption of drug via a swelling- controlled diffusion mechanism[89]. Similar to the transport of organic penetrant in glassy polymers, diffusion and swelling in glassy hydrogels generally do not follow a Fickian diffusion mechanism. The slow reorientation of polymer chains in order to accommodate the penetrating solvent molecules leads to a variety of sorption behaviors, particularly when the experimental temperatures are near or below the glass transition temperature of the hydrogel. In cases where sorption process is governed by the rate of polymer relaxation, Case-II transport is followed characterized by linear time- dependence in the amount diffused and the penetrating swelling front position, results. Generally, in

most systems, the intermediate situation, termed as non-Fickian or anomalous diffusion prevails, whenever the rates of diffusion and polymer relaxation are comparable. On segregating the study in two phases Phase-I and Phase-II, this phenomenon of drug release was very much in proximity with the theory as it is seen that in the initial phase n >>1 reflecting the non-Fickian release. With time, water penetrates into the hydrogel matrix containing dispersed drug, the polymer chains take up a finite amount of time to rearrange to an equilibrium state in order to accommodate the penetrating solvent. On significant hydration drug release tends to be linear with time giving (n~1) signifying zero-order transport mechanism.

Thus it can be concluded, that by increasing the polymer mass in the micropellets such drug delivery device could be generated which can retain a constant geometry with a constant release rate of drug following zero order kinetic model. The reproducibility of the polymers to produce micropellets of similar release mechanism was optimized statistically in the next chapter of this thesis.

9.8 REFERENCES

1. G.I.Sperandio, R.V.Evanson and H.G.Dekay, *J.Pharm. Sciences*, **37**, 1948, 71.
2. E.L.Parrot, D.E.Wurster and T.Higuchi, *J.Pharm. Sciences*, **44**, 1955, 269.
3. E.Nelson, *J.Pharm. Sciences*, **46**, 1957, 607.
4. G.Levy, R. Gumlow and Rutowski, *J. Chem. Med. Association*, **85**, 1961, 414.
5. J.Swarbrick, *Current concepts in the Pharmaceutical Science, Biopharmaceutics*, Lea & Febiger, Philadelphia, 1970, 266-276.
6. J.G.Wagner, *J.Pharm. Sciences*, **50**, 1961, 359.
7. W.I.Higuchi, *J.Pharm. Sciences*, **56**, 1967,.315.
8. J.E.Goyan, *J.Pharm. Sciences*, **54**, 1965, 645.
9. J.G.Wagner, *Drug Intell. Clinical Pharm.*, **4**,1970, 132.
10. J.Lazarus and J.Cooper, *J.Pharm. Sciences*, **50**, 1961, 715.
11. H.P.Koch, *Pharmaceutica Acta Helv.*, **59**,1984, 98.
12. M.Parnarowski, in *Industrial Pharmaceutical Technology Section*, L. Leason and J.T.Carstensen, Eds.), Academy of Pharmaceutical Sciences, Washington, 1974, 58.
13. W.Rathe and J.Schellhon, *Pharm. Ind.*, **39**, 1977, 801.
14. W.Rathe and J.Schellhon, *Pharm. Ind.*, **40**, 1978, 645.
15. W.Rathe and J.Schellhon, *Pharm. Ind.*, **41**, 1979, 785.
16. G.Detevall, *Acta Med. Scand.*, **170**, 1961, 56.
17. R.L.Altman, in *Biological Handbook*, D.S.Dilter, Eds., Federation of American Societies, Washington, 416-417.
18. H.P.Koch, *Meth. Find. Exptl. Clin. Pharmacol.*, **2**, 1980, 97.
19. H.Takenaka, Y.Kawashina and S.Y.Lin, *J.Pharm. Sciences*, **89**, 1980, 1388.
20. S.K.Das and B.K.Gupta, *Drug Dev. Ind. Pharm.*, **14(4)**, 1988, 537-544.
21. M.Abramson and C.V.King, *J. Am. Chem. Soc.*, **61**, 1939, 2290.
22. A.C.Riddiford, *J. Phy. Chem.*, **55**, 1952, 745.
23. L.J.Edwards, *Trans. Faraday Soc.*, **47**, 1951, 1191.
24. W.Nernst, *Z. Physik. Chem.*, **47**, 1904, 52.
25. D.E.Wurster and P.W.Taylor, *J.Pharm. Sciences*, **54**, 1965, 189.
26. I.Langmuir, *Physical Review*, **12**, 1918, 368.
27. N.Froessiling, *Gerlands Beitr. Geophys.*, **32**,1930,170.
28. J.M.Newton and N.A.H.Muhammad, *J.Pharm. Pharmacol.*, **36**,1984, 42.
29. N.A.H.Muhammad and J.M.Newton, J. Pharm. Pharmacol., **35**, 1983, 345.

30. P.Roller, *J.Phy. Chem.*, **39**, 1935, 221.
31. D.E.Wurster and G.P.Penlli, *J.Pharm. Sciences*, **50**,1961, 403.
32. P.Mukherjee and K.Mysels, *J.Amer. Chem. Soc.*, 77, 1955, 2937.
33. W.Harkins and H.Oppenheimer, *J.Chem. Phy.*, **6**,1948, 1000.
34. P.Ekwall and I.Danielsson, *Acta Chem. Scand.*, **5**, 1951, 976.
35. J.Mebain and H.Huft, *J.Am. Chem. Soc.*, **70**, 1948, 3838.
36. D.D.Abbott, E.W.Packman, and J.W.E.Harrison, *J. Am. Pharm. Assoc.*, **48**, 1959, 19.
37. J.H.Wood, *Pharm. Acta Helv.*, **3**,1967, 129.
38. M.Gibaldi and S.Feldman, *J.Pharm. Sciences*, **56**,1967, 1238.
39. A.Lattir, *Abrege de Pharmacie galinique*, Masson *et. al.*, Eds.,CIC, Paris, 1974,109.
40. J.A.Hersey, *Manf. Chem. Aerosol*, **40**, 1969, 32.
41. C.D.Baun and C.G.Walker, *J.Pharm. Sciences*, **58**, 1969, 611.
42. C.F.Lerk, *Pharmceutisch Weekblad*, **46**, 1976, 1157.
43. H.Stricker, in *The Quality Control of Medicines*, P.B.Deasy and R.F.Timoney, Eds., Elsevier, Amsterdam, 1976, 110.
44. W.H.Barr, *Pharmacology*, **8**, 1972, 55.
45. G.J.Wagner, *Biopharmaceutics and Relevant Pharmacokinetics*, Drug Intelligence Publications, Hamilton, 1971, 110.
46. A.C.Shah, C.B.Peat and J.F.Ochs, *J.Pharm. Sciences*, **62**, 1973, 671.
47. J.Lazarus and J.Cooper, *J.Pharm. Sciences*, **50**, 1961, 715.
48. M.Robinson, *Theory and Practice of Industrial Pharmacy*, L.Lachman, H.A.Lieberman and J.L.Kanig, Eds., Lea & Febiger , Philadelphia, 1970,.2nd Ed. 459-461.
49. J.C.Souder and W.C.Ellenbogen, *Drug Stand.*, **26**,1958, 77.
50. A.G.DeBoer and D.D.Breimer, *The Proceedings of International Conference of Drug Absorption*, L.F.Prescott and W.S.Nimmo, Eds., Aids Press, Sydney, 1980, 61-72.
51. G.Levy and B.Hayes, *N.Eng. J. Med.*, **262**, 1960, 1053.
52. S.Gerschberg and D.F.Stoll, *J.Am.Pharm.Assoc.*, **35**,1946, 284.
53. *United States Pharmacopoeia XX* and *National Formulary XV*, USP Convention Inc., Rockville, USA, 1979, 959.
54. A.A.Noyes and W.R.Whittney, *J.Am. Chem. Soc.*, **19**, 1897, 930.
55. T.J.Sullivan, E.Sakmar, K.S.Albert, D.C.Blair and J.G.Wagner, *J.Pharm. Sciences*, **64**, 1975, 1723.
56. W.Nernst and E.Brunner, *Z.Physik. Chem.*, **47**, 1940, 56.
57. A.A.Noyes and W.R.Whittney, *Z.Physik. Chem.*, **23**, 1897, 689.

58. M.Francois and R.Deneve, *F.L.P.Abstracts*, 39th International Congress of Pharmaceutical Science, Brighton, 1979, 21.
59. A. El-Yazigi, *J.Pharm. Sciences*, **70,** 1981, 535
60. A.El-Yazigi, *J.Pharm. Sciences*, **71,** 1982, 1408.
61. W.D.Rhine, D.S.T.Hrich and R.Langer, *J.Pharm. Sciences*, **69**, 1980, 265.
62. P.L.Madan, *J.Pharm. Sciences*, **70**, 1981, 430.
63. H.P.Koch and G.Hirsch, *Pharm. Ztg.*, **127**,1982, 2523.
64. W.Weibull, *J.Appl.Mech.*, **18**,1951, 293.
65. F.Langenbucher, *J.Pharm. Pharmacol.*, **24**,1972, 979.
66. K.A.Khan, *J.Pharm. Pharmacol.*, **27**,1975, 48.
67. D.J.Cutler, *J.Pharm. Pharmacol.*, **30**,1978, 478.
68. K.Yamaska, T.Nakagawa and T.Uno, *J. Pharmacokin. Biopharm.*, **8**,1980, 509
69. S.Riegelman and P.Callier, *J.Pharmacokin. Biopharm.*, **6**,1978, 547.
70. A.W.Hixson and J.H.Crowell, *Ind. Eng. Chem.*, **23**, 1931, 923.
71. G.Levy, *Am. J.Pharm.*, **135**, 1963, 78.
72. K.Heilman, in *Therapeutic System,* G.I.Thieme, Eds., Verlag, Stuttgart, 1979.
73. M.Gibaldi and S.Feldman, *J.Pharm. Sciences*, **56**, 1967, 1238.
74. J.G.Wagner, *Drug Intell. Clin. Pharm.*, **3**, 1969, 357.
75. Y.Raghunathan and C.H.Becker, *J.Pharm. Sciences,* **57**, 1968, 1748.
76. E.H.Wiseman and N.J.Federce, *J.Pharm. Sciences*, **57**, 1968, 1535.
77. T.Higuchi, *J.Pharm. Sciences,* **52**, 1963, 1145.
78. W.I.Higuchi, *J.Pharm. Sciences*, **56**, 1967, 315.
79. S.J.Desai, P.Singh, A.P.Simonelli and W.I.Higuchi, *J.Pharm. Sciences*, **54**, 1965, 1459.
80. S.J.Desai, P.Singh, A.P.Simonelli and W.I.Higuchi, *J.Pharm. Sciences*, **55**, 1966, 1230.
81. H.Fessi, J.P.Marty, F.Pusieux and J.T.Cartensen, *J.Pharm. Sciences* , **71**,1982, 749.
82. W.I.Higuchi, N.A.Mir and S.J.Desai, *J.Pharm. Sciences*, 1965, **54**, 1405.
83. T.J.Roseman and W.I.Higuchi, *J.Pharm. Sciences*, **59**, 1970, 353.
84. E.Touitou and M.Denbrow, *International J. Pharm.*, **11,** 1982, 355.
85. H.B.Hoffenberg, D.R.Paul and F.W.Harris, *Controlled Release Polymeric Formulations*, Am. Chem. Soc., Washington, 1976, 26-32.
86. B.K.Davis, *Proc. National Academy Science*, USA, **71**, 1974, 3120.
87. M. Bamba and F. Puisieux, *International J. Pharm.*, **2,** 1979, 307-315.
88. N.A. Peppas, *Pharm. Acta. Helv.*, **60 (4),** 1985, 110-111.
89. P. Costa and J.M. Souza Lobo, *Eur. J. Pharm. Science Review,* **13,** 2001, 123-133.