ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Kinetics and Mechanisms of Drug Release from Swellable and Non Swellable Matrices: A Review

Chime Salome A*, Onunkwo Godswill C and Onyishi Ikechukwu I

Department of Pharmaceutical Technology and Industrial Pharmacy, University of Nigeria, Nsukka 410001, Nigeria

ABSTRACT

Drug dissolution from solid dosage forms has been described by some kinetic models which include zero-order kinetics, first order kinetics, Higuchi model and Hixson-Crowell. Drug release from matrices may involve processes of diffusion, erosion, and leaching or dissolution. Drug release may follow mixed mechanism of release; it may involve both diffusion and dissolution controlled processes. Some parameters such as the permeability of the polymer to dissolution medium, the solubility of the drug, the dissolution medium and the molecular size of the drug may affect drug release processes. Insoluble polymers retard drug release by presenting an impermeable surface, being insoluble in water. This article however, presents various models used in studying the kinetics and mechanisms of drug release from swellable and non swellable matrices.

Keywords: Drug release kinetics; Swellable matrix; Non swellable matrix; Ritger-Peppas.

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Drugs may be released through leaching in dissolution medium which is able to enter the polymer drug matrix system through pores, cracks and inter granular spaces. The infiltration rate of the fluid into the matrix may be controlled by changes in the interspaces of the matrix [1]. Drug release from matrices may involve processes of diffusion, erosion, and leaching or dissolution [2-3]. Drug release may follow mixed mechanism of release; it may involve both diffusion and dissolution controlled processes [4]. In most of the cases the theoretical concepts does not exist and some empirical equations have proved to be more appropriate [2]. Modified drug delivery system such as sustained or controlled release tablets and capsules generally consists of drug dispersed in a polymeric matrix where the process of diffusion predominates. Drug dissolution from solid dosage forms has been described by some kinetic models which include zero-order kinetics, first order kinetics, Higuchi model and Hixson-Crowell. The mechanisms of drug release from a matrix can be interpreted using these models: Weibull model, Baker-Lonsdale model, Korsmeyer-Peppas and Ritger-Peppas model and Hopfenberg model [2-4].

Zero order:

The zero order rate (Eq. 1) describes the systems where the drug release rate is independent of its concentration [2].

$$C = k_0 t \text{ ---------- (1)}$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

A plot of amount of drug released versus time will be linear for zero-order kinetics. The dosage forms following this profile, release the same amount of drug by unit time and it is the ideal method of drug release in order to achieve a prolonged pharmacological action. This relation can be used to determine the drug dissolution from various types of modified release dosage forms such as matrix tablets with low soluble drugs, coated tablets and capsules and osmotic systems [2, 5].

First order:

The first order kinetics was first applied for drug dissolution studies by Gibaldi and Feldman in 1967 and later by Wagner in 1969 [6-7].The first order equation (Equations 2 and 3) describes the release of drug from system where release rate is concentration dependent [2].

$$\text{Log } C_t = \text{Log } C_0 - k_1 t / 2.303 \text{ ---------- (2)}$$

$$\text{Log}C_0 - \text{Log}C_t = kt / 2.303 \text{ ---------- (3)}$$

Where, C_t is the amount of drug released in time t, C_0 is the initial concentration of drug and K_1 is first order constant. Here the graphical representation of the log cumulative of % drug remaining (log $C_0 - C_t$) versus time will be linear with a negative slope [8]. The dosage form follows this profile such as those containing water soluble drug in a porous matrices release the drug that is proportional to the amount of drug released by unit time diminish [2, 9].

Higuchi models:

Higuchi in 1961 and in 1963 developed models to study the release of water soluble and low soluble drugs incorporated in semisolid and solid matrices [10-11]. To study the dissolution from a planer system having a homogeneous matrix the relation obtained is shown in equation 4:

$$Q = [D (2C-C_s) C_s t]^{1/2} \text{ ---------- (4)}$$

Where Q is the amount of drug released in time t per unit area, C is the initial drug concentration, Cs is the drug solubility in the matrix media and D is the diffusivity of drug molecules in the matrix substance. To study the dissolution from a planer a spherical 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 relation obtained:

$$Q = D\varepsilon/\tau (2C-\varepsilon C_s) C_s t \text{ ---------- (5)}$$

Where Q, D, C, C_s and t has the same meaning as in equation (4), ε is the matrix porosity, τ is the tortuosity factor of the capillary system. In general way Higuchi model can be simplified as,

$$Q = K_H t^{1/2} \text{---------- (6)}$$

Where K_H is the Higuchi dissolution constant. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. For diffusion controlled process a plot of Q versus square root of time is linear. The integral form of Higuchi equation is employed in seeking to establish whether mixed order release kinetics exists:

$$\text{Log } Q = \log k_H + 1/2 \log t \text{---------- (7)}$$

A confirmation of Higuchi diffusion is provided by the equation 7; diffusion controlled process dominates when the logarithm plot approaches 0.5 [2-3].

Hixson-Crowell cube root law:

The Hixson-Crowell cube root law (Eq. 8) describes the release from systems where there is a change in surface area and diameter of particles or tablets [12-13].

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}t \text{---------- (8)}$$

Where, Q_t is the remaining amount of drug in the dosage form at time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation. A graphical representation of the cube root of the amount remaining versus time will be linear if the equilibrium conditions are not reached and if the geometrical shape of the dosage form diminishes proportionally overtime (Cube root of initial drug load minus cube root of % drug remaining) are plotted against time (hour) to demonstrate the Hixson Crowell plot [14]. This model is used by assuming that release rate is limited by the drug particles dissolution rate and not by the diffusion [2].

Kitazawa model

Kitazawa's model reveals significant changes in the release rates of a system releasing its content under sink condition. Kitazawa' equation is expressed as:

$$\text{Log } C_S/C_S - C_t = Kt/ 2.303 \text{ ---------- (9)}$$

C_s and C_t are amount of drug dissolved at infinite time and at time t respectively, K is the dissolution rate constant derived from the slope of the regression line [3].

Ritger-Peppas and Korsmeyer-Peppas models

Ritger and Peppas (1987) and Korsmeyer and Peppas (1984) developed an empirical equation to analyze both Fickian and non-Fickian release of drug from swelling as well as non-swelling polymeric delivery systems [15-17]. The equation is represented as:

$$M_t/M_\infty = Kt^n \text{ ---------- (10)}$$

The logarithm form of equation 8 could be written as:

$$\text{Log } (M_t /M_\infty) = \text{Log } k + n \text{ Log } t \text{ ---------- (11)}$$

where M_t/M_∞ is fraction of drug released at time t, n is diffusion exponent indicative of the mechanism of transport of drug through the polymer, K is kinetic constant (having units of t^{-n}) incorporating structural and geometric characteristics of the delivery system.

For Ritger-Peppas models, the release exponent $n \leq 0.5$ for Fickian diffusion release from slab (non swellable matrix), $0.5 < n < 1.0$ for non-Fickian release (anomalous), this means that drug release followed both diffusion and erosion controlled mechanisms and $n = 1$ for zero order release, where drug release is independent of time as shown in Tables 1 and 2 [15-18]. Also, $0.45 < n < 1.0$ for non-Fickian release (anomalous) from cylinders (non swellable matrix) and $0.43 < n < 1.0$ for non-Fickian release (anomalous) from non swellable spherical samples as

shown in Table 2. For Korsmeyer-Peppas models, the release exponent n ≤ 0.45 for Fickian diffusion release and 0.45 < n < 0.89 for non-Fickian release (anomalous).

Table 1: Ritger-Peppas diffusion exponent and mechanism of diffusional release from various swellable controlled release systems

Diffusion exponent, n			Drug release mechanism
Thin film	Cylindrical sample	Spherical sample	
0.50	0.45	0.43	Fickian diffusion
0.50 < n < 1.00	0.45 < n < 0.89	0.43 < n < 0.85	Anomalous (non-Fickian) transport
1.0	0.89	0.85	Case 11 transport

Table 2: Ritger-Peppas diffusion exponent and mechanism of diffusional release from various non-swellable controlled release systems

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

Weibull model:

The Weibull equation expresses the accumulated fraction of drug 'm' in solution at time t as:

$$M = 1- \exp [-\{(t-Ti)^b\}/a] \text{ ----------(12)}$$

Where M is accumulated fraction of drug in solution at time t, 'a' is the scale parameter which defines the time scale of the process. Ti is the location parameter, represents the lag time before the onset of the dissolution or release process and in most of the cases will be zero. The shape parameter, b, characterizes the curves as either exponential (b=1), S-shaped (b>1) or parabolic (b<1) [19]. The equation (12) can be rearranged as:

$$\text{Log } [\ln - (1-m)] = b \text{ Log } (t-Ti) - \log a \text{ ---------- (13)}$$

Graphical representation of log [-ln (1-m)] versus time t gives a linear relation. Shape parameter (b) is obtained from the shape of the line and the scale parameter (a) can be estimated from the ordinate value (1/a) at time t =1[2].

Baker-Lonsdale model:

Baker-Lonsdale in 1974 developed the model from the Higuchi model and describes the controlled release of drug from a spherical matrix that can be represented as:

$$^{3/2}\,[1-(1-M_t/M_\infty)^{2/3}]-M_t/M_\infty = (3D_mC_{ms}) / (r_0^2\,C_0)\,Xt\text{----------(14)}$$

Where M_t is the amount of drug released at time t and M_∞ is the amount of drug released at an infinite time, D_m is the diffusion coefficient, C_{ms} is the drug solubility in the matrix, r_0 is the radius of the spherical matrix and C_0 is the initial concentration of the drug in the matrix [20]. Here graphical representation of the left side of the equation versus time will be linear if the established conditions were fulfilled. Baker-Lonsdale model could be redefined as:

$$^{3/2}\,[1-(1-M_t/M_\infty)^{2/3}]-M_t/M_0 = kt\text{ ----------(15)}$$

Where k is the release constant corresponds to the slope. This equation can be used to the linearization of the release data from several formulations of microcapsules [21].

Hopfenberg Model:

Hopfenberg (1976) and Katzhendler et al (1997) developed a general mathematical equation describing drug release from slabs, spheres and infinite cylinders displaying heterogeneous erosions as:

$$M_t/M_\infty = 1 - [1-k_0t/C_0a_0]^n\text{ ----------(16)}$$

Where M_t is the amount of drug dissolved in time t, M_∞ is the total amount of drug dissolved when the dosage form is exhausted, M_t/M_∞ is the fraction of drug dissolved, k_0 is the erosion rate constant, C_0 is the initial concentration of drug in the matrix and a_0 is the initial radius for sphere or cylinder or the half-thickness for a slab. The value of n is 1, 2, and 3 for a slab, cylinder and sphere respectively [2, 22-23].

Power law

Power law is a semi-empirical equation that describes drug release from polymeric system as shown in equation 17:

$$A_t/A_\infty = kt^n\text{ ---------- (17)}$$

Where A_t and A_∞ are the absolute cumulative amount of drug released at time 't' and at infinite time respectively, 'k' is a constant incorporating structural and geometric characteristics of the device and n is the release exponent, indicative of the drug release mechanism [2].

The exponent n = 1.0 for zero-order kinetics, n = 0.5 for diffusion controlled drug release and n between 0.5 and 1.0 or anomalous release mechanism. The extreme value for the exponent n, 0.5 and 1.0 are only valid for slab geometry [2, 24].

ISSN: 0975-8585

CONCLUSION

Drug release kinetics can be determined using zero-order, first order, Higuchi and Hixson- Crowell models, while the mechanisms of drug release can be determined using Weibull model, Baker-Lonsdale model, Korsmeyer-Peppas or Ritger-Peppas model and Hopfenberg model. For each model the slope (n), regression coefficient (R^2) and rate constant (k) are graphically determined and are used to predict the kinetics and mechanisms of drug release from matrices.

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