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Review Article

Mathematical Models of Drug Dissolution: A Review

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Abstract: When a new solid dosage form is developed, it is very important to study drug release or dissolution. The quantitative analysis of values obtained in dissolution or release rates is easier when mathematical formulae are used to describe the process. The mathematical modeling helps to optimize the design of a therapeutic device to yield information on the efficacy of various release models. In this paper we review the different mathematical models used to determine the kinetics of drug release from drug delivery systems such as, zero order, first order, Hixson-Crowell, Higuchi, Weibull, Korsemeyer-Peppas, Hopfenberg, Baker-Lonsdale and Gompertz model.
Keywords: Dissolution, Dissolution models, Drug release kinetics. .

INTRODUCTION

Drug dissolution is important test used to evaluate drug release of solid and semisolid dosage forms. This test is developed for quantification of the amount and extent of drug release from dosage forms. The values that are obtained from the dissolution study can be quantitatively analyzed by using different mathematical formulae. Because qualitative and quantitative changes in a formulation may alter release of drug and in vivo performance, developing tools that facilitate product development by reducing the necessity of bio-studies is always desirable. Thus mathematical models can be developed. This development requires the comprehension of all phenomena affecting drug release kinetics and this has a very important value in the formulation optimization. The model can be simply thought as a 'mathematical metaphor of some aspects of reality'. For this generality, mathematical modeling is widely employed in different disciplines such as genetics, medicine, psychology, biology, economy and obviously engineering and technology [1-6]. Model dependent methods are based on different mathematical functions, which describe the dissolution profile. Once a suitable function has been selected, the dissolution profiles are evaluated depending on the derived model parameters.
To compare dissolution profiles between two drug products model dependent (curve fitting), statistic analysis and model independent methods can be used.

MATHEMATICAL MODELS

Zero order model:

Dissolution of the drug from pharmaceutical dosage forms that do not disaggregate and release the drug slowly can be represented by the following equation:

$$W_0 - W_t = Kt \quad \text{---------- (1)}$$

Where, W_0 is the initial amount of drug in the pharmaceutical dosage form W_t is the amount of drug in the pharmaceutical dosage form at time t and K is proportionality constant. Dividing this equation by W_0 and simplifying:

$$f_t = K_0 t \quad \text{----------(2)}$$

where $f_t = 1 - (W_t / W_0)$ and f_t represents the fraction of drug dissolved in time t and K_0 the apparent dissolution rate constant or zero order release constant. In this way, a graphic of the drug-dissolved fraction versus time will be linear if the previously established conditions were fulfilled [7].

The pharmaceutical dosage forms following this profiles release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. The following relation can, in a simple way, express this model:

$$Q_t = Q_0 + K_0 t \quad \text{----------(3)}$$

Where, Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution and K_0 is the zero order release constant.

To study the release kinetics, data obtained from in vitro drug release studies were plotted as cumulative amount of drug released versus time [8-9].

Applications:

This relation 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 soluble drugs, coated forms, osmotic systems, etc [10-11].

First order model:

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967) and later by Wagner (1969). This model has been also used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualise this mechanism in a theoretical basis [12]. The dissolution phenomena of a solid particle in a liquid media imply a surface action, as can be seen by the Noyes–Whitney Equation:

$$dc/dt = K (C_S - C) \quad \text{----------(4)}$$

Where C is the concentration of the solute in time t, C_s is s order the solubility in the equilibrium at experience temperature and K is first order proportionality constant. This equation was altered by Brunner et al. (1900), to incorporate the value of the solid area accessible to dissolution, S, getting:

$$dc/dt = K_1 S (C_S - C) \quad \text{----------(5)}$$

Where, k_1 is a new proportionality constant. Using the Fick first law, it is possible to establish the following relation for the constant k_1:

$$k_1 = D/Vh \quad \text{----------(6)}$$

Where, D is the solute diffusion coefficient in the dissolution media, V is the liquid dissolution volume and h is the width of the diffusion layer. Hixson and Crowell adapted the Noyes–Whitney equation in the following manner:

$$dW/ dt = KS(C_s - C) \quad \text{---------- (7)}$$

Where, W is the amount of solute in solution at time t, dW/dt is the passage rate of the solute into solution in time t and K is a constant. This last equation is obtained from the Noyes–Whitney equation by multiplying both terms of equation by V and making K equal to k_1V. Comparing these terms, the following relation is obtained:

$$K = D/h \quad \text{----------(8)}$$

In this manner, Hixson and Crowell equation (eq.7) can be written as:

$$dW/ dt = KS/V (VC_s - W) = k (VC_s - W) \quad \text{-------(9)}$$

Where, $k = k_1S$. If one pharmaceutical dosage form with constant area is studied in ideal conditions (sink conditions), it is possible to use this last equation that, after integration, will become:

$$W = VC_s (1 - e^{-kt}) \quad \text{----------(10)}$$

This equation can be transformed, applying decimal logarithms in both terms, into:

$$\text{Log } (VC_s - W) = \log VC_s - (kt/2.303) \quad \text{--------(11)}$$

The following relation can also express this model:

$$Q_t = Q_0 e^{-K_1 t} \quad \text{or} \quad \ln (Q_t/Q_0) = K_1 t \quad \text{or} \quad \ln Q_t = \ln Q_0 K_1 t$$

Or in decimal logarithms:

$$\log Q_t = \log Q_0 + (K_1/2.303) \quad \text{----------(12)}$$

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and K_1 is the first order release constant. The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of-K/2.303[13].

Applications:

This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water soluble drugs in porous matrices [14-15].

N. Ahuja, Om Prakash Katare, B. Singh, was studied dissolution enhancement and mathematical modelling of drug release of a poorly water-soluble drug using water-soluble carriers. They studied dissolution profile of drug by using zero order, first order and Hixson- Crowell model and they found that first order model fitted well at early time periods.

The table 1 shows the kinetics parameters of different formulations which from that it is concluded that the first order model show best results than the other two [16].

Hixson and Crowell model:

Drug powder that having uniformed size particles, Hixson and Crowell derived the equation which expresses rate of dissolution based on cube root of weight of particles and the radius of particle is not assumed to be constant.

This is expressed by the equation,

$$M_0^{1/3} - M_t^{1/3} = \kappa t \quad \text{----------(13)}$$

Where, M_0 is the initial amount of drug in the pharmaceutical dosage form, M_t is remaining amount of drug in the pharmaceutical dosage form at time 't' and κ is proportionality constant.

The above equation can be rewritten as,

$$M_0^{1/3} - M_t^{1/3} = K' N^{1/3} D C_s t/\delta \quad \text{----------(14)}$$

Where K′ is a constant related to the surface, shape and density of particle, N is number of particles, D is diffusion coefficient, C_s is solubility in the equilibrium at experience temperature and δ is thickness of diffusion layer.

To study the release kinetics, data obtained from in vitro drug release studies were plotted as cube root of drug percentage remaining in matrix versus time [17].

Applications:

This is applies to different pharmaceutical dosage form such as tablets, where the dissolution occurs in planes which are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a way that the initial geometrical form keeps constant all the time [18].

I. Jalal, E. Zmaily and N. Najib was studied dissolution kinetics of commercially available controlled-release theophylline preparations by using Hixson and Crowell model. The dissolution data are plotted in accordance with the Hixson-Crowell cube root law, i.e. the cube root of the initial concentration minus the cube root of percent remained, as a function of time. The results as shown in table 2 indicates that a linear relationship was obtained in all cases [19].

Higuchi model:

This is the first mathematical model that describes drug release from a matrix system, proposed by Higuchi in 1961 [20]. This model is based on different hypothesis that (1) Initial drug concentration in the matrix is much higher than drug solubility, (2) Drug diffusion takes place only in one dimension (Edge effect should be avoided), (3) Drug particles are much smaller than thickness of system, (4) swelling of matrix and dissolution are less or negligible, (5) Drug diffusivity is constant, (6) Perfect sink condition are always attained in the release environment.

The study of dissolution from a planar system having a homogeneous matrix can be obtained by the equation:

$$f_t = Q = A\sqrt{D(2C-C_s)\,C_s t} \quad \text{----------(15)}$$

Where, Q is amount of drug release in time t per unit area A, D is diffusion coefficient of drug molecules, C is initial concentration of drug and C_s is solubility of drug in matrix media.

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:

$$f_t = Q = \sqrt{D\delta/\tau\,(2C-\delta C_s)\,t} \quad \text{----------(16)}$$

Where, D is the diffusion coefficient of the drug molecule in the solvent, δ is the porosity of the matrix, τ is the tortuisity of the matrix and Q, A, Cs and t have the meaning assigned above.

Tortuisity is defined as the dimensions of radius and branching of the pores and canals in the matrix and the Porosity is function of matrix that exist as pores or channels from which liquid penetrate inside for release of drug from granular matrix. In a general way it is possible to simplify the Higuchi model as:

$$f_t = Q = K_H \sqrt{t} \quad \text{----------(17)}$$

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. The data obtained were plotted as cumulative percentage drug release versus square root of time [21-23].

Applications:

This relationship can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs [24-25].

A. Minhaz, S. Islam, H. Rahman were studied an In vitro Release of Ketorolac from Extended Release Capsules. They found the 96.23% release of KT within 8 hrs. They applied different models for kinetic study (zero-order, first-order and Higuchi's equation).They found best fit with higher correlation with the Higuchi's equation for almost all the formulations. The result of study can be shown in table 3[26].

Weibull model:

The Weibull equation can be applied to almost all kinds of dissolution curves [27-28]. If applied to dissolution of pharmaceutical dosage form, this equation expresses the accumulation of fraction of drug in solution and is given by equation:

$$M = M_0\,[1\text{-}e^{-(t-T/a)b}] \quad \text{----------(18)}$$

Where, M is the amount of drug dissolved as a function of time t. M_0 is total amount of drug being released. T accounts for the lag time measured as a result of the dissolution process. Parameter 'a' denotes a scale parameter that describes the time dependence, while 'b' describes the shape of the dissolution curve progression. For b = 1, the shape of the curve corresponds exactly to the shape of an exponential profile with the constant k = 1/a (equation 19).

$$M = M0\,(1 - e^{-k\,(t-T)} \quad \text{----------(19)}$$

If 'b' has a higher value than 1, the shape of the curve gets sigmoidal with a turning point, whereas

the shape of the curve with 'b' lower than 1 would show a steeper increase than the one with b = 1.

The time, when 50% (w/w) and 90% (w/w) of drug being in each formulation was released, was calculated using the inverse function of the Weibull equation:

$$t_{(50\% \text{ resp. } 90\% \text{ dissolved})} = (- a \ln M- M_0 / M_0)^{1/b} + T \text{----------(20)}$$

The equation (18) may rearrange into logarithmic form,

$$\log[-\ln(1- m)] = b \log (t- T_i) - \log a \text{ -------(21)}$$

From this equation a linear relation can be obtained for a log–log plot of -ln (1-m) versus time, t. The shape parameter (b) is obtained from the slope of the line and the scale parameter, a, is estimated from the ordinate value (1/a) at time t=1. The parameter, a, can be replaced by the more informative dissolution time, T_d, that is defined by a= (T_d) d and is read from the graph as the time value corresponding to the ordinate -ln (1- m) = 1. Since -ln (1 - m) = 1 is equivalent to m=0.632, T_d represents the time interval necessary to dissolve or release 63.2% of the drug present in the pharmaceutical dosage form. To pharmaceuticals systems following this model, the logarithm of the dissolved amount of drug versus the logarithm of time plot will be linear [29-30].

Applications:

The Weibull model is more useful for comparing the release profiles of matrix type drug delivery [31-32].

Kevin J. Carroll, M.Sc. was done the analysis of survival data arising in clinical trial by using Weibull model. He found that Weibull analysis allows direct assessment and quantification of proportionality, or lack thereof and also Weibull analysis offers the opportunity to predict how data might mature over time, something that is of great interest within oncology trials, especially where a series of interim analyses are planned. The result can be shown in table 4[33].

Korsemeyer- peppas model:

Korsemeyer et al. (1983) derived a simple relationship which described drug release from a polymeric system equation.

$$ft = Kt^n \text{ ----------(22)}$$

Where, ft is fraction of drug released at time t, k is release rate constant and n is the release exponent. The drug diffusion from a controlled release polymeric system with the form of a plane sheet, of thickness δ can be represented by:

$$\partial c / \partial t = D (\partial^2 c / \partial x^2) \text{ ----------(23)}$$

Where D is the drug diffusion coefficient (concentration independent). If drug release occurs under perfect sink conditions, the following initial and boundary conditions can be assumed:

$t = 0 \quad -d / 2 < x < d/2 \quad c = c_0$

$t > 0 \quad x = \pm d / 2 \quad c = c_1$

Where c_0 is the initial drug concentration in the device and c_1 is the concentration of drug at the polymer–water interface. The solution equation under these conditions was proposed initially by Crank (1975):

$$\frac{M_t}{M_\infty} = 2 \left(\frac{D_t}{\delta^2}\right)^{\frac{1}{2}} \left[\pi - \frac{1}{2} + \sum_{n=1}^{\infty}(-1)^n \, i\,erfc \, \frac{n\delta}{2\sqrt{Dt}}\right] \text{(24)}$$

A sufficiently accurate expression can be obtained for small values of t since the second term of Eq. (24) disappears and then it becomes:

$$\frac{M_t}{M_\infty} = 2 \left(\frac{D_t}{\delta^2}\right)^{\frac{1}{2}} = a t^{\frac{1}{2}} \text{ ----------(25)}$$

Then, if the diffusion is the main drug release mechanism, a graphic representing the drug amount released, in the referred conditions, versus the square root of time should originate a straight line. Under some experimental situations the release mechanism deviates from the Ficks equation, following an anomalous behavior (non-Fickian)[34-38]. In these cases a more generic equation can be used:

$$\frac{M_t}{M_\infty} = a t^n \text{ ----------(26)}$$

'n' value is used to characterize different release for cylindrical shaped matrices; and it is describe in table 5. For the case of cylindrical tablets, $0.45 \leq n$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, $n = 0.89$ to Case II (relaxational) transport, and $n > 0.89$ to super case II transport[39-40]. To find out the exponent of 'n' the portion of the release curve, where $Mt/ M\infty < 0.6$ should only be used. To study the release kinetics, data obtained from in vitro drug release studies were plotted as log cumulative percentage drug release versus log time.

Applications:

This equation has been used to the linearization of release data from several formulations of microcapsules or microspheres.

HY Karasulu, G Ertana, T Kose were studied theophylline release from different geometrical erodible tablets. They follow the Korsemeyer- peppas model for the study and found the good results as given in table 6. They were also studied change in geometry of tablets by calculating 'n' values for each tablet, and are found to be 4, 2 and 1 for the triangular, cylindrical and half-spherical tablets respectively [41].

Hopfenberg model:

Hopfenberg developed a mathematical model to correlate the drug release from surface eroding polymers so long as the surface area remains constant

during the degradation process. He was analyzed release of drugs from surface-eroding devices with several geometries and developed a general mathematical equation describing drug release from slabs, spheres and infinite cylinders displaying heterogeneous erosion [42-43]. The drug release was expressed by equation:

$$\frac{M_t}{M_\infty} = 1 - \left[1 - \frac{k_0 t}{C_0 a_0}\right]^n \text{ ----------(27)}$$

where M_t is the amount of drug dissolved in time t, M_∞ is the total amount of drug dissolved when the pharmaceutical dosage form is exhausted, M_t / M_∞ is the fraction of drug dissolved, k_0 is the erosion rate constant, C is the initial concentration of drug in the matrix and a_0 is the initial radius for a 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. A modified form of this model was developed to accommodate the lag time (l) in the beginning of the drug release from the pharmaceutical dosage form:

$$\frac{M_t}{M_\infty} = 1 - [1 - k_1 t\,(t - l)]^n \text{ ----------(28)}$$

Where k_1 is equal to $k_0 / C_0\, a_0$. This model assumes that the rate-limiting step of drug release is the erosion of the matrix itself and that time dependent diffusional resistances internal or external to the eroding matrix do not influence it.

Applications:

This model is useful for identification of the mechanism of release from the optimized oily- spheres using data derived from the composite profile, which displayed site-specific biphasic release kinetics [44].

Baker-Lonsdale model:

This model was developed by Baker and Lonsdale (1974) from the Higuchi model and described the drug release from spherical matrices by using the equation:

$$f_1 = \frac{3}{2}\left[1 - \left(1 - \frac{M_t}{M_\infty}\right)^{\frac{2}{3}}\right] - \frac{M_t}{M_\infty} = \frac{3 D_m C_{ms}}{r_0^2 C_0} - t \text{ ----(29)}$$

Where M_t is the drug released amount 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 drug in the matrix [45].

If the matrix is not homogeneous and presents fractures or capillaries that may contribute to the drug release, the following equation is used:

$$f_1 = \frac{3}{2}\left[1 - \left(1 - \frac{M_t}{M_\infty}\right)^{\frac{2}{3}}\right] - \frac{M_t}{M_\infty} = \frac{3 D_f C_{fs}\, \varepsilon}{r_0^2 C_0 \tau} - t \text{----(30)}$$

Where D_f is the diffusion coefficient, C_{fs} is the drug solubility in the liquid surrounding the matrix, τ is the tortuosity factor of the capillary system and ε is the porosity of the matrix. The matrix porosity can be described by:

$$\varepsilon = \varepsilon_0 + KC_0 \text{ ----------(31)}$$

Where ε_0 is the initial porosity and K is the drug specific volume. If ε_0 is small, Eq. (30) can be rearranged as:

$$f_1 = \frac{3}{2}\left[1 - \left(1 - \frac{M_t}{M_\infty}\right)^{\frac{2}{3}}\right] - \frac{M_t}{M_\infty} = \frac{3 D_f K C_{fs}}{r_0^2 \tau} - t \text{-----(32)}$$

Hence, the Baker-Lonsdale model could be given by equation:

$$f_1 = \frac{3}{2}\left[1 - \left(1 - \frac{M_t}{M_\infty}\right)^{\frac{2}{3}}\right] - \frac{M_t}{M_\infty} = kt \text{ ----------(33)}$$

Where, k is release constant and is corresponds to slope.

To study the release kinetics, data obtained from in vitro drug release studies were plotted as [d (Mt / M∞)] / dt with respect to the root of time inverse[45-49].

Applications:

This equation has been used to the linearization of release data from several formulations of microcapsules or microspheres [50-51].

S. K. Singh, J. Dodge, M. J. Durrani were studied the release of drug from controlled release pellets coated with an experimental latex. They were study the kinetics of release by applying different models (Higuchi, First order, Hixon- crowell, Baker - Lonsdale), but they were found that Baker- Lonsdale model provide a best correlation from the results, given in table 7[52].

Gompertz model:

Dissolution profile of pharmaceutical dosage form can also been described by Gompertz model, expressed by equation:

$$X(t) = X_{max} \exp[-\alpha\, e^{\beta \log t}] \text{----------(34)}$$

Where X(t) = percent dissolved at time t divided by 100; Xmax = maximum dissolution; α determines the undissolved proportion at time t = 1 and described as location or scale parameter; β = dissolution rate per unit of time described as shape parameter. This model has a steep increase in the beginning and converges slowly to the asymptotic maximal dissolution [53-56].

Applications:

The Gompertz model is more useful for comparing the release profiles of drugs having good solubility and intermediate release rate [56].

Jiaxi Li, Ji-Dong Gu, Li Pan was studied transformation of dimethyl phthalate, dimethyl

isophthalate and dimethyl terephthalate by Rhodococcus rubber Sa and they studied dissolution profile of process by using modified Gompertz model, they found good results as shown in table 8[57].

Table 1: Statistical parameters of various formulations obtained after fitting the drug release data to various release kinetic models; shows first order model is best fitted [16].

Sr. No.	Formulation	Mathematical models for drug release kinetics					
		Hixson-Crowell		Zero-order		First-order	
		Slope	r^2	Slope	r^2	Slope	r^2
1	Pure RFX	0.0275	0.5522	-1.07	-0.1086	**-0.0105**	**0.7795**
2	RCA50%	0.0697	0.6257	-2.75	0.1907	**-0.0264**	**0.8017**
3	RCA25%	0.1597	0.8956	-7.01	0.7502	**-0.0651**	**0.9751**
4	RCA10%	0.3297	0.8258	-8.45	0.5127	**-0.2171**	**0.9948**
5	RNA50%	0.0346	0.5403	-1.40	-0.1031	**-0.0115**	**0.8067**
6	RNA25%	0.0493	0.6404	-1.99	0.1360	**-0.0152**	**0.8988**
7	RNA10%	0.1262	0.8380	-5.16	0.7710	**-0.0448**	**0.9823**
8	RU50%	0.0524	0.6632	-2.05	0.1610	**-0.0200**	**0.8417**
9	RU25%	0.0934	0.8680	-3.78	0.5653	**-0.0349**	**0.9604**
10	RU10%	0.1888	0.8343	-7.19	0.7615	**-0.0659**	**0.9877**

r^2, correlation coefficient

Table 2: Dissolution rate constant by using Hixson-Crowell model obtained under all test conditions [19]

Sr. No.	Name	Hixson-Crowell rate constant (K)			
		pH 1.0		pH 7.5	
		Basket	Paddle	Basket	Paddle
1	Broncho-Retard 500	0.006 r = 0.981 n=12	0.007 r = 0.999 n=12	0.005 r = 0.998 n = 27	0.006 r = 0.996 n = 24
2	Broncho-Retard 200	0.003 r = 0.998 n =12	0.005 r = 0.999 n =12	0.003 r = 0.999 n = 28	0.005 r = 0.997 n = 28
3	Theodur 300	0.001 r = 0.984 n =11	0.002 r = 0.991 n=12	0.001 r = 0.991 n = 28	0.003 r = 0.995 n = 26
4	Lasma 300	0.003 r = 0.998 n =12	0.003 r = 0.998 n =12	0.002 r = 0.999 n = 29	0.003 r = 0.996 n = 25

n, Number of data points; r, correlation coefficient.

Table 3: Kinetic parameters of the release curve showing best fit with higher correlation with the Higuchi's equation for almost all the formulations [26].

Sr. no.	Formulation	r^2 (Zero order)	r^2 (First order)	r^2(Higuchi)
1	F1	0.94	0.93	**0.98**
2	F2	0.93	0.96	**0.98**
3	F3	0.95	0.92	**0.99**
4	F4	0.97	0.93	**0.99**
5	F5	0.93	0.88	**0.95**
6	F6	0.95	0.81	**0.92**
7	F7	0.93	0.87	**0.96**
8	F8	0.92	0.82	**0.95**

r^2, correlation coefficient

Table 4: Simulated Weibull data [33].

n[a]	Weibull analysis		
	HR	5th and 95th percentiles	SE (log HR)
250	0.802	0.681, 0.935	0.0983
	0.800	0.686, 0.935	0.0955
100	0.804	0.624, 1.023	0.1516
	0.801	0.620, 1.024	0.1493
50	0.782	0.460, 1.334	0.3209
	0.800	0.494, 1.347	0.3079

a, number per group; HR, Hazard ratio; SE, Standard error.

Table 5: Interpretation of diffusional release mechanisms from polymeric films [40]

Release exponent (n)	Drug transport mechanism	Rate as a function of time
$0.45 \leq n$	Fickian diffusion	$t^{-0.5}$
$0.45 < n < 0.89$	Non-Fickian transport	t^{n-1}
0.89	Case II transport	Zero order release
$n > 0.89$	Super case II transport	t^{n-1}

Table 6: Kinetic parameters obtained by using Korsemeyer-Peppas model [41]

Sr. No.	Tablet shape	r^2	N
1	Triangle (half of side length)	0.993	4
2	Cylinder (radius)	0.924	2
3	Half-sphere (radius)	0.981	1

r^2, correlation coefficient

Table 7: Release kinetic parameters showing best fit with higher correlation with the Baker-Lonsdale equation [52].

Sr. No.	Dissolution model	Dissolution rate constant	r^2
1	Higuchi	25.179	0.9819
2	First order	0.1180	0.8403
3	Hixson-Crowell cube root law	0.2276	0.7175
4	**Baker – Lonsdale**	**0.0186**	**0.9984**

Table 8: Comparison of calculated parameters and their R^2 using the modified Gompertz model on a mixture of three isomers and the single substrata [57]

Initial concentration (mg l^{-1})	Chemicals	R^2
27	DMI	0.9999
	DMT	0.9998
	DMP	0.9995
40	DMI	0.9999
	DMT	0.9997
	DMP	0.9929
80	DMI	0.9998
	DMT	0.9944
	DMP	0.9931

CONCLUSION:

The review represents the mathematical models for the study of dissolution. From this study it is found that these dissolution mathematical models are necessary to study the release mechanism of drug from the dosage form, as it describes the pattern of release of drug mathematically. The present models can also easily be extended to study the effect of relative rate of dissolution vs. diffusion, drug loading, size and distribution of particles of drug.

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