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Review Article

A SYSTEMATIC REVIEW OF MATHEMATICAL MODELS OF PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

Description of the kinetics of drug release from pharmaceutical dosage form is a domain of steadily increasing academic and industrial importance. *In vitro* dissolution has been recognized as an important element in drug development. Several theories / kinetics models describe drug dissolution from dosage forms. The aim of this paper is to review most of the popular mathematical approaches to drug release from pharmaceutical dosage forms.

KEY WORDS: Drug-release model, Similarity, Mean dissolution time, Dissolution efficiency.

INTRODUCTION

The quantitative values obtained in the dissolution study subject to generic equation that mathematically translates the dissolution curve as a function of parameters related with the pharmaceutical dosage forms. In most cases, with tablets, capsules, coated dosages or prolonged release dosages, a more appropriate equation is used to predict release mechanism. In general the water-soluble drug incorporated in a matrix is mainly released by diffusion, while for a low water-soluble drug the self-erosion of the matrix will be the principal release mechanism. So the kind of drug, its polymorphic form, cristallinity, particle size, solubility and amount in the pharmaceutical dosage form can influence the release kinetic[1]. When a new oral dosage form is developed, one must ensure that the drug release occurs as desired by the product specification. Literature show several theories which describe the kinetic models of drug dissolution from dosage forms. Numerous methods are available to evaluate the dissolution data as a function of time but its dependence on the dosage form properties can be predicted by using equations which mathematically translates the dissolution curves as the function of other parameters related to the delivery. Several kinetic models have been proposed to describe the release characteristics of a drug from a polymer matrix. In the development of the pharmaceutical dosage forms, providing a particular drug release profile is highly desirable. Water is an important factor during hydrolysis and thus water intrusion into the matrix is of significant importance for the study of degradation kinetics as well as release kinetics.

Release kinetics

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In release kinetics, burst release is a phenomenon commonly observed in delivery of different forms and compositions. The burst effect may be favorable for certain indications or applications such as wound treatment, targeted delivery and pulsatile release. However, it is also cause negative effects such as local or systemic toxicity, short *in vivo* half-life, and shortened release profile that requires more frequent dosing[2]. Burst release is often associated with device geometry, surface characteristics of host material, heterogeneous distribution of drugs within the polymer matrix, intrinsic dissolution rate of drug, heterogeneity of matrices (pore density), *etc.* However, few studies have been conducted to develop mechanism based mathematical models for burst release. To better predict the burst release, sustained release and lag time, would be worthwhile developing models to elucidate the mechanisms of drug release. A systematic review of most of the popular mathematical models of pharmaceutical dosage forms are presented in this paper.

Empirical and Semi-Empirical Mathematical Models for Release Kinetics

In case of controlled- or sustained-release formulations, diffusion, swelling, and erosion are the three most important rate-controlling mechanisms. Formulations containing swelling polymers show swelling as well as diffusion mechanism because the kinetics of swelling includes relaxation of polymer chains and imbibitions of water, causing the polymer to swell and changing it from a glassy to a rubbery state. To determine the mechanism of release of drug from different formulae, the release data were analyzed using the linear regression according to Common empirical (zero-order, first-order and Higuchi) and semi-empirical (Ritger-Peppas, Peppas-Sahlin etc.) models.

Zero order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly can be represented by the following equation: $Q_0 / Q_t = K_t$

where Q_0 is the initial amount of drug in the pharmaceutical dosage form, Q_t is the amount of drug in the pharmaceutical dosage form at time t and K is proportionality constant.

On simplifying this equation: $f_t = K_0 t$

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. 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 [3]. The pharmaceutical 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 action. The following relation can, in a simple way, express this model:

$Q_1 = Q_0 + K_0 t$

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. An ideal matrix system is that in which the drug released constantly, from the beginning to the end, in a zero order kinetic model[1].

First order model:

Hixson and Crowell adapted the Noyes-Whitney equation and the equation is transformed, in the following manner: $\log Q_t = \log Q_0 + K_1 t / 2.303$

Where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug and K_1 is the first order release constant. The pharmaceutical dosage forms following this dissolution profile such as those containing water soluble drugs in porous matrices, release drug in a way that is proportional to the amount of drug released by unit of time diminish [4]. Kinetic models which fit first order model is more appropriate for conventional tablets [1].

Higuchi model

This model is used to study the release of water soluble and low soluble drugs incorporated in semi-solid and solid matrixes. Mathematical expressions were obtained for dug particles dispersed in a uniform matrix behaving as the diffusion media. When this model is used, it is assumed that the release rate limited by the drug particles dissolution rate and not by the diffusion that might occur through the polymeric matrix. This model has been used to describe the release profile keeping in mind the diminishing surface of the drug particles during the dissolution. Drug release from matrix tablets, in general, becomes progressively slower with time, like Higuchi's model, in which the amount of drug released is proportional to the square root of time. Kinetic models which fit zero order and Higuchi are more suitable for controlled release formulations [1].

Hixson and Crowell model:

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. *In vitro* drug release studies are plotted as cube root of drug percentage remaining in matrix versus time[5]. This 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[6]. 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.

Baker – Lonsdale model:

This model was developed by Baker and Lonsdale from the Highuchi model and describes the drug controlled release from a spherical matrix. A graphic relating the left side of the equation and time is linear if the established conditions are fulfilled. Where k, release constant, obtained from the slope. This equation has been used to the linearization of release data from microcapsules and microspheres [7].

Korsmeyer–Peppas model:

These models are generally used to analyze the release of pharmaceutical exponent, indicative of the drug release from polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomena is involved, this model yield n values that are higher than 1 and which may be regarded as super case II kinetics arising from a reduction in the attractive forces between polymer chains. The mechanism that creates the zero-order release is known among polymer scientist as case-II transport which indicates anomalous diffusion (i.e. swelling-controlled release). Here the relaxation process of the macromolecules occurring upon water inhibition into the system is the rate controlling step. The values of release parameters n and k are inversely related. A higher value of k may suggest burst release from the matrix[8].

Exponent n			
Thin film	Cylinder	Sphere	Drug release mechanism
0.5	0.45	0.43	Fickian diffusion
$0.5 < n < 1.0$	$0.45 < n < 0.89$	$0.43 < n < 0.85$	Anomalous transport
1.0	0.89	0.85	Case II transport

Hopfenberg model:

Hopfenberg [9] developed an empirical drug release model for erosion-controlled polymer by assuming that the overall release behaves as a zero-order process. This zero-order process is essentially a combination result of dissolution and erosion processes at the polymer surface. Therefore, this empirical equation is appropriately applied for the surface-eroding particles.

The release of drugs from surface-eroding devices with several geometries are analyzed by Hopfenberg, who developed a general mathematical equation describing drug release from slabs, spheres and infinite cylinders displaying heterogeneous erosion. A modified form of this model was developed to accommodate the lag time in the beginning of the drug release from the pharmaceutical dosage form. This model assumes that the rate-limiting step of drug release is the erosion of the matrix itself and that time dependent diffusion resistances internal or external to the eroding matrix do not influence it. This mathematical model, correlate the drug release from surface eroding polymers so long as the surface area remains constant during the degradation process[10]. Tlag 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. This model allow for a quantitative description of drug release from degradable drug delivery systems exhibiting a release rate which is proportional to the (time-dependent) surface area of the device. It assumes that the rate-limiting step of drug release is the erosion of the matrix itself and that time dependent diffusion resistances internal or external to the eroding matrix do not influence it. **Peppas and Sahlin:**

An interesting binomial equation model was developed by Peppas and Sahlin, similar in meaning to Korsmeyer–Peppas, in which the contribution of the relaxation or erosion mechanism and of the diffusive mechanism can be quantified, was also proposed by Hopfenberg[11] and adapted to pharmaceutical problems by Peppas and Sahlin where k1 is the diffusion constant, k2 is the relaxation constant and m is the diffusion exponent. This model accounts for the coupled effects of Fickian diffusion and case II transport [12,13]. By using the exponent coefficient (n) from Krosmeyer-Peppas model and substitution in Peppas-Sahlin model, the constants (K1&K2) can be calculated. The values of k1 indicates the contribution of diffusion (Fickian or case 1 kinetics) while the value of k2 is associated with the dissolution as well as relaxation of the polymer chains [14]. The rate of drug release from a surface eroding device is determined by the relative contribution of the drug diffusion and the degradation of the matrix**.** This model contribution to drug release could be considered additive, and it allowed the development of several other models for drug release from matrix tablets. In this model, the first term on the right hand side represents the Fickian diffusion contribution, whereas the second term represents the case-II relaxation contribution[13]

Ritger and Peppas:

Ritger and Peppas have defined the exponent ‘m’ as a function of the aspect ratio for 1-dimensional to 3-dimensional systems (slabs, cylinders, and discs). The aspect ratio is defined as the ratio of diameter to thickness. For tablets, depending

on the aspect ratio, an m value between 0.43 and 0.5 indicates Fickian diffusion-controlled drug release, and an m value ≥ 0.89 indicates a swelling controlled drug release (zero-order release or case II transport). Values of m between 0.5 and 0.89 can be regarded as an indicator of the superimposition of both phenomena, commonly called anomalous transport [15].

Makoid-Banakar model:

This model becomes identical to that of Korsmeyer-Peppas when the parameter k is zero. It follows the sole diffusion mechanism. The 'n' function governs the shape of dissolution curve [16].

Koppcha model:

Furthermore, the predominance of diffusion was confirmed by treating the release data with the empirical equation proposed by Koppcha. In this equation, M is the cumulative % of drug released at time t. A and B are diffusion and erosion terms, respectively. According to this equation, if A/B ≥1, then diffusion prevails, while for A/B ≤1, erosion predominates[17].

Gompertz model:

Dissolution profile of pharmaceutical dosage form can also been described by Gompertz model, where growth is slowest at the start and end of a time period. Where X_t = percent dissolved at time t divided by 100; X_{max} = 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. This model is more useful for comparing the release profiles of drugs having good solubility and intermediate release rate [18].

Weibull, Quadratic and Logistic

These models cannot describe drug release kinetics, but it can describe the curve in terms of applicable parameters. If β = 1 the response of release corresponds to first-order kinetics, meaning that the release rate is constant relative to the unreleased part of the drug. For β > 1 this rate will increase with time and vice versa for β < 1. If the value for shape parameter, β, is higher than 1, plots should be "S" shaped with an upward curvature. For β greater than unity, the dissolution curve becomes S-shaped as the maximum rate occurs after some time. Further, a high β will reduce the release phase and consequently lead to its abrupt termination. The Td (time interval necessary to dissolve or release 63.2% of the drug present in the tablet) values were tendencially smaller (fast dissolution process) when the stirring rate was increased. The fit of dissolution data to the Weibull distribution [19]and logistic model [20] emphasizes the S-shaped or sigmoidal dissolution profiles. In hydrophilic polymers the internal bounds between the chains are weakened and this adds to the surface erosion. The drug release mechanism within a polymer matrix depends on many factors such as the affinity of the drug with the surrounding medium (water or enzymes).The highly degradable polymers are of S-curve behavior.

Profile Comparison: The similarities between two *in vitro* dissolution profiles are also assessed by other pair wise independent- model procedures such as difference factor (f_1) [21] and Rescigno index [22]. Similarity factor,f_2, is actually insensitive to the shape of the dissolution profiles and is difficult to assess both type I and type II errors because there is no mathematical formula included for the statistical distribution of f_2 [23], which is the major drawback of f_2 [24]. The bootstrap method is proposed as a tool to estimate the statistical distribution of the data and employ a confidence interval approach of f_2. Bootstrap of f_2 generates a new population of dissolution profiles through random samples with replacement from 12 units of the test and reference batches, respectively. It is possible to assess the similarity of dissolution profiles with

large variability if the data populations are identically distributed. Compared to f_2, bootstrap-based f_2 is more accurate in similarity comparison of dissolution profiles and especially important if the f_2 value is less than 60 [25]. In general, f_1 values lower than 15 (0–15) and f_2 values higher than 50 show the similarity of the dissolution profiles.

Table 2 Mathematical model used to describe drug dissolution curves

Model	Equations
Zero order	$Q_t = Q_0 + K_0 t$
First order	$\ln Q_t = \ln Q_0 + K_1 t$
Hixson-Crowell	$Q_0^{1/3} - Q_t^{1/3} = K_s t$
Weibull	$\log [-\ln (1-(Q_t/Q_\infty))] = b \log t - \log a$
Higuchi	$Q_t = K_H \sqrt{t}$
Baker-Lonsdale	$(3/2)[1-(1-(Q_t/Q_\infty))^{2/3}] - (Q_t/Q_\infty) = Kt$
Korsmeyer-Peppas	$Q_t / Q_\infty = Kt^n$
Quadratic	$Q_t = 100 (K_1 t^2 + k_2 t)$
Logistic	$Q_t = A / [1 + e^{-k(t-y)}]$
Gompertz	$X_t = X_{max} \exp[-\alpha e\beta \log t]$
Hopfenberg	$Q_t / Q_\infty = 1 - [1 - k_0 t / C_0 a_0]^n$
Koppcha model	$M = A t^{½} + B$
Makoid –Banakar	$F = K_{MB} t^n e^{-kt}$
Peppas and Sahlin	$M_t / M_\infty = K_1 t^{½} + K_2 t$

Rescigno index (ξ) This index is 0 when the two release profiles are identical and 1 when the drug from either the test or the reference formulation is not released at all. By increasing the value of *i*, more weight will be given to the magnitude of the change in concentration, than to the duration of that change.

Other release parameters:

Other parameters used to characterize drug release profile are $t_{x\%}$, sampling time and dissolution efficiency. The $t_{x\%}$ parameter corresponds to the time necessary to the release of a determined percentage of drug (e.g. $t_{20\%}$,$t_{50\%}$, $t_{80\%}$) and sampling time corresponds to the amount of dug dissolved in that time (e.g. t_{20} min, $t_{50\ min}$, $t_{90\ min}$). Pharmacopoeias very frequently use this parameter as an acceptance limit of the dissolution test (e. g. $t_{45\ min} >= 80\ \%$).

The dissolution efficiency (DE) and mean dissolution time (MDT) parameters may be used to characterize both the drug release process and the retarding efficacy of a polymer.

MDT is a measure of the dissolution rate: the higher the MDT, the slower the release rate. DE is a dissolution parameter widely used as a significant index of drug dissolution performance. DE of a pharmaceutical dosage form is defined as the

area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time[26].

Identification of the best fit

In mathematics, a system of linear or nonlinear equations is a collection the same set of variables. The theory of linear or nonlinear systems is the basis and a fundamental part of linear algebra. A system of equation just means more than one equation. This pair of equations is called a system of linear or nonlinear equations because we are solving more than one equation simultaneously. A solution to the system consists of an ***x***-value and ***y***-value that satisfy both equations at the same time. A system of linear or nonlinear equations can be solved by many different ways e.g. Substitution, Elimination, Matrices, and Graphing [27].

The Akaike Information Criterion (AIC)is a measure of goodness of fit based on maximum likelihood. When comparing several models for a given set of data, the model associated with the smallest value of AIC is regarded as giving the best fit out of that set of models. The AIC is only appropriate when comparing models using the same weighting scheme. The more negative the value of the AIC, the better the model describes the data. Since the AIC is based on both the fit to the data and the number of estimated parameters, if 2 models each fit the data well, the AIC will be lower for the model with fewer estimated parameters. When comparing different models, the most appropriate model will be that with the largest Model Selection Criterion (MSC). It is, therefore, quite easy to develop a feeling for what the MSC means in terms of how well the model fits the data. Generally, a MSC value of more than two to three indicates a good fit [28].

The R^2 always increases or at least stays constant when adding new model parameters, R^2 adjusted can actually decrease, thus giving an indication if the new parameter really improves the model or might lead to over fitting. In other words, the ‘‘best’’ model would be the one with the highest adjusted coefficient of determination. The R^2 adjusted value was used as the model selection criterion with the best model exhibiting the R^2adjusted value closest to 1.

Among these criteria, the most popular ones in the field of dissolution model identification are the R^2adjusted, AIC [29], and the MSC [30].

Software tool for facilitating the calculations in dissolution data analysis

Until now, only one special program has been reported for fitting dissolution data, and only five release models have been implemented, and these could be applied only over a limited range [31]. Alternatively, the nonlinear fitting of dissolution data can be performed using other professional statistical software packages such as Micro-Math Scientist, Graph Pad Prism, Sigma Plot or SYSTAT, PCP Disso V 3 and the DDSolver add in program. Among those programs an easy-to-use program for fitting release data with more ready-to-use dissolution model is DDSolver and is freely available.

The illustrations given below are part of the research work of the author[32] using DDSolver software:

Table 3 Comparison of zero and Higuchi models:

Formulation	WO1		WO2		WO3		WO4	
Parameter	Zero order	Higuchi	Zero order	Higuchi	Zero order	Higuchi	Zero order	Higuchi

N_observed11	11	11	11	11	11	11	11	
DF	10	10	10	10	10	10	10	10
R_obs-pre	0.9902765	0.91026	0.9848	0.896531	0.969685	0.868198	0.968148	0.863355
Rsqr	0.9551932	0.7072866	0.9336	0.67267	0.886736	0.61257	0.877289	0.599086
Rsqr_adj	0.9551932	0.7072866	0.9336	0.67267	0.886736	0.61257	0.877289	0.599086
MSE	49.614641	324.62782	63.9446	315.7256	94.8563	324.7851	94.25474	308.4134
MSE_root	7.0065375	18.011764	7.9656	17.76318	9.716192	18.01671	9.688562	17.55837
Weighting	1	1	1	1	1	1	1	1
SS	496.14641	3246.2782	639.4461	3157.256	948.563	3247.851	942.5474	3084.134
WSS	496.14641	3246.2782	639.4461	3157.256	948.563	3247.851	942.5474	3084.134
AIC	70.039671	90.92404	72.8938	90.61839	77.29807	90.93079	77.24341	90.36592
MSC	2.8368207	0.9382417	2.4503	0.838974	1.926765	0.687426	1.850636	0.657681

Table 4 Comparison of different models

Formulation	Parameter	Korsmeyer–Peppas		Hopfenberg		Makoid-Banakar			Peppas and Sahlin		
		Mean	SD	Mean	SD	Parameter	Mean	SD	Parameter	Mean	SD
WO1	k	2.332059	0.597929	0.078869	0.0003394	kMB	2.044991	0.774236	k1	-2.2164	2.642474
	n	1.436437	0.103888	0.567447	0.0465906	n	1.604596	0.246224	k2	3.74916	1.06791
						k	0.022611	0.019959	m	0.644078	0.036196
WO2	k	1.732552	0.554712	0.07887	0.0006269	kMB	1.624314	0.766847	k1	-0.73496	2.364255
	n	1.507759	0.123723	0.459876	0.0447674	n	1.573272	0.277669	k2	1.955866	0.952063

						k	0.003 223	0.021 879	m	0.753 646	0.081 227
WO3	k	0.9732 12	0.361 536	0.0708 88	0.0000 137	kMB	1.109 034	0.708 319	k1	0.419 846	1.197 915
	n	1.6919 84	0.139 624	0.4535 87	0.0348 458	n	1.558 204	0.383 258	k2	0.480 181	0.390 362
						k	- 0.027 34	0.029 026	m	1.032 348	0.197 017
WO4	k	0.6478 82	0.260 858	0.0704 71	0.0000 764	kMB	0.697 757	0.519 877	k1	- 0.052 24	1.285 725
	n	1.8512 88	0.151 235	0.4250 38	0.0334 055	n	1.864 543	0.436 546	k2	0.574 872	0.408 713
						k	- 0.001 94	0.034 283	m	0.984 552	0.157 582

Table 5 Overall statistics of similarity factor for WO3 formulation

Overall Statistics	Mean_R vs Individual_T		Mean_R vs Mean_T
	Mean	SE	
f2	37.79	0.74	37.83
Is f2 ∈[50,100] between Mean_R and Mean_T			No
Similarity of R and T			Reject

Table 6 Overall Statistics of Rescigno index

Parameter	Mean_R vs Individual_T		Mean_R vs Mean_T
	Mean	SE	
ξ 1	0.1713	0.0087	0.1604
ξ 2	0.2161	0.0065	0.2154

Table 7 Dissolution efficiency and Mean dissolution Time of matrix tables

Formulation		WO1		WO2		WO3		WO4	
Sr.No.	Time	% DE	MDT	% DE	MDT	% DE	MDT	% DE	MDT
1	0	0	0	0	0	0	0	0	0
2	1	1.42	0.5	0.88	0.5	0.71	0.5	0.43	0.5
3	2	2.83	0.99	1.79	1.01	1.46	1.02	1.06	1.15
4	3	4.52	1.67	3.11	1.82	2.27	1.58	1.77	1.63
5	4	6.73	2.37	4.96	2.49	3.38	2.44	2.72	2.51
6	5	9.11	2.81	7.13	3.07	4.91	3.16	4.11	3.29
7	6	12.01	3.76	9.73	3.84	6.81	3.87	5.89	4
8	8	18.94	4.79	15.6	4.84	11.63	5.18	10.28	5.18
9	10	25.97	5.73	21.73	5.9	17.35	6.34	15.53	6.46
10	12	33.36	6.98	28.62	7.3	23.48	7.37	21.66	7.73
11	14	41.3	8.11	36.34	8.48	30.79	9.13	28.84	9.13

CONCLUSION

In this review on mathematical models of pharmaceutical dosage forms equation of each proposed models and its usage in accessing the drug release mechanisms are discussed. Various software tools that are used to predict the release kinetics and their availability are briefly discussed. Applications of quantitative values obtained in various drug release profiles are included along with examples.

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