IJIRR

International Journal of Information Research and Review
Vol. 04, Issue, 12, pp.4845-4850, December, 2017

REVIEW ARTICLE

DIFFERENT KINETIC MATHEMATICAL MODELS USED TO DRUG RELEASE FROM SOLID DOSAGE FORM

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ARTICLE INFO

Article History:

Received 29th September, 2017
Received in revised form
29th October, 2017
Accepted 08th November, 2017
Published online 30th December, 2017

Keywords:

Mathematical Model,
Kinetics of Drug Release,
Therapeutic Device,
Quantitative Analysis.

ABSTRACT

The mathematical models used to determine the kinetics of drug release from drug delivery systems. The quantitative analysis of the values obtained from dissolution/release rates is easier when mathematical formulas are used to describe the process. The mathematical modeling can ultimately help to optimize the design of a therapeutic device to yield information on the efficacy of various kinetic release models. Mathematical models for the drug release studies play an important role as it establishes a mechanism of drug release and provides general guidelines for the development of other systems. It is accepted that numerous successful drug delivery systems have been developed as a result of an almost arbitrary selection of components, configurations and guidelines. This review gives them an idea about the current state of mathematical (kinetic) modeling of drug delivery including empirical/semi empirical and mechanistic release models.

INTRODUCTION

Pharmaceutical drug delivery systems are the systems which deliver or drug in to the body. A drug delivery systems (DDS) consists of one or more bio-active agents and one or more excipients which forms the vehicle or medium for the administration of the active agents. The most important aim of a DDS is to undergo dissolution in a biological medium (eg: biological tissues for implants, GIT for tablets etc) in order to ensure a desired effect, there must be an appropriate rate of drug release and then proper absorption of active agents. A large number of drug delivery systems have been extensively developed in last few decades. Thus, different mathematical (kinetic) models may be an important tool for understanding the drug release from different drug delivery systems (Gautam Singhavi, 2011). Mathematical modeling and some numerical simulations of drug transport inside the human vessels and inside the arterial walls can help to the better understanding the efficiency of the treatment and guide the design of better model

Basics of kinetics of drug release

Laws in the kinetics of drug release

Noyes-Whitney law: Noyes-Whitney developed the fundamental principle of evaluation of drug release, which explains as

$$dC/dt=K\ (C_S-C_t)$$

Where dC/dt is dissolution rate of drug,

K is dissolution rate constant,
C_s is the concentration of drug in the stagnant layer (also called as the saturation or maximum drug solubility),
C_t is the concentration of the drug in the bulk of the solution at time t.

Fick's law of diffusion: According to this law drug molecules diffuse from a region of higher concentration to one of lower concentration until equilibrium is attained and that the rate of diffusion is directly proportional to concentration gradient across the membrane.

This can be expressed mathematically as

$$DQ/dt=DAK_{m/w}(C_{GIT}- C)/h$$

Where dQ/dt is rate of drug diffusion, amount per time (rate of appreance of drug in blood), D is the diffusion coefficient. Its dimension is area per unit time, so typical units for expressing it would be m^2/s (area/time), A is the surface area for absorbing membrane for drug diffusion (area), $K_{m/w}$ Partition coefficient of drug between lipoidal membrane and aqueous GI fluid (no unit), C_{GIT}- C is the difference in the concentration of drug in the GI fluid and the plasma called concentration

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gradient (amount per volume), h is the thickness of the membrane (length).

Objective of Mathematical Model

- Accurately prediction of drug release profile and improve overall therapeutic efficacy and safety of these drug (Langer, 1984).
- Designing of new drug delivery system based upon the general release expression.
- Optimization of the release kinetics
- Physical mechanism of drug transport is determined by the compare the release data with mathematical models.
- Prediction of the effect of design parameters viz. shape, size and composition on the overall drug release rate.
- Prediction of the drug release rate form and drug diffusion behavior through polymers, thus avoid excessive experiment.

Application of Mathematical Model

- The mathematical model equation can be used to design new systems by selecting the optimal geometry, size and method of formulation (Lee,).
- Mathematical modeling aids in predicting the drug release rates and diffusion behavior from these systems by the solution of an appropriate model, thereby reducing the no. of experiments needed.
- Mathematical modeling of controlled drug delivery can help provide a scientific knowledge based up on the concerning the mass transport mechanisms which are involved in the control of drug release (Cartensen, 1996).
- Thus mathematical modeling can significantly facilitate the optimization of existing and the development of new Pharmaceutical products. The systematic use of models can save money and time.
- Mathematical approaches may help for researchers to develop highly effective drug formulations and more accurate dosing regimens.

Assumption for deriving Mathematical Model

- During the release of drug, pseudo-steady state is maintained.
- Total amount of drug present per unit volume in the matrix (C_0) is greater than the saturation solubility of the drug per unit volume in the matrix (C_s), which indicates excess amount of solute present.
- At all times the release rate media is under perfect sink condition (Freguglia, 1998)
- Drug particles smaller in diameter than the average distance of diffusion.
- The value of diffusion coefficient is constant.
- Between the drug and matrix interactions are not occurred.

Mathematical Models for Drug Release Studies

A mathematical model play important role in the prediction of mechanism of drug release and also provides more general guidelines for development of other system. It is noted that, some successful drug delivery system developed as a result of almost arbitrary selection of components, configuration and geometrics (Ozturk, 1988). One of the models considered, a combination of effect of drug dissolution, diffusion and immobilization cause due to adsorption of drug from the tablet constituents which is applicable to tablet, which disintegrate into a no. of spherical fragments. Consideration of the physiological parameters or the modeling is essential for a complete model of drug release. To describe the drug release rate from different drug delivery systems of a large numbers of models were developed.

Some of important models are below

- Diffusion model
- Zero order kinetic model
- First order kinetic model
- Higuchi model
- Korsemeyer-Peppas model(The power law)
- Hixson –Crowell model
- Weibull model
- Baker –Lonsdale model
- Hopfenberg model
- Gompertz model
- Sequential layer model

Diffusion Model: Diffusion is "the process by which the mass transfer of individual molecules of a substance brought by random molecular motion and associated with a concentration gradient."""" the transfer of solute molecule is possible by either simple molecular permeation or by movement through pore and channels (Dressman, 1986). Diffusion is related with the moving of solute molecule. The diffusion mechanism can be observed, (Dressman, 1984) if in the beaker of water, a droplet of dye is placed. Diffusion of the dye molecules occurred throughout the water and form uniform color. At equilibrium condition, a uniform color is formed throughout the beaker of water, dye molecule are distributed uniformly as such there is no further net movement are occur. Same case is observed in our body for diffusion of drug molecule which is well explained by „Fick's law of diffusion."

Fick's first law of diffusion: The law is related with the diffusive flux to concentration under assumption of steady state (Noyes, 1897) It postulates that the flux goes from region of higher concentration to region of lower concentration, which is proportional to the concentration gradient. In one dimension, the law is

$$J= -D (dc/dx)$$

Where, J=amount of substance passing perpendicularly through a unit surface area per time. D=diffusion coefficient dc/dx=concentration gradient Negative sign indicate that diffusion occurred in opposite direction to the increasing concentration.

Fick's second law of diffusion: It state that, the rate of concentration is changed in the volume with the diffusional field is proportional to the rate of change in spatial concentration gradient at that point in the field. Proportionality constant is the diffusion coefficient (Nernst, 1904).
The law as…. $dc/dt = Dd^2c/dx^2$

Limitations of Fick's laws

There are some limitations in diffusion of drugs having heterogeneous structure, moving boundary condition, non-Fickian diffusion, and ionic species. In case of heterogeneous structure, each layer is made up by different material. In such

type of condition diffusion coefficient cannot be considered to be constant throughout the system.

Applications: Fick's first and second law applied to fluid flux and concentration across the membrane (Brunner, 1904)

Zero Order Kinetic Model: Zero order describes the system where the release rate of drug is independent of its concentration.

The equation is…… $C= C_0-K_0 t$

Where, C = Amount of drug release or dissolved (assuming that release occur rapidly after the drug dissolved.) C_0 = Initial amount of drug in solution (it is usually zero) K_0= Zero order rate constant t = time for study of release kinetics, the graph plotted between cumulative amount of drug released verses time.

Applications: This relationship can be applied to describe the drug dissolution of drug from several types of modified release Pharmaceutical dosage form as in the case of some transdermal system as well as matrix tablet with low soluble drugs in coated forms, osmotic system, etc.

Such models are important in certain classes of medicines intended, example for antibiotic delivery, heart and blood pressure maintenance, pain control and antidepressant (Mauger, 1986).

First Order Kinetic Model: This model is used to describe the absorption and elimination of some drugs, although it is difficult to understand the mechanism on the theoretical basis[(13)(31)] The drug release which follows the first order kinetic can be expressed by the equation…..

Log C= Log C_0-Kt/2.303

Where, C_0=Initial concentration of drug K=First order rate constant t=time. The data obtained are plotted as log cumulative percentage drug remaining verses time, which yield a straight line with slop=K/2.303.

Applications: This relationship can be use to describe the drug dissolved in Pharmaceutical dosage forms like those contained water soluble drugs in porous material.

Higuchi Model: Higuchi published the probably most famous and most often used mathematical equation to describe drug release from matrix system. This model is often applicable to the different geometrics and porous system (Costa, 2001; Crank., 1975)

The extended model is based on the following hypothesis, viz…

- Initial concentration of drug in the matrix is much higher than the drug solubility.
- Diffusion of drug occurs only in one dimension (edge effect negligible).
- Drug particles much smaller than system thickness.
- Swelling of matrix and dissolution is negligible.
- Drug diffusivity constant(Shah et al., 2001; Shoaib et al., 2006)
- In the release environment perfect sink conditions are maintained.

The basic equation of Higuchi model is…..

$C= (D (2qt-Cs) C_s t)^{½}$

Where, C=total amount of drug release per unit area of the matrix (mg/cm^2) D=diffusion coefficient for the drug in the matrix (cm^2/hr) qt=total amount of drug in a unit volume of matrix (mg/cm^3) C_s=dimensional solubility of drug in the polymer matrix (mg/cm^3) t=time (hr) Data obtained were plotted as cumulative percentage of drug release verses square root of time.

Applications By using this model dissolution of drug from several modified release dosage forms like some transdermal system and matrix tablet with water soluble drugs are studied.

Korsmeyer-Peppas Model: (The Power law) Korsmeyer et al (1983) derived a simple relationship which describes the release of drug from a polymeric system (Moore, 1996). To illustrate the mechanism of drug release, first 60% of drug release data was fitted in Korsmeyer-Peppas model. $C_t/C\infty$= ktn Where, $C_t/C\infty$=fraction of drug release at time,,t"". k=rate constant n=release exponent A modified form of this equation was developed to adjust the lag time (l) in the beginning of release of drug from the Pharmaceutical dosage form. C(t-1)/C∞= a(t-l)n Where there is possibility of a burst effect, „b"" this equation becomes…… $C_t/C\infty$= atn+b in the absence of lag time or burst effect „l""and „b"" values would be zero and only „atn"" is used. This mathematical model, also known as the „Power Law"", has been used very frequently, to describe the drug release from several different Pharmaceutical modified release dosage forms (Anonymous: Guideline for Industry, 1995; Hixson, 1931)

There are several simultaneous processes considered in this model:

- Diffusion of water into the tablet.
- Swelling of tablet as water enters.
- Formation of gel.
- Diffusion of drug and filler out of the tablet.
- Dissolution of the polymer matrix.

Following assumptions were made in this model…….

- The generic equation is applicable to small values of t or short terms and the portion of release curve, where Ct/C∞<0.6 should only use to determine the exponent „n"".
- Drug release in a one dimensional way (OíHara, 1998; Arhewoh, 2004).
- The ratio of system length to thickness should be at least. Plot made by log cumulative percentage drug release verses log time (Yuksel et al., 2000)

Table 1. Kinetic modeling on drug release from controlled drug delivery systems

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

Application This model is describing the drug release from several modified release dosage forms.

Hixson-Crowell Model: The model describes the release of dose from system, where there is change in surface area and diameter of particle or tablet. It is possible to derive an equation for a drug powder containing uniform size particles which expresses the rate of dissolution based on the cube root of the particles. The equation is…. $C0^{1/3}$-$Ct^{1/3}$= K_HC_t Where, Ct=amount of drug released in time„t". C0=initial amount of drug in the tablet. K_H=rate constant for Hixson-Crowell equation. When this model is used, it is considered the release rate is limited by the drug particles dissolution rate and not by the diffusion that might occur through the polymeric matrix (Release kinetics, 1999; Higuchi, 1963). This model is used to describe the release profile keeping in mind the surface of the drug particles is diminishes during the dissolution.

Applications It is more use full for comparing release profiles of matrix type drug release.

Baker-Lonsdale Model: This model was modified form of Higuchi model, developed by Baker and Lonsdale (1974). It described the drug release from spherical matrix (Narashimhan et al., 1999; Silvina et al., 2002)

According to the equation…..

f1= 3/2(1-(1-C_t/C∞)2/3) C_t/C∞=kt

Where,

C_t= drug release amount at time(t).
C∞= amount of drug release at an infinite time.

K= release constant, which corresponds to the graph when plotted as, (d(Ct/C∞)/dt with respect to root of time inverse.

Table 2. Mathematical models for drug release or drug dissolution

Model	Mathematical equation	Release Mechanism
Zero order	$C=C_0-K_0t$	Diffusion Mechanism
First order	$logC=logC_o-Kt/2.303$	Diffusion Mechanism
Higuchi Model	C=[D(2qt-Cs)Cs t]1/2	Diffusion medium based Mechanism in Fick's first law
Korsemeyer- Peppas Model	$C_t/C\infty=K_tn$	Semi empirical model, diffusion based mechanism
Hixson–Crowell Model	$C_0^{1/3}-C_t^{1/3}=K_HC_t$	Erosion release mechanism
Weibull Model	$C=C_0$ [1 – exp[ ]	life-time distribution function
Baker–Lonsdale Model	f1=3/2[1-(1-Ct/C∞)2/3]	Release of drug from spherical matrix
Hopfenberg Model	Ct/C∞=1-[1-K0t/CL	Erosion mechanism
Gompertz Model	Ct=Cmax exp[-αeβ log t]	Dissolution model

Plot made in between cube root of drug percentage remaining in matrix verses time.

Applications This expression is applied to Pharmaceutical dosage form such as tablet; where the dissolution occurs in planes which is parallel to drug surface if dimensions of the tablet diminish proportionality[24] in such a manner that the initial geometry form keep constant all the time.

Weibull Model (Libo, 1996**)** This model has been described for different dissolution processes as the equation…..

$C= C0 (1 – \exp (-(\underline{t-T})^{b/a}$)

Where,

- C= amount of dissolved drug as a function of time (t).
- C_0= total amount of drug being released.
- T= lag time measured as a result of dissolution process parameters.
- a= scale parameter that describe the time dependence.
- b= shape of dissolution curve.

Because of, this is an empirical model, not eliminate from any kinetic fundament, it have some deficiencies and have some limitations, such as……

- There is not any kinetic fundament which is not only describing, but also does not adequately characterize the dissolution of drug kinetic properties (Freitas, 2005; Chen, 2007).
- There is not any single parameter related with intrinsic dissolution rate of the drug and
- It is of limited for establishment of in vivo/in vitro correlations (Bourne, 2002; Polleto et al., 2007)

Applications this model used to linearization of release data from several formulations of microcapsules or microspheres.

Hopfenberg Model: This model made to correlate the release of drug from eroding surface of polymers so, surface area remains constant during the degrade process.[35] The cumulative fraction of released drug at time(t) was described as……..

Ct/C∞= 1-(1-K_0t/CL a) n

Where,

K_0=zero order rate constant, describing polymer degradation (surface erosion process.) CL=initial drug loading thought the system. a=system half thickness (that is radius for a sphere or cylinder.) n=exponent that varies with geometry, n=1, 2, 3 for slab (flat, cylindrical and spherical geometry, respectively.) Assumption of this model is the rate limiting step of release of drug is the erosion of the matrix itself and that time dependent diffusional resistance internal or external to the eroding matrix do not influence it.
Applications this model used to identify the mechanisms of release from the optimized oilisphere using derived data from the composite profile, which is essentially displayed the site specific biphasic release kinetics.

Gompertz Model (Riger, 1987) the in vitro dissolution profile is often described by simple exponential model known as, „Gompertz model" expressed by the equation.

C (t) = Cmax exp (-αeβ logt)

Where,

Ct= percent dissolved at time (t) divided by 100.

Cmax= maximum dissolution.
α= determine the undissoved proportion at time‟=1, described as location or scale parameter.
β = dissolution rate per unit of time describe shape parameter.
This model has a gradually increases in the beginning and directed slowly to the asymptotic maximal dissolution.

Applications This model is useful for compare the release profile of the drugs having good solubility and intermediate release rate (Siepmann, 2001)

Sequential Model: Sequential model is used to determine the swelling and release behavior from hydrophilic matrix tablet and to elucidate the effect of the device geometry on the drug release pattern. So, it can be facilitated the development of new Pharmaceutical products. It is used for prediction of molecules release from swelling controlled system. In this model, tablet system is considered as a certain amount of single layers penetrated by the water and model is performed in a computational grid and modified structure of the grid is required for numerical analysis. Here, it is considered that layer by layer swelling is takes place, in which the swelling of first layer is occurred followed by neighboring inner layer. This model is able to capture the major features of swelling controlled system which is the substantial change in volume of the system volume will change the concentration of all species and also influencing the mobility of the species(increasing diffusion coefficient of water and drug.). Here in the transport model only water and drug is assumed, whereas the polymer under goes a loss in molecular weight which is characterized by the constant dissolution rate constant „k‟.

Applications This model is useful for prediction of molecules release from swelling and release behavior from tablet containing hydrophilic matrix and also useful for determination of shape and dimensions of the tablet.

Other empirical model and semi empirical models are

Models developed by Peppas and Sahlin

$C_t/C_\alpha = k_1\ tm + k_2\ t2m$

Where, k1 and K2 is model constant.

First term on right side represent „Fickian diffusional contribution, f, where left side term the case II - relaxational contribution (Baker et al., 1974) (R). The ratio of both contributions can be calculated as follows.

$R/F = k_2 tm/k_1$

Model investigated by Courraze: It highlights the release of drug from bulk eroding polymer films assuming polymer degradation and drug diffusion occurred simultaneously.[40] Their assumptions for modeling were a pseudo-steady state approach for initial drug loading well above the solubility of the drug within the matrix was assumed.

- Polymer chain cleavage follows first order kinetics and
- Drug diffusion coefficient, D, increasing exponentially with time (t).

$D = D_0 \exp(kt)$

Where, D_0=diffusion coefficient of the drug at t=0(prior to degradation) and k is polymer degradation rate constant.

Selection of Best Model The selection of the suitable model in the drug release studies is difficult to ensure the effectiveness of the study. There are some criteria's for the selection of best suitable mathematical models which is based upon the statistical treatments. Determination of coefficient is most widely used method for determining R, to assess the fit of the model equation. This method also used when the model equation parameters are same. The best model is the one which have the highest adjusted coefficient of determination. Similarly other statistical methods like correlation coefficient (R), Analysis of Variance (ANOVA) and Multivariate analysis of Variance (MANOVA) are used for the comparison and selection of the suitable models (Rut Gudmundsdottir, 1897; Nernst, 1904).

Conclusion

The review study of mathematical modeling is promising which deals with the release characteristics of solid dosage forms. Assessment of pattern of release of drug is an innovative point. The mathematical modeling on drug release shows the relationship between drug dissolution and geometry on drug release patterns mathematically. The drug transport inside pharmaceutical system and its release sometimes involve multiple steps provoked by different physical or chemical phenomenon making it difficult, or even impossible to get a mathematical model describing in the correct way. The important fact that drug delivery system with multilayered tablet has shown promising results in drug delivery technology and ease of manufacturing is an added advantage to the pharmaceutical industries.

REFERENCES

Anonymous: Guideline for Industry, US Department of Health and Human Services, Food and Drug Administration (1995).

Arhewoh M.I., Okhamafe O.A. 2004. *J. Med. Biomed. Res.,* 3, 7.

Baker R.W., Lonsdale H.S. 1974. In Controlled release of biologically active agents, Tanquary A.C., Lacey R.E. Eds., Plenum Press, New York.

Bourne D.W. 2002. Pharmacokinetics. in: Modern pharmaceutics. 4th ed. Banker GS, Rhodes CT, Eds., Marcel Dekker Inc, New York.

Brunner E., Z. Physik. 1904. Chem, 47, 56.

Cartensen J.T. 1996. Modeling and data treatment in the pharma- ceutical sciences, Ed., Techno- mic Publishing Co. Inc., New York, Basel.

Chen S., Zhu J., Cheng J. 2007. Pharmazie 62, 907.

Costa P. 2001. *Int. J. Pharm.,* 220, 77.

Costa P., Lobo J.M.S. 2001. Eur. *J. Pharm. Sci.,* 13, 123.

Dressman J.B., Fleisher D. 1986. *J. Pharm. Sci.* 75, 109.

Dressman J.B., Fleisher D., Amidon G.L. 1984. *J. Pharm. Sci.* 73, 1274.

Freitas M.N., Marchetti J.M. 2005. *Int. J. Pharm.* 295, 201.

Gautam Singhavi, 2011. Review: In vitro drug release characterization models, *international journal of Pharmaceutical studies and research, January* 2: 77-84.

Grassi M. 2005. Grassi G., Curr. Drug Deliv. 2, 97.

Higuchi T. 1963. J. Pharm. Sci. 84, 1464.

Hixson A.W., Crowell J.H.1931. *Ind. Eng. Chem.* 23, 923.

Israel G. 1998. in Modelli matematici nelle scienze biologiche. Freguglia, P. Ed. Edizioni Quattro Venti, Urbino.

Korsmeyer R.W., Gurny R., Doelker E., Buri P., Peppas N.A. 1983. Int. J. Pharm. 15, 25.

Langer R.S., Wise D.L. 1984. Medical applications of controlled release, applications and evaluation, Eds., Vol. I and II, CRC Press, Boca Raton.

Libo Y., Reza F. 1996. *J. Pharm. Sci.* 85, 170.

Mauger J.W., Chilko D., Howard, S. 1986. Drug Dev. Ind. Pharm. 12, 969.

Moharram A. 2009. Khan, Role of mathematical modeling in controlled drug delivery, *J.sci.Research*, 1(3): 539-550.

Moore J.W. Flanner H.H. 1996. Pharm. Technol., 20, 64.

Narashimhan B., Mallapragada S.K., Peppas, N.A. 1999. Release kinetics, data interpretation, in: Encyclopedia of controlled drug delivery, Mathiowitz E. Ed., John Wiley and Sons, Inc, New York.

Nernst W. 1904. Z. Physik. Chem. 47, 52.

Nernst W. 1904. Z. Physik. Chem. 47, 52.

Noyes A.A., Whittney W.R. 1897. *J. Am. Chem. Soc*. 19, 930.

OíHara T., Dunne A., Butler J. 1998. Devane *J., Pharm. Sci. Technol.* Today, 1, 214.

Ozturk S.S., Palsson B.O., Donohoe B., Dressman J.B. 1988. Pharm. Res. 5, 550.

Polleto F.S., Jager E., Re M.I., Guterres S.S., Pohlmann AR., Int. J. Pharm. 345, 70 2007. 42. Paulo Costa, Modeling and comparison of dissolution profile, *European journal of Pharmaceutical sciences,* 2001; 13: 123-133.

Polli J.E., Rekhi G.S., Augsburger L.L., Shah V.P. 1997. J. Pharm. Sci. 86, 690.

Quantitative calculations in pharmaceutical practice and research. Hadjiioannou T.P., Christian G.D., Koupparis MA. Eds., VCH Publishers Inc., New York 1993.

Release kinetics, data interpretation. in: Encyclopedia of Controlled Drug Delivery. Narashimhan B., Mallapragada S.K., Peppas N.A. Eds., p. 921, John Wiley and Sons, Inc, New York 1999.

Riger P.L, Peppas N.A. 1987. *J. Control. Rel.* 5, 37.

Robinson J.R., Lee, V.H.L. Controlled drug delivery, Eds., and Marcel Dekker, Inc. New York, Basel

Rut Gudmundsdottir, Numerical model of controlled release of drug from silicon elastomers, Page no.3-6. 10. Noyes A.A., Whittney W.R., *J. Am. Chem. Soc.* 19, 930 (1897).

Shah V.P., Lesko L.J., Fan J., Fleischer N. Handerson J., et al. 1997. Dissolution Technol. 4, 15.

Shoaib H.M., Tazeen J., Merchant A.H., Yousuf I.R. 2006. *Pak. J. Pharm. Sci.* 19, 119.

Siepmann J., Peppas N.A. 2001. Adv. Drug Deliv. Rev. 48, 139.

Silvina A., Bravo M., Lamas C., Claudio J. 2002. *J. Pharm. Pharm. Sci.* 5, 213.

The mathematics of diffusion. Crank J. Ed., Clarendon Press, Oxford 1975.

Yuksel N., Kank A.E. 2000. Baykara T., *Int. J. Pharm.,* 209, 57.

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