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ROLE OF MATHEMATICAL MODELLING IN CONTROLLED RELEASE DRUG DELIVERY

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Abstract

Drug delivery is process or method of administering a drug substance to achieve a therapeutic effect in humans or animals. Since it is expensive and complicated to discover and market new drug entity, so recognition of therapeutic advantages of new drug delivery systems with control over drug release has become important, and needs greater attention to develop such delivery systems. In last few decades extensive work has been carried out in order to have spatial and temporal control over drug release from delivery systems in the body; enhance and maintain quality of drug delivery systems during manufacture and storage; protect drug from physiological degradation; improve patient compliance and therapeutic outcome. While designing such release systems, it is important to identify and understand mechanisms involved in the release process. Mathematical analysis of the dissolution data/ release rates is used to accurately predict the drug release from the drug products which can ultimately help to optimize the design of a new drug delivery systems with desired therapeutic efficacy and safety. Here, a brief review of different techniques used for obtaining controlled drug delivery will be taken up for discussion along with mathematical models employed to study the release from such delivery systems.

Introduction

From the ancient times different natural, semi synthetic or synthetic agents have been used to prevent, diagnose or cure different ailments. These agents were administered in the form of different delivery systems as pills or suitable extracts and then with advance in technology different delivery systems were developed. Traditional delivery systems were characterised by immediate and uncontrolled drug release kinetics. Accordingly, drug absorption was essentially controlled by the body's ability to assimilate the therapeutic molecule and thus, drug concentration in different body tissues such as the blood, typically undergoes an abrupt increase followed by a similar decrease. As a consequence, it may happen that drug concentration dangerously approaches the toxic threshold to subsequently fall down below the effective therapeutic level. Unfortunately, also the strategy of repeated administrations does not completely prevent the above mentioned drawbacks of traditional delivery systems [1], [2].

Since it is expensive and complicated to discover and market new drug entity, so recognition of therapeutic advantages of new drug delivery systems with control over drug release has become important, and needs greater attention to develop such delivery systems, which are able to provide therapeutic control, whether this is of a temporal nature, spatial nature or both. These systems are designated as controlled drug delivery systems [3].The purpose of controlled release system is to maintain drug concentration in the blood or in target tissues at a desired value as long as possible [4]. An ideal controlled drug delivery system is the one which delivers the drug at a predetermined rate, locally or systemically, for a specified period of time. These systems can either release drug at a slow zero or first order rate or can provide an initial rapid dose, followed by slow zero or first order release [5] such that therapeutic drug concentration in the blood or in target tissues is maintained as long as possible [1] i.e., they are able to exert a control on the drug release rate and duration [6]. The first controlled release formulation was introduced by Smith Kline & French in 1952 for 12-hour delivery of dextro-amphetamine (Dexedrine) [7].

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Controlled release systems are often confused with sustained release in the health care system. Sustained release constitutes any dosage form that provides medication over an extended time [8] and does not require any temporal or spatial control [9].

Controlled delivery of a drug can be achieved by numerous techniques depending upon the physicochemical properties and site of action of drug. Drug release from these systems (oral controlled release systems) occurs by different mechanisms. On the basis of these release mechanisms controlled drug delivery systems can be classified as:

Dissolution controlled release system

It is obvious that a drug with slow dissolution rate will reveal sustaining properties, since the release of the drug will be limited by the rate of dissolution. Thus by decreasing rate of dissolution of drugs, sustained release can be ensured. Dissolution of a drug can be limited by various approaches like preparing salts or other appropriate derivatives of the drug with limited solubility, or coating the drug with the materials which dissolve slowly [10]: where thickness of the coat can be controlled so that desired sustained/ controlled drug release profile can be achieved. Other methods of achieving sustained release are by preparing tablets of the drug with suitable slow dissolving carriers where control over drug release can be achieved by controlling thickness of layers of drug with rate controlling coats. An alternative method of controlling drug release is by administering the drug as beads that have coatings of different thicknesses so that both initial and the maintenance doses are provided [3]. Polymers employed to delay drug dissolution aim to slow the rate at which drug molecules are exposed to water from the aqueous environment surrounding the drug delivery system. This may be achieved by a polymer coating or matrix that dissolves at a slower rate than the drug [11]. Thus dissolution controlled delivery systems can be divided into two types:

Encapsulation Dissolution control Subheading

In these systems drug particles or granules are coated with slow dissolving material. Thickness of the coat applied determines the drug release from these particles or granules. Particles with thinner coating will provide initial dose while particles with thicker coatings will provide maintenance dose. These coated particles can be compressed directly into tablets or placed in capsules. Once the coating is dissolved, the drug becomes available for dissolution. These products should not be chewed as the coating may be damaged. Encapsulated products provide several advantages e.g., onset of absorption in case of encapsulated pelleted products is less sensitive to stomach emptying. The entrance of the pellets into the small intestine (where the majority of drug absorption occurs) is usually more uniform than with non-disintegrating sustained-release tablet formulations [12]. Commonly used encapsulated systems (multiparticulate systems) are micro particles (microspheres or microcapsules), nanoparticles (nano-spheres or nano-capsules) and liposomes [13].

Matrix dissolution control

Dissolution control matrix systems are generally used to control release of highly water soluble drugs. These systems are formulated by homogeneously dispersing the drug throughout a rate controlling membrane. The rate of drug release is controlled by the rate of penetration of the dissolution fluid into the matrix, porosity, presence of hydrophobic additives and the wettability of system and surface of particles [12], [13].

Diffusion controlled release system

In diffusion controlled systems release rate of a drug is dependent on its diffusion through the inert membrane of the delivery system. Diffusion systems can be divided into two major subclasses:

Matrix diffusion control

Matrix systems are the devices in which drug is dispersed homogeneously throughout a polymer matrix. These systems are widely used for sustaining and controlling release of drugs that are dissolved or dispersed [14]. In these

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systems rate of drug release is dependent on diffusion and not on rate of drug dissolution [15]. In case of hydrogel matrix systems, mechanism of release consists of exterior and interior processes of diffusion. In exterior diffusion drug molecules diffuse from surface of the hydrogel matrix into bulk of the liquid phase. Drug concentration near surface of the hydrogel matrix remains highest and it decreases with length. When the bulk of liquid is well stirred the value of drug concentration is constant. Exterior diffusion is not a general mechanism that controls drug release but it is the interior phenomenon, especially interior diffusion which controls the drug release in most of the cases [16]. Matrix diffusion systems can be classified into three types:

Hydrophobic matrix systems

In these systems water insoluble ingredients like waxes, glycerides, fatty acids, and polymeric materials such as ethyl cellulose, methyl cellulose and acrylate copolymers are used. Drug release takes place by diffusion which can be described by Higuchi square root kinetic model [17]. Diffusion of such molecules within an aqueous solution is inhibited by the insoluble polymer matrix in which drug molecules must travel through tortuous pathways to exit the device. Polymer chains such as those in a cross-linked hydrogel form the diffusion barrier. The presence of insoluble ingredient in the formulations helps to maintain the physical dimension of the hydrophobic matrix during drug release [18]. The barrier to diffusion can be decreased by swelling of the hydrogel where voids are created in the gel structure. Such hydrogels may also benefit from bio adhesive characteristics which allow them to reside within the gastrointestinal tract for extended time periods [11]. Certain soluble release rate modulators like lactose may also be used to have desired release pattern. In such systems physical dimensions in the physiological solutions is maintained by insoluble ingredients.

Hydrophilic matrix systems

Hydrophilic matrix systems are one of the most widely used systems to control the release rate of drugs because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance [18]. The primary rate limiting ingredients of hydrophilic matrix are polymers that swell when in contact with aqueous solution and form a gel layer on the surface of the system [15]. The polymers used in the preparation of hydrophilic matrices may be divided in to three broad groups [19].

Cellulose derivatives: Methylcellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose and sodium carboxymethyl cellulose etc.

Non cellulose natural or semi synthetic polymers: Alginates, agar-agar, molasses, polysaccharides of mannose and galactose, chitosan etc.

Polymers of acrylic acid: Polymers used in acrylic acid category is Carbopol 934. Other hydrophilic materials used for preparation of matrix tablet are alginic acid, gelatin and natural gums [19].

When the release medium and a polymer is thermodynamically compatible, the solvent penetrates into the free spaces between macromolecular chains. The stress caused by penetrated solvent may cause polymer relaxation and the matrix swells. This causes the drug to release more rapidly. On the other hand it takes more time for a drug to diffuse out of the matrix since matrix swelling lengthens the diffusion path [15]. Apart from swelling and diffusion mechanisms polymer dissolution is another important mechanism that can modulate the drug delivery rate. In most cases drug release kinetics is a result of a combination of these mechanisms [18].

Fat wax systems

These systems are prepared from lipid waxes or other related materials. In these systems the drug is released through both pore diffusion and erosion. These systems are more sensitive to digestive fluid in the gut than insoluble polymer matrix [20]. There are various techniques of preparing fat wax systems like spray congealing in air, blend congealing in an aqueous media and then spray drying. Granules can also be prepared by mixing the active

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ingredients with the waxy material and other suitable fillers and then compacting with roller compactor, heating in a suitable mixture such as fluidized-bed and steam jacketed blender or granulating with a solution of waxy material or other binders. In these systems desired drug release rate and drug loading can be achieved by the use of suitable surfactants [15], [19], [21], [22].

Mathematical modelling

Mathematical modelling of controlled drug delivery can help provide a scientific knowledge about the mass transport mechanisms which are involved in the control of drug release and can help to predict the drug release profile of dosage forms under investigation. If an adequate mathematical theory is identified for a pharmaceutical system it can be used to simulate the effect of the device design parameters (e.g., geometry and composition) on the resulting drug release kinetics [23]. Accurate prediction of drug release profile from the delivery systems can help improve overall therapeutic efficacy, safety of these drugs. Mathematical modelling can significantly facilitate the optimization of existing and the development of new pharmaceutical products. As mathematical modelling can help avoid excessive experimentation; thus there will be less time and money consumption.

Fundamentals of kinetics of drug release

Noyes-Whitney Rule

The fundamental principle for evaluation of the kinetics of drug release was offered by Noyes and Whitney in 1897 [24] as the equation

$$\frac{dM}{dt} = KS(C_s - C_t) \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (1)$$

Where M, is the mass dissolved in time 't' by dissolution from the solid particle of instantaneous surface, 'S' under the effect of the prevailing concentration driving force (C_s-C_t), where C_t is the concentration at time t and C_s is the equilibrium solubility of the solute at the experimental temperature. The rate of dissolution dM/dt is the amount dissolved per unit area per unit time. C_t has a negligible influence on the dissolution rate of the solid when C_t is less than 15% of the saturated solubility C_s. Dissolution under such circumstances, is said to occur under 'sink' conditions. Generally, the surface area (S), is not constant except when the quantity of material present exceeds the saturation solubility, or initially, when only small quantities of drug has dissolved [5], [25]. Particle size and surface area of the solid can be altered in order to have required dissolution rate of the drug which may further be altered by choosing a suitable polymorph or appropriate crystalline or amorphous form [24], [26].

Nernst and Brunner Film Theory

Brunner and Nernst [5], [27], [28] establish a relationship between the constant in the Noyes-Whitney equation (equation 1) and the diffusion coefficient of the solute by using Fick's law of diffusion and established the following equation:

$$\frac{dC}{dt} = DS/\gamma h(C_s - C)[29]$$

$$K = \frac{DS}{h\gamma}[25]$$

Where D is the diffusion coefficient, S is the area of dissolving surface or area of the diffusion layer, γ is the solution volume and h is the diffusion layer thickness.

Nernst and Brunner assumed that the process at the surface proceeds much faster than the transport process and a linear concentration gradient is confined to the layer of solution adhering to solid surface. The ideal condition can never be achieved as the actual surface is changed permanently with the progress of dissolution processes during the usual determination of drug release. In the Noyes-Whitney equation, the dissolution process corresponds to a first order reaction [5].

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The various methods to investigate the kinetics of drug release from controlled release formulation can be classified into three categories [25]:

Statistical methods
Repeated measures design
Multivariate approach [multivariate analysis of variance (MANOVA)]
Exploratory data analysis method

Model dependent methods
Zero order
First order
Higuchi
Korsmeyer-Peppas model
Hixson Crowell
Baker-Lonsdale model

Weibull model
Hopfenberg model
Gompertz model

Model independent methods
Difference factor (f_1)
Similarity factor (f_2)
Resign index

In this paper model dependent methods will be described. Model dependent methods are based on different mathematical functions which describe the dissolution profile [30].

Zero-order model
Zero order drug release dosage forms must be designed in such a way that they overcome Fick's law, and many creative and imaginative systems have been devised to that end [31]. Drug dissolution from dosage forms that remain intact and release drug slowly (assuming that area remains constant and no equilibrium conditions are obtained) can be represented by the following equation:

$$W_0 - W_t = kt$$

where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the amount of drug in the dosage form at time t and k is a proportionality constant [32]. Drug is released from an ideal controlled release device at a constant rate until device is exhausted [33]. Dividing above equation by W_0:

$$(W_0 - W_t)/W_0 = \mathrm{k}t/W_0$$

Rearranging the above equation gives:

$$1 - W_t/W_0 = K_0 t$$

Where 1- W_t /W_0 represents the fraction of drug dissolved in time (t) and k_0 is the zero order release constant. Plot of drug dissolved verses time, should be linear. The above relation can be used to determine the drug release from various types of modified release dosage forms e.g. some transdermal systems, matrix tablets with low soluble drugs

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[31] coated forms, and osmotic systems etc. The dosage forms that show such type of release, are ideal for achieving prolonged pharmacological action [33].

First order model

First order drug release kinetics can be expressed by the equation:

$$\frac{dC}{dt} = -k_1 C$$

Where k is first order rate constant expressed in units of time^{-1}.
This equation can be expressed as

$$log\ C = logC_0 - \frac{k_1 t}{2.303}$$

Where C_0 is the initial concentration of drug, k_1 is the first order rate constant, C is the amount of drug released in time t. The data obtained is plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of $-k_1/2.303$. The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967) [34] and later by Wagner (1969) [35][32], [36]. This model has been used to describe absorption and elimination of some drugs , although it is difficult to conceptualize this mechanism on a theoretical basis [32], [37]. This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices [30].

Higuchi model

The first example of a mathematical model aimed to describe drug release from a matrix system was proposed by Huguchi in 1961 [38] which suggests that the drug release is by diffusion. Initially the model was suggested for planar systems, which was then extended to different geometrics and porous systems. This model is based on the hypotheses that [13], [38]

(i) initial drug concentration in the matrix is much higher than drug solubility
(ii) drug diffusion takes place only in one dimension (edge effect must be negligible)
(iii) drug particles are much smaller than system thickness
(iv) matrix swelling and dissolution are negligible
(v) drug diffusivity is constant and
(vi) Perfect sink conditions are always attained in the release environment.

The Higuchi model expression is given by the equation:

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

Where Q is the amount of drug released in time t per unit area A, C is the initial drug concentration, Cs is the drug solubility in the matrix media and D is the diffusivity of the drug molecules (diffusion coefficient) in the matrix substance. 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 [26], [32], [39]:

$$f_t = Q = \sqrt{\frac{D\delta}{\tau}(2c - \delta c_S)C_s t}$$

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Where D is the diffusion coefficient of the drug molecule in the solvent, δ is the porosity of the matrix, τ is the tortuosity of the matrix. Tortuosity may be defined as the dimensions, radius and branching of the pores and canals in the matrix. Simplified Higuchi model can be written as:

$$f_t = Q = KH \times \sqrt{t}$$

Where, KH is the Higuchi dissolution constant.

Drug dissolution from several types of modified release pharmaceutical dosage forms can be described by above equation; like some transdermal systems and matrix tablets with water soluble drugs [5]. While using Higuchi model the dissolution data is plotted as cumulative percentage drug released versus square root of time [30], [39].

Hixson-Crowell model

Hixson-Crowell model was proposed by Hixon and Crowell in 1931 [40]. It describes the drug release (by dissolution) from the dosage forms where there is a change in surface area and diameter of the particles/ tablets. Hixon and Crowell recognized that the particle regular area is proportional to the cubic root of its volume and gave the following equation [33]:

$$\sqrt[3]{W_0} - \sqrt[3]{W_t} = \kappa t$$

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time t and κ (kappa) is a constant incorporating the surface-volume relation. To study the release kinetics, in vitro drug release data is plotted as the cube root of percentage drug remaining versus time [41], [42]. This expression applies to pharmaceutical dosage forms such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time [30].

Korsmeyer-Peppas model

Korsmeyer et al in 1983 [43] derived a simple relationship which described drug release from a polymeric system [44]. The equation is as follows:

$$\frac{M_t}{M_\infty} = k_{KP} t^n$$

Where, Mt and M∞ are the cumulative amounts of drug released in time t and infinite time respectively; kKP contains structural and geometric information about the device, and n is indicative of the drug release mechanism. Drug release occurs by Fickian diffusion result in when n = 0.5 [45]. When n=1, the release follows zero order kinetics. The various limits of this equation are discussed by Ritger and Peppas [46] where it has been shown that the mechanistic limits of n are dependent on the geometry of the associated release device [45]. For the case of cylindrical systems, $0.45 \geq n$ 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 [46], [47]. Anomalous diffusion or non-fickian diffusion refers to combination of both diffusion and erosion controlled rate release. To study the release kinetics, data obtained from in vitro drug release data is plotted as log cumulative percentage drug release versus log time [5].

Baker-Lonsdale model

This model was developed by Baker and Lonsdale in 1974 [48] from the Higuchi model and described the drug release from spherical matrices using the equation [32]:

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

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Where Mt is the amount of drug released in time t and M∞ is the amount of drug released at an infinite time, k is release constant and corresponds to slope.

To study the release kinetics, data obtained from in vitro drug release studies are plotted as [d (Mt / M∞)]/dt verses root of time inverse. This model has been generally used for linearization of release data from microcapsules or microspheres [25], [48].

Weibull model

The Weibull model is based on the function proposed by Weibull in 1951 [49] and later in 1972 Langenbucher [50] used it to describe the drug release curves. According to him if −ln (1−m) versus time is plotted on a log–log plot, (where m is the accumulated fraction of dissolved material) the curve will be linear which can be used for linear regression [29]. This equation can be applied to almost all kinds of dissolution curves. This equation expresses the accumulation of fraction of drug in solution at time t [32] and is given by equation:

$$M = M_0\left[1 - e^{-(t-T/a)b}\right]$$

Where, M is the amount of drug dissolved in time t; M_0 is total amount of drug being released; T is the lag time before the onset of the dissolution or release process and in most cases will be zero [32]; "a" is a scale parameter that describes the time dependence, while "b" describes the shape of the dissolution curve progression. When b = 1, the shape of the curve corresponds exactly to the shape of an exponential profile with the constant k = 1/a [5].

$$M = M_0(1 - e - k\,(t - T)$$

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 in the formulation being released is calculated using the inverse function of the Weibull equation [39]:

$$t(50\%\ resp.\ 90\%\ dissolved) = \frac{\left(-alnM - \frac{M_0}{M_0}\right)1}{b} + T$$

The equation $M = M_0\left[1 - e^{-(t-T/a)b}\right]$ may be rearranged into logarithmic form as follows

$$log[-ln(1-m)] = blog(t - T_i) - loga$$

When a log–log plot of -ln (1-m) versus time is plotted a linear curve is obtained [29], from which shape parameter b can be obtained from the slope of the line and the scale parameter, a, can be estimated from the ordinate value (1/a) at time t=1 [39].

The Weibull model is useful for comparing the release profiles of matrix type drug delivery [5], [39] but at the same time it is of limited use for establishing in vivo/ in vitro correlations; doesn't have any parameter related to the intrinsic dissolution rate and also can't characterize the dissolution kinetic properties of the drug [32].

Hopfenberg model

Hopfenberg in 1976 [51] and Katzhendler in 1997 [52] 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 [5]. Hopfenberg analyzed release of drugs from surface eroding devices with several geometries (slabs, spheres and infinite cylinders) and developed a general mathematical equation describing drug release from dosages with several geometries displaying heterogeneous erosion [30], [33], [51], [52].

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

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Where k_1 is equal to k_0/C_0 a_0. 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 a sphere or cylinder or the half-thickness for a slab. This model assumes that the rate-limiting step of drug release is the erosion of the matrix and that time dependent diffusional resistances internal or external to the eroding matrix do not influence it [37], [39]. The value of n is 1 for slab, 2 for cylinder and 3 for sphere [32]. This model is useful for identification of the mechanism of release from the optimized oily-spheres using data derived from the composite profile, which display site-specific biphasic release kinetics [53].

Gompertz model

It is a mathematical model for a time series, where release rate is slowest at the start and end of a time period [26]. The model can be expressed by following equation:

$$X_t = X_{max} \exp[-\alpha e^{\beta log t}]$$

Where X_t is the percent dissolved at time t divided by 100; X_{max} is the maximum dissolution; α is a scale or location parameter which determines the undissolved proportion at time t equaling 1; β is the shape parameter and describes dissolution rate. This model has a steep increase in the beginning and converges slowly to the asymptotic maximal dissolution [5], [26], [39]. The model is useful for comparing the release profiles of drugs having good solubility and intermediate release rate [25], [26].

Conclusion

In last few decades extensive work has been carried out in order to: have temporal and spatial control over drug release from delivery systems in the body; enhance and maintain quality of drug delivery systems during manufacturing and storage; protect drug from physiological degradation; improve patient compliance and ultimately therapeutic outcome. Since it is expensive and complicated to discover and market new drug entity, so recognition of therapeutic advantages of new drug delivery systems with control over drug release has become important, and needs greater attention to develop such delivery systems. Such delivery systems should be able to provide therapeutic control, whether of a temporal nature, spatial nature or both. These systems are designated as controlled drug delivery systems. While designing such controlled release systems, it is important to identify and understand mechanisms involved in the release process. Mathematical analysis of the dissolution data/ release rates is used to accurately predict the drug release from the drug products which can ultimately help to optimize the design of a new drug delivery systems with desired therapeutic efficacy and safety. However, drug transport inside pharmaceutical systems involves multiple steps provoked by different physical or chemical phenomenon, making it difficult, or even impossible, to get a mathematical model describing it in the correct way. The choice of the appropriate model for a particular purpose depends on various aspects. In many cases simple empirical or semi-empirical models are fully sufficient. However in some cases more complicated mechanistic theories may be applied and in such cases complete information may be needed.

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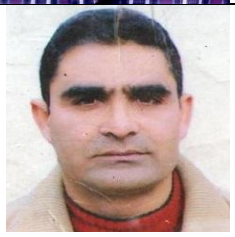	**Nisar Ahmad Khan** Senior Assistant professor at Department of Pharmaceutical Sciences, University of Kashmir. Research expertize in Nano technology, NDDS, GRDDS, TDDS, Oral films and formulation development of various other modified drug delivery systems. Email: nakhan2008@gmail.com