ABSTRACT
The release of drug from the formulations plays significant role especially when it comes to modified release as well as in immediate release dosage forms. Several factors like physicochemical properties of drugs, excipients, dosage form design, manufacturing process variables and design impact drug release from dosage form. It is essential to study the release pattern of drug from dosage form as it governs the efficacy of the dosage form. Several models facilitate the understanding of release pattern thus enabling to design an effective formulation. A few of the various models used by researchers to study the release profile are explained in this review which includes: Higuchi model - describes the drug release from a matrix system. Hixson-Crowell cube root law - describes the release from systems where there is a change in surface area and diameter of particles. Korsmeyer and Peppas developed an empirical equation to analyze both Fickian and non-Fickian release of drug from swelling and nonswelling polymeric delivery systems. Baker and Lonsdale developed the model from Higuchi model explaining the drug release from spherical matrices. The Weibull equation which describes drug dissolution and release from dosage forms, it expresses the accumulated fraction of drug ‘m’ in solution at time ‘t’. Hopfenberg model correlates the drug release from surface eroding polymers. The exponential model known as Gompertz model which describe in-vitro dissolution profile. The Gallagher and Corrigan model which describes the fraction of drug released from the biodegradable polymeric system. The Cooney model which describes about spheres and cylinders undergoing surface erosion.

Keywords: Release kinetics; Release models; Dissolution; mathematical modeling

INTRODUCTION
Dissolution and release of drugs is an important phenomenon for solid dosage forms like tablets, capsules, semisolids dosage forms like creams, ointments, and implants which deliver the drugs over the intended period of time ranges from hours, weeks and years. It is also applicable to design & optimization of all kinds of modified release dosage forms like sustained, delayed, controlled release dosage forms and novel drug delivery systems [1]. As it comes for modified release dosage forms dissolution & release becomes a crucial role as these dosage forms are designed in a complex manner which includes polymeric systems or lipid based systems where the drug is loaded into the polymeric or lipid based to achieve the purpose. The discharge of drugs is enabled by entry of fluids through the systems and the reacting the inner layers and the reaction of drug and fluid and thereby movement of molecule to surface of the system followed by complete transmit from the dosage form. The, mechanistic mathematical theories are based on real phenomena, such as diffusion, dissolution, swelling, erosion, precipitation and/or degradation [2-8]. The dissolution of a solid in a liquid involves the transfer of mass from a solid to a liquid phase. This process is composed of two consecutive stages. First is an interfacial reaction that results in the liberation of solute molecules from the solid phase. The second phase is the transport of solute away from the interfacial boundary under the influence of diffusion or convection. The overall rate of mass transfer in dissolution will be determined by the rate of the slowest stage. The Noyes-Whitney equation states that the rate of dissolution is proportional to the surface area (S) of the solid and the concentration gradient. Cs is the concentration of the boundary layer adjacent to the solid surface and C is the concentration of the medium. K is the dissolution rate constant.

Hence, rate of dissolution \( dc/dt = KS(Cs - C) \)

The rate of transfer depends on the rate at which the solute diffuses from the thin boundary layer into the bulk solution. K will depend on the diffusion coefficient of the solute and the thickness of the diffusion pathway and it will be influenced by temperature, agitation, changes in surface area, polymorphism of solids, change in viscosity of the medium [9]. Controlled release systems are usually made up of a biodegradable polymeric matrix containing the therapeutic agent as dispersed or enclosed, hence a complex heterogeneous release
pattern could be resulted. There is an initial ‘burst release’ of the drug which is not effectively protected by the carrier. This will be followed by a slow or controlled release from the polymeric matrix [10]. The common mechanisms applied to evaluate drug release from biodegradable polymeric drug delivery systems are combinations of diffusion and degradation [11]. Diffusion mechanism of drug release is surface wetting and medium ingression into the tablet; dissolution of the drug in the hydrated matrix; and diffusion of the soluble drug across the hydrated matrix into the medium.

**DRUG RELEASE KINETICS IN APPLICATION OF MATHEMATICAL MODELS TO DRUG RELEASE PROCESS**

The drug release kinetic is directed by one or more mechanisms that depend on the composition of the matrix, geometry, preparation method and dissolution media of drug release. This can be explained by mathematical models in accordance with the desired or required predictive ability and accuracy of the model [12-13].

**MATHEMATICAL MODELING**

The models are based on the main factors which affect the drug release such as the particle size distribution, the physical state and the concentration profile of the drug inside the polymeric particles, the viscoelastic properties of the polymer–penetrant system and the dissolution–diffusion properties of the loaded drug. The mathematical modeling of drug delivery has a significant potential to facilitate product development and help to understand release behavior of complex pharmaceutical dosage forms. Mathematical modeling of drug delivery can be expected to become an integral part of product development. Any one particular theory cannot be made applicable to any drug delivery system as the systems may also involve combination of models [1]. It is much more likely that there will be a broad spectrum of different mathematical models, applicable to specific types of devices differing in geometry, drug and excipient type [12]. Tool like decision tree will aid for the identification of the appropriate model for a specific type of delivery system and type of task (e.g., prediction of the effects of formulation parameters or improved understanding of the underlying drug release mechanisms) [1].

**FACTORS AFFECTING MECHANISM AND KINETICS OF DRUG RELEASE**

Mechanism and drug release kinetics are influenced by numerous factors, it is important to identify the factors to attain the purpose. For example, consider the matrix-based delivery technologies which have developed complex and customized release patterns. The basic necessity for an ideal drug delivery system is to deliver the drug at a rate dictated by the needs of the body during the entire course of treatment with spatial targeting to specific site; thus increasing therapeutic efficacy and safety of the drug. When a controlled drug delivery system is to be manufactured in large scale, diffusion devices are preferred due to its simplicity. Further the matrix devices have an edge over the reservoir devices as the drug is homogeneously dispersed in the former; hence unaffected by defects like pinholes [14].

**Drug related factors**

The basic drug related factors influencing the release are the Drug solubility, Dose or drug content, molecular weight and size; particle size and shape, physical state, diffusion in polymer and medium these are factors capable of influencing the release kinetics of a formulation. Drug solubility: Drugs with high solubility shows faster release, while poorly water-soluble drugs (<0.01 mg/mL) often result in incomplete release. Dose: An increase in drug content at constant polymer content increases the rate of release due to higher drug concentration and, thus, higher chemical gradient at the diffusion front. Molecular weight and size: The diffusion coefficient of a drug in a matrix system gradually changes from near zero in a dry matrix, to a maximum when the matrix is completely hydrated. The diffusion coefficient depends on molecular weight and diameter of the solute molecule and the viscosity of the diffusion medium. Drugs with a molecular weight of >500Da are thought to have poor diffusivity in hydrophilic matrices due to the constrain imposed by the aqueous gel structure [15]. Particle size and shape: particle size and shape of soluble drugs determine drug release in terms of effective surface area.

**Polymer related factors**

There are two mechanisms by which the release happens, the drug shall either diffuse through the polymer or the polymer shall erode. Drug diffusion increases with increase in polymer content as well as dimension proportionally; as well as the interaction between the polymer and solute. Polymers can be water-soluble or water-insoluble. Polymers that are sufficiently polar can interact with an aqueous medium and generate sufficient energy to disperse polymer chains from the glassy state. The apparent infiltration rate of aqueous medium and erosion rate of the tablet matrix depends on the type of polymer. Water-insoluble polymers such as ethyl cellulose and pH-dependent soluble polymers such as eudragits and HPMC are also in use which has various applications based on concentration. The typical properties of polymers like viscosity, gel point, hydration rate, and glass transition temperature need to be considered while selecting the polymer. The different degrees of polymer substitution lead to different hydration rates and thereby producing different viscosity grades. An increase in polymer content results in increased viscosity of the gel, leading to a decrease in the effective diffusion coefficient of the drug. Polymer swelling, chain relaxation, hydration, wetting, and enthalpy changes associated are other polymer-related factors affecting
drug release [16]. Polymers at different proportions can vary the release profile from a matrix device. An increase in polymer proportion increases the viscosity of the gel and, thereby, increases the diffusional path length. Hence diffusion coefficient decreases and rate of drug release falls. The Polymer particle property influences the availability of particle contact points, porosity, viscosity, and tortuosity of matrices. There is an increased resistance to the infiltration of aqueous medium when the bulk density increases as the porosity decreases [17].

**Formulation variables**

Major variables are formulation geometry (size & shape), processing techniques including the manufacturing variables, formulation excipients or additives quantities and their roles and physical characteristics of the dosage form. Consider the tablet formulation regardless of the tablet shape, the dissolution medium will penetrate at same rate initially. This will lead to hydration, polymer relaxation, molecular rearrangement and eventually gel formation. This gel hinders infiltration of the medium further into the tablet core and an eventual decrease in rate of drug release. The thickness of the gel layer will be similar for various system geometries but the core which should be hydrated for complete drug release will not be the same. An increased tablet size provides an increased surface area leading to an overall equilibrium in the release rate. The fraction of drug release from a planar matrix is proportional to the square root of time, and an initial portion of a similar plot for a cylindrical matrix will be similar to that of a planar one. Mathematical modeling of diffusion based in-vitro release can be used to predict the in-vivo release pattern [18, 19]. The physicochemical characteristics of excipients impact the drug release and hence to be studied and controlled. The presence of hydrophobic additives hinders infiltration of aqueous medium and insoluble fillers block the surface pores of the tablet [20]. Incorporating a surfactant may result in an increase in drug release rate through improved wetting or solubilization. Formulation constituents like Binding agents can retard drug release, plasticizers may enhance drug-release rates and lubricants will retard drug release based on the concentration in the dosage form [21].

**DRUG RELEASE MODELS AND REGULATORY PROSPECT**

Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products from the USFDA in 2003 mentions the importance of release kinetics in the determination of shelf life for both drug substance and drug product [22]. "Limited extrapolation of the real time data from the long-term storage condition beyond the observed range to extend the retest period can be undertaken at approval time if justified. This justification should be based, for example, on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, and/or existence of supporting stability data." Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms of the FDA described the Model Dependent Approaches and gives a step wise procedure to select the appropriate model to fit dissolution profiles [23]. Citations of similar kind are available in 1997 guidance for Extended Release Oral Dosage Forms [24]. In the Evaluation for Stability Data (Q1E), The International Conference on Harmonisation (ICH) has detailed the importance of mathematical and statistical modeling, linear regression and explanation on release mechanism for establishing the stability and shelf life of a product for human use [25]. The European Medical Agency (EMA) has discussed model dependant dissolution profiles with linear regression in its "Guideline on quality of oral modified release products" effected in 2014. The EMA has delineated the crucial role of release kinetics in the Development of dissolution methods [26]. Various kinetic models have been used in various studies to fit the in vitro release data obtained and to describe the release kinetics. Data obtained from the in vitro release studies can be fitted to various models such as zero order, first order, Higuchi model, Hixson-Crowell model, Korsemeyer–Peppas model, Baker and Lonsdale model, Weibull model, Hopfenberg model and Cooney model.

**CORRELATION COEFFICIENT AND COEFFICIENT OF DETERMINATION**

Correlation Coefficient and Coefficient of Determination is an important factor and is the measure of to what extent the regression line represents the data. When the regression line passes exactly though every point on the scatter plot, it would be able to explain all the variation. Further the line points away from the points, the less it is able to explain. The model that best fitted the release data was evaluated by correlation coefficient (R). The best model to describe the release pattern is the use of the coefficient of determination (R²), to assess the fit of a model equation. Usually, this value tends to get greater with the addition of more parameters, irrespective of the significance of the variable model. When comparing models with different numbers of parameters, the adjusted coefficient of determination (R² adjusted) is more appropriate:

\[ R^2_{\text{adjusted}} = 1 - \frac{\text{(n-1) / (n-p)}}{1-R^2} \]

Where 'n' is the number of dissolution data points and 'p' is the number of parameters in the model. R² adjusted decreases whereas R² always increases or remains constant when new parameters add up. Hence it helps to differentiate if the new parameter really improves the model or might lead to over fitting. It is concluded that the ‘best’ model would be the one with the highest value of adjusted coefficient.
of determination. Along with the coefficient of determination \( R^2 \) or the adjusted coefficient of determination \( R^2 \text{ adjusted} \), the correlation coefficient \( R \), the sum of squares of residues (SSR) and the mean square error (MSE) are also used to test the applicability of the release models [13].

### Sum of squares of residues (SSR)
Residual sum of squares (RSS) is also known as the sum of squared residuals (SSR) or sum of squared errors (SSE) of prediction. It is an amount of the difference between data and an estimation model. A small SSR value indicates a tight fit of the model to the data. It is used for parameter selection and model selection [27].

### Mean Square Error (MSE)
MSE measures the average of the squares of the errors or deviations. It tells you how close a regression line is to a set of points. The distances from the points to the regression line (these distances are “errors”) is taken and squared. The squaring removes any negative signs and gives more weight to large differences [27].

### RELEASE MODELS

#### 1. Zero order release kinetics
It refers to the process of constant drug release from a drug delivery device independent of the concentration. In its simplest form, zero order release can be represented as

\[
Q = Q_0 + K_0 t
\]

Where \( Q \) is the amount of drug released or dissolved, \( Q_0 \) is the initial amount of drug in solution (it is usually zero), and \( K_0 \) is the zero order release constant. The plot made: cumulative drug release vs. time [28]. Graphical representation of fraction of drug dissolved verses time will be linear. The slope of the curve gives the value of \( K \) in zero order release kinetics. This is ideal behaviour for a dosage form and leads to minimum fluctuations in drug plasma levels. This is expressed mainly by osmotic pump systems and also transdermal systems, matrix tablets with low soluble drugs and coated forms [29].

#### 2. First order release kinetics
The first order Equation describes the release from system where release rate is concentration dependent, expressed by the equation:

\[
dC / dt = -Kt
\]

Where \( K \) is first order rate constant expressed in units of time^{-1}. This equation can be expressed as:

\[
\log C_t = \log C_0 - k t / 2.303
\]

Where, \( C_0 \) is the initial concentration of drug and \( C_t \) is the concentration of drug in solution at time \( t \). The equation predicts a first order dependence on the concentration gradient \( (C_0 - C_t) \) between the static liquid layer next to the solid surface and the bulk liquid. The plot made: \log cumulative of % drug remaining vs. time which would yield a straight line with a slope of \(-K/2.303\) [28].

The dosage forms containing water soluble drug in porous matrices (Mulye and Turco, 1995) follows this profile such that the proportional to the amount of drug released by unit time diminishes.

#### 3. Higuchi Model [31]
The first example of a mathematical model aimed to describe drug release from a matrix system was proposed by Higuchi in 1963 this model is applicable to study the release of water soluble and low soluble drugs incorporated in semisolid and solid matrices

Model expression is given by the equation:

\[
Q = A \left[ D (2C - Cs) Cs \right] \frac{t^{1/2}}{t^{1/2}}
\]

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

Simplified Higuchi model describes the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Equation.

\[
Q = KH t^{1/2}
\]

The data obtained were plotted as cumulative percentage drug release versus square root of time. The slope of the plot gives the Higuchi dissolution constant KH. Professor Takeru Higuchi published the derivation of an equation that allowed for the quantification of drug release from thin ointment films, containing finely dispersed drug into a perfect sink. Despite the complexity of the involved mass transport processes, Higuchi derived a very simple equation, which is easy to use. Based on a pseudo-steady-state approach, a direct proportionality between the cumulative amount of drug released and the square root of time can be demonstrated. In contrast to various other “square root of time” release kinetics, the constant of proportionality in the classical Higuchi equation has a specific, physically realistic meaning. The major benefits of this equation include the possibility to: (i) facilitate device optimization, and (ii) to better understand the underlying drug release mechanisms. The equation can also be applied to other types of drug delivery systems, like controlled release transdermal patches or films for oral controlled drug delivery [32].

The Higuchi and zero order models are used to describe the limits for transport and drug release.

#### 4. Hixson-Crowell cube root law [33]
The cube root law was first proposed by Hixson and Crowell (1931a) as a means of representing dissolution rate that is normalized for the decrease in solid surface area as a function of time. Hixson-Crowell cube root law describes the release from systems where there is a change in surface area and diameter of particles or tablets. Provided there is no
change in shape as a suspended solid dissolves, its surface decreases as the two-thirds power of its weight. This relation has been used by Hixson and Crowell in the derivation of the cube root law. For a drug powder consisting of uniformly sized particles, it is possible to derive an equation that expresses the rate of dissolution based on the cube root of the particles. When sink conditions are applied, the cube root law can be written as:

\[ Q(t) = Q_0 \left(1 - \frac{t}{K t} \right)^{1/3} \]

where \( Q(t) \) denotes the remaining weight of solid at time \( t \), \( Q_0 \) is the initial weight of solid at time \( t = 0 \), and \( K \) represents the dissolution rate constant. The graphical plot of the cubic root of the unreleased fraction of the drug versus time should yield a straight line if the equilibrium conditions are not reached and if the geometrical shape of the dosage form diminishes proportionally overtime. This model is used by assuming that release rate is limited by the drug particles dissolution rate and not by the diffusion. The assumptions made for the validity of the law by Hixson and Crowell can be summarized as follows:

1. The law is claimed to be more suitable for monodispersed, predominantly spheroidal, materials, i.e., the solid is in the form of a single unit or all units having identical properties regarding size, shape, surface and volume characteristics [34-37].
2. The dissolution takes place normal to the surface. The difference in rates at different crystal faces is considerably less and the effect of agitation of the liquid against all parts of the surface remains same.
3. The liquid is agitated intensely to prevent stagnation in the nearest places of the dissolving particle thus resulting in a slow rate of diffusion.

<table>
<thead>
<tr>
<th>Release Exponent (n)</th>
<th>Drug transport Mechanism</th>
<th>Rate as a function of time</th>
<th>Drug release mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n &lt; 0.5 )</td>
<td>Quasi-Fickian diffusion</td>
<td>( t^n )</td>
<td>non swellable matrix-diffusion</td>
</tr>
<tr>
<td>0.5</td>
<td>Fickian diffusion</td>
<td>( t^{0.5} )</td>
<td>for both diffusion and relaxation (erosion)</td>
</tr>
<tr>
<td>0.5 &lt; n &lt; 1.0</td>
<td>Anomalous diffusion</td>
<td>( t^{n-1} )</td>
<td>Zero order release</td>
</tr>
<tr>
<td>1.0</td>
<td>Case II transport</td>
<td>(time - independant)</td>
<td>(relaxation / erosion)</td>
</tr>
<tr>
<td>Higher than 1.0</td>
<td>Super case II transport</td>
<td>( t^{n-1} )</td>
<td></td>
</tr>
</tbody>
</table>

As per Ritger-Peppas models, \( 0.45 < n < 0.89 \) for non-Fickian release (anomalous) from cylinders (non swellable matrix) and \( 0.43 < n < 0.85 \) for non-Fickian release (anomalous) from non swellable spherical samples [39, 40]. To find out the exponent \( n \), the portion of the release curve \( M_i / M_a < 0.6 \) should only be used. The model is plotted as log cumulative percentage drug release versus log time [43]. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion [38].

This model was developed by Baker and Lonsdale [44] from the Higuchi model and described the drug release from spherical matrices according to the equation:

\[ f = \frac{3}{2} \ln \left( 1 - \frac{M_i}{M_a} \right)^{2/3} - \frac{M_i}{M_a} = K t \]

\( M_i / M_a \) is the fraction of drug released at time \( t \) and can be represented as \( Q \) for a simplified appearance.
According to this model, for a drug incorporated in a spherical matrix, a straight line is expected for the 3/2 \[1 - (1 - Q)^{2/3}\] - Q versus time plot, if the drug release from the spherical matrix is based on a diffusion mechanism. The slope of the plot 3/2 \[1 - (1 - Q)^{2/3}\] - Q with respect to time gives the release constant K [28]. This model is applied for linearization of the release data from formulations of microcapsules [45, 46].

7. Weibull model
A general empirical equation described by Weibull in 1951 was adapted to the dissolution/release process by Langenbucher [47]. When Weibull equation is applied to drug dissolution and release from dosage forms, it expresses the accumulated fraction of drug ‘m’ in solution at time ‘t’ by

\[ m = 1 - \exp \left[ - \left\{ \left( \frac{t}{\alpha} \right)^b \right\} / a \right] \]

Where ‘a’ is the scale parameter defines the time scale of the process, that is, time dependence. ‘Ti’ is the location parameter, represents the lag time before the onset of the dissolution or release process and in most of the cases it will be zero. The shape parameter ‘b’ describes the shape of dissolution curve progression. When b = 1, shape of the curve is an exponential profile where the constant K = 1/a. When b is greater than 1, the shape of the curve gets sigmoidal with a turning point. When b is less than 1, shape shows a parabolic curve showing a steeper res using data derived from the composite profile, which essentially displays site-specific biphasic release kinetics [49, 50].

9. Gompertz model
The in-vitro dissolution profile is often described by a simpler exponential model known as Gompertz model, expressed by the equation: X(t) = Xmax exp \[-α e^{β \log t}\] 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 parameter (1/α) at unit of time described as shape parameter. This model has a steep increase in the beginning and converges slowly to the asymptotic maximal dissolution. The Gompertz model is more useful for comparing the release profiles of drugs increase than b = 1. The above equation can be rearranged as:

\[ \log \left[ ln \left(1 - m \right) \right] = b \log (t - Ti) - \log a \]

Graphical representation of log [ln (1 - m)] versus time ‘t’ gives a linear relation. Shape parameter (b) is 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. This is an empiric model, not deduced from any kinetic fundament. The Weibull model is more useful for comparing the release profiles of matrix type drug delivery [28].

8. 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. The cumulative fraction of drug released at time t was described as:

\[ Mt / M∞ = 1 - [1 - k0t / CL a]^n \]

where k0 is the zero order rate constant describing the polymer degradation (surface erosion) process, CL is the initial drug loading through out the system, ‘a’ is the system’s half thickness (i.e. the radius for a sphere or cylinder), and n is an exponent that varies with geometry n = 1, 2 and 3 for slab (flat), cylindrical and spherical geometry, respectively [48]. Application: This model is used to identify the mechanism of release from the optimized oil sphere having good solubility and intermediate release rate [12, 28].

10. Gallagher Corrigan model
The common mechanisms applied to evaluate drug release from biodegradable polymeric drug delivery systems are combinations of diffusion and degradation. Drug release occurs concurrently to polymer degradation. In such systems, drug release profiles usually have a sigmoidal shape. The Gallagher and Corrigan model is a mathematical model that describes the fraction of drug released from the biodegradable polymeric system. Kinetic profile described by Gallagher-Corrigan equation comprises the initial ‘burst effect’ of a drug non-bound to the drug matrix and following slow release determined by the matrix erosion (Gallagher and Corrigan, 2000)

The total fraction of drug released (f) at time t is:

\[ f = f_{t_{max}} \left[ 1 - e^{-K_1 t} \right] + \left( f_{t_{max}} - f_B \right) \left( \frac{e^{K_2 t - K_1 t_{2_{max}}} - K_2 t_{2_{max}} - K_1 t_{2_{max}}}{1 + e^{K_2 t - K_1 t_{2_{max}}}} \right) \]

ft – fraction of drug released in t time; f_{t_{max}} – maximum fraction of drug released during process; fB – fraction of drug released during 1st stage – the burst effect; k1 – the first order kinetic constant (1st stage of release); k2 – the kinetic constant for 2nd stage of release process–matrix degradation; t_{2_{max}} – time to maximum drug release rate. This calculated f is plotted against the time; and the correlation coefficient and coefficient of determination can be calculated to understand the suitability of the model [51, 52].

11. Cooney model
Cooney model is based on assumption that there is one single zero order kinetics process, which is confined to the surface of the drug delivery system. This model provides detailed analysis for spheres and cylinders undergoing surface erosion. As in the
Hopfenberg model the release rate is assumed to be proportional to the surface area of the device, which is time-dependent. For a cylinder with the initial length \( L_0 \) and initial diameter \( D_0 \), the following equation was derived quantifying the drug release rate \( f \) as a function of time \( t \):

\[
f = \frac{(D_0 - 2Kt)^2 + 2(D_0 - 2Kt)(L_0 - 2Kt)}{D_0^2 + 2D_0L_0}
\]

where \( K \) is a constant. When \( L_0/D_0 \) approaches zero (film geometry) the curves transform into a horizontal line with a constant relative drug release rate of 1. It is interesting to note that for disc-like cylinders (ratios of \( L_0/D_0 < 1 \), curves numbered 0.1, 0.2 and 0.5), the relative drug release rate remains finite up to complete drug release. In contrast, for rod-like cylinders (\( L_0/D_0 > 1 \), curves numbered 1, 2, 5 and infinity), the relative drug release rate approaches zero at late time points [53].

12. Sequential layer model
This model predicts molecule release from swelling controlled system. It 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. 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. An advantage of using computational grid is that it allows modeling of inhomogeneous swelling. Swelling is considered to take place layer by layer in which outermost layer swells first followed by neighboring inner layers. This model is able to capture the major feature of swelling controlled system, which is substantial change in volume of the system in the outer layer. The following physicochemical phenomena occurring during drug release from hydrophilic matrix tablets.

(i) At early times, significant water concentration gradients are formed at the matrix/water interface leading to water imbibition into the system. This process is taken into account considering: (i) the exact geometry of the tablet; (ii) the axial and radial direction of the mass transport; and (iii) the significant dependence of the water diffusion coefficient on the matrix swelling ratio [54]. (ii) Due to the imbibition of water HPMC swells, resulting in dramatic changes of polymer and drug concentrations, and increasing dimensions of the system..(iii) On contact with water the drug dissolves and (due to concentration gradients) diffuses out of the device.(iv) With increasing water content the diffusion coefficient of the drug increases substantially.(v) In the case of poor water-solubility, dissolved and undissolved drug co-exist within the polymer matrix. Undissolved drug is not available for diffusion. (vi) In the case of high initial drug loadings, the inner structure of the matrix changes significantly during drug release, becoming more porous and less restrictive for diffusion on drug depletion.(vii) Depending on the chain length and degree of substitution of the hydrophilic polymer used, the polymer itself dissolves more or less rapidly.Based on the reptation theory, a dissolution rate constant, \( k_{diss} \), was considered characterizing the polymer mass loss velocity normalized to the actual surface area of the system:

\[
M_{pt} = M_{po} - k_{diss} A \quad t
\]

Here, \( M_{pt} \) and \( M_{po} \) are the dry polymer matrix mass at time \( t \), and \( t = 0 \), respectively; \( A \) denotes the surface area of the device at time \( t \) [55].

SELECTING AN IDEAL MATHEMATICAL MODEL
The regulatory agency USFDA [23] suggest a step-wise procedure to do the selection of an appropriate mathematical model for the available dissolution profile. Several mathematical models have been described in the literature to fit dissolution profiles. To allow application of these models to comparison of dissolution profiles, the following procedures are suggested:Select the most appropriate model for the dissolution profiles from the standard, prechange, approved batches. A model with no more than three parameters (such as linear, quadratic, logistic, probit, and Weibull models) is recommended. Using data for the profile generated for each unit, fit the data to the most appropriate model.A similarity region is set based on variation of parameters of the fitted model for test units (e.g., capsules or tablets) from the standard approved batches.

1. Calculate the MSD in model parameters between test and reference batches. Estimate the 90% confidence region of the true difference between the two batches.
2. Compare the limits of the confidence region with the similarity region. If the confidence region is within the limits of the similarity region, the test batch is considered to have a similar dissolution profile to the reference batch.

Conclusion
The mathematical modeling in drug delivery has high potential to facilitate product development and evaluations of the same and also helps understanding the complex pharmaceutical dosage forms. The selection of the suitable model in the drug release studies is difficult, which in turn makes it difficult to ensure the effectiveness of the study. Coefficient of determination can be used to assess the fit of the model equation. This method is also applied when the model equation parameters are same. The best model shall be considered as the one which have the highest adjusted coefficient of
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