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TRANSFER OF *IN-VITRO* DRUG RELEASE PROFILE IN TO DIFFERENT STATISTICAL METHODS, MODEL DEPENDENT METHODS, & MODEL INDEPENDENT METHODS - A REVIEW

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ABSTRACT

When a new solid dosage form is developed it is important to study the drug release pattern. The objective of this review to study the kinetics of drug release from dosage form. Many mathematical models have been used to design a number of simple and complex drug delivery system and to determine the overall release behavior. It is very important to know how to use these equations to understand the release patern. The mathematical modeling help to optimize the design of dosage form. The quantitative analysis of the value obtained in dissolution rates is easier. The choice of selection best model depends upon on the desired predictive ability and accuracy of model. This review gives the idea about the kinetics of drug release namely model dependent like (zero order, first order, Hixson-Crowell, Higuchi, Weibull, Korsemeyer-Peppas, Hopfenberg, Baker-Lonsdale, Gompertz and regression models), statistical analysis (exploratory data analysis method, repeated measures design,t-test, ANOVA, MANOVA etc.) and model independent method [difference factor(f1),similarity factor(f2)] can be used.

Keywords: ANOVA, Hixson-Crowell Gompertz model, SUPAC, MANOVA

INTRODUCTION:

Drug dissolution is an important parameter used to describe the drug released from its dosage form. This test is used to quantification of amount and extent of drug release from its dosage form for absorption, distribution, metabolism and excretion, simultaneously becoming available for pharmacological action. *In vitro* dissolution study is an important parameter in drug development .Several theories describes drug dissolution from its dosage forms. There are number of factor that effects the dissolution such as physicochemical, biological, formulation etc. The data that obtained from dissolution study can be apply to different mathematical model equation to describe the mechanism of drug release **[1]**. Mathmatical model plays important role in mechanism of drug release and also provide more general guidelines for new drug development.This mathematical model require the comprehension of all phenomenon affecting drug release kinetics and this value used for formulation optimization. This kinetics models are widely used all different fields like genetics, medicines, psychology, biology, economics, pharmaceutical sciences, and engineering technology. It is noted that for successful drug delivery system result of careful selection of excipients, concentration of excipients and method **[2]**. Thus kinetic models can successfully facilitate the optimization of existing and development of new drug product. The model can simply thought as a "Mathematical metaphor some aspect of reality". To compare dissolution profile between two or more drug model dependent (zero order, first order, Hixson-Crowell, Higuchi, , Korsemeyer-Peppas, Hopfenberg, Baker-Lonsdale, Weibull and Gompertz model etc.), statistical analysis (exploratory data analysis method, repeated measures design,t-test,ANOVA,MANOVA etc.), and model independent method [difference factor(f1),similarity factor(f2)] can be used **[3]**.

Fundamentals of kinetics of drug release

Noyes-Whitney Equation

Arthur Amos Noyes and Willis Rodney Whitney in 1897 developed the formula of drug release know as Noyes-Whitney equation, which can explain by following equation

$$dc/dt=KS\ (C_S-C_b)$$

Where dc/dt= dissolution rates of drug, K= is the dissolution constant, S= surface area,C_S=Concentration of drug in stagnant layer,C_b=Concentration of drug at time " t" in bulk of solution. In order to maintain sink

condition C_s>10 C_b, than uniform rate of dissolution is obtained **[4]**.

Fick's low of Diffusion

Fick's 1st law of diffusion based on diffusion of the drug molecules from region of higher concentration to lower concentration until equilibrium exists. The rate of diffusion is directly proportional to the concentration gradient. Which can be explain by the following equation.

$$dq/dt = DAK_{M/W}(C_{git}-C)/h$$

Where dq/dt=rates of drug diffusion (Amount of drug goes in to solution), D=diffusion coefficient constant, $K_{M/W}$=Partition coefficient of drug between lipoidal membrane aqueous GI fluid (no unit), A=Surface area of absorption sites, C_{git}-C = Concentration gradient, C_{git}=Concentration of drug at the sites of absorption, C=concentration of drug in blood plasma, h=thickness of biological membrane **[5]**.

Methods to compare dissolution profile

Dissolution profile of a drug reflects its release pattern under the selected condition sets. In a number of recent guidance documents, the FDA has emphasis on the meaningful comparison of dissolution profile data **[6]**. The most important application of the dissolution profile is that by knowing the dissolution profile of particular product of the brand leader, we can make appropriate necessary change in our formulation to achieve the same profile of the brand leader. To develop *in-vitro in-vivo* correlation which can help to reduce costs, speed-up product development and reduce the need to perform costly bioavailability human volunteer studies. Establish the similarity of pharmaceutical dosage forms, for which composition, manufacture site, scale of manufacture, manufacture process and/or equipment may have changed within defined limits **[7]**. To analyze the *in vitro* release data various models were used to describe the release kinetics were recently proposed. Those methods were classified into several categories, such as

1. Statistical methods (exploratory data analysis method, repeated measures design, t-test, ANOVA, MANOVA etc.)
2. Model dependent methods (zero order, first order, Hixson-Crowell, Higuchi, Weibull, Korsemeyer-Peppas, Hopfenberg, Baker-Lonsdale, Gompertz model and regression model etc.)
3. Model independent methods [difference factor (f1), similarity factor (f2)] can be used.

1. Statistical methods

1.1 Exploratory data analysis (EDA)

Exploratory data analysis or "EDA" is a critical first step in analyzing the data from an experiment. Exploratory data analysis was

promoted by John Tukey to encourage statisticians to explore the data, and possibly formulate hypotheses that could lead to new data collection and experiments **[8]**. Exploratory data analysis (EDA) is an approach to analyzing data set to summarize their main characteristics, often with visual methods **[9]**. Now days this method is disapprove by FDA. Exploratory data analysis (EDA) is the primary investigation to compare dissolution data generally classified in to 2 ways graphical 0r non graphical numerically (Univariate or multivariate).Graphical method involve the summaries the dissolution data in a diagrammatic way while non-graphical methods involve calculation of dissolution data .if we consider one variable at a time it is called as univariate and if we consider two or more variables at a time know as multivariate methods **[10]**.

1.2 Analysis Of Variance (ANOVA)

An ANOVA test is a way to find out if survey or experiment results are significant. In other words, they help you to figure out if you need to reject the null hypothesis or accept the alternate hypothesis. Basically, you're testing groups to see if there's a difference between them. Examples of when you might want to test different groups: A manufacturer has two different processes to make tablet. We want to know if one process is better than the other. One-way or two-way refers to the number of independent variables (IVs) in analysis of Variance test. One-way has one independent variable (with 2 levels) and two-way has two independent variables (can have multiple levels). For example, a one-way Analysis of Variance could have one IV (single company of tablets dissolution data) and a two-way Analysis of Variance has two IVs (brand of 2 different company dissolution data) **[11, 12]**.

1.3 Multivariate Analysis Of Variance (MANOVA)

Multivariate analysis of variance (MANOVA) is simply an ANOVA with several dependent variables The MANOVA (multivariate analysis of variance) is a type of multivariate analysis used to analyze data that involves more than one dependent variable at a time. MANOVA allows us to test hypotheses regarding the effect of one or more independent variables on two or more dependent variables. MANOVA has several advantages over ANOVA. First, by measuring several dependent variables in a single experiment, there is a better chance of discovering which factor is truly important. Second, it can protect against Type I errors that might occur if multiple ANOVA's were conducted independently. Additionally, it can reveal differences not discovered by ANOVA tests **[13, 14]**.

2. Model dependent methods

Model dependent methods are based on mathematical equations generally used to define the dissolution data. First a suitable function has been selected than the evaluation of dissolution profile carried out, followed by the drug release profile or dissolution data can be correlated to release kinetic models. The various model dependent models included zero order, first order, Hixson-Crowell, Higuchi, Weibull, Korsemeyer-Peppas, Hopfenberg, Baker-Lonsdale, Gompertz model and regression models **[15]**.

2.1 Zero order models

Drug dissolution from dosage forms release the drug at constant rate (same amount of drug release per unit time) and release of drug is independent of the concentration of drug. When drug release follows zero order kinetics, absorption will also be a zero order. It can be represent by the following equation

$$C_0-C_t=K_0t \quad (1)$$

$$C_t=C_0=K_0t \quad (2)$$

C_t=Amount of drug release at time t,

C_0=Initial concentration of drug at time t=0,

K_0=Zero order rate constant expressed concentration/time

Hence to study the drug release kinetic data obtained from *in-vitro* dissolution study were plotted as time i.e. cumulative % drug release vs time. The slope of the above plot gives the zero order rate constant and the correlation coefficient (r^2) of plot will give information whether the drug release follow zero order kinetic or not.

The zero order kinetics can be used to establish the drug dissolution of several types of modified dosage forms like matrix tablet with low soluble drug, enteric coating tablet, transdermal drug delivery system, implants, suspension and oral osmatic system etc. Generally zero order release system is considered as ideal controlled delivery formulations. Zero order model is important in delivery of certain type of drug like antibiotic, anti-hypertensive, pain control and antidepressant **[16, 17]**.

2.2 First order model

This model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967) and later by Wagner (1969). This model has been used to describe absorption or elimination of drugs, although it is very difficult to understand the mechanism on the theoretical basis.. The release of drug which follows first order kinetics can be represent by the equation

$$Dc/dt =-K_1C \quad (3)$$

Where K_1 is the first order rate constant expressed in time^{-1}.

The above reaction indicate that the first order release rate of drug is depends on

concentration of drug only. After rearranging and integrating equation (3) can be expressed by

$$\text{Log } C = \text{Log}C_0 - K_1 t/2.303 \quad (4)$$

Where C=Initial concentration of drug

C_0=Amount of drug release at time "t"

K_1=First order rate constant

To study the drug release kinetics the data obtained from *in-vitro* dissolution is plotted against time. Graphically it represents log % drug release remaining *vs.* time which gives straight line with slope –K/2.303. The correlation coefficient (r^2) of plot will give information whether the drug release follow first order kinetic or not.

The first order kinetics can be used to establish the drug dissolution of several types of modified dosage forms like matrix diffusion controlled release, matrix dissolution controlled release, sustained release and solution etc. **[18]**.

2.3 Hixson-Crowell model

Noyes-Whitney's equation based an assumption that the surface area of dissolving drug particle remains constant during dissolution, which is practically not possible. Hixson and Crowell (1931) proposed that the during dissolution the surface area and diameter of particle change with time. According to Hixson-Crowell change in surface area of the particle is proportional to the cube root of its volume, which can be expressed by the equation as

$$W_0^{1/3} - W_t^{1/3} = Kt \quad (5)$$

Where, W_0 =Initial weight of drug in dosage form

W_t =Remaining amount of drug at pharmaceutical dosage form at time't'

K= Hixson-Crowell rate constant

The value of 'K' is a constant depends on shape, density & surface area of particle.

Hence to study the drug release kinetic data obtained from *in-vitro* dissolution study were plotted as time i.e. Cube root of drug percentage remaining in dosage form *vs.* time. This equation is used for interpretation of dissolution data of conventional dosage form, dispersible dosage form and immediate release dosage form. This model assumed that the release of drug is limited to dissolution and not by diffusion that occur the polymeric matrix **[19]**.

2.4 Higuchi model:

For coated or matrix type dosage form, the dissolution medium enters the dosage form in order for the drug to be released and diffused into the bulk solution. In such conditions involves both dissolution and diffusion. The above matrix system was first proposed by Huguchi in 1961. The first example of a

mathematical model refereed to a "Higuchi equation" intended to describe the matrix system. In modern era Higuchi equation is the most widely used and most well-known controlled release equation. Initially conceived for planar systems, it was then extended to different geometrics and pours systems. Higuchi model based on hypothesis are given below

(i) Initial drug concentration in the matrix is much higher than drug solubility.

(ii) Diffusion of drug take place only one direction, edge effect must be negligible.

(iii) The thickness of system is much higher than the drug molecules.

(iv) Matrix swelling and dissolution are negligible.

(v) Drug diffusivity is constant and

(vi) Perfect sink condition must be attained in the release environment.

The basic Higuchi equation homogenous matrix system is given at

$$f_1=Q=A\sqrt{D}\qquad (2C\text{-}C_S)C_St \quad (6)$$

Where, Q =Amount of drug release in time "t" per unit area (A), C is the initial concentration of drug,C_S is the solubility of drug in matrix and D= Diffusivity of drug molecules (Diffusion coefficient) of drug molecules.

This above equation is not valid to all matrix system. 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, it can be explain by equation:

$$f_1=Q=\sqrt{\frac{D\delta}{\tau}(2C-\delta Cs)Cs.t} \quad (7)$$

Where, δ=Porosity of matrix (pores or channels from which liquid penetrate inside for release of drug from matrix system)

τ=Tortuisity of the matrix (Dimension of radius and branching of the pores and canals in the matrix).

Higuchi 1962 proposed an equation applied to matrix saturated with drug, Where C_0 is the concentration of diffusing liquid contained in porous matrix.

$$f1=\sqrt{2Cs\ \delta\ Dt/\tau\pi} \quad (8)$$

Where π is the osmatic pressure.

Huguchi model again simplified and given below:

$$f_1=Q=K_H\qquad t^{1/2} \quad (9)$$

Where, K_H is the Higuchi dissolution constant **[20, 21]**. The dissolution data obtained from *in-vitro* dissolution study were plotted as cumulative percentage drug release versus square root of time.

This model used to describe the drug dissolution for several dosage form like transdermal systems and matrix tablets with water soluble drug.

2.5 Weibull model:

This above method was first proposed by Swedish mathematician Waloddi Weibull, who described it in detail in 1951.Weibull equation has been used to describe all kind of dissolution curve. This model adopt the function to describe the drug release from dosage form. This equation is expressed the accumulation of fraction of drug in solution on time (t). Mathematically expressed by

$$M = M_0 \left[1 - e^{-\frac{(t-T)b}{a}}\right] \quad (10)$$

Where, M=Amount of drug dissolved as a fraction of time (t)

M_0 =Total amount of drug being released.

T=Accounts for the lag time measured as a result of the dissolution process.

a=parameter 'a' denotes a scale parameter that describes the time dependence.

b=Describe the shape of dissolution curve progression.

For

- b=1, the shape of the curve corresponds exactly to the shape of an exponential profile with Constant k=1/a (exponential)
- For b>1, the shape of the curve gets sigmoidal with turning point (sigmoid with ascendant curvature delimitated by an inflection point)
- For b<1, the shape of the curve show steeper increase than the one with b=1 (parabolic, displaying high initial slope and a consistent exponential character)

$$M = M_0 \left(1 - e^{-K^{(t-T)}}\right) \quad (11)$$

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

$$t_{(50\%\ \text{resp},90\%\ \text{dissolved})} = \left(-a \ln \frac{M_0 - M}{M_0}\right)^{1/b} + T \quad (12)$$

The Weibull equation can be applied to almost all kinds of dissolution curve. This Weibull model is mostly used for comparing the release profiles of matrix type drug delivery system **[22, 23]**.

2.6 Korsemeyer-Peppas:

A simple relationship which described drug release from a polymeric matric system. The equation was derived by the Korsemeyer, Gurny, Doelker, Buri and Peppas and simultaneously by Ritger and Peppas. The resulting equation was also called as power law.

Mathematically it can be expressed by

$f_i = M_t/M_\infty = Kt^n$ (13)

Where fi=Amount of drug release

n=Release exponent (used to characterize different release for cylindrical shaped material)

k=Release rate constant

t=time

This model is designed for the describing the release of drug molecule from polymeric matrix, such as hydrogel. A modified form of this equation was developed to adjust the lag time (*l)* in the beginning of drug from the pharmaceutical dosage form.

$M_{(t-1)}/M_\infty = K(t-l)^n$ (14)

Or

$\text{Log}\ (M_{(t-1)}/M_\infty) = \text{Log}K + n\text{Log}\ (t-l)$ (15)

When drug release process is first or possibility of burst effect, 'b' the above equation becomes

$M_t/M_\infty = at^n + b$ (16)

In the absence of lag time or burst effect '*l*' and 'b' values would be zero and only 'at^n' is used. This mathematical model also knows as the 'power law', has been used very frequently to describe the drug release from several different pharmaceutical modified dosage forms **[24]**.

The power law model can be used to establish a relationship between the drug dissolution from polymeric system such as in case when release mechanism is not known or more than one mechanism of drug release is involved.it is possible to establish a classification, according to the type of observed behavior *viz*. Fickian model (Case I) and Non-fickian model (Case II, anomalous case and super case) and depending on the value of (n) whish better suits the release profile of drug.

A plot of the log % of drug release vs log time yields slope n (diffusion exponent). The 'n' value is used to characterize different release for cylindrical shaped tablets and it is describe in table (1).For the case of cylindrical tablets,

$0.45 \leq n$ correspondent to a Case I or Pure Fickian diffusion mechanism, in this case the rate controlling step is not the dissolution rate of drug but diffusion of dissolve drug molecule through the polymeric membrane. High velocity of solvent diffusion to the core of matrix and low velocity of polymeric relaxation are the result of Fickian diffusion. As a result, there is formation of gradient of solvent penetration and there is an exponential decrease of solvent concentration is observed from totally swollen region to the core of matrix. The diffusing distance is proportional to the square root of time **[25]**.

When n= 0.45 - 0.89 indicating anomalous non-Fickian transport. The mechanism of drug release is follow diffusion and swelling. The rates of solvent penetration and drug release are in same velocity. The anomalous effect due to slow rearrangement of polymeric chain and simultaneous diffusion process. This deviation is due to increase drug diffusivity from the matrix by solvent induce relaxation of the polymer.

When n=0.89 known as Case II (relaxational) transport, where drug release mechanism follow Zero order. The major mechanism driving the drug release is swelling and relaxation. In this case the drug diffusion is rapid compared to the constant rate of solvent –induced relaxation and swelling of polymer.

When n > 0.89 to super case II transport., where the velocity of solvent diffusion is much higher, causing an acceleration of solvent penetration **[26]**.

Table 1: Interpretation of drug release mechanism with different Geometry

Drug transport Mechanism	Release exponent	Geometry
Fickian diffusion	0.50	Slab
0.45	Cylindrical	
0.43	Sphere	
Non-Fickian (Anomalous)	0.5 - 1	Slab
0.45 -0.89	Cylindrical	
0.43 -0.85	Sphere	
Case II(relaxation)	1.0	Slab
0.89	Cylindrical	
0.85	Sphere	
Super Case II	n>1.0	Slab
n>0.89	Cylindrical	
n>0.85	Sphere	

There are several simultaneous process considered in this model

(i) Diffusion of water in to core of matrix tablet.

(ii) Swellings of tablet as water penetrate.

(iii) Water penetrates in to tablet first and constant velocity.

(iv) Diffusion of Drug molecule from the core of the tablet depends on type of polymer used.

(v) Diffusion distance is proportional to the time.

(vi) Drug release in a one dimensional way.

(vii) The ratio of system length to thickness should be at least. To find out the exponent of 'n' the portion of the release curve, where $M_t/M_\infty < 0.6$ should only be used.

2.7 Hopfenberg model

This mathematical model based upon assumption is that the drug release from surface eroding polymer so surface area remains constant during the degrade process.Hopfenberg was analyzed release of drug from surface- eroding devices with several geometries and developed a general mathematical equation describe drug release from spheres, slabs and infinite cylinders displaying heterogeneous erosion. **.**The Cumulative fraction of released drug at time 't' was described by following equation and is valid for spheres, cylinder and slabs**.**

$$M_t/M_\infty = 1-[1-K_0t/C_0a_0]^n \quad (16)$$

Where M_t=Amount of drug released at time't'

M_∞=Cumulative amount of drug released at infinite time

K_0=Zero order or erosion rate constant

C_0=Initial concentration of drug in matrix

a_0 =Radius for a cylinder or slab or spheres

n= Shape factor or an exponent that varies with geometry n= 1, 2 and 3 for slab, cylindrical and spherical geometry respectively.

A modified form of equation (16) has been proposed by Arini and Luenberger deciphering the latency time (*l*) at the beginning of drug release from dosage form

$$M_t/M_\infty = 1-[1-K_0t/C_0a_0(t-1)]^n \quad (17)$$

Assumption of this model is that the rate-limiting step of drug release is the erosion of the matrix itself and that time dependent diffusional resistance internal or external to the eroding matrix do not influence it.

This model is used to identify the mechanisms of drug release from the optimized oil sphere using derived data from composite profile, which is essentially displayed the site specific biphasic release kinetics **[27, 28]**.

2.8 Baker-Lonsdale Model

Taking Huguchi model for basic assumption, Baker and Lonsdale developed a mathematical model for describing the drug release from spherical matrices by using the equation given below

$$f_l = \frac{3}{2}[1-(1-\frac{Mt}{M_\infty})^{2/3}]-\frac{Mt}{M_\infty} = \frac{3\ Dm\ Cms}{ro^2 C0} - t \quad (18)$$

Where M_t= Amount of drug release at time 't',M_∞=amount of drug release at infinite time,D_m is the diffusion coefficient,C_{ms} is the drug solubility in matrix,r_0 is the radius of the

spherical matrix and C_0 is the initial concentration of drug in the matrix.

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

$$f_1 = \frac{3}{2}[1-(1-\frac{Mt}{M_\infty})^{2/3}]-\frac{Mt}{M_\infty} = \frac{3\ Df\ Cfs\ \varepsilon}{ro^2 C0\ \tau} - t \quad (19)$$

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

$$\varepsilon=\varepsilon_0+KC_0 \quad (20)$$

Where ε_0 is the initial porosity and K is the drug specific volume. Considering the fact that if (ε_0) is small the above equation (20) can be rearranged as:

$$f_1 = \frac{3}{2}[1-(1-\frac{Mt}{M_\infty})^{2/3}]-\frac{Mt}{M_\infty} = \frac{3\ Df\ KCfs}{r\ \tau} - t \quad (21)$$

Again simplify the above equation (21), the Baker-Lonsdale equation can be rewrite as:

$$f_1=\frac{3}{2}[1-(1-\frac{Mt}{M_\infty})^{2/3}]-\frac{Mt}{M_\infty} = Kt \quad (22)$$

Where, K is the release constant and is corresponds to slop. This equation can be used for linearization of release data for many micro particle formulation including microcapsule and microsphere **[29, 30]**.

2.9 Gompertz model

The *in-vitro* Dissolution profile of pharmaceutical dosage forms is described by a simpler exponential model known as Gompertz model, expressed by the equation

$$X(t) = X_{max} \exp[-\propto e^{\beta \log t}] \quad (23)$$

Where X(t), is the percentage of drug release at time t divided by 100, X_{max} is the maximum dissolution, 'α' determine the un dissolved proportion at time t =1 and described as location or scale parameter, β is the dissolution rate per unit of time described as shape parameter. This model has steep increase in the beginning and converges slowly to the asymptotic maximal dissolution**.**

This model is used for comparing the release profile of drug having good solubility and intermediate release rate **[31]**.

2.10 Regression model

For a wide variety of formulation or pharmaceutical dosage forms a number of statistical optimization design have been used. In order to optimize the formulation from *in-vitro* dissolution study several type of regression analysis being used. Some important regression model are given below.

I. Linear or First order regression model:

This method is generally used for determine for parameter having a linear data system. This model can be described by the equation

relating to the response variable to the independent variables is

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 \quad (24)$$

Where Y represents the response, X_1 and X_2 represent the two independent variables. The parameter β_0 signifies the intercept of the plan. β_1 and β_2 called partial regression coefficients, where β_1 measure the expected change in 'Y',the response per unit change in X_1 when X_2 kept constant and *vice versa* for β_2. The above equation (24) can be rewritten in a general form as:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots\ldots \beta_k X_k \quad (25)$$

The above equation is a multiple regression equation with 'k' regression variables. The model can explain a hyper-plan in the k-dimensional space. By adding interaction terms to the first order linear model a complex model can be analyzed by using multiple linear regression technique **[32]**.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 \quad (26)$$

Where X_1 and X_2 are the interaction effects of two variables acting simultaneously

II.Quadratic model or second order regression model

The explanatory and response variable may be scalars of vector, in such case where both the explanatory and response variable are scalars, then the resulting regression is called simple linear regression. When more than one explanatory variable there, than the equation is known as multiple linear regression. In both cases general formulae are the same.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X^2_1 + \beta_{22} X^2_2 + \beta_{12} X_1 X_2 \quad (27)$$

If the, $X^2_1 = X_3$, $X^2_2 = X_4$, $X_1 X_2 = X_5$ and $\beta_{11} = \beta_3$, $\beta_{22} = \beta_4$, $\beta_{12} = \beta_5$, then above equation can be reduce to linear model. Model is linear if the (β) coefficients are linear, regardless of the shape of the response surface which is generates **[33]**. The above equation can be rewritten as:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 \quad (28)$$

III.Non-linear regression model

To obtain a more accurate regression various nonlinear regression techniques may be used.in nonlinear regression model the curve in scatter plot as well as curve in residual plot. There is no significant correlation between variable. Nonlinear regression arises when predictors and response follows particular function form. Sometimes the nonlinear problem can be convert to a linear domain by a suitable transformation. There are four transformations to induce linearity are logarithmic transformation, inverse transformation, square root transformation and square transformation.

3. Model independent methods

In recent year the FDA has given more emphasis on single point dissolution profile comparison between pre change and post change of product. Single- point dissolution test and specification is employed in evaluating scale-up and post approval changes (SUPAC) such as scale-up, manufacturing site change, change in component and composition, change in equipment and process etc. A changed product may also be lower strength of a previous approved drug product but the single-point dissolution test may adequate to ensure unchanged product quality and performance **[34]**. For major change in process the dissolution profile compression carried out by SUPAC-IR guidance. The SUPAC-IR (Scale up and post approval change) guidance recommends dissolution profile comparisons for approving changes in different level and documenting the product between the test (pre change) and reference (post change).A model independent method for comparison of two dissolution profile is based on determination of difference factor f_1 and similarity factor f_2 to compare dissolution profiles (Moore 1996).The difference factor f_1 calculates the percentage of difference between 2 curves at each time point and measurement of the relative error between two curves. Mathematically it can be expressed by :

$$f_1=\{ [\sum^{n}_{t=1} (R_t - T_t)] / [\sum^{n}_{t=1} R_t]\} \text{ x}100 \quad (29)$$

The Similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of similarity in the percentage dissolution between 2 curves[35]. Mathematically it can be expressed by:

$$f_2= 50 \log \{[1+ 1/n\sum^{n}_{t=1} (R_t - T_t)^2]^{-0.5} \text{ x } 100\} \quad (30)$$

Where

n= Number of dissolution time point

R_t= Dissolution value of the reference drug product at time t

T_t=Dissolution value of the test drug product at time t

Table 2: The interpreting f_1 and f_2 values are given below:

Difference factor f_1	Similarity factor f_2	Interference
0	**100**	**Dissolution profile are identical**
≤15	**≥50**	**Similarity or Equivalence of two profile**

For determination similarity between dissolution profiles following condition must follows:

- Three or more than three dissolution time point must be measured.

- Minimum drug product tested for dissolution is 12 for both test and reference.
- Not more than one mean value of > 85% dissolved for each product.
- Standard deviation of mean of any product should not be more than 10% from second to last dissolution point.

This model independent method is suitable to compare dissolution profile when more than three dissolution points are available **[36]**.

CONCLUSIONS:

These reviews represent that kinetic model play vital role in the interpretation of mechanism of drug release from a dosage form. From this study it is found that these dissolution mathematical models are necessary to study the release mechanism of drug from the dosage form, as it describes the pattern of release of drug mathematically. The drug transport inside pharmaceutical system and its release sometimes involve multiple steps provoked by different physical or chemical phenomenon making it difficult to get a mathematical model describing in the correct way. It is prove from the pharmaceutical literature that not a single kinetic model is widely accepted to determine if dissolution profile are similar. The model dependent method and statistical method are more complicated as compared to model independent method.

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