e-Disso

QUARTERLY NEWSLETTER

SPDS — Society for Pharmaceutical Dissolution Science

Society for Pharmaceutical Dissolution Science was formed on 16th July 2012 in Mumbai with the objective of promoting science and technological development in the field of dissolution among pharmaceutical professionals, academia, students, regulatory bodies, etc.

SPDS is the only professional body dedicated to Dissolution and its application worldwide.

Vision :

To be one of the most prominent professional body focusing on Dissolution Science among the Pharmaceutical Industry and Academia

Mission :

To dissipate science & advancement taking place in the field of dissolution related to clinical application and methods.

(2)

Dear Readers

It is pleasure again to present second issue of eDisso. In the first issue, we had stalwarts writing for the delight of readers. Drs. Vinod Shah and Umesh Banakar were torch bearer for eDisso. Well begun for us and all. Now is to carry on the responsibilities ahead and with emphasis on quality.

There are going to several focus areas to be covered in the coming issues. In addition we welcome questions from readers. Experts on advisory board and international scientific advisors will be more than happy to address them

In the current issue we have Dr. Smita Nayak's article on various equations and models used for development and assessment of pharmaceutical dosage forms. Dr. Rita Lala has written concise article on IVIVC as surrogate tool for assessing bioequivalence.

We invite voluntary participation from academicians, pharmaceutical scientists and analysts and chemists to participate in forth coming issues.

Happy reading

Best wishes
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METHODOLOGIES FOR EVALUATION OF IN-VITRO DISSOLUTION DATA

Abstract:

The Pharmaceutical Industry and the Regulatory Authorities nowadays stress on in-vitro drug dissolution studies as a key parameter for assuring the therapeutic efficacy of the drug. The quantitative analysis of the values obtained in dissolution/release rate is easier when mathematical formulae are used to describe the process. In this paper we review the mathematical models used to determine the kinetics of drug release from drug delivery systems. Mathematical modelling can ultimately help to optimize the design of a therapeutic device by yielding information on the efficacy of various delivery systems by fitting them to various models thus allowing comparison of data generated by carrying out dissolution testing.

Keywords: Dissolution, biphasic release kinetics, bioequivalence interval, Rescigno index,

Dissolution of the drug in biological fluids is an important prerequisite for its absorption and subsequent action. Hence dissolution testing of formulations is a routine quality control procedure and is laid down by various Pharmacopoeias in the form of general monographs and specific drug product monographs. However, in case of conventional products, the monographs focus on a single point evaluation. During formulation development, there is a need for generation of dissolution profile of the drug due to the unique nature of the formulation under development, physicochemical characteristics of the drug and the physiological variables. Due to these factors, the kinetics of drug release varies vastly and needs to be evaluated. Depending on the nature of the formulation (for example: conventional, immediate release, fast release, modified release, sustained release, buccal, sublingual, rectal or transdermal), type of equipment used as well as selection of media, agitation conditions etc. can be varied to design methodologies unique to the product under development. Detailed dissolution techniques are available in literature and can be used as guidelines for developing these methods.

However interpretation of data requires its application to various kinetic models. The different kinetic models that can be fitted to dissolution data generated by carrying out dissolution studies are briefly reviewed here. The kinetic models help in comparing different formulations, correlating *in vitro* data with extent of *in vivo* bioavailability, and are a useful aid in justifying the role of excipients in novel drug delivery systems. They also provide additional data for applications for biowaivers for different strengths of the same drug.

MODEL DEPENDENT METHODS

Model dependent methods for analyzing dissolution profile are based on different mathematical functions. Once a suitable function has been selected, the dissolution profiles are evaluated depending on the derived model parameters. The model dependent approaches include Zero order, First order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas, Baker-Lonsdale, Weibull, Hopfenberg, Gompertz and regression models and are discussed in brief herewith.

1. Zero order model:

Ideal delivery of drugs would follow "zero order kinetics", wherein blood levels of drugs would remain constant throughout the delivery period. This ideal delivery is particularly important in certain classes of medicines intended, for example, for antibiotic delivery, heart and blood pressure maintenance, pain control and antidepressants. Consequently, there has been substantial activity by scientists searching for improved methods of achieving both controlled and sustained delivery of drugs[1].

Drug dissolution from such dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Q_0 - Qt = K_0 t$$

Rearrangement of the above equation yields:

$$Q_0 - Qt = K_0 t$$

Where Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and K_0 is the zero order release constant expressed in units of concentration/time.

To study the release kinetics as per this mechanism, data obtained from *in vitro* drug release studies was plotted as % cumulative amount of drug released versus time[2,3].

Application: This relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low solubility drugs in coated forms, osmotic systems, etc.[4,5].

2. First order model:

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to

conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by the equation:

$$\log C = \log c_0 - Kt / 2.303$$

where C_0 is the initial concentration of drug, K is the first order rate constant and t is the time[6]. The dissolution data obtained is plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of $-K/2.303$.

Application: This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices[7,8].

3. Higuchi Model:

The first example of a mathematical model aimed to describe drug release from a matrix system was proposed by Higuchi in 1961[9]. Initially conceived for planar systems, it was then extended to different geometries and porous systems[10].

This model is based on the hypotheses that (1) initial drug concentration in the matrix is much higher than drug solubility; (2) drug diffusion takes place only in one dimension (edge effect must be negligible); (3) drug particles are much smaller than system thickness; (4) matrix swelling and dissolution are negligible; (5) drug diffusivity is constant; and (6) perfect sink conditions are always attained in the release environment.

In a general way it is possible to simplify the Higuchi model as (generally known as the simplified Higuchi model):

$$F_t = Q = K_h \times t^{1/2}$$

where, K_H is the Higuchi dissolution constant, Q is the amount of drug released in time t per unit area A.

Based on the above equation, the data obtained was plotted as cumulative percentage drug release versus square root of time[11].

Application: This relationship can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs[9,10,12].

4. Hixson-Crowell Model:

Hixson and Crowell (1931) postulated that the surface area of particles is proportional to the cubic root of its volume. They derived an equation:

$$W0^{1/3} - Wt^{1/3} = k\,t$$

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. The equation describes the release from systems where there is a change in surface area and diameter of particles or tablets with time[13]. To study the release kinetics, data obtained from in vitro drug release studies was plotted as cube root of drug percentage remaining in matrix versus time.

Application: This expression applies to pharmaceutical dosage form 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[14].

5. Korsmeyer-Peppas Model:

Korsmeyer et al. (1983) derived a simple relationship which described drug release from a polymeric system equation which is given below.

To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer-Peppas model[15].

$$M_t / M_\infty = Kt^n$$

where M_t / M_∞ is a fraction of drug released at time t, K is the release rate constant and n is the release exponent. The n value is used to characterize different release for cylindrical shaped matrices.

In this model, the value of *n* characterizes the release mechanism of drug as described in Table 1.

Table 1. Interpretation of diffusional release mechanisms from polymeric films

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

In case of cylindrical tablets, $0.45 \leq n$ 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[16],[17]. To find out the exponent of n the portion of the release curve, where $M_t/M_\infty < 0.6$ should only be used.

The advantage of this model is that several simultaneous processes are considered. These include:
• Diffusion of water into the tablet.
• Swelling of the tablet as water enters.
• Formation of gel.
• Diffusion of drug and filler out of the tablet.
• Dissolution of the polymer matrix.

Key attributes of the model include:
• Tablet geometry is assumed to be cylindrical.
• Water and drug diffusion coefficients vary as functions of water concentration.
• Polymer dissolution is incorporated.
• Change in tablet volume is considered.

To study the release kinetics, data obtained from in vitro drug release studies was plotted as log cumulative percentage drug released versus log time[1].

Application: This model is generally used to analyse the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved[18]. Dissolution data of most of the dosage forms can be fitted to the Korsmeyer Peppas equation.

6. Baker-Lonsdale Model:

This model was developed by Baker and Lonsdale (1974) from the Higuchi model and described the drug release from spherical matrices according to the equation:

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

where the release rate constant, k, corresponds to the slope[19].

To study the release kinetics, data obtained from in vitro drug release studies were plotted as $[d(M_t/M_\infty)]/dt$ with respect to the root of time inverse.

Application: This equation has been used for linearization of release data from several formulations of microcapsules or microspheres[20],[21].

7. Weibull Model:

This model has been fitted to different dissolution processes. It is expressed by the equation[22,23]:

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

In this equation, M is the amount of drug dissolved as a function of time t. M_0 is total amount of drug released. T accounts for the lag time as a result of the dissolution process. Parameter a denotes a scale parameter that describes the time dependence, while b describes the shape of the dissolution curve progression. For $b = 1$, the shape of the curve corresponds exactly to the shape of an exponential profile with the constant $k = 1/a$. The equation then gets modified to

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

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 $b = 1$.

Application: The Weibull model is more useful for comparing the release profiles of matrix type drug delivery[24,25].

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[26,27]. The cumulative fraction of drug released at time t was described as:

$$M_t/M_\infty = 1 - [1 - k_0 t/C_L a]^n$$

where k_0 is the zero order rate constant describing the polymer degradation (surface erosion) process, C_L is the initial drug loading throughout 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.

Application: This model is used to identify the mechanism of release from the optimized oilispheres using data derived from the composite profile, which essentially displayed site-specific biphasic release kinetics[28].

9. Gompertz Model:

The in-vitro dissolution profile is often described by a simpler exponential model known as Gompertz model, expressed by the equation:

$$M_t/M_\infty = 1 - [1 - k_0 t/C_L a]^n$$

where $X(t)$ = percent dissolved at time t divided by 100; X_{max} = maximum dissolution; α determines the undissolved proportion at time t and described as location or scale parameter; β = dissolution rate per unit of time described as shape parameter. This model has a steep increase in the beginning and converges slowly to the asymptotic maximal dissolution[17,29].

Application: The Gompertz model is more useful for comparing the release profiles of drugs having good solubility and intermediate release rate[29].

10. Regression Model:

Statistical optimization designs have been previously documented for the formulation of many pharmaceutical dosage forms[30]. Several types of regression analysis are used to optimize the formulation from in vitro release study[20].

Linear or first order regression model[31-33].

Linear regression is a method for determining the parameters of a linear system. The empirical model relating the response variable to the independent variables are described by the following equation:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2$$

where Y represents the response, X_1 and X_2 represent the two independent variables. The parameter β_0 signifies the intercept of the plane. β_1 and β_2, called partial regression coefficients, where β_1 measures 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 can be rewritten in a general form as:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots \ldots \beta_k X_k$$

The model is a multiple linear regression model with 'k' regression variables. The model describes a hyperplane in the k-dimensional space.

Further complex model given below are often analyzed by multiple linear regression technique by adding interaction terms to the first order linear model:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1$$

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

Quadratic model or second order regression model[34-36]

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{12} X_1 X_2$$

If we put, $X_{21} = X_3$, $X_{22} = X_4$, $X_1 X_2 = X_5$ and $\beta_{11} = \beta_3$, $\beta_{22} = \beta_4$, $\beta_{12} = \beta_5$, then the above equation is reduced to a linear model. Any model is linear if the (β) coefficients are linear, regardless of the shape of the response surface that it generates.

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

The explanatory and response variables may be scalars of vectors. In the case, where both the explanatory and response variables are scalars, then the resulting regression is called simple linear regression. When there are more than one explanatory variable, then the resulting regression is called multiple linear regression. It should be noted that the general formulae are the same for both cases. The least squares and robust regression analysis are mostly used to solve linear regression models.

Non linear regression models[37,38].

A number of nonlinear regression techniques may be used to obtain a more accurate regression. Due to the large number of dissolution media available for solid dosage forms, a statistical method to choose the appropriate medium is critical for testing solid dosage forms. It should be noted that an often used alternative is a transformation of the variables such that the relationship of the transformed variables is again linear. The method was designed using software to detect factors contributing to differences in the dissolution process of the drug delivered in dosage form.

11. Other Release Parameteres :

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

The dissolution efficiency (DE) of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the release described by 100% dissolution in the same time. It is can be calculated by the following equation[39]:

$$D.E = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\%$$

Where y is the drug percent dissolved at time t.

STATISTICAL EVALUATION OF DATA[40]

After the data has been collected, statistical methods must be applied to determine the level of significance of any observed difference in the rate and/or extent of absorption in order to establish bioequivalence between two or more drug products. The commonly adopted approaches to determine statistical differences are –

1) **Analysis Of Variance** (ANOVA) is a statistical procedure used to test the data for differences within and between treatment and control groups. A statistical difference between the pharmacokinetic parameters obtained from two or more drug products is considered statistically significant if there is a probability of less than 1 in 20 or 0.05 ($p \leq 0.05$). The probability **p** is used to indicate the level of statistical significance. If $p \leq 0.05$, the differences between the two drug products are not considered statistically significant.

2) **Confidence Interval Approach-** Also called as two one- sided test procedure it is used to demonstrate if the bioavailability from the test procedure is too low or high in comparison to the reference product. The 90% confidence limits are estimated for the sample means based on Student's t distribution of data. A 90% confidence interval about the ratio of means of the two drug products must be within ± 20% for bioavailability parameters such as AUC or C_{max} i.e the difference between the bioavailabilities of the test product should not be greater than ± 20% of the average of reference product (between 80 and 120%). When log transformed data are used, the 90% confidence interval is set at 80-120%. These confidence limits are also termed as bioequivalence interval.

MODEL INDEPENDENT METHODS

Model-independent methods can be further differentiated as ratio tests and pair-wise procedures. The ratio tests are relations between parameters obtained from the release assay of the reference formulation and the release assay of the test product at the same time and can go from a simple ratio of percent dissolved drug (t) to a ratio of area under the release curve (AUC) or even to a ratio of mean dissolution time (MDT). The mean dissolution time can be calculated by the following expression:

$$MDT = \frac{\sum_{j=1}^n \widehat{t_j} \Delta M_j}{\sum_{j=1}^n \Delta M_j}$$

where j is the sample number, n is the number of dissolution sample times, t_j is the time at midpoint between t_j and t_{j-1} (easily calculated with the expression $((t_j + t_{j-1})/2)$ and ΔM_i is the additional amount of drug dissolved between t_j and t_{j-1}.

The pair-wise procedures includes the difference factor, similarity factor and the Rescigno index.

The difference factor (f_1) measures the percent error between two curves over all time points:

$$f_1 = \frac{\sum_{j=1}^n |R_j - T_j|}{\sum_{j=1}^n R_j} \times 100$$

where n is the sampling number, R_j and T_j are the percent dissolved of the reference and test products at each time point j. The percent error is zero when the test and drug reference profiles are identical and increase proportionally with the dissimilarity between the two dissolution profiles. The above equation can only be applied if the average difference between R and T is less than 100. If this difference is higher than 100 normalisation of the data is required.

The similarity factor (f_2) is a logarithmic transformation of the sum-squared error of differences between the test T_j and reference products R_j over all time points:

$$f_2 = 50 \times \log\left\{\left[1 + (1/n)\sum_{j=1}^n w_j |R_j - T_j|^2\right]^{-0.5} \times 100\right\}$$

Where w_j is an optional weight factor. The similarity factor fits the result between 0 and 100. It is 100 when the test and reference profiles are identical and tends to 0 as the dissimilarity increases. This method can be used for dissolution profile comparisons when more than three or four dissolution time points are available. In addition, it is used to compare the dissolution treatment effect when 12 individual dosage units are tested.

In order to consider the similar dissolution profiles, the f_1 values should be close to 0 and values f_2 should be close to 100. In general, f1 values lower than 15 (0-15) and f_2 values higher than 50 (50-100) show the similarity of the dissolution profiles[41].

Rescigno proposed a bioequivalence index to measure the dissimilarity between a reference and a test product based on plasma concentration as a function of time. This Rescigno index E1 can also be used based on drug dissolution concentrations:

$$\xi_i = \left\{ \frac{\int_0^\infty |d_R(t) - d_T(t)|^i \, dt}{\int_0^\infty |d_R(t) + d_T(t)|^i \, dt} \right\}^{1/i}$$

where $d_R(t)$ is the reference product dissolved amount, $d_T(t)$ is the amount of test product dissolved at each sample time point and i is any positive integer number. This adimensional, index always presents values between 0 and 1 inclusive, and measures the differences between two dissolution profiles. This index is 0 when the two release profiles are identical and 1 when the drug from either the test or the reference formulation is not released at all. By increasing the value of i, more weight will be given to the magnitude of the change in concentration, than to the duration of that change[42].

CONCLUSION

Drug transport from inside pharmaceutical systems to external environment 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 models best describing drug release phenomena are, in general, the Higuchi model, Zero order model, Weibull model and Korsemeyer-Peppas model. The Higuchi and Zero order models represent two limit cases in the transport and the drug release phenomena, while Korsemeyer-Peppas model can be a decision parameter between these two models. The Higuchi model has a large application in polymeric matrix systems, whereas the Zero order model becomes ideal to describe coated dosage forms or membrane controlled dosage forms.

To characterize drug release profile it is also possible to use other parameters such as $t_{x\%}$, sampling time (a very used parameter by the generality of the Pharmacopoeias) and dissolution efficiency. As it has been said, the information obtained from these parameters to the knowledge of the release mechanism is a very limited one, and these parameters should be used associated between themselves or associated to some of the referred models.

The pair-wise procedures, like Difference factor (f_1), Similarity factor (f_2) and Rescigno index also suffer from the same problem referred to above. Besides, these parameters are used to compare the release profiles of two different formulations, being necessary to consider one of them as the reference formulation. These pair-wise procedures reflect only the major or minor similarities between these two profiles, and can be considered as a good tool to judge its dissolution equivalence.

In the absence of a single model to define the release characteristic of the drug from the formulation, various models are fitted to the data and best fit model is selected.

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Abstract

In vitro in vivo correlations (IVIVC) play an important role in the development of pharmaceutical dosage forms. It facilitates the rationale for the development and modification of processes, evaluation of immediate release and modified release formulations, and acts as a tool for formulation screening, setting dissolution specifications and as a surrogate for in vivo bioavailability studies. It controls the quality of the product during scale up of the batch and facilitates post approval changes. It significantly reduces the number of human studies during development of new formulations and supports biowaivers. This article specifically reviews the purpose of IVIVC, the levels of IVIVC and discusses its pharmaceutical applications.

Introduction

IVIVC is today considered a key concept in drug development and optimization of formulations. Optimised formulations require modifications in composition, equipment, batch sizes and manufacturing processes. If such type of one or more changes are applied to the formulation, the in vivo bioequivalence studies in humans may need to be done to confirm the performance of the new formulation with old one. Thus, in the development of new pharmaceuticals IVIVC can be used to reduce the number of human studies during the formulation development. Hence, the main objective of an IVIVC is to serve as a surrogate for in vivo bioavailability studies and to support biowaivers (in vivo bioavailability and/or bioequivalence studies may be waived i.e. not considered necessary for product approval) [1]. Instead of conducting expensive and time consuming in vivo studies, a dissolution test could be adopted as the surrogate to decide as to whether the two pharmaceutical products are equivalent [2].

IVIVC is a mathematical relationship between in vitro properties of a dosage form with its in vivo performance. The in vitro release data of a dosage form containing the active substance serves as characteristic in vitro property, while the in vivo performance is indicated by the time course of plasma concentrations of the active substance. These in vitro and in vivo data are then correlated to each other using scientific and statistical techniques . A linear or nonlinear correlation is used to express the relationship between the in vitro and in vivo characteristics mathematically [3].

IVIVC definitions

As defined by United State Pharmacopoeia (USP):
The establishment of a rational relationship between a biological property, or a parameter derived from a biological property produced by a dosage form, and a physicochemical property or characteristic of the same dosage form [4].

As defined by Food and drug administration (FDA):

IVIVC has been defined by the Food and Drug Administration (FDA) as "a predictive mathematical model describing the relationship between an in-vitro property of a dosage form and a relevant in-vivo response". Generally, the in vitro property is the rate or extent of drug dissolution or release while the in vivo response is the plasma drug concentration or amount of drug absorbed [5].

Purpose of IVIVC

IVIVC offers the following benefits:

1. Reduction of regulatory burden concerned with in vivo experiments under certain conditions
2. Prove the validity of a new optimised formulation, which is bioequivalent with the target formulation
3. Adequate justification for therapeutic product quality
4. Justification for a biowaiver in filing of a Level 3 (or Type II in Europe) variation, either during scale up or post approval, as well as for line extensions (e.g. different dosage strengths).
5. Time and cost saving by utilising IVIVC as surrogate for in vivo bioequivalence [3].

Levels of IVIVC

There are five levels of IVIVC that have been mentioned in the FDA guidance for industry, which includes Levels A, B, C, multiple C and D. The various parameters considered in IVIVC depend on the Levels which are shown in the table below:

Table : Various parameters used in IVIVC depending on the Level [6]

Level	*In vitro*	*In vivo*
A	Dissolution curve	Input (absorption) curves
B	Statistical moments: mean dissolution time (MDT)	Statistical moments: mean residence time (MRT), mean absorption time (MAT)
C	Disintegration time, time when 10%, 50%, 90% is dissolved, dissolution rate, dissolution efficiency (DE)	Maximum observed plasma concentration(C_{max}), at time (T_{max}), absorption constant (K_a), Time when 10, 50, 90% is absorbed, AUC (total or cumulative)

Multiple Levels C

A multiple Level C correlation relates one or several pharmacokinetic parameters of interest to the amount of drug dissolved at several time points of the dissolution profile [6].

Level D

Level D correlation is a rank order and qualitative analysis and is not considered useful for regulatory purposes. It is not a formal correlation but serves as an aid in the development of a formulation or processing procedure [1].

Applications of IVIVC in drug delivery

1. **Early stages of drug delivery technology development: Proof-of-concept**

   A drug candidate selection is the most crucial phase in the life cycle of drug development. During this step, exploring the relationship between *in vitro* and *in vivo* properties of the drug in animal models gives an idea of the feasibility of the drug delivery system for a given drug candidate [7].

2. **IVIVC and Parenteral drug delivery**

   IVIVC can be developed and applied also to parenteral dosage forms, such as controlled release, particulate systems, implants, etc, which are either injected or implanted. However, the chances of success are fewer in the development of IVIVC for such dosage forms [8].

3. **Formulation assessment:** *in vitro* **dissolution**

   A suitable dissolution method which is capable of distinguishing the performance of formulations with different release rates *in vitro* and *in vivo* is an important key factor in the development of a product. IVIVC facilitates the process of such method development [9].

4. **Dissolution specifications**

   The FDA guidance describes the dissolution specifications in cases of level A, multiple level C, level C co-relations, and, where there is no IVIV co-relation.

   For level A: a minimum of three time points is recommended to establish the specifications. These time points should cover the early, middle and late stages of the dissolution profile. The last time point should be the time point where at least 80% of drug has dissolved. If the maximum amount dissolved is less than 80%, then the last time point should be the time where the plateau of the dissolution profile has been reached. After the IVIVC has been developed, it is used to set specifications in such way that the fastest and slowest release rates as presented by the upper and lower dissolution specifications results in a difference in the maximum predicted plasma concentration and AUC of not more than 20%.

   For Multiple Level C: the specifications at each time point are such that there is a maximal difference of 20% in the predicted C_{max} and AUC. Additionally, the last time point should be the time point where at least 80% of drug has dissolved.

   For Level C: Based on Single Time Point - It may be used to establish the specification such that there is not more than a 20% difference in the predicted AUC and C_{max}. At other time points, the maximum recommended range at any dissolution time point specification should be ± 10% of label claim deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. Reasonable deviations from ± 10% may be acceptable if the range at any time point does not exceed 25%.

   Without an IVIV co-relation : The recommended range at any dissolution time point specification is ± 10% deviation from the mean dissolution profile obtained from the clinical/bioavailability lots [10].

5. **Future biowaivers**

   Frequently, drug development requires modifications in formulations due to a variety of reasons, such as unpredicted problems in stability and development, inadequately superior materials, poor processing results, etc. Having an established IVIVC can facilitate and evade bioequivalence studies by using the dissolution profile from the modified formulation and subsequently predicting the *in vivo* concentration-time profile. This predicted profile could perform as a surrogate for *in vivo* bioequivalence studies [8].

Conclusion

The process of new formulation development is time-consuming and the expenditure on product development is high. IVIVC is a tool which can be used at various stages and areas in the development of dosage forms; that can be accepted by regulatory bodies of the world. It can serve as a surrogate to the *in vivo* bioavailability studies and supports biowaiviers. It allows setting the dissolution media, method and specifications in dissolution studies. IVIVC can be used in early stages of drug development as proof of concept. IVIVC principles and guidelines are applicable to oral drug delivery and there is need to develop the guidelines for non-oral delivery, inhaled medicines and dermatological medicaments which concentrate on permeation and dissolution methods.

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UPCOMING COURSES

- **COURSE V**
  QbD in Dissolution Method Development:
  QTTP, Critical Method Attributes,
  Discriminatory Method.
  DOE's, Method Finalization
  - **Course Director:**
    - Mr. Vijay Kshirsagar, CEO & Director, TRAC Consulting, Mumbai

- **COURSE VI**
  IVIVC, BIOWAIVERS AND CLINICAL APPLICATIONS OF IVIVC
  - **Course Director:**
    - Umesh V. Banakar Ph.D., Professor and President, Banakar Consulting Services, USA

OTHER EVENTS

Disso India - Ahmedabad 2016
26th & 27th July, 2016 at Ahmedabad

Disso Europe - Romania 2016
20th & 21st October, 2016 at Bucharest

Disso America 2017
21st & 22nd June, 2016

Poster Abstract : Fabrication and Evaluation of Apparatus for Simultaneous Dissolution and Permeation studies-A feasibility study

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Key Words: In vitro Dissolution-permeation, Permeation, Diltiazem, Ketoprofen, Hydrochlorothiazide

Introduction:

Oral administration is one of the most convenient and practical route of administration, from the point of view of both the patient and the manufacturer. Good oral bioavailability occurs when the drug has maximum solubility/dissolution in the g.i. fluids and good permeability through the intestinal mucosal membrane. The extent of absorption of drug in vivo thus, could be predicted based on permeability and solubility measurements. Stephan A. Motz has reported the simultaneous dissolution and permeation of dosage form by coupling Type IV dissolution apparatus with CaCO-2 permeation cell; such equipments would be useful in - screening of new API and innovative formulations to detect if any of the excipients interact with intestinal epithelia and alter the absorption of various drugs.

Objective:

In present research work, an attempt has been made to fabricate a simple Dissolution-Permeation Apparatus, wherein a modified permeation cell has been combined with the USP Type IV dissolution apparatus (Flow though cell), for simultaneous dissolution and permeation evaluation of oral drugs and formulations.

General Features Of The Apparatus:

The apparatus (Figs 1A & B) consists of: 1)Dissolution unit, and 2) Permeation unit. The Dissolution unit consists of the USP apparatus 4 (flow through cell, Sotax, Germany) equipped with a 12 mm dissolution cell (C). The Permeation unit is subdivided into two compartments: Donor compartment (D) and Receiver compartment (R) with an intestinal membrane segment or other suitable membrane (M) mounted between these both compartments.
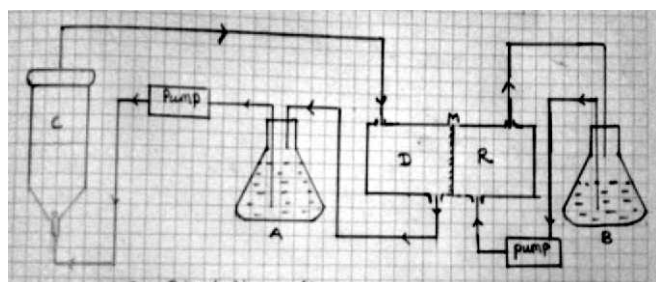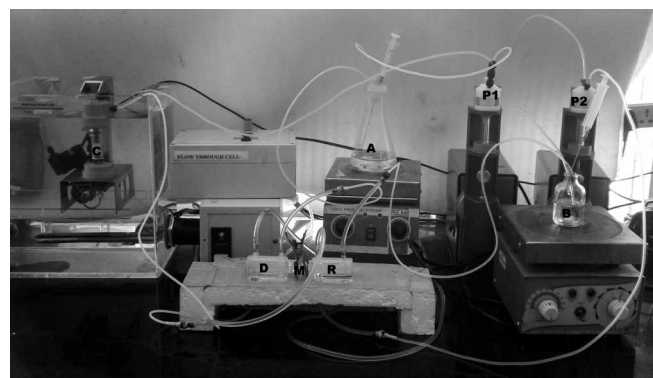

Fig 1A Schematic Diagram

Fig 1B Fabricated Apparatus

Dissolution-Permeation Apparatus
(C =Flow through cell (12mm), A = Dissolution media reservoir, B = Permeation media reservoir, D = Donor Compartment, R = Receiver compartment M = Intestinal membrane segment)

Working Principle:

- A Pump P1 continuous circulates medium for dissolution (mimics gi fluids) from reservoir A to flow through cell C to donor compartment D.
- As the medium moves through D, based on permeability, dissolved drug will permeate through membrane (M) to the receptor compartment R, where there is a constant circulation of permeation medium by pump P2 from reservoir B.(mimics Blood compartment).
- With periodic sampling from A (dissolved drug) and B (permeated drug), we can calculate amount of drug dissolved and permeated and thereby simultaneous assessment of dissolution and permeation is possible.

Experimental :

In vitro Dissolution-Permeation studies:

The *in vitro* dissolution-permeation studies were carried out in triplicate, on 30 mg drugs belonging different BCS Class, viz Diltiazem (DLTZ)) (BCS Class 1), Ketoprofen (KTF) (BCS Class 2) and Hydrochlorothiazide (HTZ) (BCS Class 3) using the fabricated dissolution– permeation apparatus

Medium and conditions:

Medium and conditions:

Dissolution Medium :- 100 ml Kreb-Ringer Buffer solution pH 7.4; Permeation Medium :- 50 ml Kreb-Ringer Buffer solution pH 7.4; Temp :- 37±0.5˚C; Glass beads :- 4 gm; Flow rate :- 4ml/min; Filters used :- GF-D and GF-F

Results :

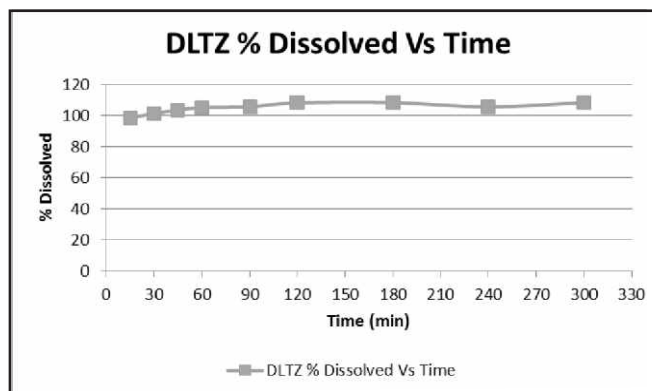Dissolution and permeation plots of drugs are depicted in Fig 2 (A-D)
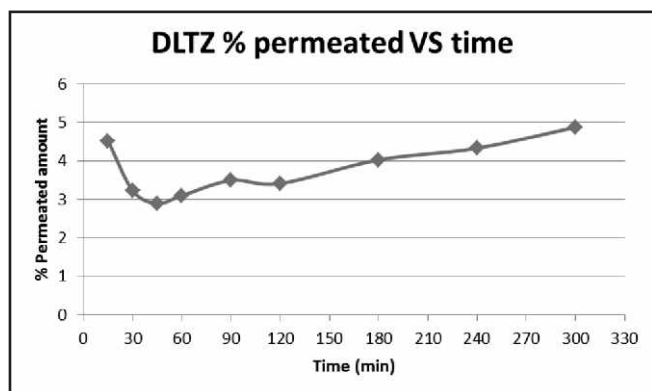

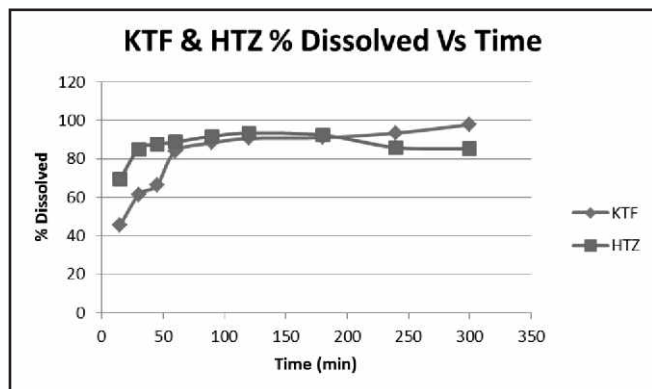**Fig 2 A Dltz Dissolution Plot**

Fig 2 B Dltz Permeation Plot

Fig 2 C KTF & HTZ Dissolution plot
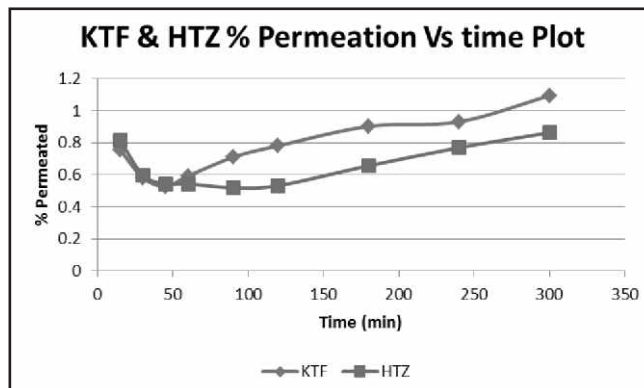
Fig 2 D KTF & HTZ Permeation Plot

Dissolution and Permeation plots :

It was observed that depending upon class of each drug, its dissolution and permeation curves varied (Fig 2); percent dissolution of the drugs in about 30 min was found to be 100%, 61% and 85% for DLTZ, KTF and HTZ respectively, which are in accordance to solubility characteristics. % permeability of the same drugs in about 120 min was found to be 3.4 %, 0.78% and 0.53% for DLTZ, KTF, and HTZ respectively which again are indicative of permeability characteristics.

Conclusion:

With these preliminary studies using only API it can be concluded that the fabricated instrument is simple, and capable of distinguishing simultaneously dissolution and permeation characteristics. However, further studies are necessary with different drugs as well as their formulations and further improvements in the instrument are also being explored.

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P001-Lyophilization Monophase Solution Technique for Improvement of the Solubility and Dissolution of Piroxicam

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Introduction:-

Piroxicam, an anti-inflammatory drug, exhibits poor water solubility, dissolution and flow properties [1]. The aim of the present study was to improve the solubility and dissolution rate of Piroxicam by preparing crystals using the freeze drying technique, and employing solvents DMF and chloroform. [2].

Key words: - Piroxicam, Lyophilization monophase solution, Direct compression tablets, freeze dried crystal

Experimental Methods:-

Preparation of freeze dried crystals of Piroxicam : Piroxicam (2.5g) was dissolved in 25 ml of is DMF heated at 45^0 until a clear solution was obtained. The drug solution was poured in to 68 ml solvent mixture consisting of water and chloroform (7ml) maintained at room temperature. The resulting solution was shifted to 100 ml glass bottle and then transferred to and maintained in an ultra low freezer at - 40 ^{0}C for 24 hr. The frozen drug solution was placed in a lyophilizer for 72 hr (IISHIN Lab. Co. Ltd. Korea), with a condenser temperature of - 40^0C and a pressure of 7×10^{-2} mbar followed by a secondary drying at 25 ^{0}C for 24 hr. The resulting crystals were stored in desiccators at room temperature until further experiment.

Recrystallized Piroxicam:-Recrystallized sample of Piroxicam was prepared by using Piroxicam and various solvent compositions with occasional shaking with glass rod to find out the impact of solvents and process on Piroxicam.

Determination of residual solvents in Freeze dried crystals by gas:- GC studies were carried out on SHIMADZU model 2014 gas chromatograph.

Characterization of freeze dried crystals:-Freeze dried crystals were characterized by Differential scanning calorimetry, Fourier transform infrared spectroscopy, X-Ray Diffraction, and Scanning electron microscope.

Solubility studies:-The solubility of freeze dried crystals in distilled water was determined by taking excess quantity of freeze dried crystals. The vials were shaken for 24 hours on mechanical shaker (Presto Testing Instruments, Mumbai) and the drug concentration was determined spectrophotometrically at 332 nm.

Dissolution studies of agglomerates:-The dissolution of Piroxicam pure sample, freeze dried crystals and recrystallized sample was determined by using USP dissolution apparatus Type II (Electro Lab, Mumbai). Dissolution medium was 900 ml of Phosphate buffer (pH 7.4). The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 332 nm.

Determination of the physical stability:-To determine the physical stability of freeze dried crystals, they were packed in suitable packaging (sample were kept in 10 ml transparent glass bottle and covered by aluminum foil) and placed in a stability chamber maintained at 40^0C and 75% relative humidity (RH) for 90 days.

Preparation of tablets:-Piroxicam tablets containing different crystals were prepared by direct compression with directly compressible tablet excipients using Single Rotary Tablet Punching Machine (Riddhi Pharma Machinery Limited, Mumbai).

Results and Discussion:-

The solvent system involved in preparation of freeze dried crystals was DMF, chloroform and water in ratio of (25:7:25). The selection of these solvents was based on the miscibility of the each of the solvents and the solubility of Piroxicam in individual solvent.The resulting crystals were small in size, and were found to be free flowing compared to commercial Piroxicam. The % yield found to be in the range of 60-80% and drug content was in the range of 97-99%. Gas chromatography results confirmed that there were 3.8 and 2.4 ppm residual of DMF and chloroform present in the freeze dried crystals respectively, which was much lower than the permitted limits i.e. 880 & 60 ppm respectively.The DSC thermograms showed a sharp endothermic peak for all the Piroxicam crystals. This one step melt is due to only one crystal form (Triclinic) of the Piroxicam formed during the crystallization process.

Specific changes in IR spectra are not very clear, could be due to variations in the resonance structure, rotation of a part of a molecule or certain bonds. Alteration could be due to minor

distortion of bond angles, or even a result of the presence of a solvent of crystallization.

The characteristic peak of the Piroxicam appeared in the 2θ range of 0–60°. All the prepared crystals of Piroxicam showed similar peak positions (2θ) in X-ray diffraction.(Fig 1)
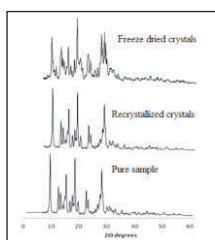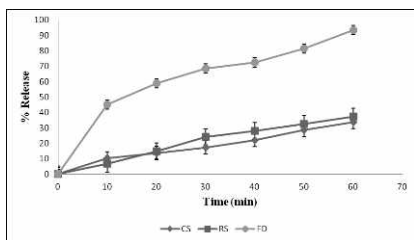

Fig.1:X-ray diffraction spectra of Piroxicam Samples

Fig. 2: Dissolution of different Piroxicam Crystals

In SEM study showed that crystals of pure sample are of the smallest size (5-10 μm) and they have irregular shapes. Recrystallization crystals were of intermediate size (7-18 μm) and appeared rod like. The freeze dried crystals were formed by microcrystalline precipitates, with a smooth surface and average (particle size of around 365 nm). Freeze dried crystals showed increased solubility compared to the **commercial piroxicam** in distilled water **which was more than ten folds**

(0.0924 mg/ml) than commercial piroxicam (0.0084 mg/ml), and dissolution rate was increased four fold; also, the dissolution rate of tablets prepared from freeze dried crystals showed marked improvement in dissolution rate. Stability studies indicated that the freeze dried crystals of Piroxicam were stable for 90 days.

Conclusion:-
Freeze dried crystals of Piroxicam were found to possess decreased crystallinity and improved mechanical properties, enhanced solubility, were safe in terms of solvent residuals, and the dissolution of tablets containing freeze dried Piroxicam showed improved release compared to tablets containing pure sample. In conclusion, freeze drying technique can be used for Piroxicam to enhance the solubility and to achieve better dissolution from tablets prepared by direct compression.

Acknowledgements
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