



A REVIEW ARTICLE ON STATISTICAL COMPARISON OF DISSOLUTION PROFILE

Asla C. K.*, Rashidah K. Ansari¹, Dr. Nishad K. M.¹, Dr. Shijikumar P. S.² and Dr. Sirajudheen M. K.¹

¹Department of Pharmaceutics, Jamia Salafiya Pharmacy College, Pulikkal, Malappuram, India, 673637.

²Department of Pharmaceutical Analysis, Jamia Salafiya Pharmacy College, Pulikkal, Malappuram, India, 673637.

***Corresponding Author: Asla C. K.**

Department of Pharmaceutics, Jamia Salafiya Pharmacy College, Pulikkal, Malappuram, India, 673637.

Article Received on 11/02/2020

Article Revised on 01/03/2020

Article Accepted on 21/03/2020

ABSTRACT

Solid dosage forms are mainly taken orally to get its therapeutic action. After the administration the drug undergoes disintegration, followed by dissolution and then diffuses into the systemic circulation. Dissolution testing is an *in vitro* method that deals with how an active molecule is extracted from a solid dosage form. The comparison of dissolution profiles can be done by model-dependent and model-independent approaches. In the model-dependent approach including zero order, first order, Hixson-Crowell, Higuchi, and Weibull models are applied to the utilization of fit factors. Model-independent approaches including ANOVA-based procedures, ratio test procedure, and pair wise procedure. The ratio test includes percentage, area under the curve, mean dissolution time, while the pair wise procedure includes difference factor (f1), similarity factor (f2), and Rescigno index *e.t.c.* All these approaches are valuable in statistical and clinical aspects, supporting the objectives of current dissolution profiles.

KEYWORDS: Dissolution comparison, Model dependent and independent method, f2 similarity.

INTRODUCTION

In vitro dissolution is an analytical methodology to measure drug release and bioavailability in liquid media. The ability to compare the *in vitro* dissolution profile and demonstrate the similarity of formulation is most important in the pharmaceutical industry^[1] while regulatory authorities in the European Union (EU) and the United States of America (USA) have always been the most prominent countries of dissolution guidelines, current trends indicate a proliferation of suitable dissolution similarity requirements from regulatory authorities around the world. This results in differences in the requirements for dissolution profiles and a significant amount of unnecessary and redundant work which does not help to guarantee the safety or efficacy of the product.^[2] In 1997 FDA testing guidelines of dissolution describe three important uses: (1) evaluate the batch - the quality of a batch of drug, (2) guide the development of new formulations, and (3) ensure the continuous quality and performance of the product after certain events, such as formulation changes, the manufacturing process. The results of the *in vitro* dissolution may be sufficient to obtain regulatory approval of the post-marketing changes and waive of the bioequivalence requirements for the dosage forms.^[3]

The dissolution tests play a chief role in these three situations: (i) formulation and optimization decisions:- during formulation and product development, where dissolution performance is a main quality attribute, the formulation of product and the manufacturing process

are optimized based on the achievement of respective dissolution targets. (ii) Equivalence decisions:- during the development of the generic product, and bringing of the post-approval process or changes in formulation, similarity of the *in vitro* dissolution profiles between the reference product and its generic or modified version are one of the major requirements for regulatory approval decisions. (iii) Product compliance and release decisions:- during periodic manufacturing, dissolution outcomes are very often one of the criteria used to make drug release decisions.^[4,5,6]

If dissolution profile similarity is established for the formulations before and after the changes, then expensive *in vivo* bioequivalence testing can be waived. Various methods have been proposed for statistical assessment of dissolution profile similarity. Comparison of various profiles describing a cumulative event over time is not unique to the pharmaceutical sciences. For equivalence dissolution profile, use to assure similarity in product performance, regulatory interest is in knowing how similar the two curves are, and to have a measure that is more sensitive to large differences at any particular time point.^[7-14]

However, before begin with a further discussion of statistical method significance, it is useful to consider the different meanings of the term "significance" in the circumstances of new formulation development.

- Statistical significance, used for assessing the reliability of a scientific outcome, is a measurement

of the probability that the observed result actually exists. Statistical significance and statistical reliability, depends on four factors – how much data has been gathered, how the experimental space has been sampled, how much variability is present in the collected data, and how large are measurement errors relative to the magnitude of the effect.

- The clinical importance, in the context of pharmaceutical product development, product equivalence, product release and quality control, is linked to a completely different question: whether the effect is large enough to have a significant effect on a patient's health. statistical significance can be differentiated from clinical significance: with enough data, even very small effect can be evaluated in a statistically significant way, but this does not make them clinically relevant.
- Finally, regulatory importance should ideally be the answer to another question. That point to recent testing studies - that of knowing whether the observed effects, known with a given degree of reliability, are significant enough to justify regulatory action or inaction.

The aim of this work is to understand the statistical, clinical and regulatory significance to increase the statistical significance of the comparison of dissolution profiles so that the effect can be easily obtained by independent and model-dependent approaches.^[1]

Statistical comparison methods of the dissolution profile

1. model-dependent methods

Zero order

First order

Higuchi model

Hixson - Crowell model

Weibull model

2. model independent methods

ANOVA-based procedure

Ratio test procedure

Pair wise procedure

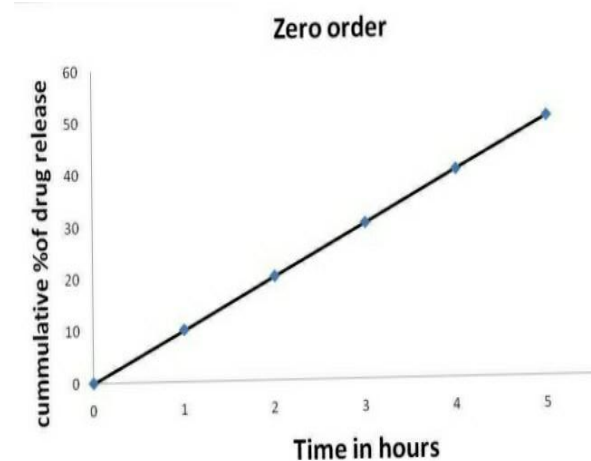
Resicigno Index

Post hoc analysis

1. Model-dependent methods^[15]

a) Zero order model

Zero order release kinetics describe a system where the drug release rate is constant over a period of time. The drug release rate is independent of its concentration of dissolved substance.



$$Q_t = Q_0 + K_0t$$

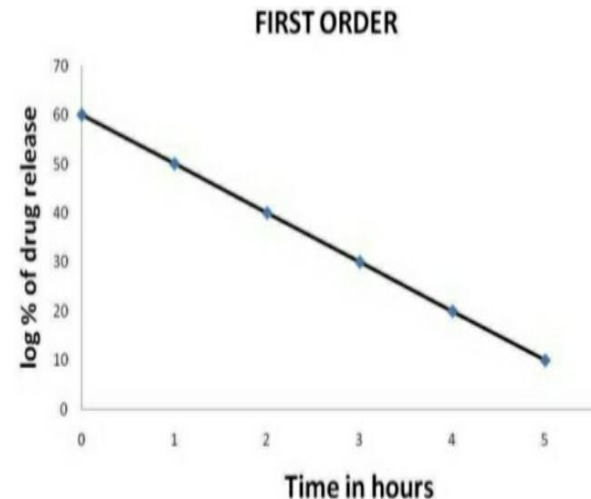
Q_t - amount of drug dissolved over time

Q_0 - initial amount of drug in the given solution

K_0 - zero order rate constant

b) First order model

The drug release rate depends on concentration of one reactant and used to describe dissolution of pharmaceutical dosage form.



$$\log C = \log C_0 - Kt \div 2.303$$

C - drug release at time t

C_0 - Initial concentration of drug

K - First order rate constant

c) Higuchi model

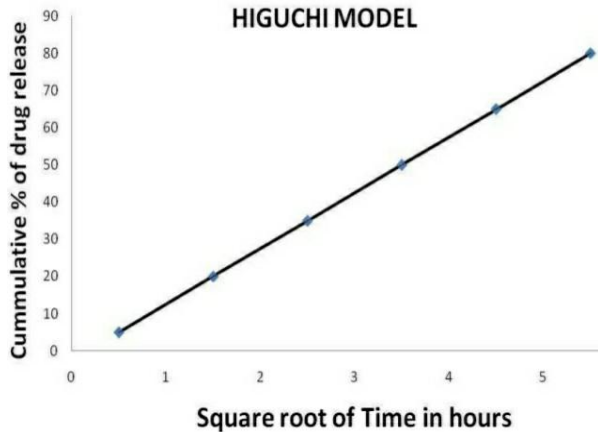
Drug dissolution from dosage form that do not disaggregate and release the drug slowly. This mathematical model describe the release of water soluble and low water soluble drugs in incorporated into semi solid or solid dispersed in a uniform matrix behaving as diffusion media.

$$Q = K\sqrt{T}$$

Q - Amount of drug released in the time ' t ' per unit area

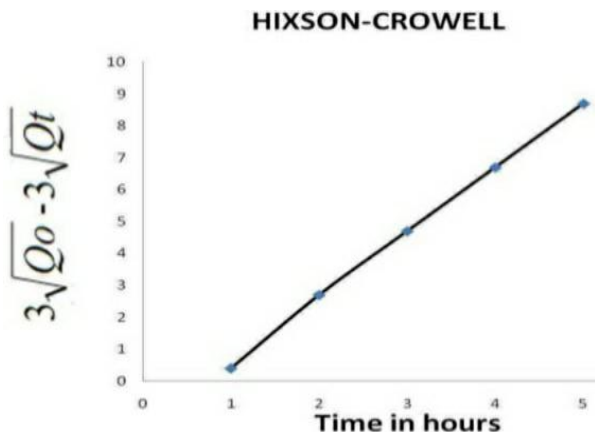
K - higuchi constant

T - time in hour



d) Hixson - Crowell model

Hixson-Crowell model states that the drug release from the particle is proportional to cubic root of it's volume. It describe a correlation between drug release from the particle and surface area and diameter of the particle.



$$Q^{1/3} - Q_0^{1/3} = Kt$$

Q_0 - initial amount of drug

Q_t - amount of drug release at time t

e) weibull model

The Weibull function is a mathematical model lacking physicochemical fundament and can be used to study the dissolution rate. It is very useful for comparison of release profile of matrix type drug.

$$m = 1 - e^{-(t - T)^{b/a}}$$

m - % dissolved at time t

T - location parameter

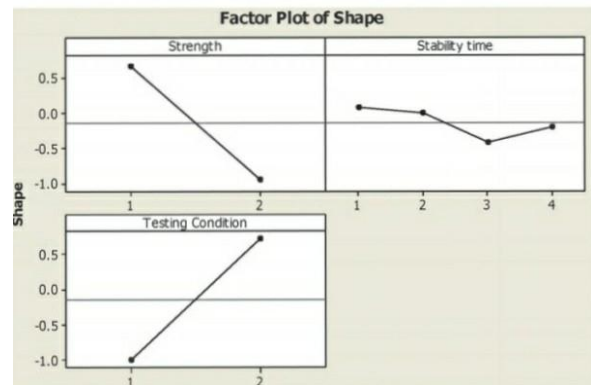
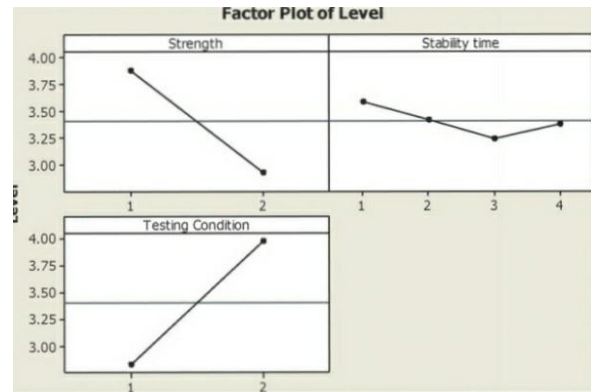
a - scale parameter

b - shape procedure

2. Model independent Method

a) ANOVA method (analysis of variance)

Generally applied to different group of data. we compare the variance of different group of data and predict whether the data are comparable or not. Minimum three sets of data required. Here first we have to find the variance within each individual group and then acompare them with each other. If the calculated value is less than the tabulated value, then the degree of variance is considered as insignificant.^[15]



ANOVA methods can be used to test the effect of treatment on level and shape. By now, level and shape factors have been calculated separately for each individual profile, and comparing dissolution profiles is transformed into comparing the two descriptive values (level value and shape score).^[1]

b) Ratio test procedure

Mainly 3 types

Ratio test of percentage dissolved

Ratio test of AUC

Ratio test of mean dissolution time

Each of these procedure compares the dissolution profile of two formulation at a particular time point. Descriptive static form data analysis tool on three types ratio test were performed to analyses standard error and a 90% confidence level for the mean value of ratio percentage dissolved, AUC and mean distribution time.

c) Pair wise procedure^[3]

Moore and Flanner proposed two new indices (f1 and f2) to compare dissolution profiles of a test and a reference formulation. These fit factors, the similarity factor (f2) and the difference factor (f1), that compare the dissolution profiles of a pair of drug products were applied to the dissolution data.

Difference factor(f1)

Difference factor (f1) calculates the percent difference between the two curves at each time point and is a measurement of relative error between the two curves.

$$f_1 = \left\{ \frac{\sum_{t=1}^n |R_t - T_t|}{\sum_{t=1}^n R_t} \right\} \times 100$$

n - number of time points

R - dissolution value of reference (pre change) batch at time t

T - dissolution value of the test (post change) batch at time t

Similarity Factor (f2)

The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent dissolution between the two curves. The concept of similarity factor (f2) has been endorsed by Food and Drug Administration (FDA); therefore, it is widely adopted in formulation and development and dossier preparation.^[2]

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum (R_t - T_t)^2 \right)^{-0.5} \times 100 \right\}$$

d) resicigno index

A bio equivalence index to measure the dissimilarity between reference and a test procedure -based on the plasma concentration as function of time. Index is also be used for comparison of dissolution data.^[16]

Post hoc procedure

post hoc analysis (from Latin post hoc means "after this") consists of statistical analyses that were specified after the data was seen. This typically produces a multiple testing problem because each potential analysis is effectively a statistical test. Multiple testing procedures are sometimes used to recompensate, but that is often difficult or impossible to do precisely. Interpretation and conduction of post hoc analysis without any proper consideration lead to data dredging by critics because the statistical associations that it finds are often spurious.^[17-19]

They are generally based on a familywise error rate; the probability of at least one Type I error in a set (family) of comparisons. The most common post-hoc tests are:

- Bonferroni Procedure
- Duncan's multiple range test (MRT)
- Dunn's Multiple Comparison Test
- Fisher's Least Significant Difference (LSD)
- Tukey's Test
- Rodger's Method.^[20]

COMPARISON OF DISSOLUTION PROFILES - REQUIREMENTS

The dissolution of the test and reference products must be carried out in the apparatus USP I at 100 rpm or the apparatus II at 50 rpm using 900 ml of the following dissolution medium:

- Acid media such as 0.1 N HCl or USP simulated gastric fluid without enzyme
- Acetate buffer pH 4 and Phosphate buffer of pH 6.8 or simulated intestinal fluid USP without enzyme.

If the test and the reference product show a dissolution greater than 85% in 15 minutes, the profiles are considered to be similar (no calculation required). If not, Calculate the value f2. If $f_2 \geq 50$, the profiles are considered to be similar and no further in vivo study is necessary. Note that only one measurement must be considered after 85% of dissolution of the two products and outside zero point. A minimum of 12 dosage units of the drug product should be evaluated.^[2]

Current approaches to the dissolution profile similarity test

Similarity f2 is a relatively simple and widely accepted method for comparing dissolution profiles. so many regulatory authorities require the use of the f2 test for this purpose. However, the rules and criteria associated with the application of this test are not harmonized worldwide. The following aspects associated with the similarity factor approach are compared to obtain a exact result. They are

- ★ criteria f2 to demonstrate the similarity
- ★ Exemption criteria for f2 comparisons
- ★ Minimal number of time points required for an f2 calculation
- ★ Determination of the last time point for a f2 calculation
- ★ Coefficient of variation criteria

It is easy to calculate and a clear acceptance criterion for the similarity of the profile (i.e. $f_2 \geq 50$) has been established. An f2 value of 50 corresponds to an average difference of 10% at all the specified times.

In general, the f2 test is an acceptable approach to assess the similarity of product quality and performance characteristics after post-approval modifications. Similarly, the f2 test offers the possibility of obtaining an exemption from in vivo bioequivalence studies for additional assays according to certain criteria of biowavers specified in the appropriate directives.

The f2 assessment should be performed with a specified number of reference (before exchange) and test (after exchange) drug lots. In Japan and Korea, for example, three production lots before exchange are tested and the batch with the intermediate dissolution rate is selected as the batch reference; similarly, three post-exchange production batches are tested and the batch with the intermediate dissolution rate is selected as the test batch.

The dissolution profiles of the reference and test products are produced with a validated dissolution method using the medium described in the regulatory application as well as two additional media. The purpose of testing the product in these three media is to assess its performance of dissolution across the physiologically relevant pH range. In cases where several time points and several media tests are necessary, special attention must be paid to the selection of media.

To accurately compare two profiles using these adjustment factors, the dissolution results must be obtained at a sufficient number of time points to correctly characterize the shape of the dissolution profiles. Since the average dissolution profiles are compared using these adjustment factors, the variability associated with the dissolution results of the individual dosage forms at each time must also meet certain regulatory criteria.^[2]

f2 Criteria for demonstrating similarity

According to the guidelines issued by the 14 regulatory authorities evaluated in this study, f1 values up to 15 (0,15) and f2 values greater than 50 (50,100) guarantee the similarity or equivalence of the two profiles. Values less than 50 may be acceptable if they are justified.^[2]

Disadvantages of the f2 method for the development of pharmaceutical products

Because of its simplicity and adoption by various regulatory agencies, the f2 method has grown in popularity and is widely used to guide similarity decisions, but it is not a good statistical estimator of similarity.

First, f2 is limited to a pairwise comparison. When there are N groups of dissolution profiles, the values $N * (N-1) / 2$ f2 must be calculated. However, in cases where the similarity is studied among groups of dissolution profiles without obvious reference, the matrix f2 cannot provide a direct interpretation.^[1]

Part of the formulation study based on the comparison of the drug profile is given below:

Statistical comparison of the dissolution profile of marketed products aceclofenac

In vitro dissolution study Dissolution was carried out on five formulations of aceclofenac 100 mg tablets, one branded coded formulation (reference) and four generic formulations. The dissolution was carried out on six units of each formulation using the apparatus USP II (Paddle) at 37.6 ± 0.58 ° C in 900 ml of phosphate buffer medium of pH 6.8 at 50 rpm. After an appropriate time interval, a sufficient volume of sample was taken and filtered through the Whatman # 41 filter. Immediately, the same volume of fresh dissolution medium was transferred to the dissolution flask. The samples were taken at an appropriate time interval and analyzed by spectrophotometry at 275 nm.

Statistical evaluation

ANOVA-based procedures

One-way ANOVA plus Tukey's post hoc tests on dissolved percentage data were applied using Microsoft Excel 2007.

Model independent methods

Report test procedures

Three types of ratio test procedures were performed: dissolved percentage ratio test, area under curve curve test, and average dissolution time ratio test. Each of these procedures compares the dissolution profile of two formulations at a given time. A descriptive statistical data analysis tool on three types of ratio test was performed to analyze the standard error and a 90% confidence level for the mean value of the ratio of the dissolved percentage, AUC and the average dissolution time.

Paired procedures

These include the difference factor f1, the similarity factor f2 and two rescigno indices. Rescigno proposed a bioequivalence index to measure the dissimilarity between a reference product and a test product based on the plasma concentration as a function of time. This index can also be used for drug dissolution data. Like the ratio test procedure, pair procedures compare the dissolution profile of a pair of products and use 90% approach to trust. The main advantage of equations f1 and f2 is to provide a simple way to describe the comparison of the data. The factor f1 measures the percentage of error between two curves at all points. And measures the differences between two dissolution profiles. This index is 0 when the two release profiles are identical and when the drug coming either from the test or from the reference formulation is not released at all.

Model-dependent methods

Model dependent approaches, including zero order, first order, Hixson-Crowell, Higuchi and Weibull models, as described in Table 1, were applied taking into account the amount of drug release from 0 to 90 mins. The following graphs were produced: cumulative% of drug release as a function of time (zero order kinetic model); cumulative log of the remaining drug as a function of time (first order kinetic model); cumulative% of drug release relative to the square root of time (Higuchi model), cubic root of the drug% remaining in the matrix relative to time (law of the Hixson Crowell cubic root) and logarithm of the dissolved amount of drug with respect to the logarithm of time (Weibull model From the mean ratio of the model parameter and the ES of the mean ratio, a confidence level of 90% was assessed.^[16]

RESULTS

The FDA suggests some acceptable approaches for establishing similarity in dissolution profiles, such as model-independent or model-dependent approaches, although any of the approaches will be considered once justified. Due to the emphasis on comparing dissolution

profile data in the FDA guidelines, the interest of pharmaceutical scientists has focused on the methodology used to compare the dissolution profile. The FDA states that in cases where the intra-batch variability is greater than 15% coefficient of variation (CV), a procedure independent of the multivariate model is more appropriate for the comparison of dissolution profiles. It is further stated in the guidance document that to allow the use of average data, the percentage coefficient of variation (% CV) should not be greater than 20% at previous times, and at other time points, the % CV should not be higher than 30%.

Table 1: Mathematical models used to describe dissolution curves

Zero order	$Q_t = Q_0 + K_0 t$
First order	$\ln Q_t = \ln Q_0 + K_1 t$
Hixson-crowell	$Q_0^{1/3} - Q_t^{1/3} = K_2 t$
Higuchi	$Q_t = K_H t^{1/2}$
Weibull	$\text{Log}[-\ln(1-(m))] = \text{blogt} - \text{loga}$

Table 2: Results of one-way ANOVA

ANOVA						
Source of variation	SS	df	MS	F	P-value	Fcrit
Between groups	6072.356	4	1518.089	3.325194	0.038708	3.055568
Within groups	6848.123	15	456.5415			
Total	12920.48	19				

SS - Sum of squares; MS - Mean square error; df - Degree of freedom

Table 3: Descriptive statistic for the ratio test procedure

Ratio	T1/S1	T2/S1	T3/S1	T4/S1
Percentage				
Mean	1.0124	0.7919	0.5521	0.7568
Std. error	0.0367	0.0188	0.0399	0.0303
90% CL	0.0863	0.0442	0.0804	0.0611
Area under the curve				
Mean	1.0243	0.7903	0.5534	0.7423
Std. error	0.0301	0.0158	0.0444	0.0239
90% CL	0.0708	0.0373	0.0896	0.0481
Mean dissolution time				
Mean	0.9973	1.2587	1.8589	1.3908
Std. error	0.0409	0.0336	0.1339	0.025
90% CL	0.0963	0.0791	0.2698	0.0503

Table 4: Mean values of f_1 , f_2 and two indices of rescigno

	T1 vs S1	T2 vs S1	T3 vs S1	T4 vs S1
f_1	5.60483	20.49834	48.56718	30.01353
f_2	59.48955	34.95411	16.65016	26.47835
ζ_1	0.028063	0.031224	0.037012	0.032972
ζ_2	0.16752	0.176704	0.192385	0.181583

Similarity can be claimed when the lower limit of 95% for f_2 is greater than or equal to 50. The result obtained will be biased low, making it a conservative estimate. This means that the lower bound of f_2 will be lower by more than 50 more often than expected in cases where the differences in the actual dissolution profiles would give values of f_2 close to 50.

These values can be considered as the maximum admissible % CV in various research works. To assess the difference between the four lots, the Tukey test can be performed on the results of the ANOVA. The results of Tukey's test would show that there could be a statistically significant difference between the batches. The ANOVA methods take into account the variability of the dissolution profile data in the comparison at each instant, they ignore the correlation between the instant of dissolution.

According to FDA guidelines, the values of f_1 must be between zero and 15 and f_2 between 50 and 100 guarantee the similarity or the equivalence of the two dissolution profiles.^[2]

Graphical representation

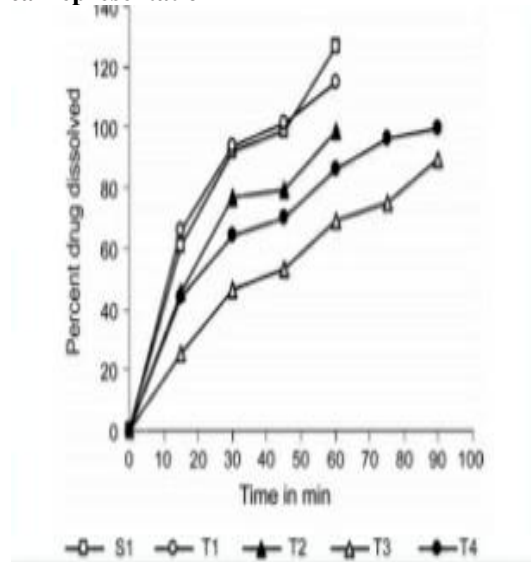


Figure 1: Mean dissolution profile of percentage dissolved

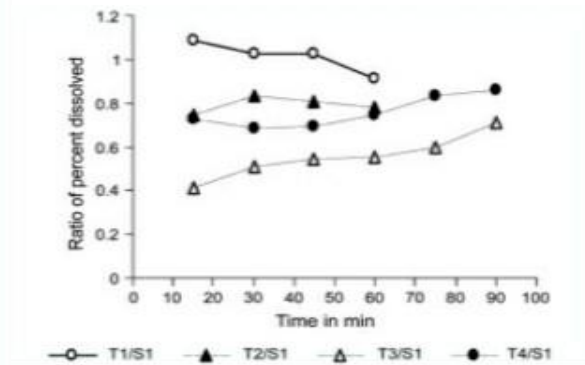
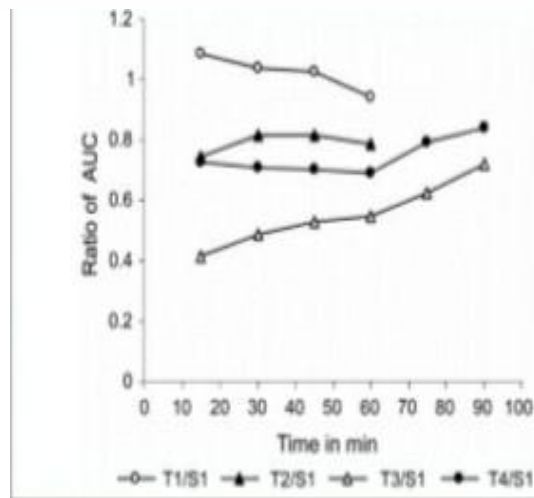
Figure 2: Mean dissolution profile of the ratio of percentage dissolved
[Note: The percent coefficient of variance at the earlier time points should not be more than 20% and at the other time points should not be more than 10%]

Figure 3: Mean dissolution profile of the ratio of AUC

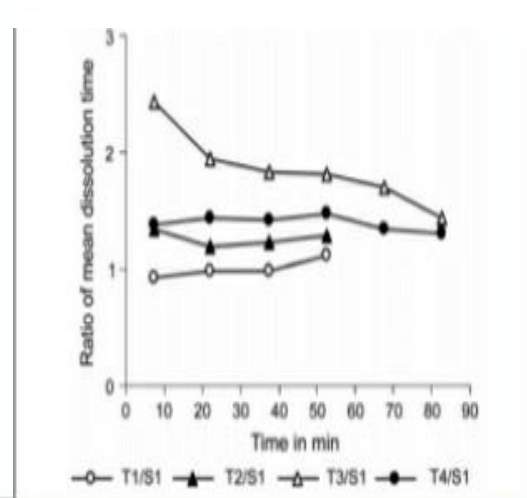


Figure 4: Mean dissolution profile of the ratio of mean dissolution time

CONCLUSION

General approaches for comparing dissolution profiles were discussed; they have proven to be model dependent and model independent approaches. Dissolution tests are generally used to direct the development of new formulations, examine the quality of drugs, assess the potential impact and effect of post-approval changes on product performance and, in some cases, predict the in vivo performance of the drug also. It is often necessary to collect dissolution data at several times to adequately characterize the in vitro performance of the drug product more precisely than the point estimation approach. This study was planned in order to study several methods, to become familiar with the numerical results and to evaluate the advantages and disadvantages of these methods.

The study showed that the analysis of dissolution profiles depends on the target information and must take into

account the applicable decision scenario as well as the intrinsic data structure. Critically, if the objective is to optimize a product or a process, the method used to analyze the data must take into account the multivariate nature of the information, the intrinsic auto-correlated nature of the dissolution profiles and the availability of the intra-group variability as a means to determine reliability and importance.

The evaluation and direct application of model dependent methods and statistical methods are more complicated. While model dependent methods present an acceptable model approach to the true relationship between dependent and independent variables, statistical methods include post hoc procedures for comparing dissolution data. The disadvantages of model independent methods are the values of f_1 and f_2 are sensitive to the number of dissolution points and the basis of the criteria for deciding the difference or

similarity between the dissolution profiles is unclear. The limitation is that, only when the intra- batch variation is less than 15%, the equation f_2 should be used.^[21]

REFERENCES

1. Statistical comparison of dissolution profiles-Yifan Wang¹, Ronald D. Snee², Golshid Keyvan¹, and Fernando J. Muzzio¹; 20 Aug 2015, pg no 2.
2. Dissolution Similarity Requirements: How Similar or Dissimilar Are the Global Regulatory Expectations? Dorys Argelia Diaz, Stephen T.Colgan, [...], and Leslie Van Alstine, 2015 Nov; 18: 15.
3. Moore, J. W.; Flanner, H. H. Mathematical Comparison of Curves with an Emphasis on In-Vitro Dissolution Profiles. *Pharm. Technol*, 1996; 20(6): 64–74.
4. FDA. Guidance for Industry: Modified Release Solid Oral Dosage Forms: Scale- up and Post Approval Changes (SUPAC- MR): Chemistry, Manufacturing and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation. 1997.
5. FDA. Guidance for Industry: Extended Release Oral Dosage Forms Development, Evaluation, and Application of In Vitro/In VivoBCorrelations, 1997.
6. FDA. Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms. 1997.
7. O'Hara T, Dunne A, Kinahan A, Cunningham S, Stark P, Devane J. Review of methodologies for the comparison of dissolution profile data. *Adv Exp Med Biol*, 1997; 423: 167-718.
8. Mauger JW, Chilko D, Howard S. On the analysis of the dissolution data. *Drug Dev Ind Pharm*, 1986; 12: 969-92.
9. Polli JE, Rekh G, Augsburger LL, Shah VP. Methods to compare dissolution profiles and a rationale for wide dissolution specifications for metoprolol tartarate tablets. *J Pharm Sci.*, 1997; 86: 690-700.
10. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. *Eur J Pharm Sci.*, 2001; 13: 123-33.
11. Chow SC, Ki F YC. Statistical comparison between dissolution profiles of drug product. *J Biopharm Statist*, 1997; 7: 241-58.
12. Gill JL. Repeated measurement: Split-plot trend analysis versus analysis of first difference. *Biometrics*, 1998; 44: 289-97.
13. Liu JP, Ma MC, Chow SC. Statistical evaluation of similarity factor f_2 as a criterion for assessment of similarity between dissolution profiles. *Drug Inform J*, 1997; 31: 1255-71.
14. Yuksel N, Kanik AE, Baykara T. Comparison of in vitro dissolution profiles by ANOVA-based model-dependent and independent methods. *Int J Pharm*, 2000; 209: 57-67.
15. Thomas O.H Adrian D, Jackie B and john D.A review of method used to compare dissolution profile data. *PSIT*, 1998: 214-223.
16. Assessment of Dissolution Profile of Marketed Aceclofenac Formulations Soni T, Chotai N1 Department of Pharmaceutics, India, correspondence: Dr. Narendra Chotai, 2010; (1): 21-26.
17. Wang, Yifan; Snee, Ronald D.; Keyvan, Golshid; Muzzio, Fernando J. (2016-05- 03). "Statistical comparison of dissolution profiles". *Drug Development and Industrial Pharmacy*, 42(5): 796–807.
18. Anand, Om; Yu, Lawrence X.; Conner, Dale P.; Davit, Barbara M. (2011-04-09). "Dissolution Testing for Generic Drugs: An FDA Perspective". *The AAPS Journal*, 13(3): 328.
19. Zhang, X.; Duan, J.; Kesisoglou, F.; Novakovic, J.; Amidon, G. L.; Jamei, M.; Lukacova, V.; Eissing, T.; Tsakalozou, E. (2018). "Mechanistic Oral Absorption Modeling and Simulation for Formulation Development and Bioequivalence Evaluation: Report of an FDA Public Workshop". *CPT: Pharmacometrics & Systems Pharmacology*, 492–495.
20. Statics how to, by Stephanie, June 10, 2015 report, google search point.
21. Evaluation of in Vitro Dissolution Profile Comparison Methods of Immediate Release Gliclazide Tablet Formulations, Nov 1, 2005; 25.