IJBPAS, November, 2024, 13(11): 5831-5843

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

COMPARISON AND ANALYSIS OF SIMILARITY FACTOR OF IN-VITRO DRUG RELEASE PROFILE USING CUBIC SPLINE INTERPOLATION METHOD

ACHARYA F. S. AND SHETH T. S.*

Department of Applied Sciences and Humanities, Parul Institute of Engineering and Technology, Parul University, Vadodara 391760, Gujarat, India

***Corresponding Author: Ms. Tulsi Sagar Sheth: E Mail:** tulsi.sheth12725@paruluniversity.ac.in

Received 24th Sept. 2023; Revised 25th Nov. 2023; Accepted 1st March. 2024; Available online 1st Nov. 2024

https://doi.org/10.31032/IJBPAS/2024/13.11.8473

ABSTRACT

This paper compares and analyses the similarity factor of drug release profiles for modified-release (MR) dosage forms using the Cubic Spline Interpolation method. The Cubic Spline Interpolation (CSI) method is employed to approximate the percentage drug release at intermediate time points of in-vitro drug release profiles; the changes in the similarity factor f_2 is noted. To test the method, percentage drug release of Quetiapine Fumarate MR tablets is considered. The CSI method explains the interpretation and comparison of supplemental mediating timepoint observations in the ex-vivo environment. This method may aid industries in monitoring the characteristics of in-vitro release studies with a few changes in timepoint selection or to achieve comparative drug release profile for early-stage drug dosage form preparation.

Keywords: Drug release profiles, Similarity factor f_2, Cubic spline interpolation

MSC: 03C40, 41A15

INTRODUCTION

For more than 50 years, scientists in the drug development process have used mathematical models of drug release in the drug delivery (DD) fields. These models not only assist scientists in learning the dynamics of drug release, but they also assist them in saving money and time by assisting in the design of more effective experiments **[9]**. Marketed generic drugs must undergo continuous monitoring to ensure their safety, consistency, and potency to meet bioequivalence and pharmacopeia criteria

[21]. Employing in-vitro dissolution to enhance post-approval adjustments is encouraged by the FDA guidance on Scale-Up and Post-Approval Changes (SUPAC) for (MR) oral dosage forms **[14]**. Dissolution testing plays significant role in identifying the need for the bioequivalence (BE) studies related to Scale-Up and Post-Approval Changes (SUPAC) **[10]**.

The mathematical model is crucial in interpreting drug release mechanisms. Several models are available for comparing drug release profiles, including the Zero order, First order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas, Weibull model, and others (**[2], 13]**). The best model for each formulation is chosen based on the highest adjusted root mean square and the lowest Akaike Information Criterion (AIC) (**[24], [4]**).

Using 'In-vitro /In Vivo Correlations (IVIVC)' can drive down costs in the introduction of new dosage forms, and that is why it has gained importance from regulatory systems in past few decades **[6, 20]**. In the 1990s, scientists began to develop methods for comparing dissolution profiles (**[13], [25]**), varying from the similarity factors to more unique and powerful computer software **[29]**. Similarity factors have gained notoriety because they reduce the difficulty of constructing a dissolution profile by offering a single value describing two curves of several points each **[6]**. The methods used to study dissolution profile comparison include a Model dependent method, Model-independent method, and Statistical methods based on ANOVA (**[7], [27]**).

Empirical data were recorded at uneven timepoints to check percentage drug release profiles. The data can be made evenly distributed by using mathematical techniques. In mathematics, estimation of intermediate value is done by using interpolation technique. Several interpolation methods are available to calculate intermediate values, like Polynomial Interpolation, Divided Difference method, Spline Interpolation etc. To this end, the Cubic Spline Interpolation (CSI) method is used, as it minimizes the oscillations and preserves the concavity of the graph **[5]**. The percentage drug release at intermediate time points is predicted for empirical data, and the similarity factor f_2 is examined **[12]**. CSI is generally preferred over Polynomial Interpolation because it reduces the error in fitting the higher degree polynomial. The current study looks at a pair-wise comparison of formulation of Quetiapine Fumarate MR tablets. This analysis demonstrates the significance and similarity of the additional intervening time points. The cubic spline interpolation method may be preferable for industries to compare drug release profiles with few modifications in timepoint selection to

provide a pair-wise comparison between the data sets **[27]**. This paper is an expanded version of the authors previously presented Linear Regression Model **[27]**.

This paper is structured as follows, in section 2 preliminaries of Interpolation method and the process of Cubic Spline Interpolation method are discussed. Section 3 then explains the methodology. Section 4 discusses the result and shows importance of time point selection for similarity factor f_2 calculation, and section 5 presents the conclusion drawn from the CSI method.

Preliminaries:

Interpolation is the determination or estimation of the value of $f(t)$, or a function of t, from certain known values of the function. If $t_0 < \ldots < t_n$ and $y_0 = f(t_0), \ldots, y_n = f(t_n)$ are known, and if $t_0 < t < t_n$, then the estimated value of $f(t)$ is said to be an interpolation **[1]**. Interpolation problems are frequently solved by dividing the points in a specified range into several subintervals and approximating with low-order polynomials at each subinterval **[11]**. These resulting polynomials are known as splines. There is a polynomial that is as "similar" to the given function as desirable for each given function that is continuous, finite, and bounded on an interval. The Weierstrass Approximation Theorem perfectly describes this conclusion.

Weierstrass Approximation Theorem [5]:

Suppose that the function f is defined and continuous on $[a, b]$. For each $\epsilon > 0$ there exist a function $P(t)$ with the property,

$$|f(t) - P(t)| < \epsilon, for\ all\ t\ in\ [a, b]$$

Theorem [5]:

For $t_0, t_1, \ldots, t_r$ are $(r + 1)$ discrete values of t-coordinate (x-axis) and the function f whose values are given at these coordinates, then a unique polynomial $P(t)$ of degree at most r exists with $f(t_k) = P(t_k), for\ k = 0, 1, \ldots, r$.

These interpolating polynomial $P(t_k)$ can be obtained by using the Polynomial Interpolation method (Lagrange interpolation or Newton's Divided Difference method). To implement these methods, MATLAB (Matrix Laboratory) is used. Polynomial interpolation fits higher degree polynomial for large amount of data. It is not always preferred to fit higher degree polynomial as it overshoots the data and gives error in the calculation as shown in **Figure 1**. This error can be minimized by using Piecewise-Polynomial Interpolation. Linear interpolation is used for first-degree polynomials, while Quadratic and Cubic Spline Interpolation is used for a second-and third-degree polynomial, respectively **[1]**.

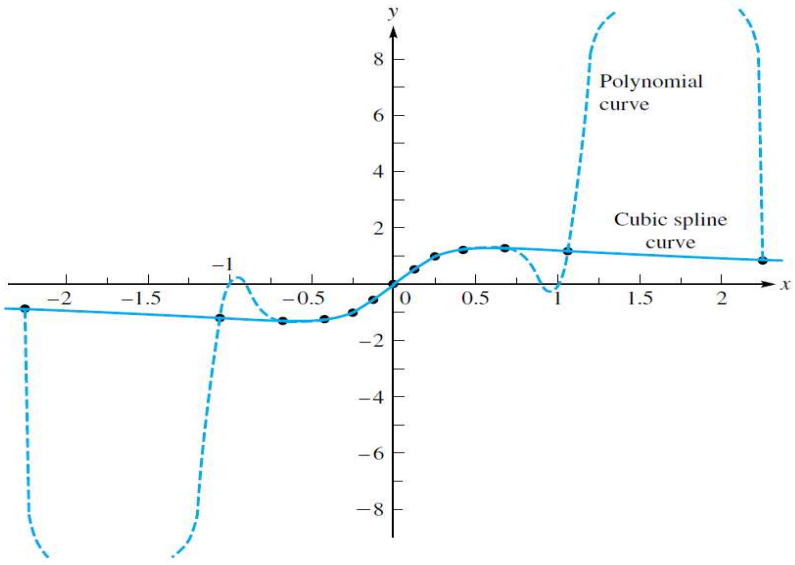


Figure 1: Representation of Polynomial curve and Cubic spline curve [5]

The possibility of no invariance at the endpoints of the subintervals is a limitation of linear interpolation. The interpolating function in a mathematical context is not smooth. Physical conditions frequently make it very clear because smoothness is necessary; hence, the approximation function must be continuously differentiable. This criterion is satisfied by the third-degree polynomial hence CSI method is used to interpolate the data.

Theory of Spline Interpolation with natural boundary condition [17]:

The cubic spline interpolation gives a continuous smooth curve passing through all the given data points. The process is described as below:

For a function f defined on $[a, b]$ and a set of nodes $a = t_0 < t_1 < t_2 < \ldots < t_r = b$, a cubic spline interpolation function $S(t)$ for f is given below:

$$S(t)=\begin{cases} S_0(t)=a_0+b_0(t-t_0)+c_0(t-t_0)^2+d_0(t-t_0)^3;\ [t_0,t_1] \\ S_1(t)=a_1+b_1(t-t_1)+c_1(t-t_1)^2+d_1(t-t_1)^3;\ [t_1,t_2] \\ \vdots \\ S_{r-1}(t)=a_{r-1}+b_{r-1}(t-t_{r-1})+c_{r-1}(t-t_{r-1})^2+d_{r-1}(t-t_{r-1})^3;\ [t_{r-1},t_r] \end{cases} \quad \ldots\ldots\ldots\ldots (1)$$

The natural cubic spline $S(t)$ for the function f satisfies the criteria listed below:

(a) $S(t)$ is a piecewise cubic polynomial. It is denoted by $S_i(t)$, on the subinterval $[t_i, t_{i+1}]$, for $0 \le i \le r-1$;

(b) $S_i(t_i) = f(t_i)$ and $S_i(t_{i+1}) = f(t_{i+1})$ for $0 \le i \le r-1$;

(c) $S_{i+1}(t_{i+1}) = S_i(t_{i+1})$, $0 \le i \le r-2$;

(d) $S'_{i+1}(t_{i+1}) = S'_i(t_{i+1}), 0 \le i \le r-2$;

(e) $S''_{i+1}(t_{i+1}) = S''_i(t_{i+1})$, $0 \le i \le r-2$;

(f) $S''(t_0) = S''(t_r) = 0$ (Natural boundary condition). The boundary conditions given by (f) imply that $c_0 = c_r = 0$. Assemble these two equations and the conditions (b) to (e) produce a tridiagonal system of linear equations $AX = B$, where, A is $(r+1) \times (r+1)$ coefficient matrix, X and B are $(r+1) \times 1$ column vectors.

To find the unique solution for $c_0, c_1, c_2, \dots, c_r$, the Gauss Elimination method is used **[3]**.

$$A = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & \dots & \dots & 0 & 0 & 0 \\ m_0 & 2(m_0+m_1) & m_1 & 0 & 0 & \dots & \dots & 0 & 0 & 0 \\ 0 & m_1 & 2(m_1+m_2) & m_2 & 0 & \dots & \dots & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \dots & \dots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \dots & \dots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & 0 & \dots & \dots & m_{r-2} & 2(m_{n-2}+m_{r-1}) & m_{r-1} \\ 0 & 0 & 0 & 0 & 0 & \dots & \dots & 0 & 0 & 1 \end{bmatrix}$$

$$X = \begin{bmatrix} c_0 \\ c_1 \\ c_2 \\ \vdots \\ c_{r-1} \\ c_r \end{bmatrix}, B = \begin{bmatrix} 0 \\ \frac{3}{m_1}(a_2 - a_1) - \frac{3}{m_0}(a_1 - a_0) \\ \frac{3}{m_2}(a_3 - a_2) - \frac{3}{m_0}(a_2 - a_1) \\ \vdots \\ \frac{3}{m_{r-1}}(a_r - a_{r-1}) - \frac{3}{m_{r-2}}(a_{r-1} - a_{r-2}) \\ 0 \end{bmatrix}$$

Algorithm of the Natural Cubic Spline [5]:

For the function f, defined at the values of $t_0, t_1, t_2, \ldots, t_r$, the cubic spline interpolant S for the defined at the numbers satisfying the natural boundary condition $S''(t_0) = S''(t_r) = 0$ is presented below:

Input: r; $t_0, t_1, t_2, \ldots, t_r$; $a_0 = f(t_0), a_1 = f(t_1), \ldots, a_r = f(t_r)$.

Output: a_i, b_i, c_i, d_i for $i = 0, 1, \ldots, r-1$.

Step 1: For $j = 0, 1, \ldots, r-1$ set $m_j = t_{j+1} - t_j$

(Here, m is the difference between two t values)

Step 2: For $j = 0, 1, \ldots, r-1$ set

$$\alpha_j = \frac{3}{m_j}(a_{j+1} - a_j) - \frac{3}{m_{j-1}}(a_j - a_{j-1}).$$

Step 3: (Solving tridiagonal system using linear algebra)

Set $\beta_0 = 1; \gamma_0 = 0; \delta_0 = 0;$

Step 4: $For\ j = 1, \ldots, r-1$

set $\beta_j = 2(t_{j+1} - t_{j-1}) - m_{j-1}\gamma_{j-1};$

$\gamma_j = m_j/\beta_j;$

$\delta_j = (\alpha_j - m_{j-1}\delta_{j-1})/\beta_j.$

Step 5: Set $\beta_r = 1; \delta_r = 0; c_r = 0.$

Step 6: For $i = r-1, r-2, \ldots, 0$

set $c_i = \delta_i - \gamma_i c_{i+1};$

$b_i = (a_{i+1} - a_i)/m_i - m_i(c_{i+1} + 2c_i)/3;$

$d_i = (c_{i+1} - c_i)/3m_i).$

Step 7: Output (a_i, b_i, c_i, d_i for $i = 0, 1, \ldots, r-1$);

Stop.

Methodology:

Various theories and kinetics models represent drug dissolution from ancient and modified release dosage forms **[17]**.

Model Independent Methods: The difference factor (f_1), similarity factor (f_2), and dissolution efficiency (D.E.) are theories and kinetic models associated with drug release forms and drug solubility **([8], [27])**.

Difference factor (f_1): The difference factor is a measure of the relative errors between the two curves **[8]**.

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

where, n is the number of sample points, R_j is the reference dissolution value at time t, and T_j is the test dissolution value at time t.

Similarity factor (f_2): A similarity factor is a logarithmic reciprocal square root transformation of the sum of squared errors. It compares the percentage dissolution of two curves to determine the similarity of two drug profiles (**[8], [28]**).

$$f_2 = 50\ log\ \{(1 + \frac{1}{n}\sum_{j=1}^{n}(R_j - T_j)^2)^{-0.5} \times 100\}$$

The similarity factor f_2 assumes the value 100 when the fit is perfect, and the value decreases when the profiles become more unsimilar.

Dissolution Efficiency (D.E.): The area under the dissolution curve, up to a certain time t of dissolution efficiency of a drug dosage form is known as the dissolution efficiency **([18], [27])**.

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

where, y is the percentage of drug dissolved at time t, y_{100} is the maximum percentage of drug release.

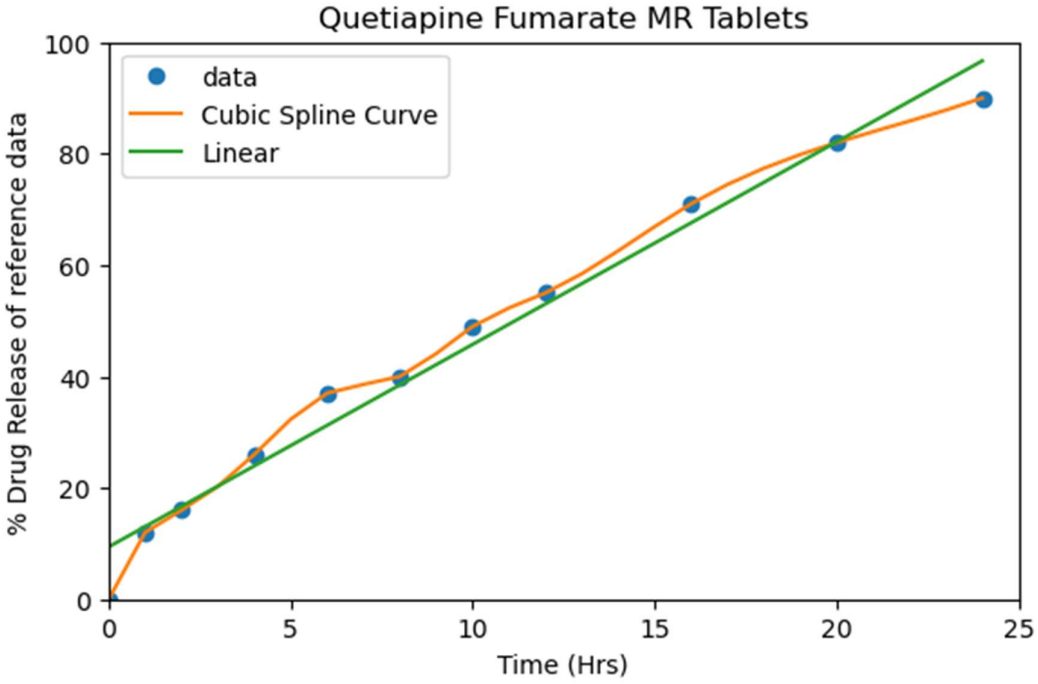
Out of all above methods, the Similarity factor (f_2) is adopted by industries. So, in this paper we have considered f_2 for pairwise comparison between two drug release profiles. In **[22]** Moore and Flanner projected the comparison of pairwise dissolution profiles through indices f_1 and f_2, while in **[23]** the comparison is performed using dissolution efficiency and fit factors f_1 and f_2. In **[21]** it is represented that the similarity factor and the difference factor can easily estimate the similarity between pairs of dissolution profile; however, their values are subtle to the choice of number of time points. This limitation of f_1 and f_2 opens further scope of research in the area of effectiveness of data variability. According to the FDA guideline, the range of f_1 and f_2 lies within 0 to 15 and 50 to 100 respectively **[10]**. The range of 50 and 100 is the range where similarity can be assumed. The f_2 value of 50 represents a 10% variation in the mean between predetermined points **[19]**.

RESULT:

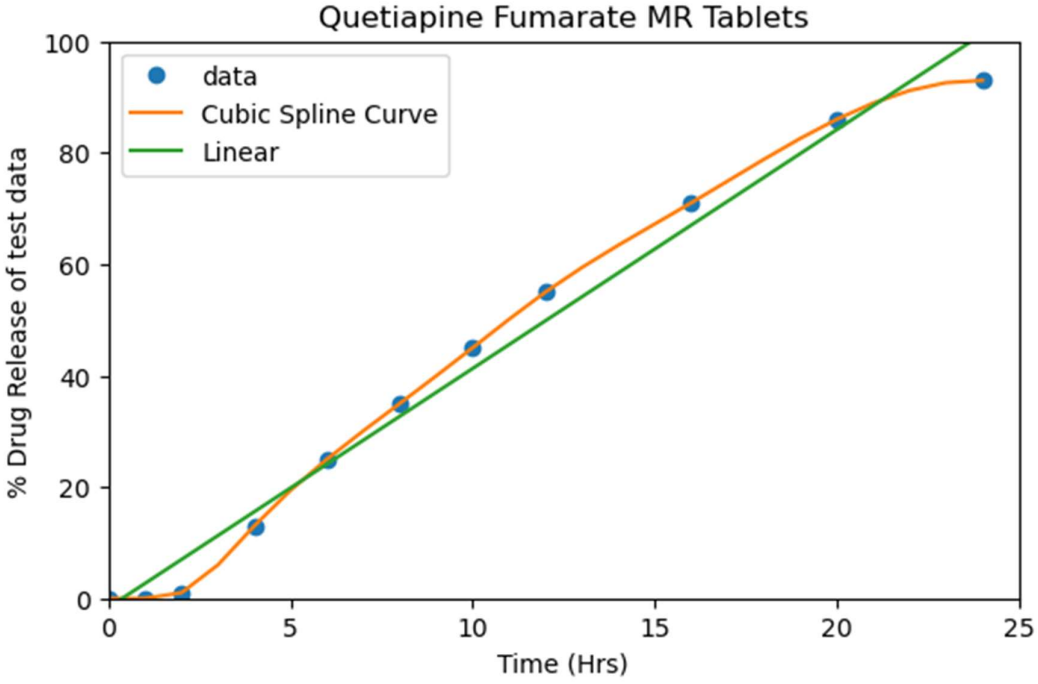
As a continuation of previous work **[27]**, in this paper, the CSI method was used to compare and analyse the similarity factor f_2 of in-vitro drug release profiles for MR dosage form. Interpolation is used because it accurately represents the value of a drug release at the given timepoint, whereas Linear Regression accepts approximate drug release values. To represent the comparison and analysis, the drug release profiles of Quetiapine Fumarate MR tablets was considered in the paper. The graphical representation of reference and test data is presented in **Figure 2**. Calculation of percentage drug release at evenly distributed timepoints were noted and variation in f_2 was found with choice of different timepoint (as shown in **Table 1**). The straight line represents the linear regression curve, while the other depicts the cubic spline interpolation curve. The number of timepoints (n) relates to the sample points of an experiment. Total ten timepoints were considered for the calculation; it was at 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 hrs. The percentage drug release by CSI curve were calculated for n=24 and f_2 value is analysed as 56.21, which was changed by 10.60%; at this end, the study shows the importance of timepoint selection during the experiment.

Table: 1 f_2 Calculation using CSI method for Quetiapine Fumarate MR Tablets

f_2 Value	Number of Timepoints (n)	Discussion
53.01	n = 10	n is taken as per number of timepoints for empirical data
56.21	n = 24	n is chosen from interpolated data with interval size 1
55.41	n = 13	n is chosen from interpolated data with interval size 2



(a)



(b)

Figure 2 Graphical representation of drug release profiles of Quetiapine Fumarate MR Tablets
(a) Cubic spline curve and Linear curve for experimental reference data
(b) Cubic spline curve and Linear curve for experimental test data

CONCLUSION:

The present work is of assistance to pharmaceutical industries where selection of timepoints is important to compare in-vitro drug release profiles. The present study approximates percentage drug release by fitting a cubic polynomial in each subinterval and shows impact of timepoint

selection in the analysis of similarity factor f_2. In this study, similarity factor f_2 was analysed for MR dosage form of in-vitro drug release profiles. Drug release profiles of Quetiapine Fumarate MR tablets was compared, and the similarity factor f_2 was measured between drug release profiles. There is a significant transformation in the similarity factor of the predicted data compared with experimental data by approximately 10.60% for (n=24 to that of n=10) and, which indicates the significance of selecting limited time points; however, this study could be further developed using other robust methods to achieve more accurate results. Finally, the study concludes that companies may use the CSI method to calculate the similarity factor with only a few changes in the time points. The CSI method helps in predicting the percentage drug dissolution at intermediate timepoints and in this way it suggests to take observation at different timepoint for f_2 calculation. The CSI method overcome the overshooting, so it is concluded that it is preferable than Linear regression model which was presented by the authors in the previous work **[27]** to find the intermediate value.

Ethical approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Acknowledgements: The authors would like to thank School of Pharmacy, Parul University, Vadodara, Gujarat for the data.

Funding: No funding to report.

Availability of data and material:

Data used in this article are experimental data of School of Pharmacy, Parul University.

Data Availability:

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Competing interest:

The authors declare that they have no competing interest.

Authors' contributions:

The authors have jointly carried out research and worked together on the manuscript. All authors read and approved the final manuscript.

Author's Information:

Department of Applied Sciences and Humanities, Parul Institute of Engineering and Technology, Parul University, Vadodara, Gujarat, India.

REFERENCES:

[1] Ahmad, N., and Deeba, K. F. (2017): Applications of cubic splines in the numerical solution of polynomials; International Journal of Engineering, Science and Mathematics, 6, 99-106.

[2] Amidon, G. L., Lennernas, H., Shah, V. P., & Crison, J. R. (1995): A theoretical basis for a

biopharmaceutic drug classification: the correlation of in-vitro drug product dissolution and in vivo bioavailability; Pharmaceutical Research, 12(3), 413–420. https://doi.org/10.1023/a:1016212804288 .

[3] Anton, H., and Rorres, C., (2000): Elementary linear algebra: Applications version.

[4] Benomar, A., Adade, C. A., Elalaoui, Y., Cherkaoui, N., Rahali, Y., Laatiris, A., & Fahry, A. (2021): Hierarchical Bayesian approach applied to the formulation of sustained-release suppositories and dissolution profile modeling. Journal of Applied Pharmaceutical Science, 11(07), 055–062. https://dx.doi.org/10.7324/JAPS.2021.110705.

[5] Burden, R. L., & Faires, J. D., (2011): Numerical analysis: Ninth Edition; Brooks/Cole, Pacific Grove.

[6] Cascone, S., (2017): Modeling and comparison of release profiles; Effect of the dissolution method. European Journal of Pharmaceutical Science, 106, 352-361 https://doi.org/10.1016/j.ejps.2017.06.021.

[7] Costa, P., & Sousa Lobo, J. M., (2001): Modeling and comparison of dissolution Profiles; European Journal of Pharmaceutical Sciences, 13(2), 123-133. https://doi.org/10.1016/S0928-0987(01)00095-1.

[8] Diaz, D. A., Colgan, S. T., Langer, C. S., Bandi, N. T., Likar, M. D., & Van Alstine, L. (2016): Dissolution Similarity Requirements: How Similar or Dissimilar Are the Global Regulatory Expectations; The AAPS Journal, 18(1), 15–22. https://doi.org/10.1208/s12248-015-9830-9.

[9] Elmas, A., Akyuz, G., Bergal, A., Andac, M., & Andac, O. (2020): Mathematical Modelling of Drug Release; Research on Engineering Structures & Materials; 6(4), 327-350. http://dx.doi.org/10.17515/resm2019.156ic2809

[10] 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. US Food and Drug Administration, Rockville, MD, USA, 1997.

[11] FDA Guidance for Industry: Waiver of in vivo bioavailability and bioequivalence studies for

immediate-release solid oral dosage forms based on a biopharmaceutics classification System, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), December 2017.

[12] Fenton, J. D., (2015): Approximating splines and the representation of scattered and not-so-scattered data; Redirected from: http://johndfenton.com/Approximating-splines/Approximating-splines.pdf

[13] Gouda, R., Baishya, H., & Qing, Z. (2017): Application of Mathematical Models in Drug Release Kinetics of Carbidopa and Levodopa ER Tablets; Journal of Developing Drugs; 6(2): 171. doi:10.4172/2329-6631.

[14] https://lubrizolcdmo.com/technical-briefs/in-vitro-dissolution-testing-for-solid-oral-dosage-forms/

[15] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m9-biopharmaceutics-classification-system-based-biowaivers-step-5_en.pdf

[16] Jain, A., & Jain, S. K., (2016): In-vitro Release Kinetics Model Fitting of Liposomes; An Insight; Chemistry and Physics of Lipids; 201, 28– 40. https://doi.org/10.1016/j.chemphyslip.2016.10.005

[17] Jain, M.K. & Iyenger, S.R.K. (2015): Numerical methods for Scientific and Engineering Computation. New Age International Publishers.

[18] Khan, K., (1975): The concept of dissolution efficiency. Journal of Pharmacy and Pharmacology; An International Journal of Pharmaceutical Science, 27(1).

[19] Krkobabic, M., Medarevic, D., Cvijic, S., Grujic, B., & Ibric, S. (2019): Hydrophilic excipients in digital light processing (DLP) printing of sustained release tablets: Impact on internal structure and drug dissolution rate; International Journal of Pharmaceutics. 572, 118790. https://doi.org/10.1016/j.ijpharm. 2019.118790

[20] Logoyda, L. (2020): Efficient validated method of HPLC to determine amlodipine in combinated dosage form containing amlodipine, enalapril and bisoprolol and in-vitro dissolution studies with in-vitro / in vivo correlation; Pharmacia 67(2), 55-61. https://doi.org/10.3897/pharmacia.67.e48220

[21] Maryana, S., & Youssef, A., (2020): Assessment and Comparison of Pharmaceutical Equivalence of Amlodipine Besylate Tablets Available in Syria under Biowaiver Coditions; Research Journal of Pharmacy and Technology, 13(4), 1720-1724. https://doi.org/10.5958/0974-360X.2020.00310.8

[22] Moore, J.W., Flanner, H. H., (1996): Mathematical comparison of dissolution profiles; Pharm Tech, 20 (6), 64-74.

[23] O'Hara, Thomas, Adrian, Dunne, Jackie, Butler, John, Devane, (1998): A Review of Methods Used to Compare Dissolution Profile Data; Pharmaceutical Science and Technology Today, 1(5), 214–23.

[24] Paarakh, M. P., Jose, P. A., Setty, C. M., and Christoper, G. V., (2019): Release kinetics- concepts and applications: International Journal of Pharmacy Research and Technology, 8(1). https://doi.org/10.31838/ijprt/08.01.02

[25] Ruiz, M. E., & Volonte, M. G., (2014): Biopharmaceutical relevance of dissolution profile comparison: Proposal of a combined approach; Dissolution Technologies, 21, 32-43. https://doi.org/10.14227/DT210114P32

[26] Shah, J. C., & Deshpande, A., (2014): Kinetic modelling and comparison of in-vitro dissolution profiles; World Journal of Pharmaceutical Sciences., 2(4), 302-309. https://wjpsonline.com/index.php/wjps/article/view/kinetic-modeling-comparison-invitro-dissolution-profiles.

[27] Sheth, T. S., Acharya, F., (2021): Optimizing similarity factor of in-vitro drug release profile for development of early-stage formulation of drug using linear regression model; Journal of Mathematics in Industry ,11(9) https://doi.org/10.1186/s13362-021-00104-9 .

[28] Zeeshan, F., Lin, P. Y., & Sheshala, R., (2020): Application of similarity factor (f2) and time required to drug Release (t%) indicators for dissolution profiles comparison of Paracetamol tablets; Indian Journal of Pharmaceutical Education and Research; 54(3): 647-53 http://dx.doi.org/10.5530/ijper.54.3.114 .

[29] Zhang, Y., Huo, M., Zhou, J., Zou, A., Li, W., Yao, C., & Xie, S., (2010): DD Solver: an add-in

program for modeling and comparison of drug dissolution profiles. The AAPS journal, 12(3), 263–271. https://doi.org/10.1208/s12248-010-9185-1