Comparison of the Use of Kinetic Model Plots by DD Solver Software to Evaluate the Drug Release from Rutin-Mesoporous SBA-15 Complex

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Abstract- The understanding of the release kinetics of active drugs is crucial for developing dosage forms that deliver drugs effectively and for predicting their behaviour *in vivo*. This study aims to investigate the mechanism of drug release from a complex of Rutin and mesoporous SBA-15 (MSBA-15) using mathematical models, and to compare the use of graphs and DD solver software in fitting dissolution profiles to kinetic models. The Rutin was loaded into MSBA-15 using the solvent evaporation technique, and a control batch of pure Rutin was also prepared for comparison.

The dissolution profiles showed that the complexed formulation improved the release of Rutin compared to pure Rutin. The researchers used Excel add-in DD solver and kinetic plots to determine the kinetic model that best fits the data. The results indicate that the first-order model and the Korsmeyer-Peppas model have the highest goodness of fit parameters, with Rsqr values of 0.9742 and 0.9747, respectively. This suggests that these models are the most appropriate for describing the release kinetics of the Rutin-MSBA-15 complex from the DD solver.

Keywords: Rutin, Mesoporous SBA-15, Kinetics, Models, DD solver, Dissolution profile, mathematical models

INTRODUCTION

Rutin poor solubility in aqueous media is the reason for its poor bio-availability. Enhancing the lower bioavailable Rutin with mesoporous SBA-15 inclusion complex helps in various pharmacological activity such as antiallergic, anti-inflammatory, vasoactive, antitumor, antibacterial, antiviral, anti-protozoal, hypolipidemic, cyto-protective, antispasmodic and anticarcinogenic effects [1,2]. Overcoming the problem of poor solubility in aqueous media helps in enhancing the usage/ administration of Rutin orally and thereby increasing the patient compatibility [3].

Mesoporous SBA refers to a class of porous materials that are characterized by a highly ordered array of uniform-sized pores in the mesoscale range (typically 2-50 nm in diameter) and a high surface area. The name SBA stands for Santa Barbara Amorphous, which was coined by researchers at the University of California, Santa Barbara who first synthesized these materials.

SBA materials are synthesized through a sol-gel process, where a precursor solution containing inorganic and organic components is hydrolysed and polymerized to form a three-dimensional network of interconnected nanoparticles. The nanoparticles are then removed through calcination or other methods, leaving behind the mesoporous structure. The high surface area and ordered pore structure make them useful for a variety of applications, such as catalyst supports, drug delivery, solubility enhancement. The concept of mesoporous silica as a drug delivery carrier was utilized by Vallet-Regi and colleagues in the year of 2001[4]. Subsequently, the research on their biomedical applications has increased exponentially, and successfully applied to a variety of poorly water-soluble drugs for improved the rate of dissolution [5,6].

Thus, the combination of the essential properties of mesoporous silica with natural products has provoked interest in studies concerned with the spread of these molecules from a controlled release system.

Drug release is a crucial process in which the active drug in a medication is released through dissolution or diffusion into the body's aqueous medium[7]. Immediate release formulations do not delay drug absorption and availability, whereas delayed-release formulations have an intended delay in drug absorption. Extended-release formulations are designed to make the drug available over an extended period, and controlled

release formulations regulate the quantity and timing of drug release, which could be pulsatile or extended [8].

Since a drug must solvate before it can be absorbed, tablets must dissolve in the gastrointestinal tract's contents before systemic absorption can occur. Dissolution studies provide valuable information on drug release patterns, and several mathematical kinetic models have been published to study drug release kinetics [9,10]. Some commonly used models include the Hixon-Crowell model, Higuchi model, first-order kinetics, and zero-order kinetics. Additionally, the Korsmeyer-Peppas model and the Weibull model have been utilized to interpret drug release mechanisms [11].

In-vitro drug release kinetics

The cumulative amount of Rutin release at different time intervals from the different formulation of were fitted to zero order kinetics, first order kinetics, Hixson-Crowell Kinetics, Higuchi's model and korsmeyer-Peppas model to characterize mechanism of drug release.

a) Zero order release kinetics: Zero order release kinetics describes the constant release of a drug from a delivery device, where the release rate is independent of the drug's concentration. This can be represented as: $Q = Q0 + K0t$

Where Q is the amount of drug released in time t, Q0 is the initial amount of drug in the device, and K0 is the zero-order release constant. If the zero-order drug release kinetics is followed, the plot of cumulative drug release (Q) vs. time (t) will be a straight line with a slope of K0 and an intercept at Q0.

Zero order release kinetics may be desired for slow and prolonged delivery of drugs like antibiotics, antidepressants, pain management, maintaining blood pressure, and cancer therapy [12,13].

b) First order release kinetics: First order release kinetics describes drug release from a system in which the release rate is dependent on the drug's concentration. The drug's release pattern, which follows first order kinetics, can be expressed by the equation: $dC/dt = -K1C$

This equation can also be expressed as: $Log\ C = log\ C0 - K1t/2.303$ Where C is the amount of drug released in time t, C0 is the initial amount of drug in the device, and K1 is the first-order release constant.

If the release pattern of the drug follows first-order kinetics, then the plot of the logarithm of cumulative drug remaining [log (C0 - C)] vs. time (t) will be a straight line with a slope of K1/2.303 and an intercept at t=0 of logC0.

First order release kinetics is commonly used to study drug absorption and elimination, and it is relevant in drug delivery systems where a rapid initial release of the drug is required, such as in pain management or treatment of acute conditions.

c) Hixson-Crowell Kinetics: Hixson and Crowell (1931) proposed that the rate of drug release from a solid dosage form can be related to the surface area of the drug particles and the cube root of the amount of drug remaining in the dosage form. The Hixson-Crowell equation is given as: $(W_0 - W_t)^{1/3} = KHC * t$

where W_0 is the initial amount of drug in the dosage form, W_t is the amount of drug released at time t, and KHC is the Hixson-Crowell rate constant. If the Hixson-Crowell drug release kinetic is obeyed, then the plot of the cube root of the remaining drug amount $(W_0 - Wt)^{1/3}$ versus time (t) will be a straight line with a slope of KHC and an intercept at $(W_0)^{1/3}$.

d) Higuchi Model: Higuchi (1961 & 1963) proposed a theoretical model to study the release of drugs from insoluble matrices based on Fickian diffusion. The Higuchi model describes the release of drugs from a solid dosage form as a square root of a time-dependent process. The equation for the Higuchi model is: $Mt/M\infty = KH * t_{1/2}$

where Mt and M∞ are the cumulative amount of drug release at time t and infinite time, respectively. KH is the Higuchi release constant. If the Higuchi model of drug release is obeyed, then the plot of Mt/M∞ versus $t_{1/2}$ will be a straight line with a slope of KH. The Higuchi model is often used to describe drug release from insoluble matrices such as tablets and implants [14].

e) Korsmeyer-Peppas Model: Korsmeyer et al. (1983) derived a simple relationship which describes the fractional drug release as a function of time. It adequately describes the release of drug from a polymeric system of slabs, cylinders and spheres, as expressed in the following equation: $Mt/M\infty = Kt^n$ or $Log\ (Mt/M\infty) = log\ K + n\ log\ t$ Where, Mt/M∞ - fraction of drug released at time 't', K - the rate constant, and n - the diffusion exponent indicative of the mechanism of drug release. If the Korsmeyer-Peppas model of drug release is obeyed, then a plot of log cumulative % drug release [log (Mt/M∞)] vs. log time [log t] will be a straight line with a slope of n.

Alternatively, the model can also be expressed as: F = (Mt/M∞) = K' * t^n Where, K' - a modified rate constant incorporating drug loading and tablet geometry. The Korsmeyer-Peppas model is widely used for describing drug release from polymeric systems, and can help in optimizing drug delivery systems for controlled release.

Table 1: Mechanism of Drug Release as per Korsmeyer Peppa's model

S. No	'n' value	Drug release Mechanism
1.	0.45	Fickian release, Diffusion release Square root of time depended
2.	0.45 <n<0.89	Diffusion and swelling, Non- Fickian release, Time depended/First order
3.	n>0.89	Swelling controlled, Independent of time/ Zero order Case II transport

d) Weibull Model: The Weibull model is an empirical model used for different dosage formulations to describe drug release kinetics. Its equation is: F = 100*{1 - exp[-((t-Ti)^β)/α]} Where, F = accumulated portion of the drug, β = shape parameter, α = scale parameter or apparent rate constant, Ti = location parameter or time lag (usually zero), t = time in hours. The α value in the Weibull model represents the time scale or apparent rate constant, while the β value characterizes the shape of the release curve. When β = 1, the curve is exponential and corresponds to first-order kinetics. A value of β > 1 indicates a sigmoidal curve, with an increasing rate of drug release over time. β < 1 indicates a parabolic curve, with a decreasing rate of drug release over time. A plot of log of dissolved amount of drug vs log time gives a linear graph, with β obtained from the slope of the graph and α obtained from the y-axis (1/α) at time t = 1. The time taken for 63.2% of the drug to be released, Td, can be used to replace the parameter α and can be obtained from the y-axis.

In this study, the ability of Mesoporous SBA-15 to improve the dissolution of Rutin was evaluated using the Excel add-in app DD Solver and kinetic graphs to analyze the release kinetics of the Rutin-Mesoporous SBA-15 complex.

Experimental

Materials

Rutin and Pluronic P123(Yarrow Chem, Mumbai), Tetraethyl orthosilicate (Otto Chem pvt ltd), Ethanol (Indian Fine Chemicals), Sodium hydroxide and Potassium dihydrogen phosphate (Karnataka Fine Chem), Disodium hydrogen phosphate and Hydrochloric acid (SD Fine Chem. Limited)

Methods

Rutin loading into mesoporous SBA-15

The mesoporous SBA-15 was dispersed in a Rutin containing ethanol. Then this solution was dried by fast solvent evaporation by heating for obtaining drug-loaded in mesoporous silica material. He *et al* suggested that the solvent evaporation method gives the drug molecules enough time to rearrange and aggregate inside the mesopores [15].

Determination of the drug loading efficiency

The drug loaded efficiency (EE) was calculated after extracting the drug from the prepared inclusion complex. Equivalent to 100 mg Rutin from the final product were insulated in 100 ml of phosphate buffer (pH 6.8) and stirred magnetically at 500 rpm for 6 h for completely extracted Rutin. After completion of 6 hours these solutions were diluted and analyzed by a UV-VIS spectrophotometer at 360 nm. All trails were done in triplet. The percentage of drug loaded was calculated by using below equation [16]

$$\text{Drug loaded (\%)} = \frac{\text{Practical drug loading}}{\text{Theoretical drug loading}} \text{X } 100$$

Dissolution study of Rutin Mesoporous SBA-15 complex

The rate of dissolution of Rutin from SBA-15 in comparison to pure Rutin was assessed using a dissolution apparatus I. A volume of 900 mL of HCl 0.1 N (pH 1.2) for 2 h and replaced by phosphate buffer (6.8pH) for 7 h was used as dissolution medium at 37°C with a speed of 100 rpm. About 100 mg of pure Rutin and equivalent to 100 mg of Rutin complex were packed in muslin cloth and placed in each dissolution basket. The samples of 5 ml were taken every 1 h interval and in order to maintain a constant volume fresh medium was added (at 37°C). The Rutin concentration was measured with a UV-VIS spectrophotometer at 360 nm. The assays were done in triplicate and mean values were calculated [17].

Kinetics of drug release

The dissolution profiles of the formulated batches with untransformed data were fitted to different kinetic models: zero order, first order, Higuchi model, Hixon-Crowell model, Korsmeyer -Peppas model and the Weibull kinetic model using the Excel Add-in DD solver version 1.00 [18]. Lowest Akaike information criterion (AIC), highest model selection criterion (MSC) and highest adjusted coefficient of determination (R2 adj) values were used in selecting the model with the best fit [19, 20]. The correlation coefficient of highest degree establishes the kinetic model that best fits the drug's release [21]. The release exponent (n) of the Korsmeyer -Peppas model and shape parameter (β) of the Weibull model were obtained from the slope of their respective plots [22].

RESULTS AND DISCUSSION

Drug loading efficiency:

The percentage of drug loading efficiency of MSBA-15 was 71.2%. A high drug loading efficacy is desirable for many applications since it can lead to a higher concentration of the active drug in the target tissue, which may improve the efficacy of the drug. However, a lower drug loading efficacy may be acceptable if the formulation still achieves the desired therapeutic effect.

In-vitro drug release study:

Figure1 shows the *in-vitro* drug release study of Rutin and formulation, where the concentration of the drug is measured at different time intervals.

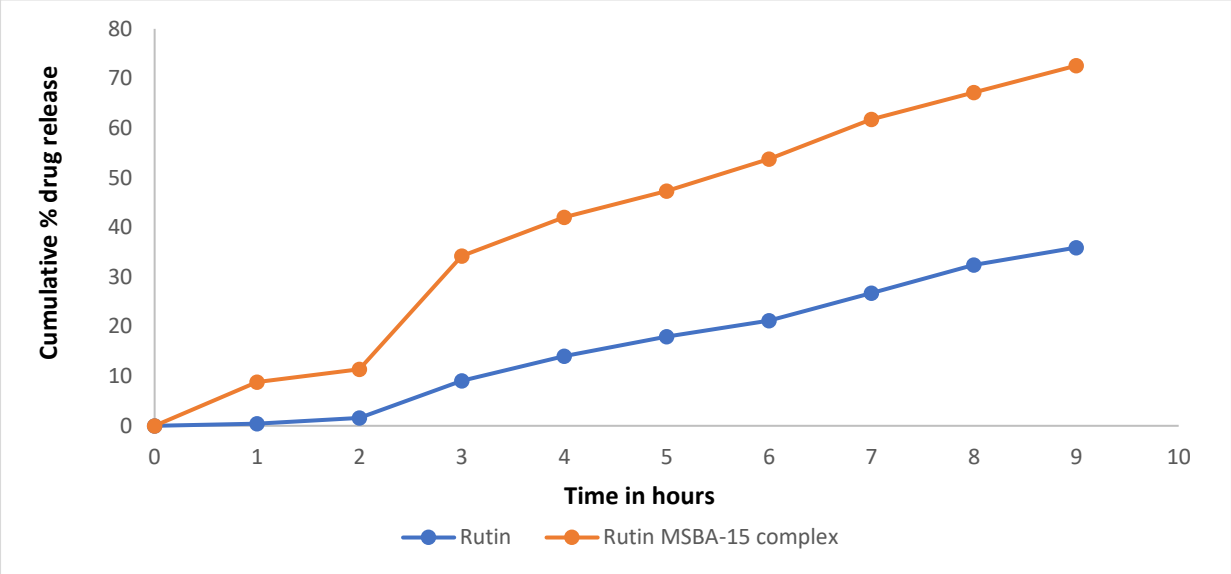

Figure1: *In-vitro* drug release study of Rutin and Formulation

From the data, we can see that the percentage of drug release of Rutin increases with time in the given formulation. At 1 hour, the percentage of drug release is 0.45%, which gradually increases to 35.92% at 9th hour.

In terms of the formulation, at 1 hour, the formulation shows an 8.84% drug release, which gradually increases to 72.58% at 9th hour.

Comparing the values, we observed that as the time increases, the percentage of drug release of Rutin increases in the given formulation. This indicates that the Rutin MSBA-15 complex is effective in releasing the drug over a period of time, and the drug release kinetics can be further optimized for better performance.

Kinetics of drug release:

The table 2 showed that a kinetic drug release study of Rutin was conducted using a DD (differential dissolution) solver. The study tested various models and equations to determine the goodness of fit parameters for the release of Rutin. The models tested include zero-order, first-order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell, Hopfenberg, Baker-Lonsdale, and Weibull. The goodness of fit parameters evaluated include R_obs-pre, Rsqr, MSE, MSE_root, SS, AIC, and MSC.

Table 2: Kinetic drug release study of Rutin from DD solver Goodness of fit parameters

Model & Equation	Goodness of fit parameters						
	R_obs-pre	Rsqr	MSE	MSE_ root	SS	AIC	MSC
Zero-order	0.9961	0.9501	8.0160	2.8313	64.1280	39.4479	2.7758
First-order	0.9946	0.9218	12.5653	3.5448	100.5225	43.4934	2.3263
Higuchi	0.9841	0.6921	49.4818	7.0343	395.8545	55.8294	0.9557
Korsmeyer-Peppas	0.9933	0.9849	2.7730	1.6652	19.4113	30.6927	3.7486
Hixson-Crowell	0.9953	0.9320	10.9313	3.3063	87.4505	42.2397	2.4656
Hopfenberg	0.9911	0.9742	4.7340	2.1758	33.1377	35.5060	3.2138
Baker-Lonsdale	0.9819	0.6710	52.8719	7.2713	422.9749	56.4258	0.8894
Weibull	0.9972	0.9945	1.1881	1.0900	7.1284	23.6767	4.5282

The results indicate that the Weibull model had the highest goodness of fit parameters, with an R_obs-pre of 0.9972 and an Rsqr of 0.9945. The Korsmeyer-Peppas model also had high goodness of fit parameters, with an R_obs-pre of 0.9933 and a Rsqr of 0.9849. The other models tested had varying levels of goodness of fit parameters, with the zero-order, first-order, and Hixson-Crowell models showing relatively high goodness of fit as well. Overall, these results suggest that the Weibull and Korsmeyer-Peppas models may be effective for modeling the kinetic release of Rutin from the DD solver.

Table 3: Kinetic drug release study of Rutin from DD solver Best- fit Values

Zero order	First order	Higuchi	Korsmeyer-Peppas		Hixson Crowell	Hopfenberg		Baker-Lonsdale	Weibull		
k0	k1	kH	KkP	n	kHC	kHB	n	kBL	α	β	Ti
3.767	0.043	9.083	1.972	1.335	0.014	0.080	0.366	0.002	1.012	1.575	17.342

The table 3 shows the best-fit values of the kinetic drug release models for Rutin from DD solver. Starting with the zero-order model, the best-fit value of k0 is 3.767, which means that the drug release rate is constant over time. For the first-order model, the best-fit value of k1 is 0.043, indicating that the drug release rate decreases exponentially with time. The Higuchi model has a best-fit value of kH of 9.083, indicating that the drug release follows a square root of time pattern.

Moving on to the Korsmeyer-Peppas model, the best-fit value of KkP is 1.972, suggesting that the drug release follows a non-Fickian diffusion mechanism. The parameter n has a value of 1.335, indicating that the drug release follows a quasi-Fickian diffusion mechanism.

For the Hixson-Crowell model, the best-fit value of kHC is 0.014, suggesting that the drug release depends on the square root of the difference in volume between the initial and remaining particles. The Hopfenberg model has a best-fit value of kHB of 0.080, indicating that the drug release follows a power law pattern. The parameter n has a value of 0.366, indicating that the drug release follows a non-Fickian diffusion mechanism.

For the Baker-Lonsdale model, the best-fit value of kBL is 1.575, suggesting that the drug release follows a surface erosion mechanism. The Weibull model has a best-fit value of α of 17.342 and β of 1.012, indicating that the drug release follows a sigmoidal pattern. Finally, Ti is the initial lag time before the drug release starts, and its value is 7.1284 for the Weibull model.

Overall, the best-fit values provide insight into the release kinetics of Rutin from the DD solver, which can be useful for optimizing drug delivery systems. However, it is important to note that the best-fit values should be interpreted with caution and validated with experimental data.

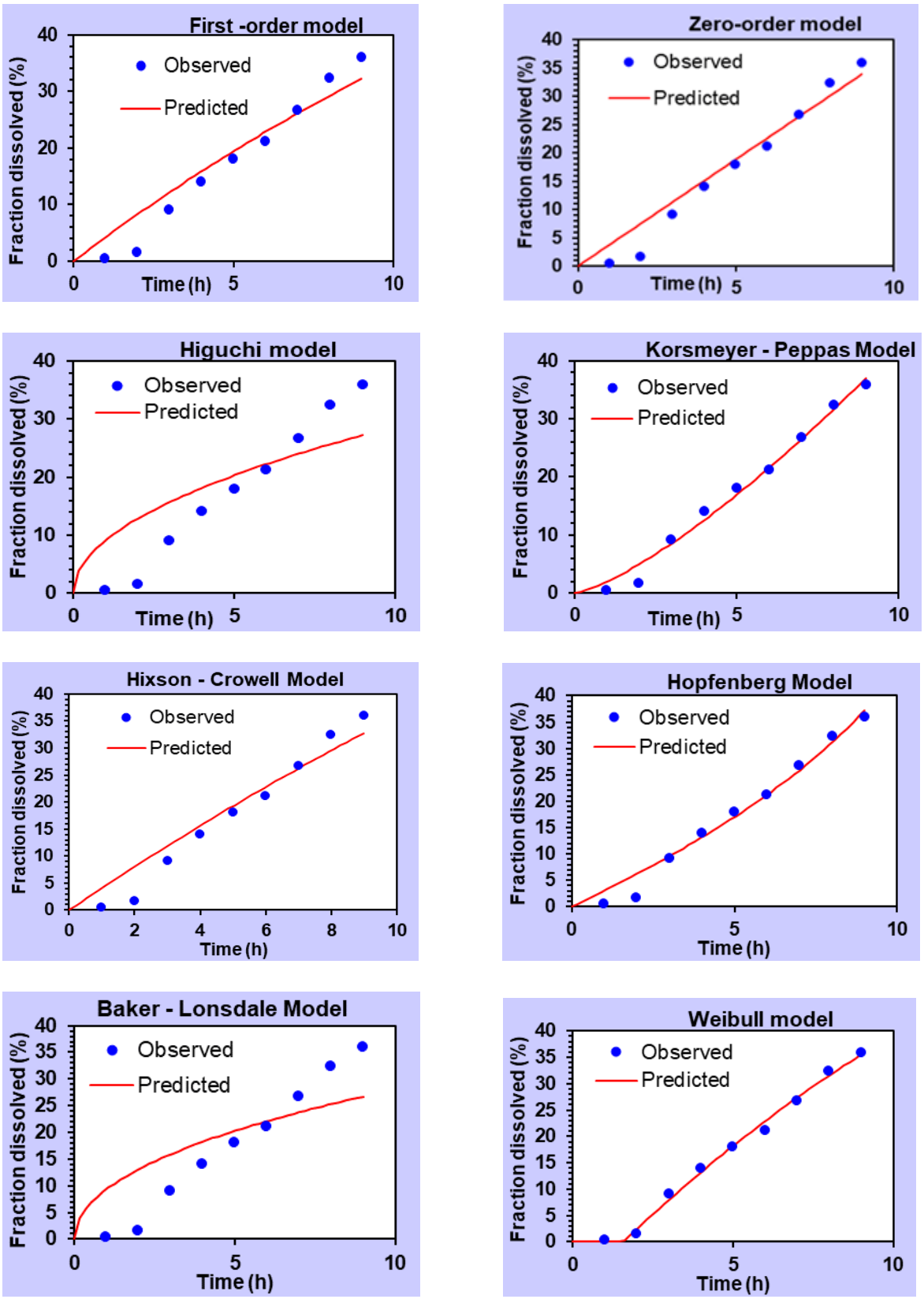

Figure 2: Graph for release kinetics obtained automatically by the DD Solver software for Rutin

Table 4: Kinetic drug release study of Rutin MSBA-15 complex from DD solver Goodness of fit parameters

Model & Equation	Goodness of fit parameters						
	R_obs-pre	Rsqr	MSE	MSE_ root	SS	AIC	MSC
Zero-order	0.9835	0.9646	23.3465	4.8318	210.1182	55.4767	2.8297
First-order	0.9910	0.9742	17.0545	4.1297	153.4908	52.3364	3.1438
Higuchi	0.9634	0.8888	73.3676	8.5655	660.3085	66.9271	1.6847
Korsmeyer-Peppas	0.9876	0.9747	18.7664	4.3320	150.1310	54.1151	2.9659
Hixson-Crowell	0.9907	0.9791	13.7911	3.7136	124.1198	50.2125	3.3561
Hopfenberg	0.9904	0.9801	14.7839	3.8450	118.2714	51.7298	3.2044
Baker-Lonsdale	0.9477	0.8491	99.6062	9.9803	896.4562	69.9845	1.3789
Weibull	0.9925	0.9850	12.6955	3.5631	88.8682	50.8715	3.2902

Based on the values in the table 5, the first-order model shows the best fit with the highest R_obs-pre (0.9910), Rsqr (0.9742), and lowest MSE (17.0545) and MSE_root (4.1297) values. The Weibull model also shows a good fit with high R_obs-pre (0.9925) and Rsqr (0.9850) values and a low MSE_root (3.5631) value.

On the other hand, the Higuchi model shows a relatively poor fit with lower R_obs-pre (0.9634) and Rsqr (0.8888) values and a higher MSE (73.3676) and MSE_root (8.5655) values. The Baker-Lonsdale model also shows a relatively poor fit with a lower Rsqr value (0.8491) and higher MSE (99.6062) and MSE_root (9.9803) values.

The values of the goodness-of-fit parameters for the Weibull model are used to evaluate how well the model fits the experimental data. The R_obs-pre and Rsqr values are measures of the correlation between the predicted and observed drug release data, with higher values indicating better correlation. The MSE and MSE_root values are measures of the goodness of fit of the model, with lower values indicating better fit. The SS value is a measure of the sum of squares of the residuals, with lower values indicating better fit. The AIC and MSC values are measures of the relative quality of the model, with lower values indicating better quality. Based on these parameters, the Weibull model appears to provide a good fit to the experimental data, with high values for R_obs-pre and Rsqr, and low values for MSE, MSE_root, SS, AIC, and MSC.

Table 5: Kinetic drug release study of Rutin MSBA-15 from DD solver Best-fit Values

Zero-order	First-order	Higuchi	Korsmeyer-Peppas		Hixson-Crowell	Hopfenberg		Baker-Lonsdale	Weibull		
k0	k1	kH	KkP	n	kHC	kHB	n	kBL	α	β	Ti
8.716	0.015	21.706	11.490	0.855	0.038	0.053	2.069	0.010	7.679	1.067	0.465

The best-fit values of Rutin MSBA-15 complex showed in table 6. Zero-order model, the best-fit value of the rate constant (k0) is 8.716. In the First-order model, the best-fit value of the rate constant (k1) is 0.015. In the Higuchi model, the best-fit value of the rate constant (kH) is 21.706, and the square root of the mean square error (MSE_root) is 11.490.

Similarly, for the Korsmeyer-Peppas model, the best-fit values of the rate constant (KkP) and the exponential constant (n) are 0.855 and 0.038, respectively. In the Hixson-Crowell model, the best-fit values of the rate constant (kHC) and the cube root of the mean square error (MSE_root) are 2.069 and 7.679, respectively.

For the Hopfenberg model, the best-fit values of the rate constant (kHB) and the exponential constant (n) are 1.067 and 0.465, respectively. In the Baker-Lonsdale model, the best-fit value of the rate constant (kBL) is 0.465. Finally, in the Weibull model, the best-fit values of the scale parameter (α), the shape parameter (β), and the lag time (Ti) are 88.8682, 50.8715, and 3.2902, respectively. These best-fit values provide insight into the kinetics of drug release from the DD solver, which can be used to optimize the release profile of the drug.

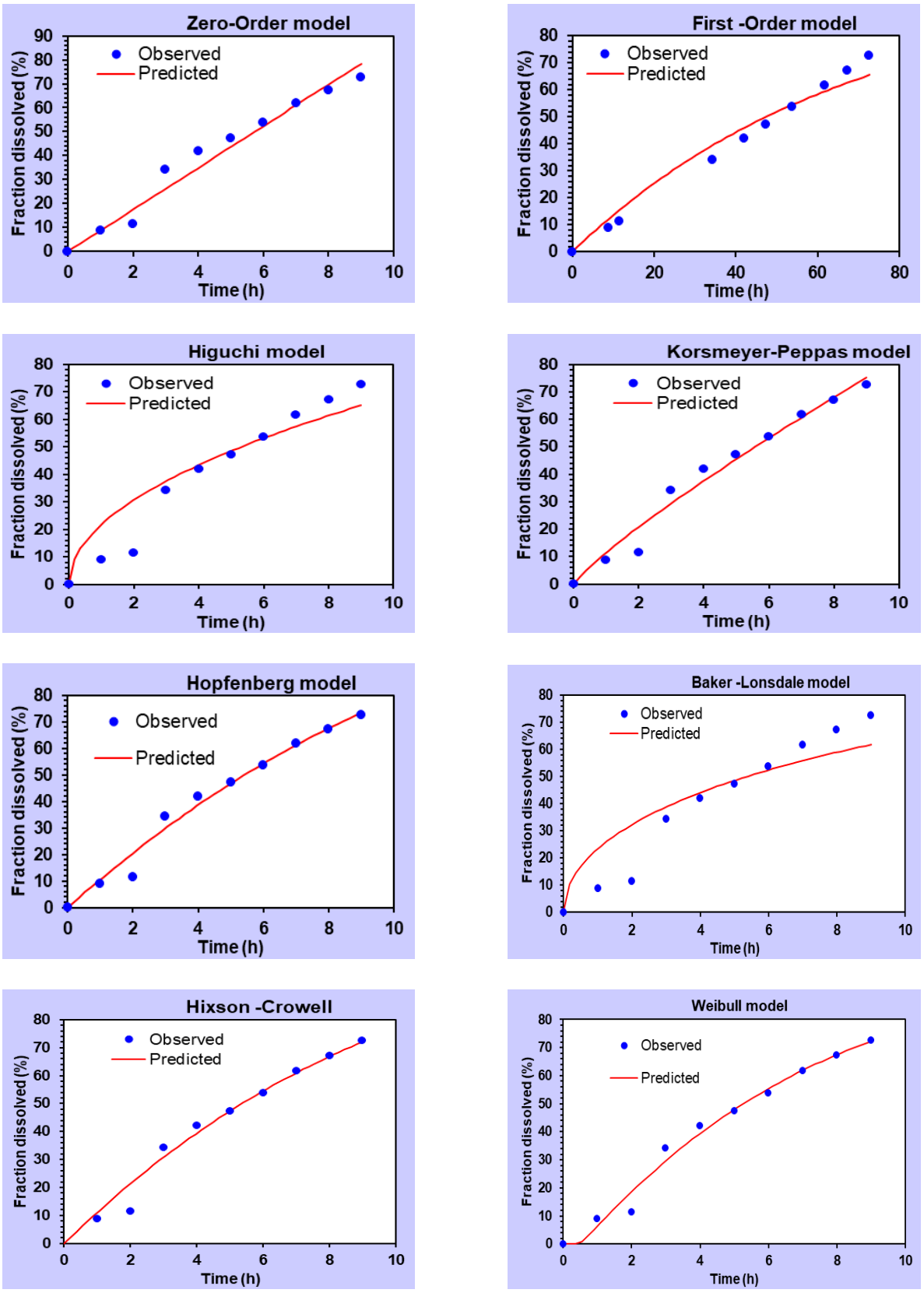

Figure. 3: Results for release kinetics obtained automatically by the DD Solver software for Rutin MSBA-15 complex

CONCLUSION

The dissolution studies were conducted for 9 hours, with 2 hours in pH 1.2 buffer and 7 hours in pH 6.8 buffer. The results showed a significant increase in the release rate of the loaded drug approximately 72.58% of the drug at the end of 9 hours, in comparison to pure Rutin.

Based on the analysis of the goodness-of-fit parameters for the different models, it can be concluded that the Weibull model provides the best fit to the experimental data for drug release. This is evident from the high R_obs-pre and Rsqr values, which indicate a strong correlation between the predicted and observed drug release data. Additionally, the low values of MSE, MSE_root, SS, AIC, and MSC further support the superior fit of the Weibull model compared to the other models evaluated.

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