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Determination of *In- Vitro* Release Kinetics of Metformin Hydrochloride from Six Brands of Metformin Hydrochloride Tablets Available in Bangladesh Using Water Media: A UV Spectroscopic Analysis

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Abstract: The purpose of this study was to determine the *in vitro* release kinetics of different brands of metformin HCl tablets available in the local pharmaceutical market of Bangladesh. For this study, six widely prescribed brands M1, M2, M3, M4, M5 and M6 were chosen. All of these brands were of 500 mg metformin HCl with strip packaging. The dissolution was carried out using USP apparatus-II and the analysis was performed with the UV spectroscopy. To find out the release kinetics K_0 (for zero order), K_1 (for first order), K_h (for Higuchi model), K and n (for Korsmeyer-Peppas model) and K_{HC} (for Hixon Crowell model) were determined. The R^2 value for each kinetics was also determined which indicated the linearity of release kinetics for each brand. The study found no brand to follow the zero order kinetics mostly. Brand M1 mainly followed the first order (R^2=0.982) and the Hixon-Crowell model (R^2=0.982) whereas M2 followed the Higuchi model (R^2=0.979). At the same time brands M3 and M4 were found to follow Korsmeyer-Peppas (R^2=0.996 and 0.992 respectively) and Hixon-Crowell model (R^2=0.992 and 0.991 respectively). However, brand M5 and M6 followed Hixon-Crowell equation with the R^2 value of 0.984 and 0.988 consecutively. So this study assumes that the available metformin HCl tablet brands available in Bangladesh generally follow the Hixon-Crowell release kinetics.

Key words: Metformin, UV, Zero order, First order, Higuchi, Korsmeyer-Peppas, Hixon Crowell, R2, kinetics

INTRODUCTION

Within Metformin is a first line oral anti-hyperglycemic agent used in the treatment of non-insulin dependent Type-2 diabetes mellitus and thus lowering the blood glucose concentration without causing hypoglycemia.(Wadher et al., 2010) It has relatively short plasma half life, low absolute bioavailability(Wadher et al., 2011) that mechanizes by decreasing the intestinal absorption of glucose, increased glucose uptake from the blood into the tissues, decreased glucose production in the liver, and decreased insulin requirements for glucose disposal. It is contraindicated for lactic acidosis. (Klepser et al., 1997, (Salpeter et al., 2010) During its initial use, it shows symptoms like abdominal discomfort, nausea, diarrhea etc. (Gusleret al., 2010). For better tolerance in GIT, it is dosed in an escalated manner with each

meal. (Odidi et al., 2001) Metformin shows anti-hyperglycemic activity by suppressing glucose production by the liver (hepatic gluconeogenesis). It activates adenosine monophosphate-activated protein kinase; an enzyme that helps in insulin signaling and also by glucose and fats metabolism etc. (Cusi et al., 1996), (Davidsonet al., 1997), (Setter et al., 2003).

Dissolution is the process of how the active pharmaceutical ingredient is released from the solid-state matrix of the dosage form into media within the gastrointestinal tract. In other words, dissolution testing is an *in vitro* method of how much an active pharmaceutical ingredient is solubilized into the GI media under specified standard condition. (Roy et al., 2013). Physiological availability of the drug substance along with its product release and stability testing is measured and signified by dissolution testing especially in case of oral solid dosage forms. (Roy et al., 2013).

Release kinetics can be defined as the reaction rate or order by which a drug is extracted out from the solid-state matrix of the dosage form. *In vitro* dissolution testing helps to determine the percent drug release from a tablet (for oral solid dosage form) and also to find out their release kinetics. It also guides the optimization of drug release as well dissolution efficiency from formulations. (Sheorey et al., 1991), (Khan et al., 1975).

In Bangladesh, a lot of national and multinational companies having different brands of metformin hydrochloride are available. This paper shows the *in vitro* dissolution study and determination of release kinetics of six brands of metformin hydrochloride in deionized water media of six different national brands.

Materials and methods:

All the materials and equipment's are mentioned in the table 1.

Standard Active drug	Metformin hydrochloride
Solvents and reagents	Deionized water/distilled water.
Equipment	UV spectrophotometer, Tablet dissolution tester, Analytical Balance.

Table 1: Materials and equipment's

Six national brands of marketed metformin hydrochloride tablets of the test drug were collected from various pharmaceutical stores. These were randomly coded as (M1, M2, M3, M4, M5, M6) in table 2.

Brand Names	1. M1 2. M2 3. M3 4. M4 5. M5 6. M6
API in each tablet	500 milligram
Packaging	Strip

Table 2: Coded brand names of six brands of metformin HCl tablets

In vitro dissolution study:

The *in vitro* dissolution study performed at USP type II apparatus (paddle type) at 100 rpm with a temperature of 37±0.5°C was divided into six sections assembly. Dissolution was carried out in 900 ml deionized water in each of the assembly. 5ml of dissolution medium was withdrawn by pipette at specific time intervals during 50 minutes of dissolution study. It was analyzed at 233.5 nm after filtration. The drug release data of the six brands were given input in various release kinetics equation such as zero order, first order, Higuchi, Korsmeyer-Peppas, Hixson Crowell equations to interpret their release kinetics of each. (Wadher et al., 2010), (Wadher et al., 2011), (Roy et al. 2013), (Biswas et al., 2008), (Mandal et al., 2008).

Determination of Release Kinetics:

Equation for Zero order kinetics:

The zero order equation assumes that the rate of drug release is independent of drug amount in the tablet matrix and the cumulative amount of drug release is directly proportional to time. The equation may be as follows:

$C=K_o t$; Where, C= cumulative drug release at 't' time; $K_{0=}$ zero order rate constant, t =time. A graph of cumulative drug release *vs* time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes. (Mandal et al., 2008), (Espenson, 1995).

Equation for first order kinetics:

The release behavior of first order equation expressed as log cumulative percentage of drug remaining against time. The equation may be as follows:

$\log C=\log C_o - k_1 t/2.303$; Where, C=amount of drug undissolved at 't' time, C_0 is drug amount at $t = 0$, k1 is the first order release rate constant. A graph where log C is plotted against time, would yield a straight line with a slope $-k_1/2.303$ and an intercept of logarithm of C_o. (Mandal et al., 2008), (Espenson, 1995).

Higuchi Equation for Drug Release:

The Higuchi release model is described as cumulative percentage of drug release versus square root of time. The equation may be written as:

$Q=K_h\sqrt{t}$; Where, Q = the amount of drug dissolved at time t. K_h is the constant reflecting the design variables of the system. Hence, drug release rate is proportional to the reciprocal of the square root of time. (Vanderpoel et al., 2004), (Kumar et al., 2008), (Siepmann et al., 2011), (Higuchi et al., 1963).

Korsmeyer-Peppas Equation for Drug Release:

The Korsmeyer-Peppas Model was developed to specifically model the release of a drug molecule from a polymeric matrix, such as a hydrogel. Korsmeyer et al. developed the following equation:

$\log (M_t/M_f) = \log k + n \log t$; Where $M_{t=}$amount of drug release at time t; $M_{f=}$ amount of drug release after infinite time; K= release rate constant incorporating structural and geometric characteristics of the dosage form; n= diffusional exponent indicative of the mechanism of drug release.

The log value of percentage drug dissolved is plotted against log time for each formulation according to the equation. A value of n less than 0.45 indicates Fickian (case I) release; n value ranging from 0.45 to 0.89 indicates non-Fickian (anomalous) release; n greater than 0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled drug release. (Basak et al., 2008), (Peppas et al., 1989).

Hixson-Crowell Cube Root Law for Drug Release:

It is the law that provides idea about the evaluation of drug release pattern changes with the surface area and the diameter of the particles/tablets. It is mentioned as the (cube root of the percentage of initial drug - cube root of the percentage of drug remaining in the matrix) *vs* time. The equation may be as follows:

$Q_o^{1/3} - Q_t^{1/3} = K_{HC}.t$; Where Q_0 is initial amount of the drug in the tablets, Q_t is the amount of drug remaining in time t and k_{HC} is rate constant for the Hixson-Crowell cube root law. (Singhvi et al., 2011), (Niebergall et al., 1963).

Result:

For the determination of drug release from metformin hydrochloride tablet, a standard curve was prepared using a concentration range of 0-10 microgram per milliliter. The pure active ingredient was supplied by Incepta Pharmaceuticals Ltd. which is one of the leading pharmaceutical companies in Bangladesh. The dissolution media used in the release kinetics determination was water. That is why, same deionized water was used for the preparation of standard curve. The standard curve provided an equation: y=0.074x-0.005 with a R^2 value of 0.999 which indicates sufficient linearity of the standard curve.

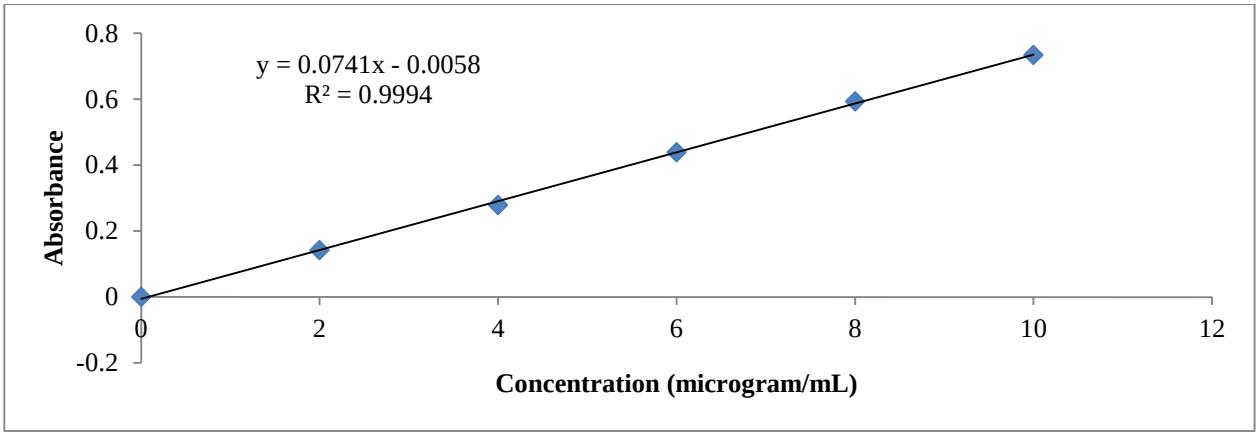

Figure 01: Standard curve of Metformin HCl

Time (minute)	Cumulative percentage of drug released from Metformin HCl Tablets					
	M1	M2	M3	M4	M5	M6
0	0	0	0	0	0	0
10	15.44	32.04	21.39	17.22	17.07	15.52
20	40.98	38.88	32.89	32.4	46.61	43.65
30	50.29	47.26	44.1	40.09	53.57	57.18
40	57.42	60.78	53.09	56.37	67.62	66.85
50	71.02	72.56	65.72	62.64	81.11	81.79

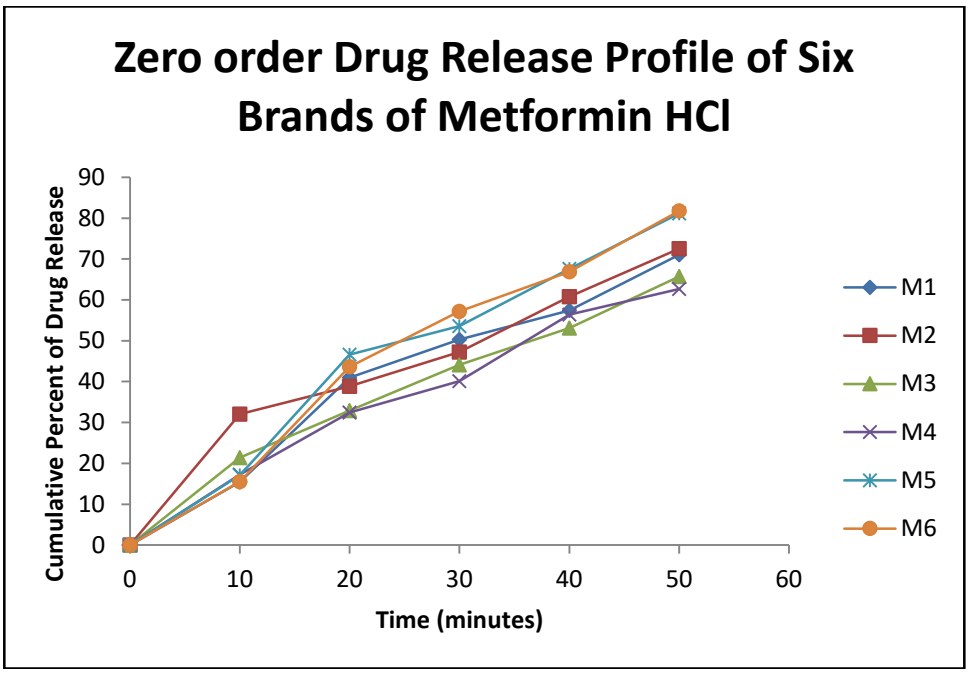

Figure 2: Zero Order Plot of Six Brands of Metformin HCl Tablets

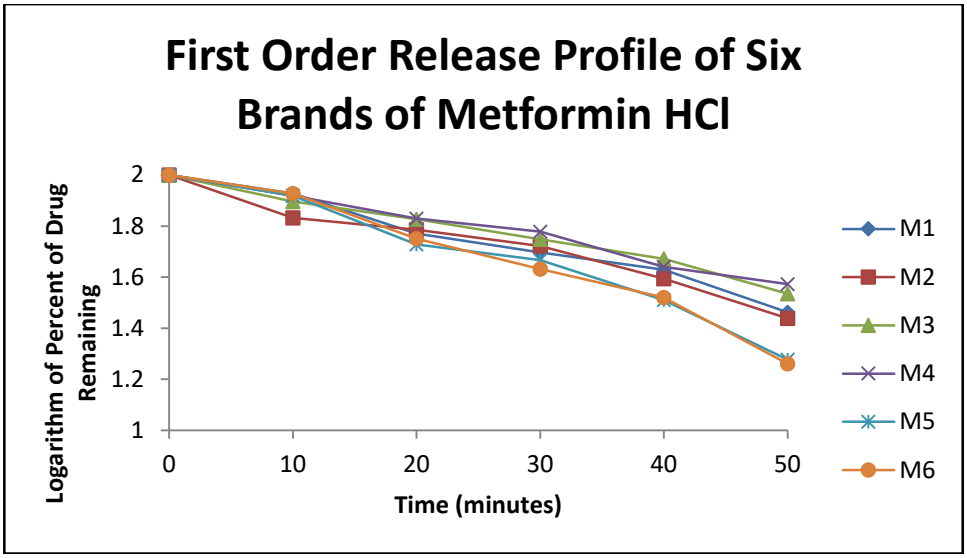

Figure 3: First Order Plot of Six Brands of Metformin HCl Tablets

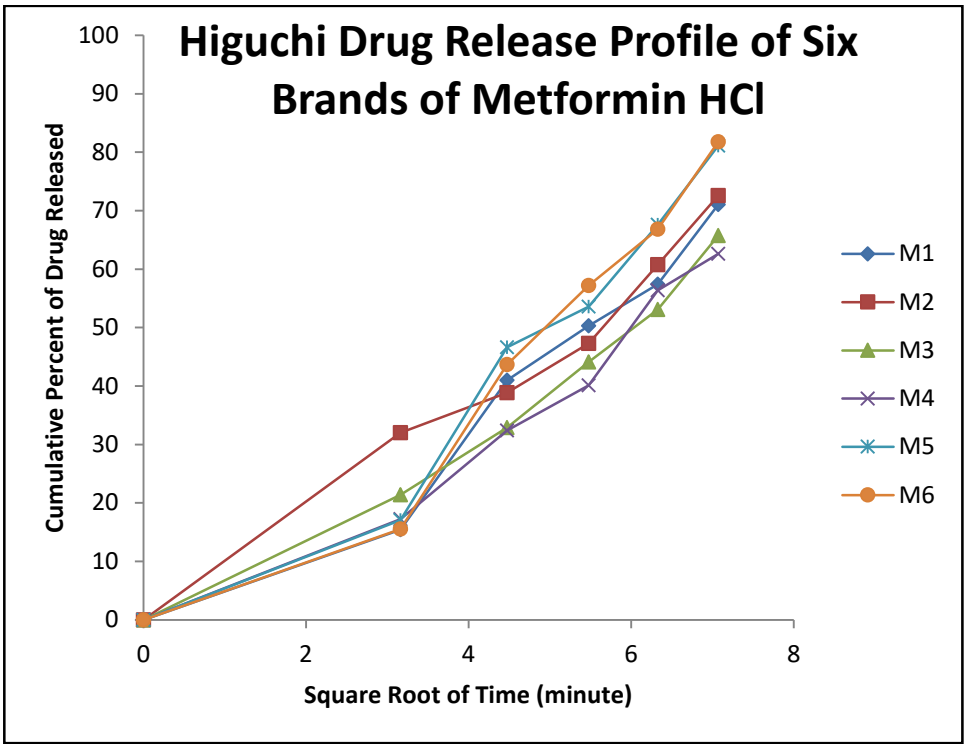

Figure 4: Higuchi Plot of Six Brands of Metformin HCl Tablets

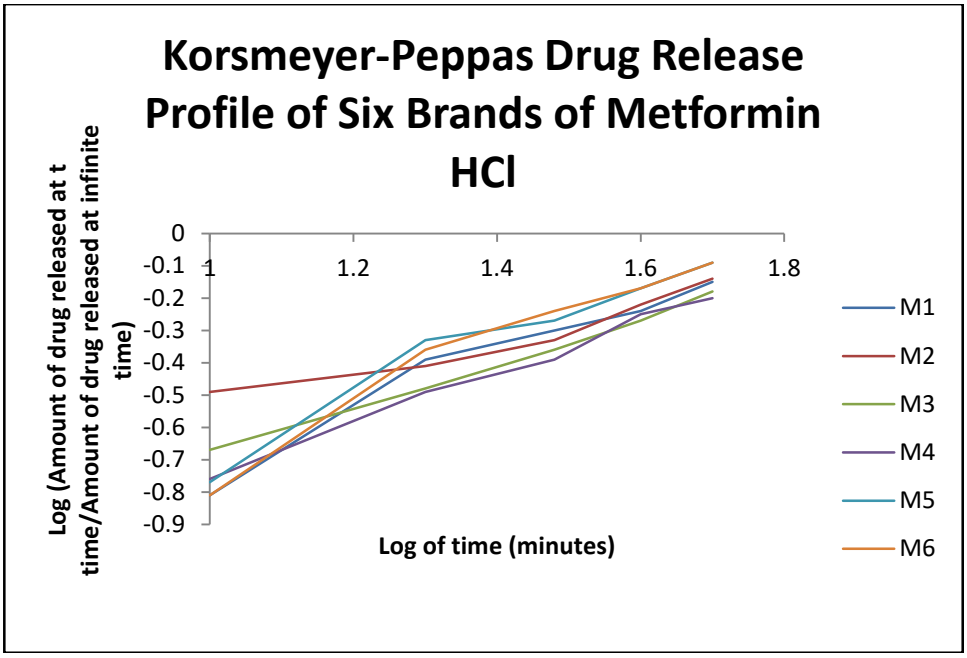

Figure 5: Korsmeyer-Peppas Plot of Six Brands of Metformin HCl Tablets

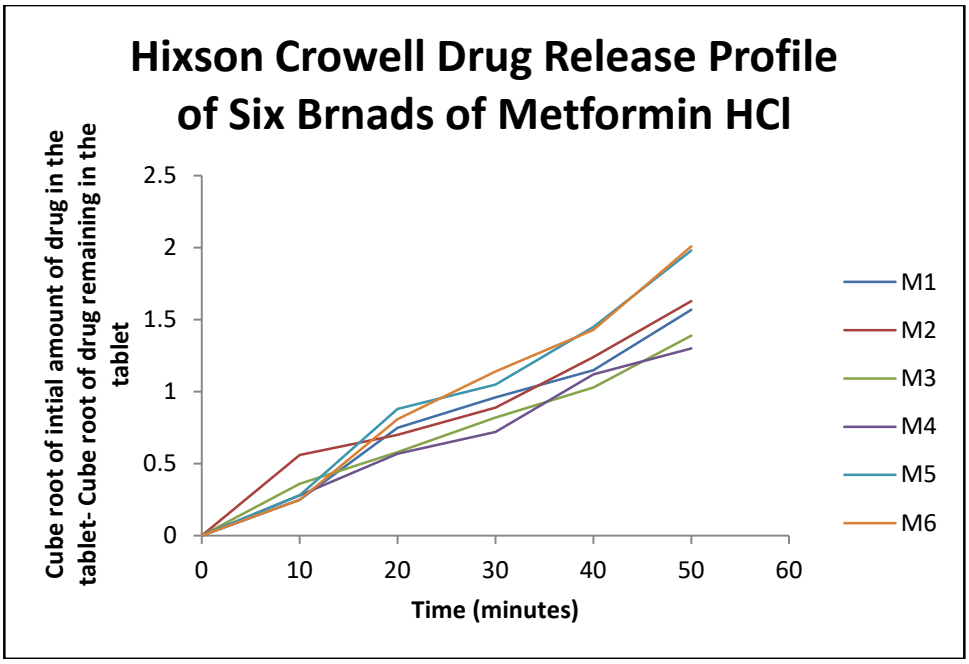

Figure 6: Hixson Crowell Plot of Six Brands of Metformin HCl Tablets

There are a number of commercially available metformin HCl tablets in Bangladeshi pharmaceutical market. The aim of this recent experiment was to evaluate the release kinetics as well as release mechanism of drugs from the drug matrix. Five mathematical equations were used to determine the release kinetics of drugs from the drug matrix. The R^2 value obtained from the curves are the indicative of drug release kinetics. And Korsmeyer-Peppas equation was used to determine the release mechanism.

The cumulative drug release against time is shown in table 4. A zero order graph was prepared using the cumulative drug release pattern against time. After 10 minutes, all the brands provided drug release less than 20% except brand M2 (32.04%) and brand M3 (21.39%). After 50 minutes of drug dissolution, six brands showed a cumulative drug release of 71.02%, 72.56%, 65.72%, 62.64%, 81.11% and 81.79% respectively. Zero

order rate constants and R^2 values were determined from the graph. Brand M4 provided the highest R^2 value of 0.982. And brand M2 displayed least R^2 value of 0.938. The release rate constants range from 1.243 to 1.647.

According to the first order drug release kinetics, the rate of drug release is directly proportional to the amount of drug remaining in the drug matrix. (Mandal et al., 2008), (Espenson, 1995). A graph was prepared plotting time on the X axis and Logarithm of % drug remaining on the Y axis. For the six brands, first order release rate constants were determined and R^2 values were obtained from the graph. Brand M3 and M4 provided highest R^2 value of 0.989 indicating sufficient linearity of the release kinetics. The first order release rate constants range from -0.009 to -0.014.

In the Higuchi plot, square root of time was plotted along X axis. The cumulative percent of drug release was plotted along Y axis. (Vanderpoel et al., 2004), (Siepmann et al., 2011), (Higuchi et al., 1963). The Higuchi rate constants for the six brands range from 9.007 to 11.793. The highest R^2 value was provided by the brand M2. The least linearity was displayed by the brand M6 (R^2=0.939).

In the Hixson-Crowell graphical representation, time was plotted along X axis. Difference between cubic root of initial amount of drug and cubic root of drug remaining in the tablet at 't' time was plotted along Y axis. Six lines were obtained from the graph slopes of them are the release rate constants. The K_{HC} values range from 0.026 to 0.040. The R^2 value of brand M3 (0.992) was maximum and brand brand M2 (0.968) was minimum. (Singhvi et al., 2011), (Niebergall et al., 1963).

The release mechanisms from the six brands of metformin HCL were determined by the Korsmeyer-Peppas equation. (Basak et al., 2008), (Peppas et al., 1989). The value of 'n' was obtained from the slop of the Korsmeyer-Peppas plot. Brand M2, M3 and M4 showed value of 'n' 0.49, 0.69 and 0.80 respectively. The release mechanism of these brands should be non- Fockian or anomalous type which means simultaneous erosion of polymeric matrix and diffusion of drug particles. On the other hand, brand M1, M5 and M6 provided 'n' value of 0.91, 0.93 and 1.01. This means super case II type release which denotes the polymeric erosion.

Conclusion:

Our aim of this thesis was to elucidate the release kinetics of six brands of metformin HCL available in Bangladeshi pharmaceutical market. The R^2 value is the indicative of the release kinetics for the different brands. For M1, the highest R^2 value was found for first order and Hixson-Crowell plot. We can conclude, this brand follows both first order and Hixson-Crowell release kinetics. Brand M2 was found to follow Higuchi equation most (highest R^2 value of 0.979). Again, the R^2 values of M3and M4 for Korsmeyer-Peppas plot as well as Hixson-Crowell plot were found very close to 1 (0.996 and 0.992 respectively for M3; 0.992 and 0.991 respectively for M4). We can suggest, these brands follow both of these equations. Lastly, Brand M5 and M6 follow Hixson-Crowell equation because of the highest R^2 value of 0.984 and 0.988 respectively.

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