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Novel Mathematical Method for Quantitative Expression of Deviation from the Higuchi Model

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ABSTRACT A simple mathematical method to express the deviation in release profile of a test product following Higuchi's kinetics from an ideal Higuchi release profile was developed. The method is based on calculation of area under the curve (AUC) by using the trapezoidal rule. The precision of prediction depends on the number of data points. The method is exemplified for 2 dosage forms (tablets of diltiazem HCl and microspheres of diclofenac sodium) that are designed to release the drug over a 12-hour period. The method can be adopted for the formulations where drug release is incomplete (<100%) or complete (100%) at last sampling time. To describe the kinetics of drug release from the test formulation, zero-order, first-order, Higuchi's, Hixson-Crowell's, and Weibull's models were used. The criterion for selecting the most appropriate model was based on the goodness-of-fit test. The release kinetics of the tablets and microspheres were explained by the Higuchi model. The release profiles of the test batches were slightly below the ideal Higuchi release profile. For the test products, observed percentage deviation from an ideal Higuchi profile is less than 16% for tablets and less than 11% for microspheres. The proposed method can be extended to the modified release formulations that are designed to release a drug over 6, 18, or 24 hours. If the data points are not evenly separated, the ideal drug release profile and AUC are calculated according to the specific sampling time. The proposed method may be used for comparing formulated products during the research and development stage, for quality control of the products, or for promoting products by comparing performance of the test product with that of the innovator's product.

KEYWORDS: Diltiazem HCl, Modified release, Higuchi model, Kinetics of drug release, Mathematical model

INTRODUCTION

Ideally, controlled drug-delivery systems should deliver the drug at a controlled rate over a desired duration. The primary objectives of the controlled drug-delivery systems are to ensure safety and to improve efficacy of drugs, as well as to improve patient compliance. Of the approaches known for obtaining controlled drug release, hydrophilic matrix is recognized as the simplest and is the most widely used. Hydrophilic matrix tablets swell upon ingestion, and a gel layer forms on the tablet surface. This gel layer retards further ingress of fluid and subsequent drug release. It has been shown that in the case of hydrophilic matrices, swelling and erosion of the polymer occurs simultaneously, and both of them contribute to the overall drug-release rate [1]. It is well documented that drug release from hydrophilic matrices shows a typical time-dependent profile (ie, decreased drug release with time because of increased diffusion path length) [2, 3]. This inherent limitation leads to first-order release kinetics.

Many controlled-release products are designed on the principle of embedding the drug in a porous matrix. Liquid penetrates the matrix and dissolves the drug, which then diffuses into the exterior liquid [4].

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Wiegand and Taylor [5] and Wagner [6] showed that the percentage of drug released versus time data for many controlled-release preparations reported in the literature show a linear apparent first-order rate. Higuchi tried to relate the drug release rate to the physical constants based on simple laws of diffusion. Release rate from both a planar surface and a sphere was considered. The analysis suggested that in the case of spherical pellets, the time required to release 50% of the drug was normally expected to be 10% of the time required to dissolve the last trace of solid drug in the center of the pellet [7].

Higuchi [7, 8] was the first to derive an equation to describe the release of a drug from an insoluble matrix as the square root of a time-dependent process based on Fickian diffusion (Equation 1).

$$Q_t = [2DS\varepsilon(A - 0.5S\varepsilon)]^{0.5} \times t^{0.5} = k_H\sqrt{t} \quad (1)$$

Where, Q_t is the amount of drug released in time t, D is the diffusion coefficient, S is the solubility of drug in the dissolution medium, ε is the porosity, A is the drug content per cubic centimeter of matrix tablet, and k_H is the release rate constant for the Higuchi model.

Considerable attention has been given to describing drug release by the Higuchi equation. To the best of our knowledge, no research has been reported that quantifies the percentage deviation from the ideal Higuchi release pattern. In the present study, a simple mathematical method is proposed to quantitatively express the deviation from Higuchi kinetics. The method is exemplified for 2 dosage forms (tablets and microspheres) that are designed to release drug over a 12-hour period. It may also be extended to other systems.

MATERIALS AND METHODS

Materials

Diltiazem HCl USP and hydroxypropyl methylcellulose (HPMC K4M) were received as gifts from Cadila Health Care Pvt. Ltd (Ahmadabad, India). Guar gum IP (5400-cPs viscosity, 2% wt/vol aqueous solution) was received as a gift from H. B. Gum Industries Ltd (Kalol, India). Magnesium stearate IP, talc IP (JC's Reagent, Baroda, India) and succinic acid (E. Merck Ltd, Mumbai, India) were used as received. All other solvents and chemicals were of analytical grade. Deionized double-distilled water was used throughout the study.

Assay

Aqueous solutions of diltiazem HCl in distilled water were prepared and the absorbances were measured at 237 nm using a Hitachi U-2000 UV-VIS double-beam spectrophotometer (Hitachi, Tokyo, Japan)[9]. An equation was generated by fitting a weighted linear regression model to the data obtained in triplicate (n = 3)[10].

Tablet preparation

Diltiazem HCl (43.18% wt/wt), alkali-treated guar gum (43.18% wt/wt), and succinic acid (10.64% wt/wt) were physically admixed. The blend was then lubricated with 1% wt/wt talc and 2% wt/wt magnesium stearate. The method for preparation of alkali-treated guar gum is reported in our previous work [11]. The tablets were prepared by direct compression on a 16-station rotary tablet press equipped with concave punches of 9-mm diameter. Fifteen die cavities were blocked with stainless steel solid blocks. The batch size was 250 tablets. The compression force was adjusted so that the crushing strength of the tablets was in the range of 50 ± 10 N. The average weight and the drug content of the tablets were 375 mg and 162 ± 5 mg respectively.

Dissolution study

In vitro release of diltiazem HCl from the matrix tablets was measured according to the USP XXIII paddle apparatus (Electrolab, model TDT-06 T, Mumbai, India) at 37°C ± 0.5°C and at 50 rpm using 900 mL of distilled water as a dissolution medium (n = 3). Samples (5 mL) were withdrawn at predetermined time intervals, filtered through a 0.45 μm membrane filter, diluted suitably (absorbance in the normal range of 0.2 to 0.8), and analyzed spectrophotometrically. An equal volume of fresh dissolution medium, maintained at the same temperature, was added after withdrawing each sample to maintain the volume. Percentage of drug dissolved at different time intervals was calculated using the equation generated from the standard curve.

Kinetics of drug release

To describe the kinetics of the drug release from the test formulation, mathematical models such as zero-order, first-order, Higuchi's, Hixson-Crowell's, and Weibull's models were used. The criterion for selecting the most appropriate model was based on a goodness-of-fit test [12].

THEORETICAL CONSIDERATION

The first step is to calculate the theoretical percentage of drug released using the Higuchi equation (Equation 1). The straight line of percentage of drug released versus square root of time is considered as a reference line (**Figure 1**). Because the relationship between the percentage of drug released and the square root of time is linear, the entire dissolution profile may be compared using area under the curve (AUC), calculated by the trapezoidal rule. The precision of prediction can be increased by using a large number of data points. The shaded area of **Figure 1** can be calculated using the following equations.

$$AUC_{t\ hr,\ 0\%\ deviation} = \left(\frac{k_H\sqrt{t} + k_H\sqrt{t-n}}{2}\right) \times \left(\sqrt{t} - \sqrt{t-n}\right) \quad (2)$$

$$AUC_{t\ hr,\ 0\%\ deviation} = \frac{k_H}{2} \times n \quad (3)$$

Where, k_H, t, and n are Higuchi rate constant, time, and difference between two successive sampling time points respectively. The AUC for α% deviation from the Higuchi release profile is represented by equation 4.

$$AUC_{t\ hr,\ \alpha\%\ deviation} = \left(\frac{k_H}{2}\right) \times n \times \left(1 + \frac{\alpha}{100}\right) \quad (4)$$

From equation 4 it is evident that the AUCs for α% deviation is independent of time point (t); however, it depends on the difference between two successive sampling time points (n). It is important to note that the AUC increases with an increase in percentage deviation from the reference line (**Figure 2**). The average absolute difference between AUCs (AADA) of the reference line and that of lines showing ± α% deviations at any time point can be calculated by using equation 5.

$$AADA_{\alpha\%deviation} = \frac{\left\{\left(AUC_{+\alpha\%} - AUC_{0\%}\right) + \left(AUC_{0\%} - AUC_{-\alpha\%}\right)\right\}}{2} \quad (5)$$

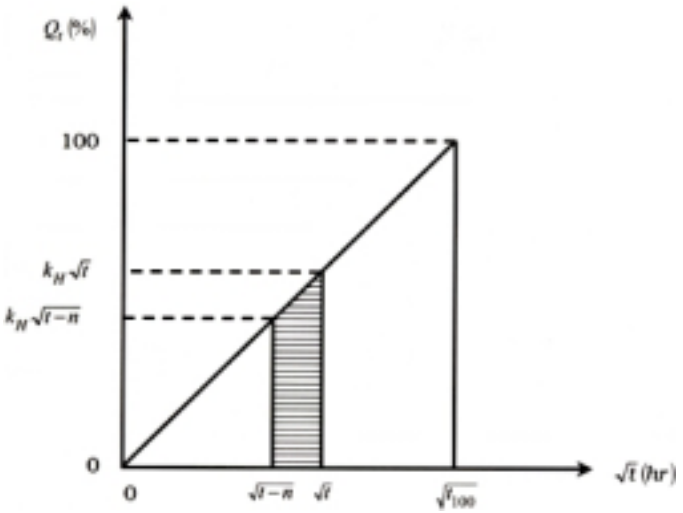

Figure 1. Area under the curve for an ideal Higuchi model.

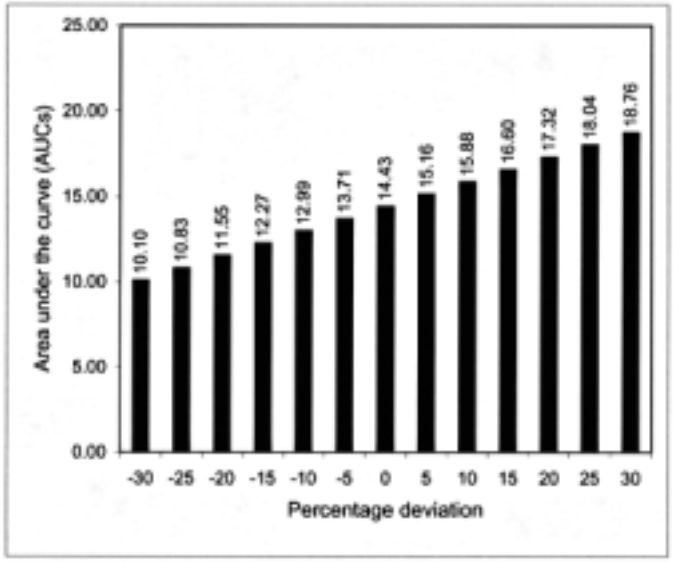

Figure 2. Relationship between area under the curve and percentage deviation.

Equation 6 is evolved using equations 3, 4, and 5.

$$AADA_{\alpha\%\ deviation} = \frac{k_H}{2} \times n \times \frac{\alpha}{100} \quad (6)$$

For an ideal 12-hour Higuchi release profile, k_H is equal to $100/\sqrt{12}$. Equation 7 is derived from equation 6 by substituting k_H with $100/\sqrt{12}$ and n with 1 (ie, the difference between two successive time points is 1 hour).

$$AADA_{\alpha\%\ deviation,\ 12\ hr\ system} = \frac{1}{2\sqrt{12}} \times \alpha = 0.1443 \times \alpha \quad (7)$$

For the 12-hour release profile, the AADA of the reference line and that of lines showing different percentage deviations from the reference line were calculated using equation 7. For example, the calculated value of AADA was 0.722 for 5% deviation (ie, 0.1443 x 5). Accordingly, calculated AADA for 10%, 15%, 20%, 25%, and 30% deviations were 1.443, 2.165, 2.887, 3.608, and 4.330.

Equation 6 can be rearranged as shown below:

$$AADA_{\alpha\%\ deviation} = \frac{k_H}{200} \times n \times \alpha \qquad (8)$$

For an ideal t_{100} hour release profile (where t_{100} is the time required for 100% drug release), k_H is equal to $100/\sqrt{t_{100}}$. For special cases, where percentage drug released at the last sampling time point is X%, modification such as k_H is equal to $X/\sqrt{t_X}$ shall be made in equation 8. For an ideal t_{100} hour release profile, equation 9 is obtained by substituting k_H with $100/\sqrt{t_{100}}$ into equation 8.

$$AADA_{\alpha\%\ deviation} = \frac{n}{2 \times \sqrt{t_{100}}} \times \alpha \qquad (9)$$

Equation 9 represents that AADA is a linear function of α (slope = n/[2 x $\sqrt{t_{100}}$], intercept = 0). For the ideal 12-hour Higuchi release profile (t_{100} = *12*), equation 9 can be written as:

$$AADA_{\alpha\%\ deviation,\ 12\ hr\ system} = \frac{n}{2\sqrt{12}} \times \alpha = 0.1443 \times n \times \alpha \qquad (10)$$

$$\alpha = \frac{AADA_{\alpha\%\ deviation,\ 12\ hr\ system}}{0.1443 \times n} \qquad (11)$$

If the observed absolute difference of AUCs between the test and the ideal 12-hour Higuchi release profile at any time point is 1.732 (*n = 1*), the deviation from the ideal Higuchi release profile is 12% (α = 1.732 ÷ [0.1443 x 1].

It is important to note that equation 11 is applicable for the ideal 12-hour Higuchi release profile only. The values of slope for the different Higuchi release profiles for *n = 1* can be generated using equation 9 (**Table 1**).

Table 1. Values of slope for different Higuchi release profiles (*n = 1*)

Hour	6	8	10	12	14	16	18	20	22	24
Slope	0.2041	0.1768	0.1581	0.1443	0.1336	0.1250	0.1179	0.1118	0.1066	0.1021

RESULTS AND DISCUSSION

The drug-release profile of the tablets containing untreated guar gum showed a tailing effect in the terminal phase, which was not observed in the tablets containing alkali-treated guar gum. The purpose of adding succinic acid was to investigate the influence of microenvironmental pH. The details of this effect are discussed in our earlier study [11].

The percentage diltiazem HCl released as a function of time from the prepared tablet is shown in **Table 2**. The dissolution data were fitted to the different models (**Table 3**). The value of r^2 (0.9944) was found to be highest for the Higuchi model. The sum of square residuals (SSR = 41.03) and F value (3.73) were lowest for the Higuchi model, which also indicates that the test product follows Higuchi release kinetics. The values of slope and intercept obtained from the nonlinear equation of the Higuchi model were found to be 3.154 and 1.5095 respectively.

From the absolute difference of AUCs, the percentage deviations for the test product from the ideal 12-hour Higuchi release profile were calculated by using equation 11. As shown in **Table 2**, the deviation from the ideal 12-hour Higuchi release profile is less than 16% at any time point.

The proposed method is also exemplified for microspheres of diclofenac sodium. The method of preparation of microspheres (best batch – No. 9) is given in our earlier work [13]. The percentage of diclofenac sodium released as a function of time from the microsphere is shown in **Table 2**; the deviation from the ideal 12-hour Higuchi release profile calculated using the proposed method is less than 11% at any time point. The model illustrated in **Table 3** reveals that the release of diclofenac sodium from the microspheres follows Higuchi's equation.

Table 2. Percentage deviation for the test products from the ideal 12-hour Higuchi release profile

Time	Square root time	Ideal Higuchi release profile		Test product		Absolute difference of AUCs	% deviation from Higuchi model
(hour)	(hour)	CPR*	AUC*	CPR	AUC		
Tablets of diltiazem HCl							
0	0.00	0.00	-	0.00	-	-	-
1	1.00	28.87	14.43	26.51	13.26	1.18	8.17
2	1.41	40.82	14.43	33.76	12.48	1.95	13.52
3	1.73	50.00	14.43	43.38	12.26	2.18	15.07
4	2.00	57.74	14.43	53.26	12.95	1.49	10.30
5	2.24	64.55	14.43	58.32	13.17	1.26	8.76
6	2.45	70.71	14.43	64.43	13.10	1.34	9.25
7	2.65	76.38	14.43	67.62	12.96	1.48	10.23
8	2.83	81.65	14.43	69.00	12.48	1.96	13.55
9	3.00	86.60	14.43	73.43	12.22	2.22	15.35
10	3.16	91.29	14.43	78.19	12.30	2.13	14.77
11	3.32	95.74	14.43	81.86	12.35	2.08	14.43
12	3.46	100.00	14.43	84.43	12.26	2.17	15.05
Microspheres of diclofenac sodium							
0	0.00	0.00	-	0.00	-	-	-
1	1.00	28.87	14.43	29.71	14.86	0.42	2.38
2	1.41	40.82	14.43	39.92	14.42	0.01	0.07
3	1.73	50.00	14.43	46.08	13.67	0.77	4.34
4	2.00	57.74	14.43	53.16	13.30	1.14	6.44
5	2.24	64.55	14.43	58.94	13.23	1.20	6.80
6	2.45	70.71	14.43	61.82	12.89	1.55	8.75
7	2.65	76.38	14.43	67.07	12.65	1.79	10.10
8	2.83	81.65	14.43	73.07	12.80	1.63	9.24
9	3.00	86.60	14.43	77.38	12.91	1.53	8.64
10	3.16	91.29	14.43	81.42	12.88	1.55	8.76
11	3.32	95.74	14.43	85.27	12.86	1.57	8.88
12	3.46	100.00	14.43	88.95	12.85	1.59	8.98

*CPR indicates cumulative percentage drug released; AUC, area under the curve.

Table 3. Results of model fitting for the test products

Model	r^2	SSR*	F	Slope	Intercept
Tablets of diltiazem HCl					
Higuchi	0.9944	41.03	3.73	3.1540	1.5095
Weibull	0.9855	42.27	4.23	0.7397	-1.8819
First-order	0.9885	171.93	15.63	-0.0024	4.4856
Hixson-Crowell	0.9734	334.12	30.38	0.0027	0.2625
Zero-order	0.8953	766.02	69.64	0.1000	20.4768
Microspheres of diclofenac sodium					
Higuchi	0.9971	22.33	2.03	3.2188	2.5798
Weibull	0.9630	120.65	12.06	0.7243	-1.8080
First-order	0.9812	209.00	19.00	-0.0027	4.5213
Hixson-Crowell	0.9813	321.27	29.21	0.0030	0.2521
Zero-order	0.9057	716.95	65.17	0.1025	21.7745

*r^2 indicates square of correlation coefficient, SSR, sum of square residuals.

The comparative release profiles of the ideal and the test batches are shown in **Figure 3** for tablets and **Figure 4** for microspheres. The release profiles of the test batches were slightly below the ideal Higuchi release profile. The values of SSR also indicate that there is some difference between the ideal and the test-release profiles and this difference can be calculated by the proposed method.

For a 12-hour controlled release formulation, ideally the percentage drug released at 12 hours should be 100. If the percentage drug released at 12 hours is less than 100 (ie, 84%), one should generate an ideal release profile accordingly.

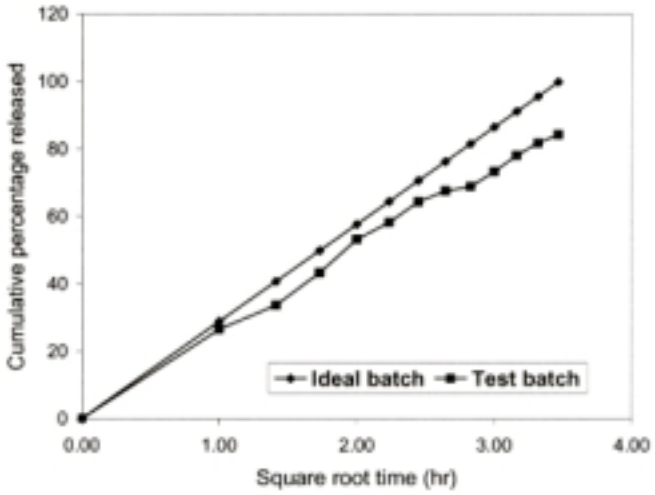

Figure 3. Comparison of dissolution profiles of ideal and test batch (tablets of diltiazem HCl).

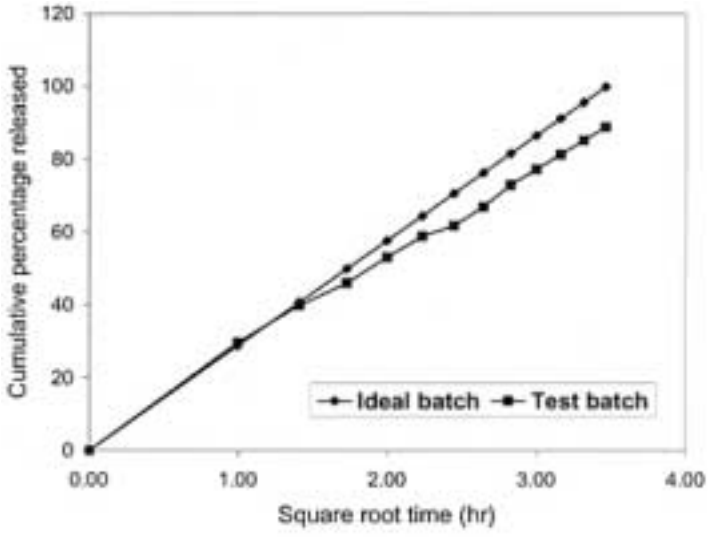

Figure 4. Comparison of dissolution profiles of ideal and test batch (microspheres of diclofenac sodium).

Table 4. Percentage deviation for uneven sampling time points*

Time (hour)	Square root time (hour)	Ideal Higuchi release profile		Test product		Absolute difference of AUCs	% deviation from Higuchi model
Tablets of diltiazem HCl		CPR	AUC	CPR	AUC		
0	0.00	0.00	-	0.00	-	-	-
1	1.00	28.87	14.43	26.51	13.26	1.18	8.17
2	1.41	40.82	14.43	33.76	12.48	1.95	13.52
4	2.00	57.74	28.87	53.26	25.49	3.38	11.71
6	2.45	70.71	28.87	64.43	26.45	2.42	8.38
7	2.65	76.38	14.43	67.62	12.96	1.48	10.23
8	2.83	81.65	14.43	69.00	12.48	1.96	13.55
10	3.16	91.29	28.87	78.19	24.57	4.30	14.89
11	3.32	95.74	14.43	81.86	12.35	2.08	14.43
12	3.46	100.00	14.43	84.43	12.26	2.17	15.05

*hr indicates hour; CPR, cumulative percentage drug released, AUC, area under the curve.

If the data points are not evenly separated, the ideal drug release profile and AUCs are generated according to the sampling time points of dissolution study of the test batch. Then, for a particular time point, percentage deviation can be calculated using equation 11, where *n* is the difference between 2 successive time points. The application of our method, for time points that are not evenly separated, is shown in **Table 4.**

In summary, a simple mathematical model is proposed for the comparison of formulated products during the research and development stage, for quality control of matrix tablets, or for promoting products by comparing the performance of the test product with that of the innovator's product.

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