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Preparation and In Vitro Evaluation of Controlled Release Hydrophilic Matrix Tablets of Ketorolac Tromethamine Using Factorial Design

Lütfi Genç and Esmaeil Jalvand
Anadolu University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Eskişehir, Turkey

Controlled release matrix tablets of ketorolac tromethamine (KT) were prepared by direct compression technique using cellulose derivatives as hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HEC), and carboxymethyl cellulose (CMC) in different concentrations (10–20%). The effect of polymer type and concentration was investigated on drug release by 2^3 factorial design. For the quality control of matrix tablets, weight deviation, hardness, friability, diameter–height ratio, content uniformity of KT, and in vitro dissolution technique were performed. UV Spectrophotometric method was used to detection of KT in matrix tablets. This method was validated. Dissolution profiles of the formulations were plotted and evaluated kinetically. An increase in polymer content resulted with a slow release rate of drug as was expected. According to the dissolution results, tablets prepared with HPMC + HEC + CMC (F1 and F8) were found to be the most suitable formulation for KT. About 99.27% KT was released from F8 in 7 h.

Keywords ketorolac tromethamine; hydrophilic matrix tablet; factorial design; cellulose derivatives; controlled release

INTRODUCTION

Diffusion-controlled delivery systems have been used in controlled release matrix tablets in which the drug is uniformly dissolved or dispersed. When designing an oral sustained release formulation, the hydrophilic matrices present an alternative to other monolithic or multiparticulate pharmaceutical dosage forms. They have several advantages such as ease of manufacture, low production cost, the possibility of introducing large proportions of the drug and the wide range of release profiles, and the manufacturing processes are relatively straight forward (Hashim & Wan Po, 1987 ; Vazquez et al., 1992).

Cellulose derivatives may be used for hydrophilic matrices for controlled release oral delivery (Ford, Rubinstein, Mclaul, Hogan, & Edgarp, 1987; Kibbe, 2000). Çelebi and Ünlü (1999) evaluated hydrophilic matrix tablets of diltiazem using three grades of hydroxypropylmethyl cellulose (HPMC) according to 3^2 factorial design. They reported the effect of the polymer ratio on diltiazem release from matrix tablets.

Hydrophilic matrix systems have attracted considerable attention in recent years as sustained release devices for the delivery of water soluble drugs. Various types of polymers used as hydrophilic matrices and their modeling aspects were reviewed. Cellulose derivatives are the most commonly used hydrophilic polymers for oral sustained-release tablet formulations (Baveja, Ranga-Rao, & Padmalatha Devi, 1987; Bettini, Colombo, Massimo, Catellani, & Vitali, 1994; Bravo, Lamas, & Salomon, 2002; Vázquez et al., 1996; Reynolds, Mitchell, & Balwinski, 2002; Tiwari, Murthy, Pai, Mehta, & Chowdary, 2003). Heng et al. prepared swellable hydrophilic matrix tablets of aspirin. The effects of HPMC of different particle size ranges, size distributions, and concentrations on the release behavior of aspirin from matrix tablets were investigated (Heng, Chan, Easterbrook, & Li, 2001). The behavior of gel layer thickness in swellable HPMC matrices loaded with increasing amounts of soluble and colored drug and exhibiting swelling, diffusion, and erosion fronts was studied using a colorimetric technique (Colombo, Bettini, & Peppas, 1999). Juárez et al. investigated the influence of admixed CMC on release of 4-aminopyridine from HPMC matrix tablets (Juárez, Rico, & Villafuerte, 2001).

Ketorolac tromethamine (KT) was absorbed rapidly (Tmax < 1.0 h) and efficiently (>87%) following oral and intramuscular doses. Its plasma half-life ranged from 1.1 to 6.0 h and its single dose was 10–30 mg (Mroszczak et al., 1987). KT was 36 times more potent than phenylbutazone, approximately twice as potent as indomethacin and three times more potent than naproxen in systemic anti-inflammatory activity. Its analgesic activity was stronger than aspirin. Clinical studies indicated that single-dose efficacy of KT was greater than that of morphine, pethidine, and pentazocine in moderate to severe postoperative pains (Buckley & Brogden, 1990). For this reason, KT was used in our study. UV spectrophotometric method was used for the assay of KT (Kamath, Shivram, & Vangani,

Address correspondence to Lütfi Genç, Anadolu University, Faculty of Pharmacy, Department of Pharmaceutical Technology, 26470 Eskişehir, Turkey. E-mail: lgenc@anadolu.edu.tr

1994). This method is validated (Caporal-Gautier et al., 1992; Riley & Rosanske, 1996; The United States Pharmacopeia [USP 24-NF 19], 2000).

Matrix tablets of KT were prepared using direct compression technique. The objective of this work is to outline 2^3 factorial design and to study the effect of three factors: HPMC, hydroxyethyl cellulose (HEC), and carboxymethyl cellulose (CMC) on the dissolution rate of KT in matrix tablets. In this case, there are eight treatment combinations: (1), a, b, ab, c, ac, bc, abc. The ideal matrix tablet formulation was found by evaluating these findings and were evaluated kinetically. For the quality control of tablets, physical control and in vitro dissolution techniques were performed. Dissolution profiles of each tablet were plotted. The influence of polymer type and concentration on dissolution rate of matrix tablets was investigated.

MATERIALS AND METHODS

Materials

KT: Dr. Reddy's laboratories (TD), HPMC (80,000–120,000 mPa s): Shin-Etsu Chemical Company; Tokyo-Japan, HEC (Type HR, 1,500–2,500 mPas): Hercules BV; The Netherlands (HEC-NF); CMC (1,500–2,000 mPa s): 7LF Aldrich; Starch: (Soluble, S 9765) Sigma. All the other chemicals were of analytical grade.

Methods

Factorial Design

The effect of HPMC (A), HEC (B), and CMC (C) were studied in separate 2^3 factorial experiments. The levels and variation intervals for the eight treatment combination are the calculation matrix for a 2^3 factorial design (Table 1), with the following combinations of factors A, B, and C at two levels (10–20%): (1), a, b, ab, c, ac, bc, and abc. These levels are polymer concentrations, "high" and "low" levels of a factor, or presence and absence of factors (Montgomery, 1997). Every factors was investigated one by one (a [F2], b [F3], c [F5]), two factors together (ab [F4], ac [F6], bc [F7]), and three factors together (abc [F1, F8]). F0 was prepared without polymer or absence of factor. The effects on drug release of polymer type and concentrations were investigated by 2^3 factorial design.

TABLE 1
Factorial Design Parameters and Experimental Conditions

	Level	
Factors	Low (−)	High (+)
A) HPMC	%10	%20
B) HEC	%10	%20
C) CMC	%10	%20

Preparation of Matrix Tablets

Nine formulations were prepared on an instrumented single-punch tablet machine by direct compression technique (granulator: Erweka; tablet machine: Korsch with Erweka Motor, Maximum load of the punch is 30 kN). Magnesium stearate was used as the lubricant (2.5%), and HPMC, HEC, and CMC were the polymers in different concentrations (10–20%). Contents of matrix tablet formulations are given in Table 2.

Physical Tests

The following tests were applied to the tablets (n = 10): amount of KT, crushing strength, diameter–height ratio and friability (friabilator: Roche; UV spectrophotometer: Shimadzu UV-visible recording spectrophotometer 160 A). Tablet weight uniformity was calculated according to USP 24, and tablet thickness was determined using a micrometer. Tablet hardness tests were carried out using a Monsanto hardness tester (hardness apparatus: Monsanto). Friability tests were performed using a Roche friabilator.

Amount of KT

Spectrophotometric method was used for KT assay (Kamath et al., 1994). For this purpose, 20.0 mg KT was weighed accurately and dissolved in distilled water and the volume adjusted to 100 mL. Eight samples of 0.5–5.0 mL were taken from this stock solution and diluted to 50 mL with distilled water. Absorbances of these samples were measured at 323.0 nm and the quantitative assay results were plotted therefrom. Regression equation and regression coefficient were then calculated.

In Vitro Dissolution Test

Dissolution tests were performed according to the basket method described in USP 24, Apparatus II (dissolution apparatus: Aymes; pH meter: Bilmar model 101). The rotating speed was 50 rpm and the temperature was 37 ± 0.5°C. Dissolution studies were carried out in 600 mL distilled water. About 5 mL of samples was taken from the dissolution media at appropriate time intervals with the aid of an injector fitted with a Schleicher–Schuell filter paper (0.2 μm). An equal volume of the same medium was returned to the system after each withdrawal. Absorbances of the samples were measured at 323.0 nm against blank by using an UV spectrophotometer. Placebo tablets corresponding to each formulation were used as blank. The amounts of KT released were evaluated by using the standard calibration curve equation (n = 6).

Validation of UV Spectrophotometric Assay

Validation of an analytical method is the process by which it is established, by laboratory studies, that the performance characteristics of the method meet the requirements for the intended analytical applications. The validation of the types of methods is accuracy, precision, specificity, detection limit, quantitation limit, and linearity and range (Beuving, 2001; Caporal-Gautier et al., 1992; Riley & Rosanske, 1996; USP 24-NF 19, 2000).

TABLE 2
Content of Matrix Tablet Formulations

	Tablet Code Number								
Contents	F0	F1(1)	F2(a)	F3(b)	F4(ab)	F5(c)	F6(ac)	F7(bc)	F8(abc)
KT (mg)	21	21	21	21	21	21	21	21	21
Starch(mg)	50	50	50	50	50	50	50	50	50
HPMC (%, wt/wt)	–	10	20	–	10	–	10	–	20
HEC (%, wt/wt)	–	10	–	20	10	–	–	10	20
CMC (%, wt/wt)	–	10	–	–	–	20	10	10	20
Mg Stearate (%, wt/wt)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Precision. The precision of an analytical method is the degree of agreement among individual test results when the method is applied repeatedly to multiple sampling of a homogenous sample. About 4.0, 10, and 16.0 μg/mL solutions were prepared using 200.0 μg/mL stock solution of KT. Absorbances of these samples were measured at 323.0 nm. The standard deviation or relative standard deviation (RSD) (coefficient of variation) of a series of measurement was calculated. Same procedure was made different days.

Accuracy. The accuracy of an analitycal method is the closeness of the test results obtained by that method to the true value. About 2.0–20.0 μg/mL solutions were prepared using 200.0 μg/mL stock solution of KT. Absorbances of these samples were measured at 323.0 nm. Regression equations and regression coefficients were then calculated. Accuracy is calculated as the percentage of recovery by the assay of the known added amount of analyte (three concentrations: 4.0, 1.0, 16.0 μg/mL) in the sample using regression equation ($n = 6$).

Specificity. The specificity of an analytical method is its ability to measure accurately and specifically the analyte in the presence of components that may be expected to be present in the sample matrix. Specificity may often be expressed as the degree of bias of test results obtained by analysis of samples containing added impurities, degradation products, related chemical compounds, or placebo ingredients when compared with test results from samples without added substances. This bias may be expressed as the difference in assay results between the two groups of samples.

Detection and Quantitation Limits. The limit of detection is a parameter of limit tests. It is the lowest concentration of analyte in a sample that can be detected. Limit of quantitation is a parameter of quantitative assays for the low levels of compounds in sample matrices, such as impurities in bulk drug substances and degradation products in finished pharmaceuticals.

Evaluation of Release Kinetics

The results thus obtained were evaluated kinetically using zero-order, first-order, Hixson Crowell, RRSBW(Rosin–Rammler–Sperling–Bennet–Weillbull) distribution, Q Square Root of Time, Higuchi equation, Spherical, Cylindrical and Slab Erosion (the rate constants k′, k″, and k‴ were obtained according to Hopfenberg). The release rate constants (k), correlation coefficients (r), and determination coefficients (r^2) were calculated by means of a computer program (Ağabeyoğlu, 1984). The in vitro release profiles (percentage of drug released versus time) obtained from the KT matrix tablet formulations were fitted to the main models which have been proposed to describe drug release kinetics from tablets and other polymer matrices.

RESULTS AND DISCUSSION

Factorial designs are used in experiments where the effects of different factors, or different conditions, on experimental results are to be elucidated. Factorial designs are the designs of the choice for simultaneous determination of the effects of several factors and their interactions. Application of factorial design experiments to pharmaceutical problems has appeared to be extremely useful. The effects of several factors (A, B, and C) and their interactions (ab, bc, ac, and abc) can be determined simultaneously by factorial design experiments (Montgomery, 1997). Calculation of total effects for 2^3 factorial design and the effects of A, B, and C and their interactions on the T values (min) are summarized in Table 3. The differences of importance between T values have also been examined and for the factors polymer type, and concentration F values have been calculated. F4 and F8 have been found as the most appropriate formulations according to T values. This model was applied to the evaluation of the dissolution rate of matrix tablets.

The physical characteristics of the KT tablets are given in Table 4. These tablets provided good weight uniformity and friability ($F < 0.5\%$). These results were in accordance with the pharmacopoeia limits.

Regression equation is $C = 19.825 \times \text{Abs} - 0.1523$, regression coefficient (r) is = 0.9999 (C = concentration [μg/mL]), Abs = absorbance.

In the validation parameters, the RSD for the sample preparation step might be approximately 1% (Beuving, 2001; USP 24-NF 19, 2000). As summarized in Table 5, these results are

TABLE 3
Analysis of Variance for 2^3 Factorial Experiments for the Time at Which 63.2% of the Active Ingredient Dissolved (Minutes) (T Values)

	T Values						
Source of Variation	Exp. 1	Exp. 2	Exp. 3	D.F.	Sum of Square	Mean Square	F
(1)	30.000	29.318	30.999	1			
a	106.877	104.633	107.222	1	2,200.4882	2,200.4882	53.891
b	150.379	152.444	151.100	1	23,033.630	23,033.630	564.110
ab	121.421	121.017	122.010	1	5,707.743	5,707.743	139.786
c	51.642	50.928	50.438	1	1,348.261	1,348.261	33.019
ac	74.802	74.200	75.363	1	225.743	225.743	5.528
bc	115.205	115.954	114.866	1	235.1005	235.1005	5.757
abc	122.857	120.844	121.654	1	2,941.1219	2,941.1219	72.030
Residual				16	653.3096	40.8318	
Total				23	36,345.397		

suitable for method validation. Reproducibility refers to the use of UV spectrophotometric assay method for KT in different laboratories, as in a collaborative study. An important step in the validation of any analytical method is the establishment of the relationship between released % (y) and the concentration of the analyte (x) and the method may be calibrated. When correlation coefficient is above 0.9990, the assay method was acceptable. The satisfying recoveries confirm the suitability of the proposed method for the routine analysis of KT in pharmaceuticals (Table 6). According to the results, the proposed method is able to access the analyte in the presence of common excipients, and hence, it can be considered specific. Results in Table 7 indicate that KT showed good detection limit.

Cellulose derivatives are ofen used to modify the release of drugs in tablet and capsule formulations. For tablets, cellulose derivatives provide utility as matrix components and coating. These systems benefit from ease of manufacture, low cost, and predictable in vivo performance. Cellulose derivatives such as HPMC and HEC are used in hydrophilic matrix systems. As the polymers are exposed to water, they form a gel layer that will retard or control the release of the active ingradients. Drug release with these systems involves two simultaneous processes: Fickian diffusion and matrix relaxation and erosion. Along with drug load and solubility, polymer swelling, concentration and particle size, pH effects, other excipients and processing are important factors when formulating these systems.

The effects of cellulose esters (CEs) on in vitro release of KT have also been investigated. Drug release profiles are given in Figure 1–3 (n = 6). The drug release from matrix tablets depended upon the concentration and type of cellulose derivatives. Approximately 100% KT was released in the first 60 min from F1 (without polymer). The release of KT from matrix tablets was slower than that of control tablets (F1).

On the other hand, as observed in F1–F8 formulated tablets, the type of cellulose has an important effect on the release rate of the drug. All of KT was released from F5 (%20 CMC) in the first 90 min. But, 96.16% KT from F2 (%20 HPMC) in 3.5 h and 94.57% KT from F3 (%20 HEC) in 4.5 h were released. The mixture of polymers at low concentration content resulted with a slow release rate of drug as was expected. According to dissolution results, tablets prepared with HPMC + HEC + CMC (F1 and F8) were found to be the most suitable formulation for KT. Because, 99.27% KT was released from F1 in 7 h and 100.56% KT was released from F8 in 7.5 h. Figures 1–3 show release profiles of matrix tablets. F1 and F8 have good dissolution profiles. The main factor controlling drug release was the concentration and type of the polymer. Mechanisms for drug release from matrices of CEs imply water penetration in the matrix (with drug dissolution on the surface, causing its immediate release), hydration and swelling of CEs, diffusion of the dissolved drug, and the erosion of gelatinous polymer layer. When the hydrophilic matrix tablet is conducted in an aqueous environment, firstly KT is released from the surface of the matrix tablet and then water penetrates into the matrix. The polymer swells to form a gel layer and the matrix increases, KT releases through the gel barrier and this process continues until the tablet is completely eroded. The release of KT from formulations F1, F2, F3, F4, F7, and F8 were found to be 93.27, 97.82, 94.57, 94.32, 100.7 and 90.87%, respectively, in 4.5 h. F0, F5, and F6 were disintegrated after 1.0, 1.5, and 2.0 h, respectively. The in vitro release of KT was changed as the polymer ratio and mixture changed. When the polymer ratio increased, the in vitro release of KT was decreased (F1, F8). It was also observed that complete KT release from mixed polymer containing tablet formulation (F1, F8) lasted for 7.0, 7.5 h. From these results it appears that polymer type, concentrations and mixing ratio are the main factors for improving the formulation and also effecting time-dependent characteristic changes such as the drug release rate from dosage forms.

TABLE 4
Tablet Specifications (n = 10)

Tablet Specifications	Tablet Code Number								
	F0	F1	F2	F3	F4	F5	F6	F7	F8
KT Amount (mg)	19.24 ± 0.774	22.51 ± 0.539	20.23 ± 0.204	22.51 ± 0.219	22.17 ± 0.531	21.77 ± 0.278	21.97 ± 0.518	21.87 ± 0.697	2142 ± 0.539
Breaking Force (kg)	1.00 ± 0.250	1.00 ± 0.000	1.00 ± 0.176	1.00 ± 0.120	0.75 ± 0.000	0.75 ± 0.024	0.90 ± 0.122	0.80 ± 0.104	1.00 ± 0.000
Friability (%)	0.69 ± 0.031	0.52 ± 0.022	0.03 ± 0.004	0.09 ± 0.034	0.09 ± 0.108	0.01 ± 0.089	0.23 ± 0.205	0.42 ± 0.134	0.48 ± 0.022
Diameter–Height Ratio	1.91 ± 0.016	2.32 ± 0.033	2.27 ± 0.046	2.32 ± 0.061	2.29 ± 0.064	2.29 ± 0.064	2.34 ± 0.059	2.32 ± 0.018	2.48 ± 0.051
Tablet Weight (mg)	73.7 ± 0.26	91.0 ± 0.6	90.3 ± 1.2	88.2 ± 1.3	91.6 ± 1.6	88.8 ± 1.2	94.5 ± 0.6	87.3 ± 0.6	131.0 ± 0.8

TABLE 5
Repeatability and Precision of UV Absorbances (Medium: Distilled Water)

Concentration (µg/mL)	RSD %
Repeatability (day = 3, n = 6)	
4	0.0172
10	0.0305
16	0.0695
Precision (day = 3, n = 6)	
4	0.0111
10	0.0303
16	0.0692

TABLE 6
Accuracy Results (n = 6)

Regression Equation	Regression Coefficient	Recovery Values
$C = 19.825 \times Abs - 0.1523$ (1 day)	0.9999	100.11 ± 0.15% (for 4.0 µg/mL)
$C = 18.309 \times Abs - 0.2043$ (2 days)	0.9999	99.85 ± 0.11% (for 10.0 µg/mL)
$C = 19.217 \times Abs - 0.0784$ (3 days)	0.9997	99.35 ± 0.09% (for 16.0 µg/mL)

C = Concentration (µg/mL), Abs = Absorbance.

TABLE 7
Detection Limit (LOD) and Quantitation Limit (LOQ) Results (n = 6)

Parameters	Results
Linear range (µg/mL)	4.0–16.00
LOD (µg/mL)	5.676×10^{-2}
LOQ (µg/mL)	0.172

F8 showed the best fit to Higuchi kinetic according to the Akaike's information criteria (AIC = –27.40), weighted sum of squared deviations (WSSD = 0.1294), and R square (r^2 = 0.9873) results (Ağabeyoğlu, 1984). Kinetic assessment of release data for formulation F4 and F8 are given in Table 8. As for the kinetic evaluations, the highest determination coefficient and the best linear relation were observed for matrix tablet (F8) using Higuchi equation (Higuchi, 1963). Graphically Higuchi distribution gave a straight line (Figure 4).

In this investigation, controlled release tablet forms containing different types of polymers were developed. Using different types and concentrations of polymers, it was planned to control the drug release and compare the effect of polymer type and concentrations.

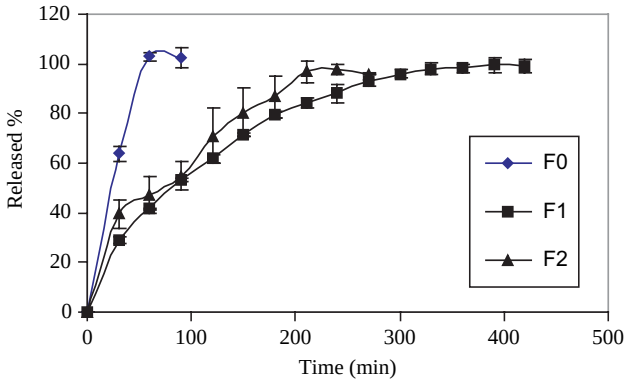

FIGURE 1. Dissolution profiles of F0, F1, and F2.

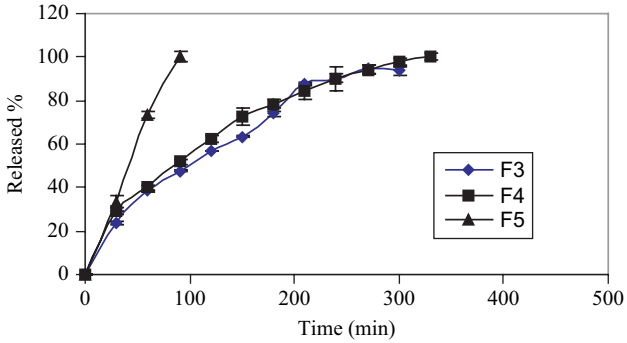

FIGURE 2. Dissolution profiles of F3, F4, and F5.

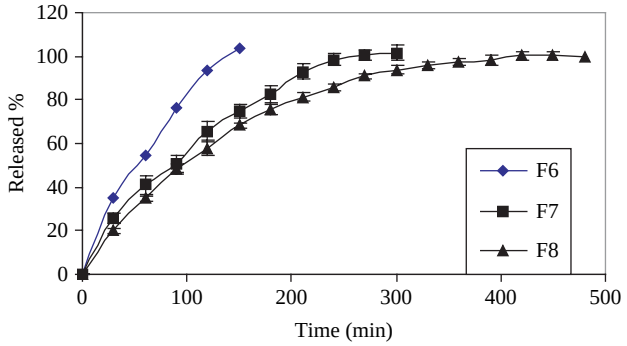

FIGURE 3. Dissolution profiles of F6, F7, and F8.

The combination of diffusion and erosion release mechanisms in matrix systems comprising an insoluble hydrophobic and a hydrophilic gel-forming part depends greatly on the wettability of the added drug. Furthermore, with wettable and water-soluble drugs, the matrices swelled and releases were mainly achieved by diffusion and erosion because of dissolution of the gel formed. However, with less wettable drugs, the matrix erodes, because of deaggregation caused by the inability of the matrix to accomodate the swelling of gel forming hydrophilic part.

TABLE 8
Kinetic Assessment of Release Data for Formulation F4 and F8

Kinetics	Parameters	F4	F8
Modified Hixson-Crowell	r^2	0.9819	0.9923
	A	0.9906	0.8152
	B	2.3851×10^{-3}	1.8898×10^{-3}
	AIC	–32.0224	–74.6666
	WSSD	1.8064×10^{-2}	0.0239
First Order	r^2	0.7704	0.9501
	Kr^1	1.5124 h^{-1}	0.7638 h^{-1}
	AIC	–5.1224	–29.1208
	WSSD	11.7974	0.7470
Zero order	r^2	0.9203	0.8769
	Kr^0	2.5124 mg/h	2.1920 mg/h
	AIC	–5.7922	–2.8657
	WSSD	0.2575	0.7269
Hixson-Crowell (Sink)	r^2	0.9812	0.9884
	Slope	2.6081×10^{-3}	1.9230×10^{-3}
	Rate	0.2843 mg/h/cm^2	0.2444×10^{-2} mg/h/cm^2
	AIC-6.3	31.4544	–48.6569
	WSSD0.8	2.8908×10^{-2}	0.0947
RRSBW	r^2	0.9069	0.9685
	$T_{\%63.2}$ min	112.315 min	122.9063 min
	B	1.474	1.0819
	AIC-17	–20.645	–53.7024
	WSSD0.1	0.1290	0.0780
Q $\sqrt{t}$	r^2	0.9727	0.9573
	K	21,475.7305	1051.7305
	AIC	–27.4029	–43.9504
	WSSD	3.7335×10^{-2}	–0.1911
Higuchi	r^2	0.9873	0.9940
	Slope	3.2074×10^{-3}	2.5240×10^{-3}

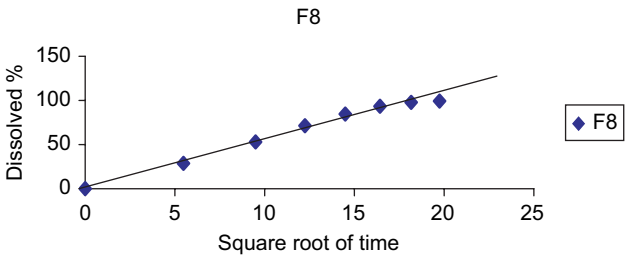

FIGURE 4. The release of KT from F8 according to Higuchi equation.

CONCLUSION

In conclusion, it was shown that the addition of different types and concentrations of polymer to tablet formulations could result in controlled drug release and thus different release profiles obtained could best explain the effects of different types, concentrations, and mixing ratios of the polymer in matrix tablet formulations.

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