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Effect of HPMC 4 Cps and Carbopol 974p NF On Release Kinetics Of Ciprofloxacin From Kollidon® SR Embedded Matrix Tablets

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ABSTRACT
Controlled release (CR) Ciprofloxacin (CFX) matrix tablets were prepared using Ciprofloxacin betaine as a model drug and Kollidon® SR as a core matrix former. Kollidon® SR embedded CFX matrix tablets were then characterized with Carbopol 974P NF, Cetyl alcohol, Hydroxypropyl methyl cellulose (HPMC 4.5 cps). CFX release was 74% after 10 hours dissolution in 0.01 N HCl solution from the tablets containing only Kollidon® SR. Though addition of only HPMC 4.5 cps increased the release rate of CFX, combination of HPMC 4.5 cps, cetyl alcohol and Carbopol 974P NF, Cetyl alcohol decreased the release rate of CFX. The increased released rate of CFX from the former formulations might be due to the hydrophilic nature of HPMC 4.5 cps and the reduced CFX release from the latter formulations might be due to the hydrophobic and release retarding nature of Carbopol 974P NF and Cetyl alcohol. Highest MDT value and lowest release rate was 13.54 hour and 14.21 $\%hr^{-0.5}$ respectively for 9% Carbopol 974P NF-18% cetyl alcohol containing tablet. Whereas lowest MDT value and highest release rate was 4.7 hour and 28.48 $\%hr^{-0.5}$ respectively for 27% HPMC 4.5 cps-0% cetyl alcohol containing tablet. CR tablets of CFX followed non-Fickian or anomalous type release. But, polymer relaxation dominated more on CFX release than diffusion from HPMC containing tablets (n were nearer to 0.7) whereas diffusion dominated more on CFX release than polymer relaxation from Carbopol containing tablets (n were nearer to 0.6).
Key Words: Carbopol 974P NF, Cetyl alcohol, Ciprofloxacin, HPMC 4.5 cps, Kollidon® SR, Matrix Tablet.

Introduction

Many strategies are available for the design and development of modified-release drug delivery formulations. The primary purpose of these drug delivery devices is to improve the state of disease management by modifying the pharmacokinetic profiles of therapeutic agents normally administered as conventional tablets or capsules. Conventional oral dosage forms often produce fluctuations of drug plasma level that either exceed safe therapeutic level or quickly fall below the minimum effective level; this effect is usually totally dependent on the particular agent's biologic half-life, frequency of administration, and release rate. It is recognized that many patients can benefit from drugs intended for chronic administration by maintaining plasma levels within a safe and effective range [1]

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Ciprofloxacin (CFX) is a fluoroquinolone derivative with outstanding antibacterial activity against gram-negative and some gram-positive bacteria as well as on some Chlamydia and Mycoplasma, and many mycobacterium species [2-4].
Its action takes place via the inhibition of the bacterial DNA gyrase which is an essential enzyme for DNA replication and synthesis. In animals Quinolones, especially CFX, exhibit favorable pharmacokinetic properties, their apparent volume of distribution suggested substantial tissue penetration [5, 6].

Kolidon® SR, which is a Polyvinyl acetate and polyvinyl pyrrolidone (Povidone) based matrix polymer, has already been established as sustain release polymer. This water insoluble polymer (povidone part is water soluble but polyvinyl acetate part is water insoluble) can be used in different types of sustain release dosage forms like tablets, pellets, and granules.[3] But its excellent flowability and compressibility

makes it suitable for sustain release matrix tablet by direct compression [7-10].

The USP describes ethyl cellulose (Ethocel™ 7 cps and 20 cps) as an ethyl ether of cellulose which is long chain polymer of –anhydroglucose units joined together by acetal linkages. Ethyl cellulose is a tasteless, free-flowing, white to light tan colored powder [11]. Ethyl cellulose is widely used in oral and topical pharmaceutical formulations. But the main use of these polymers in oral formulations is as a hydrophobic coating agent for tablets and granules. Modified release tablet formulations are also produced using ethylcellulose as a matrix former [12-14].

The PhEur describes hydroxypropyl methyl cellulose (**HPMC** 4.5 cps and 15 cps) as a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades which vary in viscosity and extent of substitution. Hydroxypropyl methyl cellulose is an odorless and tasteless, white or creamy-white colored fibrous or granular powder which is soluble in cold water forming a viscous colloidal solution, practically insoluble chloroform, ethanol (95%), and ether [11]. Hydroxypropyl methyl cellulose is widely used as a tablet binder, in film coating and as an extended release tablet matrix [15-19].

The USP describes cetyl alcohol (CA) as a mixture of solid aliphatic alcohols comprising mainly 1-hexadecanol ($C_{16}H_{34}O$). The USP specifies not less than 90% of cetyl clcohol and the remainder consisting chiefly of related alcohols. It is an emulsifying and stiffening agent. It occurs as waxy, white flake which is practically insoluble in water [11]. Cetyl alcohol is also used as sustained release excipient in extending the release of the drug [20, 21].

Several kinetic models have been proposed to describe the release characteristics of a drug from a CR polymer matrix. The following 3 equations are commonly used, because of their simplicity and applicability [22, 23]: Equation 1, the zero-order model equation; Equation 2, Higuchi's square-root equation; and Equation 3, the Ritger-Peppas empirical equation.

$$M_t/M_\infty = K_0 t \quad \ldots\ldots\ldots (1)$$
$$M_t/M_\infty = K_H t^{1/2} \quad \ldots\ldots\ldots (2)$$
$$M_t/M_\infty = K t^n \quad \ldots\ldots\ldots (3)$$

where M_t/M_∞ is the fraction of drug released at any time t; and K_0, K_H, and K are release rate constants for Equations 1, 2, and 3, respectively. In Equation 1, n is the diffusional exponent indicative of mechanism of drug release. In the case of cylindrical tablets, a value of $n = 0.45$ indicates Fickian or case I release; $0.45 < n < 0.89$ indicates non-Fickian or anomalous release; $n = 0.89$ indicates case II release; and $n > 0.89$ indicates super case II release.

EXPERIMENTALS

Materials

Ciprofloxacin betaine was purchased from Organo-Chem Pvt. Ltd. India. Kollidon® SR (BASF, Germany), Ethyl cellulose (Ethocel™ 7 cps) (Colorcon, UK), Ethyl cellulose (Ethocel™ 20 cps) (Colorcon, UK), Carbopol 974P (Noveon, USA), Hydroxypropyl methyl cellulose (HPMC 15 cps) (Samsung, Korea), Hydroxypropyl methyl cellulose (HPMC 4.5 cps) (Samsung, Korea), Cetyl Alcohol (BDH Chemicals Ltd., England), Talc (Whittaker, Clark and Daniels Inc, USA), Aerosil 200 (Degussa, Germany) Magnesium Stearate (Wilfrid Smith Ltd, UK) were used as gift.

Preparation of matrix tablets of Ciprofloxacin betaine

Matrix embedded controlled release tablets of CFX were prepared using different matrix former (see table 1) and different coating

Table 1 Core Tablet Formulation of Ciprofloxacin Betaine*

Chemicals	CFX_K (F1)	CFX _E7	CFX _E20	CFX _H15
Ciprofloxacin betaine	250	250	250	250
Kollidon SR	250			
Ethocel 07		250		
Ethocel 20			250	
HPMC 15cps				250
	500	500	500	500

* Each formula also contains 1 mg of each of aerosil 200, magnesium stearate, and talc

polymers (see table 2). CFX tablets of different compositions were compressed by a Perkin- Elmer laboratory hydraulic press equipped with a 10 mm flat faced punch and die set. Compression pressure and time were 5 ton and 1 minute respectively. Prepared tablets were then preserved in a desiccators for further experiments.

Physical Characterization of Designed Tablets

The drug content of the manufactured tablets of each batch was determined in duplicate. For each batch, 10 tablets were taken, weighed, and finely powdered. An accurately weighed quantity of this powder was taken and suitably dissolved in 0.01 N hydrochloric acid solution and analyzed after making appropriate dilutions. The weight variation was determined by taking 10 tablets using an electronic balance (AY 120, Shimadzu Corp., Japan). Tablet thickness, diameter, and hardness were determined for 6 tablets using a DR. SCHLEUNIGER PHARMATRON Tablet Tester 8M (UK). Friability was determined by testing 10 tablets in a friability tester (FTA-20, Campbell Electronics) for 4 minutes at 25 rpm.

Release Rate Studies

Release rate for all the designed formulations was studied up to 10 hours using a USP tablet dissolution tester (Dissolution Tester TDT-08L, Electrolab, Mumbai, India), type 2 (paddle method), in 900 mL of 0.01 N hydrochloric acid solution at 37.5 ± 0.5°C. The stirring speed was set at 50 rpm. At predetermined time intervals, a 10 mL sample was withdrawn and replaced with fresh dissolution medium. After appropriate dilution the samples were analyzed. Cumulative percentage of the drug released was calculated, and the mean of 6 tablets was used in data analysis.

Statistical Analysis of the Release Curves

Release datas were statistically evaluated with the help of 1-way analysis of variance (ANOVA).

RESULTS AND DISCUSSIONS

Physical Properties of the Designed Tablets

The physical appearance, tablet thickness, diameter, hardness, friability, and weight variation of all tablet formulations were found to be satisfactory and reproducible as observed from the data in Table 3. Average thickness of the tablets of formulation 1 was 3.4 mm. As the weight of the tablets was increased, thickness was also increased. Tablet diameter values were also found uniform which was around 12.00 mm. Tablet hardness was found to be good (between 169 and 450 newton) for different compositions. Average hardness value of the formulation F1 was 325 newton. Incorporation of lower viscosity grade of

Table 2 Formulation with Different amounts of HPMC 4.5 cps, Carbopol 974P NF and Cetyl Alcohol*.

CHEMICALS (mg)	F2[Ψ]	F	F4[Ψ]	F	F6[§]	F	F	F9[§]
Ciprofloxacin Betaine	250	25	250	25	250	25	25	250
Kollidon SR	150	15	150	15	150	15	15	150
Cetyl Alcohol	-	50	70	10	-	50	70	100
HPMC 4.5 cps	150	10	80	50	-	-	-	-
Carbopol 974P NF					150	10	80	50
	550	55	550	55	550	55	55	550

* Each formula also contains 1 mg of each of aerosil 200, magnesium stearate, and talc

[Ψ] These formulas are also represented as 27%H4.5_0%CA, 18%H4.5_9%CA, 14%H4.5_12%CA, and 9%H4.5_18%CA.

[§] These formulas are also represented as 27%C974_0%CA, 18% C974_9%CA, 14% C974_12%CA, and 9% C974_18%CA.

Table 3 Tablet Properties of Different Formulations

Tablet Properties	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight Variation (%)[¥]	± 1.1	± 2.5	± 1.7	± 1.3	± 2.2	± 2.1	± 1.2	± 1.4	± 0.9
Thickness (mm)[Ψ]	3.4 ± 0.05	3.78 ± 0.11	3.93 ± 0.04	4.05 ± 0.8	4.12 ± 0.03	3.63 ± 0.1	3.9 ± 0.1	3.85 ± 0.1	4.05 ± 0.1
Diameter (mm)*	12.99 ± 0.15	12.96 ± 0.19	12.99 ± 0.32	13.00 ±	12.98 ± 0.15	13.00 ± 0.25	13.00 ± 0.22	12.99 ± 0.19	12.99 ± 0.17
Hardness (newton)[§]	325 ± 5	269 ± 11	169 ± 10	175 ± 9	180 ± 11	450 ± 12	413 ± 10	322 ± 12	245 ± 10
Friability (%)	< 0.5	< 0.5	< 0.5	< 0.5	< 0.5	< 0.5	< 0.5	< 0.5	< 0.5

[¥] Weight variation ± standard deviation (SD) from mean values (n=10)

[Ψ] Mean thickness of tablets ± SD (n=6)

* Mean diameter of tablets ± SD (n=6)

[§] Mean hardness values of tablets ± SD (n=3)

HPMC (4.5 cps) reduced the tablet hardness values. As the concentration of HPMC was decreased and concentration of cetyl alcohol was increased, tablet hardness values were found to be decreased gradually. But presence of Carbopol 974P NF increased the hardness values of the tablets. It was maximum of 450 newton while 150 mg of Carbopol 974P NF was incorporated in the tablet formulations (formula F6). But as the concentration of Carbopol 974P NF was decreased and concentration of cetyl alcohol was increased, tablet hardness values were decrease gradually. Friability value of all the tablets was less than 0.5% (wt/wt). The manufactured tablets showed low weight variation indicating that direct compression is an acceptable method for preparing good-

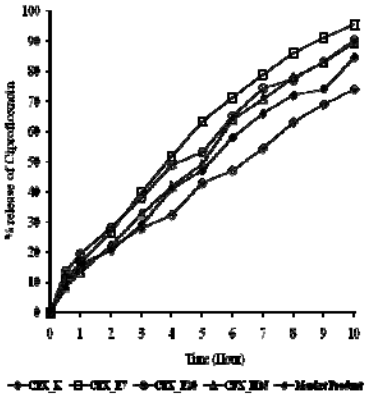

Figure1: Comparative release profile of Ciprofloxacin from controlled release matrix tablets prepared using different matrix former. Each data point represents the average release value ±SD (n = 6).

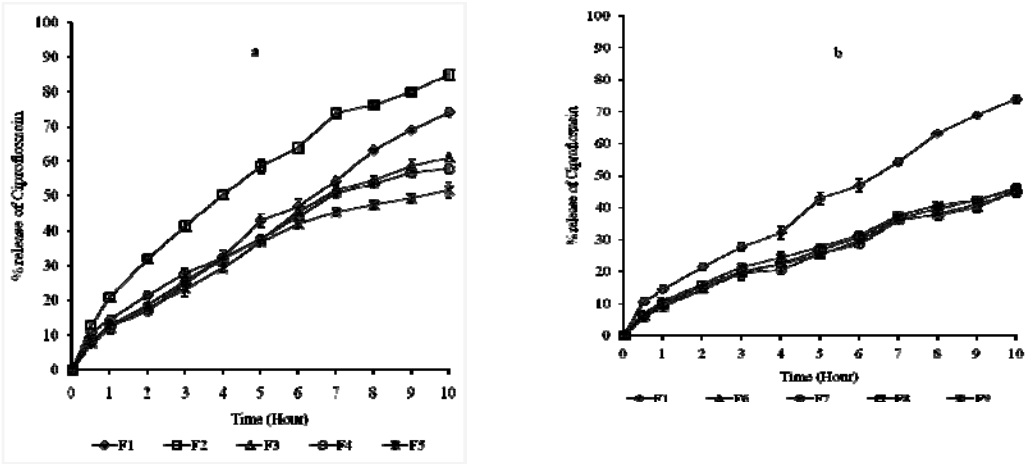

Figure 2: Zero Order release model of Ciprofloxacin from controlled release matrix tablets prepared using different concentration of HPMC 4.5 cps (a) and Carbopol 974P NF (b). Each data point represents the average release value ±SD (n = 6).

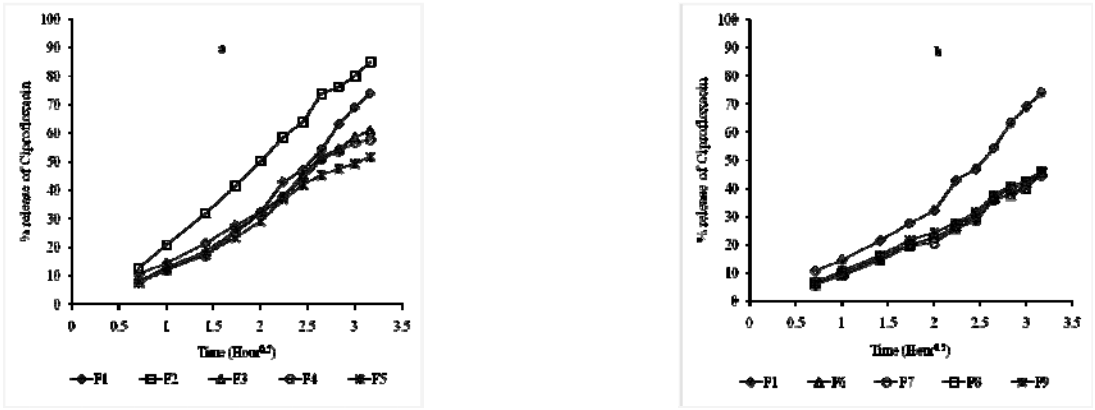

Figure 3: Higuchi release model of Ciprofloxacin from controlled release matrix tablets prepared using different concentration of HPMC 4.5 cps (a) and Carbopol 974P NF (b).

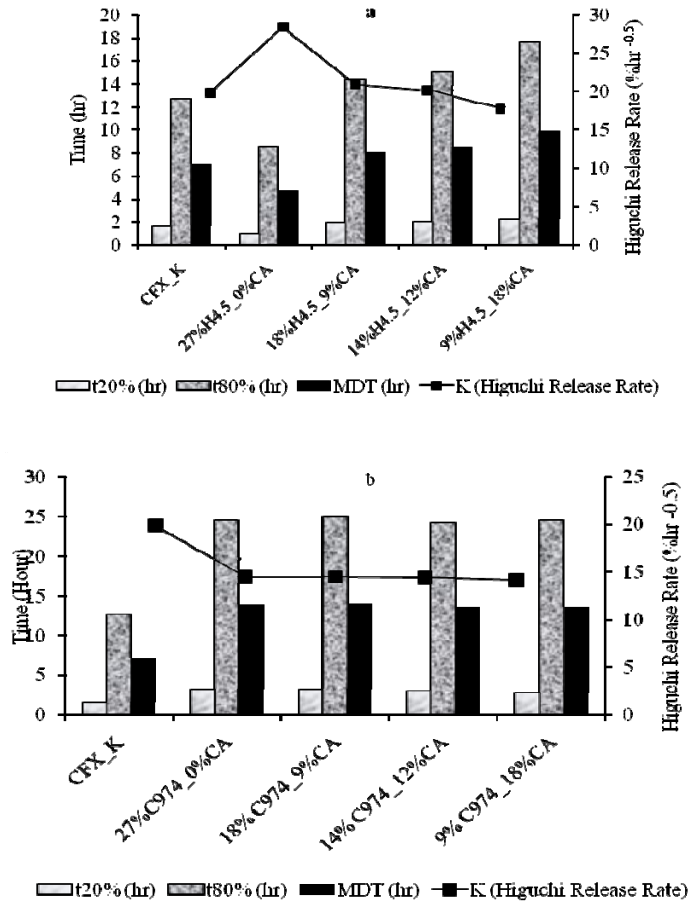

Figure 4: Release kinetics parameters of Ciprofloxacin matrix tablets formulated with different amounts of HPMC 4.5 cps (a) and Carbopol 974P NF (b)

quality matrix tablets of Ciprofloxacin using Kollidon® SR as the matrix former.

Release Rate

A plot of cumulative percentage released vs time for matrix-embedded CR tablets of CFX prepared using different matrix former (Kollidon SR, Ethocel 7 cps, Ethocel 20 cps, HPMC 15 cps) and for a market product is shown in Figure 1. A significant ($P<0.8$; $F_{crit} = 2.53$) and similar type of release was observed. After 10 hours of dissolution, 74% CFX was released from Kollidon® SR embedded matrix tablet (CFX_K/F1), 95.5% CFX was released from Ethocel™ 7 cps embedded matrix tablets (CFX_E7), 90.33% CFX was released from Ethocel™ 20 cps embedded matrix tablets (CFX_E20), 89.42% CFX was released from HPMC 15 cps embedded matrix tablets (CFX_H15), 84.54% CFX was released from market product. Formulation CFX_K/F1 released comparatively less amount of ciprofloxacin indicating that Kollidon® SR formed better matrix tablet of ciprofloxacin than others.

Figure 2 shows the cumulative percentage released vs time for matrix-embedded CR tablets of CFX prepared using HPMC 4 cps (a) and Carbopol 974P NF (b). In case of figure 2a where concentration of HPMC 4 cps and cetyl alcohol were varied to optimize the designed tablets, formulation F2 showed faster release of CFX than F1.

After 10 hours, CFX release was 86.01% for F2 and 74% for F1. Besides 150 mg of Kollidon® SR, F2 contained 150 mg of HPMC and no cetyl alcohol where as F1 contained only 250 mg of Kollidon® SR. It might be due to the hydrophilic nature of the HPMC which helped CFX to be released faster from the matrix tablets than those containing no HPMC (formula F1) [11]. But as the concentration of HPMC was decreased and cetyl alcohol was increased, CFX was found to be released at a slower rate from the tablets gradually (see F3, F4, and F5 in figure 2a). Formulation F3, F4, and F5 contain 50 mg, 100 mg and 150 mg of cetyl alcohol respectively. It might be due to the hydrophobicity of cetyl alcohol in aqueous media which retarded the CFX release from the CR matrix tablets [11, 20, 21]. The release of CFX from the formulations was statistically significant also ($P< 0.3$, $F_{crit} = 2.53$ and $F_{cal} = 1.36$).

In case of figure 2b where concentration of Carbopol 974P NF and cetyl alcohol were varied to optimize the designed tablets, a linear releation between the increment of these two excipients and percent release of CFX was observed e.g. as the content of Carbopol 974P NF and cetyl alcohol was increased alternatively, CFX release was found reduced gradually. After 10 hours, CFX release was 74% for F1 and was 45.35%, 44.64%, 42.51%, 42.44% for F6, F7, F8, F9 respectively. Formulation F1 contains no Carbopol 974P NF or cetyl alcohol and formulation F6, F7, F8, F9 contain 150 mg, 100 mg, 80 mg, 50 mg of Carbopol 974P NF. In CR tablet formulations, Carbopol 974P NF is widely used as dry binder for rate controlling purpose and this might be attributed for this reduced CFX release from Carbopol 974P NF containing tablets [11]. Though amount of Carbopol was less in formulation F6, F7, F8, and F9, presence of cetyl alcohol in these formulations caused the reduced release of CFX20-21 as formulation F6, F7, F8, F9 also contain 0 mg, 50 mg, 70 mg, 100 mg of cetyl alcohol respectively. This reduced release of CFX from F6 to F9 was also significant statistically ($P< 0.2$ and F $F_{crit} = 2.53$ and $F_{cal} = 1.6$).

Incorporation of Carbopol and cetyl alcohol also slowed down the release rate (K value, higuchi release rate) of CFX from the matrix tablets (see Figure 3b). But, incorporation of HPMC 4 cps increased the CFX release rate. As HPMC 4 cps was added in formulation F2, CFX was released at faster rate (Figure 3a). But, while cetyl alcohol was added in the same formulations, CFX was released at reduced rates from formulation F3 to formulation F5. Formulation F5 slowed down the release rate most which contained 100 mg of Cetyl alcohol and 50 mg of HPMC 4 cps.

$t_{20\%}$, $t_{80\%}$, and MDT values of the designed tablets are also shown in figure 3. In case HPMC 4 cps containing formulations, formulation F2 showed lowest MDT values of all as it increased the release rate of CFX. But, as the concentration of HPMC 4 cps was decreased and concentration of Cetyl alcohol was increased in the latter formulations (F3, F4, F5), MDT values were increased. Formulation F5 showed highest MDT (9.85 hr) value. However, Carbopol 974P NF containing formulations increased the MDT values of all. Formulation F9 showed highest MDT value (13.54 hr). It might be due to the presence of both Carbopol 974P NF and Cetyl alcohol as both act as release retardant [11].

The n values for HPMC 4 cps containing formulations ranged from 0.61 to 0.72, indicating that the release mechanism was non-Fickian or anomalous release ($0.45 < n < 0.89$). It can be inferred that the release was dependent on both drug diffusion and polymer relaxation. The poor correlation coefficients (r values were ≤ 0.97) observed

for the kinetic parameters based on the zero-order model equation were mainly due to the drug release mechanism. Though the values of n were closer to 0.7 in most cases, good correlation coefficients (r values ranged from 0.970 to 0.995) were even obtained for the kinetic parameters based on Higuchi's square-root equation. But it cannot be concluded that the drug release was totally based on diffusion, which generally is the case in Higuchi's square-root kinetics and correlation coefficient values based on Korsmeyer model were better (r values were > 0.99). However, it can be concluded that the effect of polymer relaxation on drug release was more than the effect of diffusion as the values of n were nearer to 0.7.

The n values for Carbopol 974P NF containing formulations ranged from 0.63 to 0.68, indicating that the release mechanism was non-Fickian or anomalous release ($0.45 < n < 0.89$). This is why, poor correlation values were obtained for the kinetic parameters based on the zero-order model equation (r values were mostly ≤ 0.98). But, correlation coefficients were also poor (r values were mostly ≤ 0.97) for the kinetic parameters based on Higuchi's square-root equation. However, considering the good fitting of the release data with Korsmeyer model (r values were > 0.99), it can be concluded that the effect of diffusion on drug release was more than the effect of polymer relaxation as the values of n were nearer to 0.6.

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