

Once-Daily Tablet Formulation and In Vitro Release Evaluation of Cefpodoxime Using Hydroxypropyl Methylcellulose: A Technical Note

Submitted: February 13, 2006; Accepted: June 5, 2006; Published: September 22, 2006

Hamid A. Merchant,¹ Harris M. Shoaib,¹ Jaweria Tazeen,¹ and Rabia I. Yousuf¹

¹Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi, Karachi-75270, Pakistan

KEYWORDS: Cefpodoxime proxetil, hydroxypropyl methylcellulose (HPMC), hydrophilic matrix tablets, in vitro sustained drug release, once-daily tablet, Cefpo SR.

INTRODUCTION

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because they make it easier to achieve a desirable drug-release profile, they are cost-effective, and they have broad US Food and Drug Administration acceptance.¹ The hydrophilic polymer matrix system consists of hydrophilic polymer, drug, and other excipients distributed throughout the matrix. This dynamic system is dependent on polymer wetting, hydration, and dissolution for controlled release of drug. At the same time, other soluble excipients or drug substances will also wet, dissolve, and diffuse out of the matrix, whereas insoluble excipients or drug substances will be held in place until the surrounding polymer, excipients, or drug complex erodes or dissolves away.²

Hydroxypropyl methylcellulose (HPMC), which is commonly used in hydrophilic matrix drug delivery systems, is a mixed alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxypropyl groups. The hydration rate of HPMC depends on the nature of these substituents, such as the molecular structure and the degree of substitution. Specifically, the hydration rate of HPMC increases with an increase in the hydroxypropyl content. The solubility of HPMC is pH independent.¹ HPMC has been found to be a very versatile material for the formulation of soluble matrix tablets. It is a widely accepted pharmaceutical excipient and is included in all major compendia. Because HPMC is available in a wide range of molecular weights, effective control of gel viscosity is easily provided.²

Cefpodoxime proxetil is an orally administered, extended-spectrum, semisynthetic antibiotic of the cephalosporin class. Cefpodoxime is a prodrug; its active metabolite is cefpodoxime.³ Cefpodoxime proxetil, a relatively new broad-spectrum third-generation cephalosporin, has very good in

vitro activity against *Enterobacteriaceae*, *Hemophilus* spp, and *Moraxella* spp, including lactamase producers and many strains resistant to other oral agents. It also has activity against Gram-positive bacteria, especially against *Streptococci*. It is well tolerated and is one of the first third-generation cephalosporins to be available in oral form. While the compound has been used most widely in the treatment of respiratory and urinary tract infections, its utility has also been demonstrated in the treatment of skin structure infections, acute otitis media, pharyngitis, tonsillitis, and sexually transmitted diseases.⁴ In a multicenter study, the in vitro activity of cefpodoxime was compared with that of cefixime, cefuroxime, cefaclor, cefadroxil, and clarithromycin against 5556 recent clinical isolates. Cefpodoxime demonstrated potent activity against members of the *Enterobacteriaceae*, in particular against species generally resistant to the established oral cephalosporins such as *Proteus vulgaris* (minimum inhibitory concentration (MIC) 50, 0.12 g/mL), *Providencia rettgeri* (MIC50, 0.015 g/mL), and *Serratia marcescens* (MIC50, 2 g/mL). Cefpodoxime was very effective against the fastidious organisms most frequently associated with respiratory infections, such as *Streptococcus pneumoniae* (MIC90, 0.12 g/mL), *Hemophilus influenzae* (MIC90, 0.12 g/mL), and *Moraxella catarrhalis* (MIC90, 1 g/mL). In contrast to other orally administered third-generation cephalosporins (cefixime or ceftibuten), cefpodoxime demonstrated reasonable activity against oxacillin-susceptible *Staphylococci*, with MIC90 ranging from 1 to 2 g/mL. All cephalosporins tested demonstrated poor activity against *Pseudomonas* spp, *Xanthomonas* spp, *Enterococcus* spp, and oxacillin-resistant *Staphylococci*. Cefpodoxime had the widest spectrum of activity of all tested oral cephalosporins.⁵

Considering the wide range of activity of cefpodoxime proxetil, the objective of this study was to decrease the dose frequency and increase the speed of recovery from the indications by increasing the rate of bacterial killing and thereby increasing patient compliance. The prospective sustained-release formulation of cefpodoxime proxetil named Cefpo SR is expected to produce a peak plasma concentration of 1.2 mg/L and then sustain that concentration for 24 hours. After 100 mg of the conventional-release dosage form of cefpodoxime is administered, the peak plasma concentration achieved is 1.2 mg/L, and this concentration slowly declines below minimum effective concentration (MEC) within 12 hours.^{6,7} The steady-state maintenance of plasma

Corresponding Author: Harris M. Shoaib, Assistant Professor, Faculty of Pharmacy, University of Karachi, Department of Pharmaceutics, University Road, Karachi-75270, Pakistan. Tel: +9221-4816410; Fax: +9221-4987344; E-mail: harrisshoaib2000@yahoo.com

concentration will increase the rate of bacterial killing and more quickly relieve the excruciating symptoms of bacteremia. One tablet of Cefpo SR will be sufficient for 24 hours' maintenance where 100 mg twice-daily doses of conventional-release dosage forms are recommended for conditions such as pharyngitis, tonsillitis, uncomplicated urinary tract infections, uncomplicated gonorrhoea, and rectal gonococcal infections. Two tablets of Cefpo SR taken as a straight dose can replace a 200 mg twice-daily dose regimen in acute community-acquired pneumonia and acute bacterial exacerbations of chronic bronchitis. However, this will not be suitable for indications like skin/skin structure infections requiring higher doses, such as 400 mg every 12 hours.³

In the present study, the formulation (Cefpo SR) was designed for 24-hour sustained release of cefpodoxime proxetil, and the sustained pattern was evaluated by in vitro drug release for 24 hours. The drug release data were plotted using various kinetic equations (zero order, first order, Higuchi's kinetics, Korsmeyer's equation, and Hixson-Crowell cube root law) to evaluate the drug release mechanism and kinetics. In vivo drug release, biopharmaceutical evaluation, and in vivo/in vitro correlations were beyond the scope of this study and will be considered in future work.

MATERIALS AND METHODS

Materials

HPMC 4000 cps (USP Type-2208) was purchased from Dow Chemicals (Midland, MI); Avicel PH-101 from FMC Biopolymer Corporation (Philadelphia, PA); and magnesium stearate from Merck KGaA (Darmstadt, Germany). Cefpodoxime proxetil (Orchid Chemical, India) was a gift from S.J. and G. Fazul Ellahie (Pvt) Ltd (Karachi, Pakistan). All other materials used in analysis of Cefpo SR were of analytical grade.

Methods

Calculation of the Sustained Dose

Per the zero-order release principle, the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. The release from the dosage form should follow zero-order kinetics, as shown by the following equation:

$$K_r^0 = \text{Rate in} = \text{Rate out} = k_e \cdot C_d \cdot V_d \quad (1)$$

where K_r^0 is the zero-order rate constant for drug release (amount/time), k_e is the first-order rate constant of overall drug elimination (h^{-1}), C_d is the desired drug level in the body (amount/volume), and V_d is the volume in which the

drug is distributed.⁸ If the elimination half-life of cefpodoxime proxetil is 2.4 hours ($k_e = 0.693/2.4$), C_d is 1.4 mg/L, and V_d is 32.3 L, then K_r^0 is 13.05 mg/h.⁶ The elimination constant (K_r^0) calculated was 13.05 mg/h, so the drug release constant should also have been equal to the elimination constant so as to maintain the steady-state condition. Cefpodoxime is not completely absorbed if taken orally; only 50% of the drug is absorbed in fasting conditions. The percent absorbed is improved if the drug is taken with food, to ~75% of the dose administered.⁹ Hence, the drug release rate should be 25% more than the elimination rate, which would be $13.05 \text{ mg/h} \times 125/100$, or 16.32 mg/h.

For a system in which the maintenance dose releases drug by a zero-order process for a specified period of time, the total dose is as follows:

$$W = (D_i - K_r^0 T_p) + K_r^0 T_d \quad (2)$$

where D_i is the initial dose, K_r^0 is the same zero-order rate constant, and T_d is the total time desired for sustained release from 1 dose (ie, 24 hours). If the maintenance dose begins release of the drug at the time of dosing ($t = 0$), it will add to that which is provided by the initial dose, thus increasing the initial drug level. In this case, a correction factor is needed ($K_r^0 T_p$) to account for the added drug from the maintenance dose. This correction factor is the amount of drug provided during the period from $t = 0$ to the time of the peak drug level, T_p .⁸

If D_i is 100 mg, K_r^0 is 16.32 mg/h, T_p is 2.5 hours, and T_d is 24 hours, then per Equation 2 the total dose would be 450.88 mg of cefpodoxime. Since 130 mg of cefpodoxime proxetil is equivalent to 100 mg of cefpodoxime,¹⁰ the required quantity of cefpodoxime proxetil would be (450.88×1.3) , or 586 mg (the quantity used was 590 mg/tablet).

Manufacturing of Tablets

Tablets were prepared by direct compression, the recommended process for working on a matrix system with HPMC; in wet granulation, unwanted swelling of HPMC could occur because of granulation fluid.¹¹ The tablet formula consisted of cefpodoxime proxetil (53.6%), HPMC 4000 cps (35%), Avicel PH 101 (10.4%), and magnesium stearate (1%). The HPMC manufacturer JRS (Rosenberg, Germany) recommended 20% to 50% matrix former for optimum release.¹¹ Materials were blended in a polybag using the geometric dilution principle. The blend was compressed using a single-punch tablet machine (KORSCH Erweka, Frankfurt, Germany) using 19.0 mm \times 8.8 mm caplet-shaped concave punches (although we recommend using 22 mm \times 10 mm punches for ease of filling) with a target weight of 1.1 g/tablet.

Evaluation of Tablets

Physical Evaluation. Using official British Pharmacopoeia methods, we evaluated tablets' physical parameters, including weight (Mettler Toledo B204-S, Zurich, Switzerland) and hardness (OSK Fujiwara Hardness Tester, Tokyo, Japan) variation, thickness, length, breadth, and friability (H. Jurgens GmbH and Co, Bremen, Germany).¹²

Assay for Cefpodoxime. An assay was performed on HPLC as per the official monograph requirement for cefpodoxime proxetil in USP 27.¹³ System suitability was checked prior to sample injections. Resolution factor *R* between the cefpodoxime proxetil S and R epimer peaks, and tailing factor *t* for cefpodoxime R epimer, were calculated.

In Vitro Dissolution Studies. In vitro drug release of Cefpo SR was evaluated using USP official method Drug Release <724> Method A using USP Apparatus-II, following general dissolution procedure USP <711>. The only exception was that a stationary basket was suspended in the vessel of Apparatus-II (Erweka ZT-2, Heusenstamm, Germany) because of the floating character of the tablet in the dissolution medium during paddle rotation at 100 rpm. The tablet was placed in a specially made basket of stainless steel wire gauze (8 mesh) with rod assembly through the cover of the dissolution vessel and fixed at 3.2 cm away from the center of the vessel; the lower end of the bottom of the basket was adjusted to ~1 cm above the top of the paddle blade. The largest side of the basket was oriented tangentially to the flow stream, with the tablet standing on its edge.¹³

Qiu et al found that factorial studies have indicated that higher pH, addition of sodium lauryl sulfate (SLS) to the dissolution medium, and higher agitation intensity increased the release rate from the matrix tablet. Use of SLS led to not only increased release rates that were closer to in vivo absorption rates but also improved differentiation among formulations with varying release rates.¹⁴ Hence, drug release for Cefpo SR was studied for the first 45 minutes in an

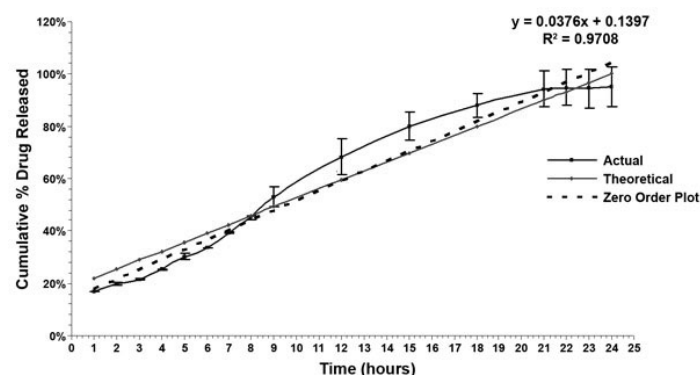


Figure 1. Cefpo SR release profile vs theoretical profile and zero order plot.

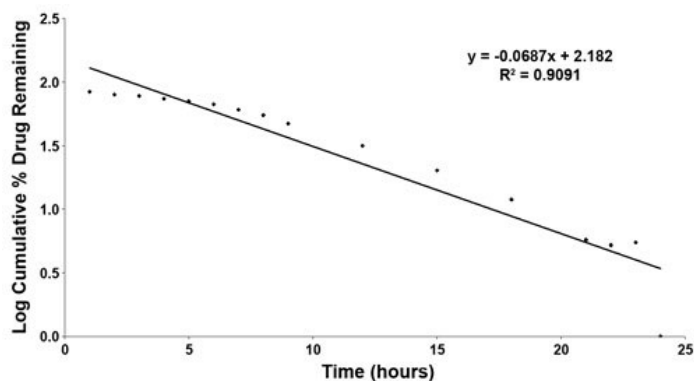


Figure 2. First-order kinetics (log cumulative percent drug remaining vs time).

acidic medium containing 1% SLS and then for the rest of the 24-hour period in phosphate buffer (pH 6.8 ± 0.05) having 0.75% SLS. A 10-mL aliquot was withdrawn from the dissolution medium at predetermined intervals throughout the 24-hour period; at each interval, the withdrawn medium was replaced with blank dissolution medium. Drug release was then analyzed by measuring the absorbance through a spectrophotometer (UV 150-02, Shimadzu Corporation, Kyoto, Japan) at wavelength 259 nm after suitable dilution. Drug content (assay) was determined through High Performance Liquid Chromatography (HPLC) (LC-5A, SPD-2A, Shimadzu Corporation, Kyoto, Japan) using official methods for cefpodoxime proxetil tablets.¹³

Drug Release Kinetics. To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models: zero order (Equation 3) as cumulative amount of drug released vs time, first order (Equation 4) as log cumulative percentage of drug remaining vs time, and Higuchi's model (Equation 5) as cumulative percentage of drug released vs square root of time.

$$C = K_0 t \tag{3}$$

where K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.¹⁵

$$\text{Log}C = \text{Log}C_0 - kt/2.303 \tag{4}$$

where C_0 is the initial concentration of drug, k is the first order constant, and t is the time.¹⁶

$$Q = Kt^{1/2} \tag{5}$$

where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release

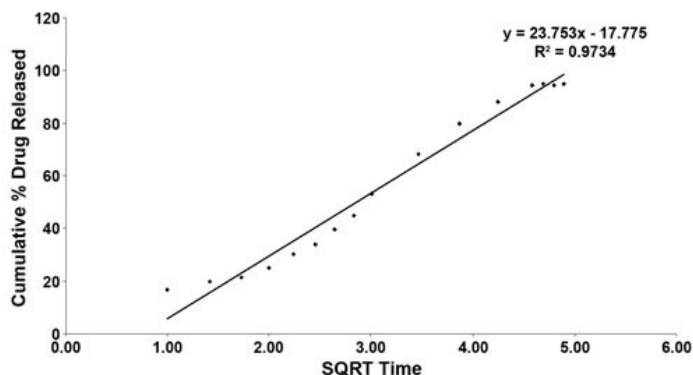


Figure 3. Higuchi (square root) kinetics (cumulative percent drug released vs square root of time). SQRT indicates square root.

rate is proportional to the reciprocal of the square root of time.¹⁷

To evaluate the drug release with changes in the surface area and the diameter of the particles/tablets, the data were also plotted using the Hixson-Crowell cube root law:

$$\sqrt[3]{Q_0} - \sqrt[3]{Q_t} = k_{HC} \times t \quad (6)$$

where Q_t is the amount of drug released in time t , Q_0 is the initial amount of the drug in the tablet, and K_{HC} is the rate constant for the Hixson-Crowell rate equation,¹⁸ as the cube root of the percentage of drug remaining in the matrix vs time.

Mechanism of Drug Release. To evaluate the mechanism of drug release from Cefpo SR, data for the first 60% of drug release were plotted in Korsmeyer et al's equation (Equation 7) as log cumulative percentage of drug released vs log time, and the exponent n was calculated through the slope of the straight line.

$$M_t/M_\infty = Kt^n \quad (7)$$

where M_t/M_∞ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers.¹⁹ For cylindrical matrix tablets, if the exponent $n = 0.45$, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release.²⁰

RESULTS AND DISCUSSION

Manufacturing and Evaluation of Tablets

The physical attributes of the tablet were found to be satisfactory. Typical tablet defects, such as capping, chipping, and picking, were not observed, but for ease of filling we recommend using 22 mm × 10 mm instead of 19 mm × 8.8 mm punches. Results for other physical evaluations were also found to be within an acceptable range. For instance, weight variation was calculated as 1.68% (range ± 5%), where average weight was 1.1015 ± 0.0185 g ($n = 20$). Hardness of the tablet was found to be 18.5 ± 5 kg ($n = 20$). Thickness, length, and breadth were found to be fixed during the compression cycle; values were 9.8 mm, 19.0 mm, and 8.8 mm, respectively. Friability of the tablet was calculated as 0.1613% ($n = 10$), which was well within the acceptable range of 1% and indicates that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage and transportation and until they are consumed.¹²

Assay for Cefpodoxime Proxetil

The resolution factor R between the cefpodoxime proxetil S and R epimer peaks was 2.538 (not less than (NLT) 2.5), and the tailing factor for cefpodoxime proxetil R epimer was 1.04 (not more than (NMT) 1.5). The assay percentage was 90.04% (90% to 110%), with relative standard deviation (RSD) of 1.06% (NMT 1%). The fact that the assay results were close to the lower limit of the range may have been due to manual bag blending of the formula ingredients.

In Vitro Dissolution Studies

Ideally, an extended-release tablet should release the required quantity of drug with predetermined kinetics in order to maintain an effective drug plasma concentration. To achieve this, the tablet should be formulated so that it releases the drug in a predetermined and reproducible manner. By considering the drug's biopharmaceutic and pharmacokinetic profile, one can determine the required release from the tablet.²¹ Figure 1 shows the in vitro drug release profile of Cefpo SR. It was found that ~99.45 mg (16.86%) of the drug was released during the first hour, which is in accordance with the conventional dose of a 100-mg tablet. During the initial 9 hours, ~50% of the drug was released. After 9 hours, the release rate increased slightly, until the 21st hour, and then release slowed but continued until the

Table 1. Release Kinetics of Cefpo SR

Zero Order		First Order		Higuchi		Korsmeyer-Peppas			Hixson-Crowell	
r^2	$K_o (h^{-1})$	r^2	$K_l (h^{-1})$	r^2	$K_H (h^{-1/2})$	r^2	n	$K_{KP} (h^{-n})$	r^2	$K_{HC} (h^{-1/3})$
0.9708	3.7574	0.9091	0.1582	0.9734	23.753	0.9006	0.57	0.1309	0.9878	0.1325

24-hour mark. Hence, a sustained-release pattern was observed throughout the 24-hour dissolution study. The *in vitro* release behavior of Cefpo SR was also compared with the theoretical (predictive) profile and found to be quite similar; a very close relationship was noted between the test and theoretical release patterns (Figure 1).

Drug Release Kinetics

The zero-order rate (Equation 3) describes the systems where the drug release rate is independent of its concentration. Figure 1 shows the cumulative amount of drug release vs time for zero-order kinetics. The first order (Equation 4), which describes the release from systems where the release rate is concentration dependent, is illustrated by Figure 2, which shows the log cumulative percent drug remaining vs time. Higuchi's model (Equation 5) describes the release of drugs from an insoluble matrix as a square root of a time-dependent process based on Fickian diffusion. Figure 3 illustrates the Higuchi square root kinetics, showing the cumulative percent drug release vs the square root of time.²² The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r^2) was determined (Table 1). It was found that the *in vitro* drug release of Cefpo SR was best explained by Higuchi's equation, as the plots showed the highest linearity ($r^2 = 0.9734$), followed by zero order ($r^2 = 0.9708$) and first order ($r^2 = 0.9091$). This explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as square root kinetics (or Higuchi's kinetics). However, drug release was also found to be very close to zero-order kinetics, indicating that the concentration was nearly independent of drug release. Figure 1 also verifies the correlation of the Cefpo SR release profile with the theoretical profile.

The dissolution data were also plotted in accordance with the Hixson-Crowell cube root law (Equation 6). The ap-

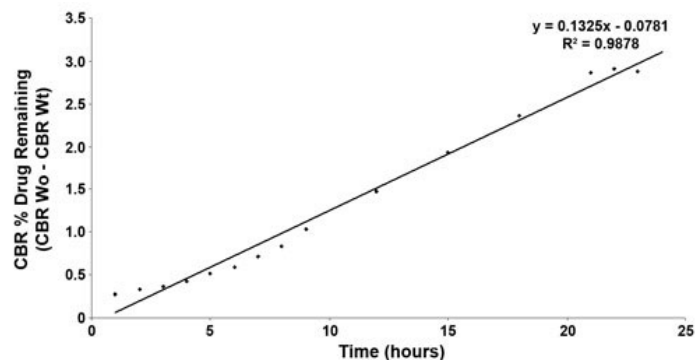


Figure 5. Hixson-Crowell cube root plots (CBR percent drug remaining vs time). CBR indicates cube root, W_0 indicates initial drug load at time zero, taken as 100%, and W_t indicates percentage drug undissolved at time t .

plicability of the formulation to the equation indicated a change in surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time (Figure 4).

Mechanism of Drug Release

The corresponding plot (log cumulative percent drug release vs time) for the Korsmeyer-Peppas equation¹⁹ indicated a good linearity ($r^2 = 0.9006$). The release exponent n was 0.57, which appears to indicate a coupling of the diffusion and erosion mechanism—so-called anomalous diffusion—and may indicate that the drug release is controlled by more than one process (Figure 5). Reddy et al observed similar results with a matrix tablet of nicorandil with an n value of 0.71,²³ and Fassihi and Ritschel with a matrix tablet of theophylline with an n value of 0.7.²⁴ Both these groups of researchers also considered the corresponding n values to indicate an anomalous release mechanism.

SUMMARY AND CONCLUSIONS

Decreasing the dose frequency of cefpodoxime proxetil increases patient compliance; patients prefer to take the drug once daily. It also improves the rate of bacterial killing and hastens the cure from the indications, and therefore increases compliance. The hydrophilic matrix of HPMC controlled the cefpodoxime proxetil release effectively for 24 hours; hence, the formulation can be considered as a once-daily sustained-release tablet of cefpodoxime proxetil. The formulation showed acceptable pharmacotechnical properties and assay requirements. *In vitro* dissolution studies indicated a sustained-release pattern throughout 24 hours of the study that was comparable to the theoretical release profile. Drug release kinetics indicated that drug release was best explained by Higuchi's equation, as these plots showed the highest linearity ($r^2 = 0.9734$), but a close relationship was also noted with zero-order kinetics ($r^2 = 0.9708$).

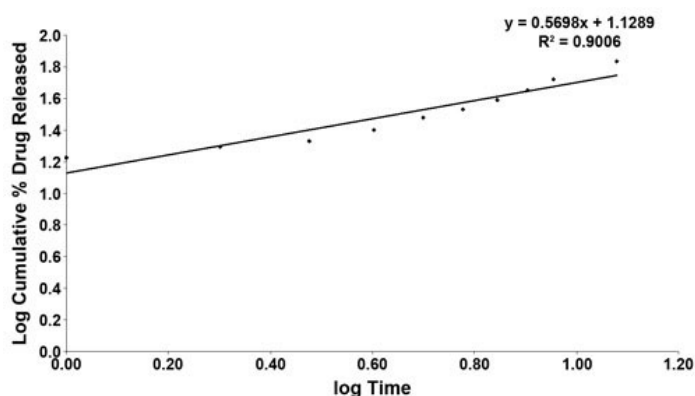


Figure 4. Korsmeyer et al kinetics (log cumulative percent drug released vs log time).

Korsmeyer's plots indicated an n value of 0.57, which was indicative of an anomalous diffusion mechanism or diffusion coupled with erosion; hence, the drug release was controlled by more than one process. Hixson-Crowell plots indicated a change in surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time.

ACKNOWLEDGMENT

The authors gratefully acknowledge the support of M/s S.J. and G. Fazul Ellahie (Pvt) Ltd (Karachi, Pakistan), which provided cefpodoxime proxetil for this research.

REFERENCES

1. Alderman DA. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. *Int J Pharm Tech Prod Mfr*. 1984;5:1-9.
2. Dow Chemical Company. Using methocel cellulose ethers for controlled release of drugs in hydrophilic matrix systems. Available at: http://www.dow.com/PublishedLiterature/dh_01e7/09002f13801e718c.pdf?filepath=methocel/pdfs/noreg/198-02075.pdf&fromPage=GetDoc. Accessed: August 24, 2006.
3. Dollery C. *Therapeutic Drugs*. Edinburgh, Scotland: Churchill Livingstone; 1999:C113-C117.
4. Todd WM. Cefpodoxime proxetil: a comprehensive review. *Int J Antimicrob Agents*. 1994;4:37-62.
5. Sader HS, Jones RN, Washington JA, et al. In vitro activity of cefpodoxime compared with other oral cephalosporins tested against 5556 recent clinical isolates from five medical centers. *Diagn Microbiol Infect Dis*. 1993;17:143-150.
6. Orelox. Electronic medicines compendium, Aventis Pharma Ltd. Available at: <http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=8940>. Accessed: January 8, 2005.
7. Saathoff N, Lode H, Neider K, et al. Pharmacokinetics of cefpodoxime proxetil and interactions with an antacid and an H₂ receptor antagonist. *Antimicrob Agents Chemother*. 1992;36:796-800.
8. Wai-Yip Lee T, Robinson RJ. Controlled drug delivery systems. In: Gennaro AR, ed. *Remington: The Science and Practice of Pharmacy*. 20th ed. Philadelphia, PA: University of Sciences in Philadelphia; 2000:903-929.
9. Vantin. Pharmacia & Upjohn Company, Pharmacia Corporation. Available at: http://www.pfizer.com/download/uspi_vantin.pdf. Accessed: August 24, 2006.
10. Martindale. *The Extra Pharmacopoeia*. 31st ed. London, UK: Royal Pharmaceutical Society; 1996:193.
11. VIVAPHARM, cellulose-based polymer for film-coating and sustained release application. Available at: <http://www.jrspharma.de>. Accessed: January 8, 2005.
12. British Pharmacopoeia (B.P.). London, UK: Stationary Office London; 2004.
13. *United States Pharmacopoeia-27*. Rockville, MD: US Pharmacopoeial Convention; 2004:377-379. Also pp778-780.
14. Qiu Y, Garren J, Samara E, et al. Once-a-day controlled-release dosage form of divalproex sodium II: development of a predictive in-vitro drug release method. *J Pharm Sci*. 2003;92:2317-2325.
15. Hadjiioannou TP, Christian GD, Koupparis MA. *Quantitative Calculations in Pharmaceutical Practice and Research*. New York, NY: VCH Publishers Inc; 1993:345-348.
16. Bourne DW. Pharmacokinetics. In: Banker GS, Rhodes CT, eds. *Modern Pharmaceutics*. 4th ed. New York, NY: Marcel Dekker Inc; 2002:67-92.
17. Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J Pharm Sci*. 1963;52:1145-1149.
18. Hixson AW, Crowell JH. Dependence of reaction velocity upon surface and agitation: I-theoretical consideration. *Ind Eng Chem*. 1931;23:923-931.
19. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. *Int J Pharm*. 1983;15:25-35.
20. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Adv Drug Deliv Rev*. 2001;48:139-157.
21. Saravanan M, Nataraj KS, Ganesh KS. Hydroxypropyl methylcellulose based cephalixin extended release tablets: influence of tablet formulation, hardness and storage on in-vitro release kinetics. *Chem Pharm Bull (Tokyo)*. 2003;51:978-983.
22. Sood A, Panchagnula R. Drug release evaluation of diltiazem CR preparations. *Int J Pharm*. 1998;175:95-107.
23. Reddy KR, Mutalik S, Reddy S. Once-daily sustained-release matrix tablets of nicorandil: formulation and in vitro evaluation. *AAPS PharmSciTech*. 2003;4:E61.
24. Fassih RA, Ritschel WA. Multiple layer, direct compression controlled release system: in vitro and in vivo evaluation. *J Pharm Sci*. 1993;82:750-754.