Intragastric Floating Drug Delivery System of Cefuroxime Axetil: In Vitro Evaluation

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ABSTRACT

This investigation describes the development of an intragastric drug-delivery system for cefuroxime axetil. The 3^2 full factorial design was employed to evaluate contribution of hydroxypropyl methyl cellulose (HPMC) K4M/HPMC K100 LV ratio (polymer blend) and sodium lauryl sulfate (SLS) on drug release from HPMC matrices. Tablets were prepared using direct compression technique. Formulations were evaluated for in vitro buoyancy and drug release study using *United States Pharmacopeia (USP*) 24 paddle-type dissolution apparatus using 0.1N HCl as a dissolution medium. Multiple regression analysis was performed for factorial design batches to evaluate the response. All formulations had floating lag times below 2 minutes and constantly floated on dissolution medium for more than 8 hours. It was found that polymer blend and SLS significantly affect the time required for 50% of drug release, percentage drug release at 12 hours, release rate constant, and diffusion exponent ($P < .05$). Also linear relationships were obtained between the amount of HPMC K100 LV and diffusion exponent as well as release rate constant. Kinetic treatment to dissolution profiles revealed drug release ranges from anomalous transport to case 1 transport, which was mainly dependent on both the independent variables.

KEYWORDS: hydroxypropyl methylcellulose (HPMC), sodium lauryl sulfate (SLS), factorial design, floating tablets.

INTRODUCTION

Cefuroxime is a broad-spectrum, β-lactamase-stable cephalosporin that has well-defined pharmacokinetics after intramuscular and intravenous administration in the form of sodium salt.[1,2] In humans, gastrointestinal absorption of cefuroxime is negligible,[1,3] whereas the acetoxyethyl ester of cefuroxime (cefuroxime axetil), an oral prodrug shows a bioavailability of 30% to 40% when taken on fasting and 5% to 60% when taken after food.[4-7] Also, the extent and bioavailability rate of the drug vary according to the dosage form used.[8] The molecule is de-esterified during absorption, either in the mucosal cells, the portal blood, or the liver such that only cefuroxime circulates systemically. The cefuroxime axetil esterase can hydrolyze cefuroxime axetil to the nonabsorbable cefuroxime in the gut lumen and is, therefore, suspected as a possible cause of incomplete bioavailability.[9] The absolute bioavailability of all newer oral ester prodrug cephalosporins is below 50% to 60%,[10] which suggests an absorption mechanism through the mucosa with limited capacity. Indeed, β-lactam has been shown to be excreted by the renal anionic transport system, and administration of increasing doses of these drugs results in a nonlinearity of β-lactam elimination. Results reported from GlaxoSmithKline's laboratories (Madrid, Spain) have confirmed that an increase in the dose of cefuroxime axetil is not accompanied by a proportional increase in serum drug concentration, probably because of a loss of absorption capacity.[11] Merino and coworkers[12] studied the hydrolysis of the cefuroxime axetil, and this process was mathematically separated from the absorption process. Therefore, according to the reported results, the luminal degradation of the prodrug does not seem to be responsible for the nonlinear absorption. The improvement in bioavailability after ingestion would be justified by the spreading of the hydrolytic activity of the esterase on the food and the prodrug; on the other hand, by the slowing of the gastric emptying, the prodrug arrives slowly at its absorption site and, in this way, in the case of a specialized transport mechanism, the carriers are not saturated.

Adams and coworkers[13] had to terminate prematurely a trial of cefuroxime axetil on patients with urinary tract infections because of the incidence of antibiotic-associated colitis, which might have been caused by the high concentration of antibiotic entering the colon, absorption high up in the gut not having taken place. It was suggested that if the drug exhibits reduced or no absorption in the colon then a gastro-retentive dosage form would be required to ensure drug delivery within drug-absorbable intestinal regions.[14] Sommers and coworkers[4] reported that the bioavailability of cefuroxime axetil was reduced more than 65% when administered with 300 mg of ranitidine and 4 g of sodium bicarbonate, which might be the result of elevation of gastric pH responsible for low dissolution and of reduced

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bioavailability as the absorption of drug is confined mainly to the upper part of the gastrointestinal (GI) tract. A direct correlation exists between the duration the β-lactam antibiotic concentrations are maintained above the therapeutic concentration and the clinical outcomes. Unlike aminoglycosides, the kinetics of bactericidal effect is slow and requires prolonged maintenance of effective concentrations of the drug in order to achieve onset of effect.[15]

From examination of the above-mentioned characteristics of cefuroxime bioavailability, it was clear that cefuroxime axetil had saturation kinetics that could be overcome by slow release of drug from the formulation, by incorporating cefuroxime axetil in sustained drug-delivery system. Also, because cefuroxime axetil had higher absorption in the proximal region of the GI tract and poor absorption, as well as antibiotic-associated colitis, when a large amount of drug entered the colon suggest it is an ideal candidate for a gastroretentive drug-delivery system that will prolong the gastric residence time of the dosage form, giving prolonged drug release in the upper GI tract, where absorption of cefuroxime is well confined.

The gastroretentive drug-delivery system can be retained in the stomach and assists in improving the oral sustained-delivery of drugs that have an absorption window in a particular region of the GI tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Several approaches are currently used to prolong gastric retention time. These include floating drug-delivery systems, swelling and expanding systems, polymeric bioadhesive systems, high-density systems, and other delayed-gastric-emptying devices.[16] The principal of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for dosage form and sustained drug release.[17] The present investigation describes the formulation development of an intragastric floating drug-delivery system for cefuroxime axetil.

Materials and Methods

Materials

Cefuroxime axetil was received as a gift sample from Zorex Pharmaceutical Ltd (Ahmedabad, India). Methocel K4M (4000 mPa.s) and Methocel K100 LV (100 mPa.s) were received as a gift sample from Colorcon Asia Pvt Ltd (Goa, India). Tablettose 80 was received as a gift sample from Meggle Gmbh (Wasserburg, Germany). Sodium lauryl sulfate and all other ingredients were purchased from S. D. Fine Chemicals (Mumbai, India). All ingredients used in study are of *USP* 24 standards.

Methods

Full Factorial Design

A 3^2 randomized full factorial design was used in development of the dosage form. In this design, 2 factors were evaluated each at 3 levels and experimental trials were performed using all possible 9 combinations. In the present investigation, the ratio of hydroxypropyl methyl cellulose (HPMC) K4M:HPMC K100 LV(X_1) and content of sodium laurel sulfate (SLS) (X_2) were selected as independent variables. The time required for 50% of drug release ($t_{50\%}$), percentage drug release at 12 hours (Q_{12}), release rate constant (k), and diffusion exponent (n) were selected as dependent variables. The experimental design with corresponding formulations is outlined in Table 1. Content of polymer blend was 15% of total tablet weight. Blends of HPMC K4M and HPMC K100 LV were evaluated at 85:15, 75:25, and 65:35, while constant of SLS was evaluated at 0%, 1%, and 2% of total tablet weight. A statistical model incorporating interactive and polynomial terms was used to evaluate the response (Equation 1).

$$Y = b0 + b1X1 + b2X2 + b12X1X2 + b11X1X1 + b22X2X2 \quad (1)$$

where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_i is the estimated coefficient for the factor X_i. The main effect (X_1 and X_2) represents the

Table 1. Formulation and Dissolution Characteristics of Batches in a 3^2 Full Factorial Design*

Batch Code	Coded Value X_1	Coded Value X_2	$t_{50\%}$ (minutes)	Q_{12} (%)	Release Rate Constant (k)	Diffusion Exponent (n)
B1	+1	+1	100	88.90	0.684	0.303
B2	+1	0	45	110.17	0.800	0.240
B3	+1	–1	110	90.48	0.688	0.305
B4	0	+1	215	79.38	0.610	0.356
B5	0	0	225	88.43	0.553	0.500
B6	0	–1	230	74.59	0.549	0.450
B7	–1	+1	330	71.82	0.555	0.396
B8	–1	0	230	80.00	0.548	0.550
B9	–1	–1	450	65.34	0.493	0.470

Coded Values	**Actual Values** X_1	X_2
–1	**85:15**	0%
0	**75:25**	1%
1	**65:35**	2%

*$t_{50\%}$ indicates the time required for 50% of drug release; and Q_{12}, percentage drug release at 12 hours. X_1 is ratio of HPMC K4M to HPMC K100 LV, and X_2 is content of SLS. All batches contained 300 mg cefuroxime axetil (equivalent to 250 mg of base), 10% sodium bicarbonate, 15% polymer blends, 1% magnesium stearate, and quantity sufficient of lactose.

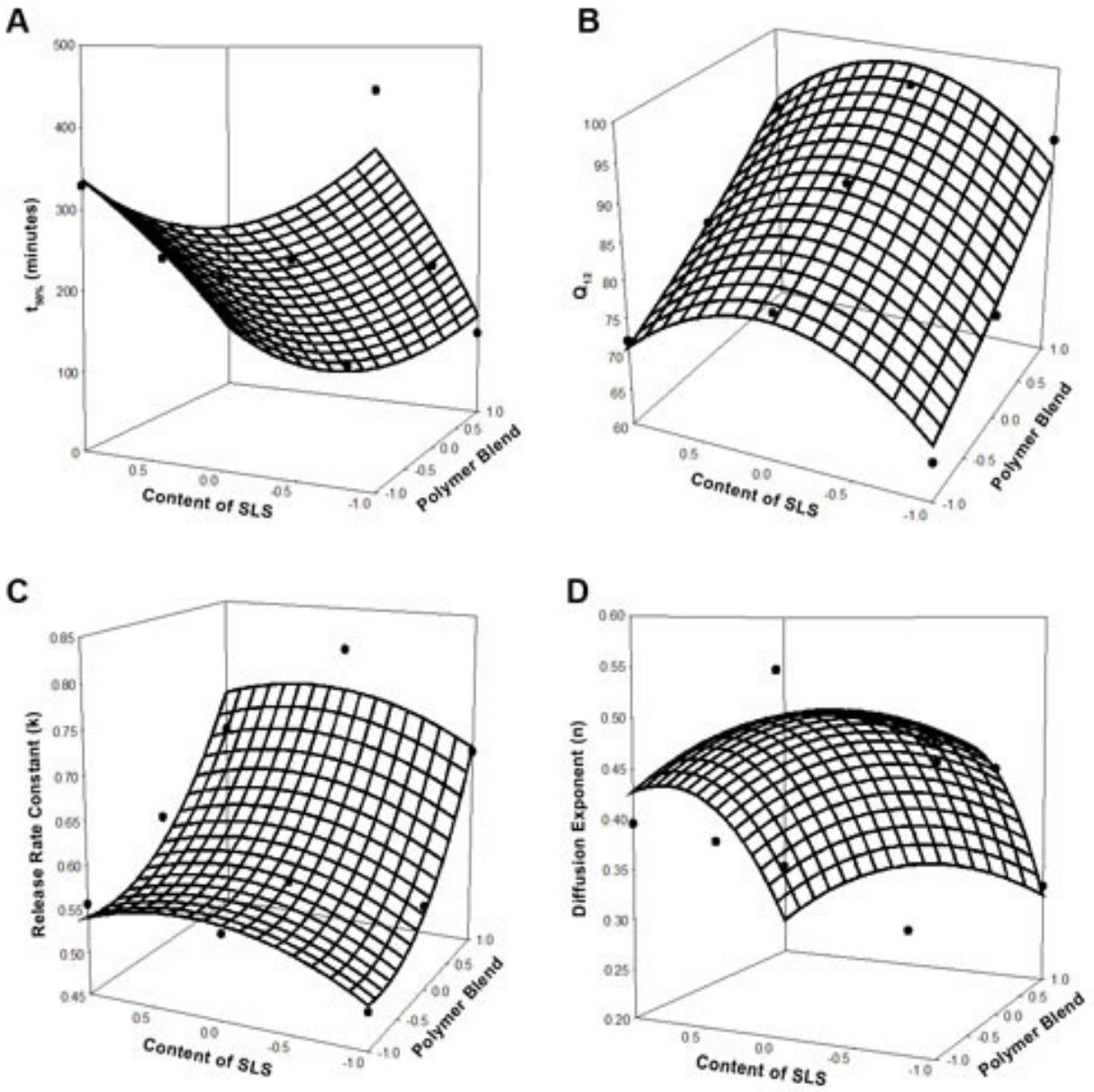

Figure 1. Influence of polymer blend and content of SLS on (A) $t_{50\%}$, (B) Q_{12}, (C) *k,* and (D) *n*.

average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when 2 factors are changed simultaneously. The polynomial terms (X_1X_1, X_2X_2) are included to investigate nonlinearity.

Preparation of Cefuroxime Axetil Floating Tablets

Cefuroxime Axetil (300 mg equivalent to 250 mg of cefuroxime base) was mixed with the required quantities of polymer blend, SLS, sodium bicarbonate (10%), and lactose by geometric mixing. The powder blend was then lubricated with magnesium stearate (1%) and compressed on a 10-station rotary tablet machine (Rimek, Ahmedabad, India) using a 12-mm standard flat-face punch. Lactose, being a water-soluble filler, was used to maintain constant tablet weight as well as to counterbalance the poor water solubility of drug. The tablet characteristics were weight, 600 ± 2 mg; shape, round and flat faced; size, average diameter of 12 ± 0.1 mm and thickness of 4.5 ± 0.2 mm; and hardness, range of 5 to 6 kg/cm^2.

In Vitro Buoyancy Study

The in vitro buoyancy was characterized by floating lag time and total floating time. The test was performed using a *USP* 24 type-2 paddle apparatus using 900 mL of 0.1N HCl at paddle rotation of 100 rpm at 37°C ± 0.5°C. The time required for the tablet to rise to the surface of the dissolution medium and the duration of time the tablet

Table 2. Multiple Regression Output for Dependent Variables*

Parameters	Coefficient of Regression Parameters							
	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}	r	P
$t_{50\%}$	175.01	–125.82	–24.16	27.5	–12.5	72.5	0.920	0.041
Q_{12}	90.43	12.07	1.62	–2.02	3.65	–14.44	0.973	0.015
k	0.595	0.096	0.020	–0.017	0.057	–0.037	0.906	0.044
n	0.49	–0.095	–0.028	0.018	–0.058	–0.050	0.835	0.040

*$t_{50\%}$ indicates the time required for 50% of drug release; Q_{12}, percentage drug release at 12 hours; k, release rate constant; and n diffusion exponent.

constantly floated on the dissolution medium were noted as floating lag time and total floating time, respectively (n = 3).

In Vitro Drug Release Study

The in vitro drug release was performed using *USP* 24 type-2 paddle apparatus using 900 mL of 0.1N HCl at paddle rotation of 100 rpm at 37°C ± 0.5°C. The samples were withdrawn at predetermined time intervals for a period of 12 hours and replaced with the fresh medium. The samples were filtered through a 0.45-μm membrane filter, suitably diluted, and analyzed at 280 nm using double-beam UV/visible spectrophotometer (UV-1601, Shimadzu, Kyoto, Japan). The content of drug was calculated using equation generated from standard calibration curve.

Statistical Analysis

The statistical analysis of the factorial design batches was performed by multiple regression analysis using Microsoft Excel. To evaluate the contribution of each factor with different levels on responses, 2-way analysis of variance (ANOVA) followed by Tukey test was performed using Sigma Stat software (Sigma Stat 2.03, SPSS, Chicago, IL). To demonstrate graphically the influence of each factor on responses, the response surface plots were generated using Sigma Plot software Version 8.0, (Jandel Scientific Software, San Rafael, CA). The $P < .05$ was considered to be significant.

Results and Discussion

In the present investigation, the ratio of HPMC K4M to HPMC K100 LV and the content of SLS was studied using 3^2 full factorial design. Tablets of all formulations had floating lag time below 2 minutes regardless of ratio of HPMC K4M to HPMC K100 LV and content of SLS. Also, all formulations had to constantly float on dissolution medium for more than 8 hours. The $t_{50\%}$, Q_{12}, release rate constant (k), and diffusion exponent (n) showed wide variation (Table 1). The data clearly indicate that the dependent variables are strongly dependent on the independent variables. The fitted equation relating the response $t_{50\%}$, Q_{12}, k,

Table 3. Results of Analysis of Variance for Measured Response*

Parameters	df	SS	MS	F	Significance F
		For $t_{50\%}$			
Regression	5	112358.33	22471.66	6.884	0.041
Residual	3	9797.66	3263.88		
Total	8	122150			
		For Q_{12}			
Regression	5	1349.45	269.89	21.19	0.015
Residual	3	38.20	12.73		
Total	8	1387.66			
		For n			
Regression	5	0.0716	0.0143	3.031	0.040
Residual	3	0.0142	0.0047		
Total	8	0.0857			
		For k			
Regression	5	0.0680	0.0136	5.757	0.044
Residual	3	0.0070	0.0023		
Total	8	0.0752			

*df indicates degree of freedom; SS, sum of square; MS, mean sum of square; and F, Fischer's ratio. All other abbreviations are explained in the footnote to Table 2.

and n to the transformed factor are shown in Equation 2 to Equation 5.

$$t50\% = 175 - 125.82X1 - 24.16X2 + 27.50X1X2 - 12.5X1X1 + 72.5X2X2, r = 0.920 \quad (2)$$

$$Q12 = 90.43 + 12.07X1 + 1.62X2 - 2.02X1X2 - 14.44X1X1 + 3.65X2X2, \; r = 0.973 \quad (3)$$

$$k = 0.595 + 0.096X1 + 0.020X2 - 0.017X1X2 + 0.057X1X1 - 0.037X2X2, \; r = 0.906 \quad (4)$$

$$n = 0.49 - 0.095X1 - 0.028X2 - 0.018X1X2 - 0.058X1X1 - 0.050X2X2, \; r = 0.835 \quad (5)$$

The value of the correlation coefficient indicates a good fit. The polynomial equation can be used to draw a conclusion after considering the magnitude of coefficient and the mathematical sign it carries (positive or negative).

To demonstrate graphically the effect of the amount of HPMC K100 LV and SLS, the response surface plots (Figure 1) were generated for the dependent variables, $t_{50\%}$, Q_{12}, k, and n using Sigma Plot software. Multiple regression analysis was performed using Microsoft Excel, and it was found that the ratio of HPMC K4M to HPMC K100LV and SLS had significant influence for time required for 50% drug release ($P < .05$, Table 2). Results of ANOVA for the measured responses are provided in Table 3. To evaluate the contribution of different levels of factor (X_1) and factor (X_2), 2-way ANOVA followed by Tukey test was performed using Sigma Stat software. For factor X_1, it was found that there is a statistically significant difference between the 1 and −1 levels, ($P < .05$). For factor X_2, it was found that there is a statistically significant difference between levels 0 and −1 ($P < .05$). From the results, it was clear that the release rate was higher at SLS concentration of 1% compared with 2% and without SLS. This finding may be owing to the solubilization effect of SLS at the 1% level, which was not observed at 2%; drug may have been entrapped within a micelle formation causing a decrease in the rate of drug release. For percentage drug at 12 hours, it was found that the ratio of HPMC K4M to HPMC K100 LV and content of SLS had significant influence ($P < .05$, Table 2). From the results of the Tukey test, it was found that for X_1, there is significant difference between levels of

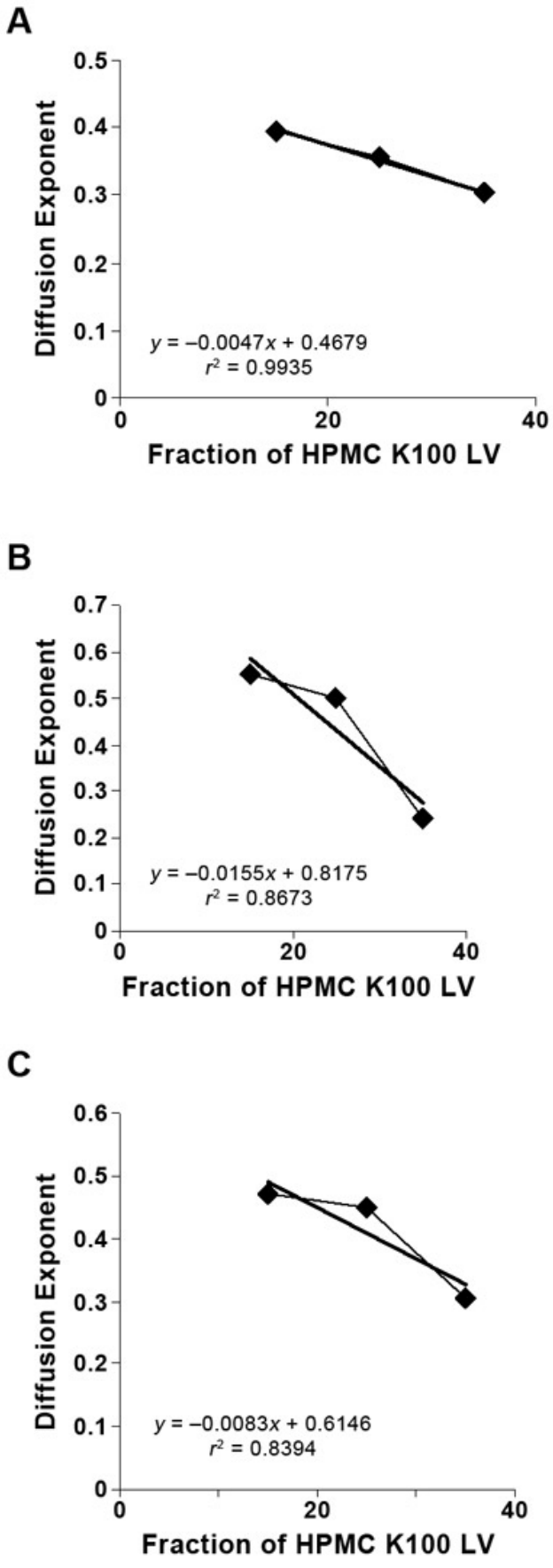

Figure 2. Influence of fraction of HPMC K100 LV on diffusion exponent at SLS (A) 2%, (B) 1%, and (C) 0%.

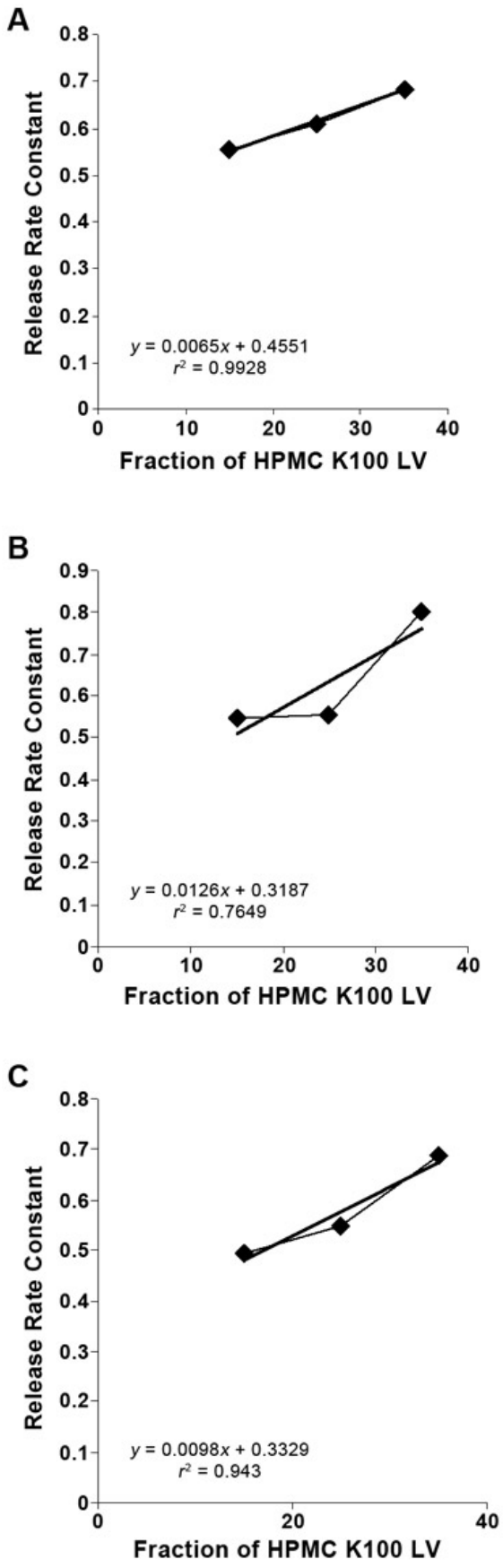

Figure 3. Influence of fraction of HPMC K100 LV on release rate constant at SLS (A) 2%, (B) 1%, and (C) 0%.

0 and 1 as well as 1 and −1 indicating that the fraction of HPMC K100 LV at higher levels significantly contributed to Q_{12}, while for X_2 only the difference observed significantly between the 0 and −1 levels indicated that the content of SLS above 1% does not significantly contribute to Q_{12}.

There has been considerable interest in using different grades of HPMC in controlled-release drug-delivery systems because of their hydrophilic nature and fast hydration.[18] The release profiles appear to be biphasic with initial burst effect followed by a polymer-controlled slower release in the second phase. The difference in burst effect of the initial time is a result of the difference in the viscosity of the polymeric mixtures[19] as well as the amount of SLS, which mainly contributes to the dissolution of drug in the initial period. The polymeric system with higher content of HPMC K100 LV yielded a faster initial burst effect. Dortunc and Gunal[20] have reported that increased viscosity resulted in a corresponding decrease in the drug release, which might be to the result of thicker gel layer formation. On other hand, the apparent drug release rate observed in the second phase from different polymeric mixtures is quite similar, which indicates that once the gel layer forms there is no difference in the release rate from drug-delivery system.

Dissolution profiles were fitted with the power law equation given by Korsmeyer and Peppas equation. Diffusion exponent ranges from 0.24 to 0.55, while release rate constant ranges from 0.493 to 0.800, which indicates that independent variables had a significant effect on mechanism and kinetics of drug release. Both variables significantly affect the release rate constant and diffusion exponent ($P < .05$, Table 2). Linear relationship was obtained between the fraction of HPMC K100 LV and the diffusion exponent, and it was observed that as the fraction of HPMC K100LV increased, the value of the diffusion exponent decreased (Figure 2) at all 3 levels of SLS and release mechanism changes from anomalous transport to case-1 transport, which might be due to dominance of chain disentanglement leads to chain relaxation and subsequent dissolution of polymer. The similar phenomenon was also observed in case of release rate constant. Linear relationship was obtained between fraction of HPMC K100 LV and release rate constant. It was observed that as the fraction of HPMC K100 LV increased, the rate of drug release was also increased at all the 3 levels of SLS which might be due to lowering of viscosity of polymeric mixtures (Figure 3).

CONCLUSION

Overall it was cleared that for the development of controlled-release dosage form for poorly soluble drug, polymer blends of different viscosity grade of HPMC and presence of surfactant appears necessary, which imparts hydrophilic

environment and wettability to molecules of drug leads to more uniform drug release, respectively.

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