Statistical Evaluation of Influence of Viscosity and Content of Polymer on Dipyridamole Release From Floating Matrix Tablets: A Technical Note

Received: October 31, 2006; Final Revision Received: March 30, 2007; Accepted: April 3, 2007; Published: August 24, 2007

Viral F. Patel[1] and Natavarlal M. Patel[1]

[1]Shri B. M. Shah College of Pharmaceutical Education and Research, Modasa, India.

KEYWORDS: Hydroxypropyl methylcellulose (HPMC), factorial design, floating tablets, dipyridamole

INTRODUCTION

The real issue in the development of oral controlled release dosage forms is not just to prolong the delivery of drugs for more than 12 hours, but to prolong the presence of the dosage forms in the stomach or upper gastrointestinal (GI) tract until all the drug is released for the desire period of time.[1] Controlling the residence time of a drug delivery system in a particular region of GI tract can be achieved via intragastric floating system, altered density system, mucoadhesive system, unfolding, extendable, or expandable systems and superporous hydrogels. From the technological point of view, floating drug delivery system is a more convenient and logical approach to prolong gastric residence time.[2]

Dipyridamole is a poorly water soluble weak base with pK_a of 6.4 reported to be altered to a considerable extent by the pH of different digestive fluids (ie, dipyridamole dissolves readily in the stomach but incompletely in intestine).[3] He and coworkers[4] reported that the extent of absorption of dipyridamole was remarkably lower when gastric pH was continuously elevated to 6.0, whereas absorption increased when gastric pH temporarily decreased to 1.8. This finding may be due to the contribution of the precipitation potential of drug when pH changes from acidic to neutral. Because of above reported facts about dipyridamole bioavailability, it would be beneficial to develop a floating drug delivery system that prolongs gastric residence time and releases drug in proximal GI tract (pH ≈5.5), where absorption of dipyridamole is more confined.

The factors influencing the release of drugs from hydrophilic matrices include viscosity of the polymer, ratio of the polymer to drug, mixtures of polymers, compression pressure, thickness of the tablet, particle size of the drug, pH of the matrix, entrapped air in the tablets, molecular size of the drug, molecular geometry of the drug, solubility of the drug, the presence of excipients or additives, and the mode of incorporation of these substances. Among all the factors influencing the drug release from matrix tablets, the viscosity and content of hydroxypropyl methylcellulose (HPMC, Methocel) had a dominant role, while others acted as auxiliary components.[5,6] Hence in the present investigation, the influence of viscosity and content of HPMC on dipyridamole release was statistically evaluated using 3^2 full factorial design.

Corresponding Author: Viral F. Patel, Department of Pharmaceutics, Shri B. M. Shah College of Pharmaceutical Education and Research, Dhansura Road, Modasa 383 315, Gujarat, India. Tel: +91 98 79248887; Fax: +91 27 74249482; E-mail: mviral27@yahoo.co.in

MATERIALS AND METHODS

Dipyridamole was received as a gift sample from Sun Pharmaceutical Ltd (Vadodara, India). Methocel K4M CR (4000 mPa.s), Methocel K15M CR (15 000 mPa.s), and Methocel K100M CR (100 000 mPa.s) were received as gift samples from Colorcon Asia Pvt Ltd (Goa, India). Tablettose 80 was received as a gift sample from Meggle GmbH (Wasserberg, Germany). All excipients used in study were of directly compressible grade. All other ingredients were procured from local market and of analytical grade.

Full Factorial Design

A 3^2 randomized full factorial design was used in development of dosage form. In the present investigation, viscosity of HPMC (X_1) and content of HPMC (X_2) were selected as independent variables. The diffusion exponent (n), release rate constant (k), and percentage drug release at 1 hour (Q_1), 4 hours (Q_4), 6 hours (Q_6), and 12 hours (Q_{12}) were chosen as dependent variables. The experimental design with corresponding formulations is outlined in Table 1. Viscosity of HPMC was evaluated at 4000 mPa.s (−1), 15 000 mPa.s (0), and 100 000 mPa.s (+1), while content of HPMC was evaluated at 20% (−1), 30% (0), and 40% (+1) of total tablet weight. A statistical model incorporating interactive and polynomial terms was used to evaluate the response (Equation 1).

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1X_1 + b_{22}X_2X_2 \ , \quad (1)$$

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 average result of changing 1 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 change simultaneously.

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

Batch Code	Coded Value		Diffusion Exponent (n)	Release Rate Constant (k) ($hours^{-1}$)	Percentage Drug Release			
	X_1	X_2			Q_1	Q_4	Q_6	Q_{12}
H1	–1	–1	0.725	0.153	16.00	44.99	63.33	100
H2	–1	0	0.767	0.137	13.76	38.55	54.28	90.04
H3	–1	1	0.846	0.109	10.51	36.35	51.64	85.76
H4	0	–1	0.738	0.139	14.67	36.90	52.07	87.14
H5	0	0	0.778	0.117	12.03	33.30	48.00	80.00
H6	0	1	0.896	0.088	07.76	31.50	45.20	76.70
H7	1	–1	0.794	0.110	11.73	32.37	44.26	82.83
H8	1	0	0.820	0.097	09.69	29.81	41.84	73.58
H9	1	1	0.919	0.072	06.64	27.20	36.42	68.23

The polynomial terms (X_1X_1, X_2X_2) are included to investigate nonlinearity.

Preparation of Dipyridamole Floating Tablets

Tablets were prepared using direct compression technique. Dipyridamole (30% [150 mg]) was mixed with the required quantity of polymer having different viscosity grade, sodium bicarbonate (10%), and lactose (quantity sufficient to 500 mg of tablet weight) by mixing in laboratory cube blender for 15 minutes. The powder blend was then lubricated with magnesium stearate (1%) and manually compressed on 10 station rotary tablet machine (Rimek, Ahmedabad, India) using a 12-mm standard flat face punch. Compression force was adjusted to obtain tablets with hardness in range of 5 to 6 kg/cm^2. The batch size was 100 tablets for each formulation. The lactose, being water-soluble, filler was used to maintain constant tablet weight as well as to counterbalance the poor water solubility of drug. The round flat-faced tablets weighed 500 ± 2 mg, and had an average diameter of 12 ± 0.1 mm and a thickness of 4.5 ± 0.2 mm.

In Vitro Buoyancy Study

The in vitro buoyancy test was performed using United States Pharmacopeia (USP) 24 paddle-type apparatus using 900 mL of 0.1 N HCl at rotation of 100 rpm at 37°C ± 0.5°C. The time required for tablet to rise to surface of dissolution medium and duration of time the tablet constantly floated on 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 paddle-type apparatus using 900 mL of 0.1 N HCl at 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 then analyzed at 283 nm using double-beam UV/Visible spectrophotometer (UV-1601, Shimadzu Corp, Kyoto, Japan). The content of drug was calculated using calibration curve. High reproducibility of data was obtained (standard deviation [SD] <3%, n = 3), hence only average value was considered.

Statistical Analysis

The statistical analysis of the factorial design batches were performed by multiple regression analysis using Microsoft Excel. To evaluate relative 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 Inc, Chicago, IL). To demonstrate graphically the influence of each factor on responses, the response surface plots were generated using Sigma Plot software (Sigma Plot Software 8.0, Jandel Scientific Software, San Rafael, CA). The value of $P < .05$ was considered to be significant.

Results and Discussion

HPMC was selected as a matrix-forming material because it has a pH-independent and reproducible drug release profile. Tablets of all 9 batches had floating lag time below 2 minutes regardless of viscosity and content of HPMC because of the evolution of CO_2 resulting from interaction between sodium bicarbonate and dissolution medium; entrapment of gas inside the hydrated polymeric matrices enables the dosage form to float by lowering the density of the matrices. No variability in floating lag time was observed with tablets prepared by using different viscosity grades of HPMC at variable polymer levels (data are not shown because all the tablets had floating lag time below 2 minutes). It was reasoned that as for HPMC content of 20% or more, the particles of HPMC are close enough to permit a faster establishment of the gel layer in a manner that minimizes the effect of different viscosities of polymer, although the

rate of swelling of particles with high viscosity grade was slow compared with low viscosity HPMC.[7] The total floating time was more than 12 hours for tablets of all batches, which indicates a stable gel layer formation by HPMC that persists for a longer time.

The drug diffusion through most types of polymeric systems is often best described by Fickian diffusion, but other processes in addition to diffusion are important. There is also a relaxation of the polymer chains, which influences the drug release mechanism. This process is described as non-Fickian or anomalous diffusion. A simple, semi-empirical equation given by Korsmeyer and Peppas[8] can be used to analyze data of controlled release of drugs from polymer matrices.

The results of diffusion exponent (n), release rate constant (k), and percentage drug release at 1 hour (Q_1), 4 hours (Q_4), 6 hours (Q_6), and 12 hours (Q_{12}) showed wide variation (Table 1). Results of multiple regression analysis revealed that both viscosity and content of HPMC had statistically significant influence on all dependent variables ($P < .05$, Table 2), while interaction terms and polynomial terms appeared to be insignificant ($P > .05$). The latter effect was cleared from response surface plot showing negligible curvature on both axes in all graphs, which indicates little contribution of interaction terms along with linearity of responses.

Figure 1 shows the influence of viscosity and content of HPMC on the diffusion exponent. It was found that the diffusion exponent rises with increase in viscosity and content of HPMC. Although the viscosity and content of HPMC had significant influence ($P < .05$) on the diffusion exponent, it ranged from 0.725 to 0.919, indicating anomalous drug release to case-II transport. Results of Tukey test revealed that all levels of content of HPMC had significant influence, but the difference was not found to be significant between all levels of viscosity of HPMC. There is no influence of viscosity on the diffusion exponent between matrices prepared with either HPMC K4M or HPMC K15M ($P > .05$), while the difference was observed amongst other levels. Regarding the overall effect of both factors, it appeared that the diffusion exponent was affected more by the content level of HPMC, which was cleared from the response surface plot

Table 2. Summary of Regression Output of Significant Factors for the Measured Response

	Coefficient of Regression Parameters				
Response	b_0	b_1	b_2	r	P
n	0.783	0.033	0.067	0.992	.0067
k	0.118	–0.023	–0.022	0.997	.0018
Q_1	11.89	–2.033	–2.915	0.994	.0043
Q_4	33.23	–5.085	–3.202	0.995	.0034
Q_6	47.90	–7.789	–4.399	0.989	.0098
Q_{12}	79.79	–8.525	–6.548	0.996	.0023

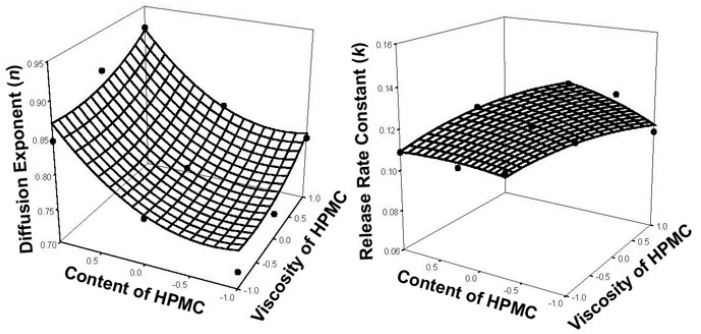

Figure 1. Response surface plot for influence of viscosity and content of HPMC on diffusion exponent (n) and release rate constant (k). HPMC indicates hydroxypropyl methylcellulose.

(Figure 1), as the decline of the diffusion exponent value was more extreme on the axis of content of HPMC compared with the viscosity of HPMC. When the viscosity and content of HPMC are increased, the rate of dissolution of disentangled chains decreases with increase in the diffusion path length of the aqueous channel, which leads to an increase in the value of the diffusion exponent and results in shifting of the mechanism of drug release from anomalous transport to zero-order drug release or super case-II transport.

Figure 1 shows the influence of viscosity and content of HPMC on the release rate constant. When the viscosity and content of HPMC are increased, the release of drug tends to become slower. For release rate constant, all 3 levels of both variables had statistically significant influence ($P < .05$). HPMC particles of increasing viscosity grades will swell more slowly and produce swollen particles of smaller volume; then matrices made of particles of HPMC with higher viscosity grade will contain pores of smaller diameters and will show slower release rate than those made of HPMC particles with lower viscosity grades. Increases in the polymer level from 20% to 30% and to 40% dramatically retarded the release of dipyridamole from matrix tablets. This finding might be due to the increase in resistance of the gel layer to drug dissolution and gel erosion. At a higher polymer level, formation of tightly swollen gel layer caused by more intimate contact between the particles of HPMC results in decrease mobility of insoluble drug particles in swollen matrices, which leads to decreased release rate.

Figure 2 shows the influence of viscosity and content of HPMC on percentage drug release from floating matrix tablets. Multiple regression analysis for percentage drug release at 1 hour, 4 hours, 6 hours, and 12 hours showed that both viscosity and content of HPMC had significant influence ($P < .05$). For Q_1, Tukey test indicated that all levels of both factors had significant contribution on drug release at 1 hour, which is generally termed as a period of burst effect. The coefficients of both factors are negative, indicating an antagonistic effect. Among the magnitudes of coefficients

and values of Tukey test for both factors, it was found that Q_1 is more dependent on content of HPMC compared with viscosity of HPMC. It was reasoned that the content of HPMC used in the study was from 20% to 40%, which was great enough to permit a faster establishment of gel barrier, in a manner that minimized the effect of the different viscosities of polymers.

Both factors had significant contribution for Q_4 and Q_6 ($P < .05$). Results are in contrast to Q_1, as the drug release is more dependent on viscosity of HPMC for Q_4 and Q_6. Results of Tukey test revealed that the difference was not found to be significant when the content of polymer increased from 30% to 40% in case of Q_4, and the difference was also not found to be significant when the content of the polymer increased from 20% to 30% and 30% to 40% ($P > .05$) for Q_6. The observed effect can be explained the on basis that dipyridamole is a poorly soluble drug that is mainly release by erosion mechanism and/or diffusion and erosion of polymeric material. Diffusion/erosion properties of the gel layer is more sensitive to the strength of the gel layer formed by the viscosity of polymer, although the overall release of drug at 4 hours and 6 hours is controlled by both factors ($P < .05$).

Multiple regression analysis for percentage drug release at 12 hours (Q_{12}) showed the significant contribution of both the factors on response ($P < .05$). Tukey test (Table 3) revealed that all the levels of both factors significantly contributed to drug release at 12 hours. Among the levels of viscosity of HPMC, it was observed that changing of viscosity of HPMC from 4000 mPa.s to 15 000 mPa.s and from 4000 mPa.s to 100 000 mPa.s was more sensitive compared with 15 000 mPa.s and 100 000 mPa.s for overall drug release. A similar finding was also observed among the levels of content of HPMC as overall release of drug was more sensitive when content of HPMC changed from 20% to 30% and 20% to 40% compared with 30% to 40%. From the study results, it was apparent that above certain threshold values for both viscosity and content of HPMC, the effect of these variables becomes nonlinear.

Table 3. Tukey Test Performed Using 2-way Analysis of Variance

Response	Comparison for Levels	*P*	
		Viscosity of HPMC (X_1)	Content of HPMC (X_2)
n	–1 vs 1	.006	.001
	–1 vs 0	.032	.001
	0 vs 1	.135	.046
k	–1 vs 1	.001	.001
	–1 vs 0	.006	.008
	0 vs 1	.003	.001
Q_1	–1 vs 1	.001	.001
	–1 vs 0	.019	.010
	0 vs 1	.013	.002
Q_4	–1 vs 1	.001	.006
	–1 vs 0	.007	.024
	0 vs 1	.026	.160
Q_6	–1 vs 1	.001	.010
	–1 vs 0	.014	.058
	0 vs 1	.017	.155
Q_{12}	–1 vs 1	.001	.001
	–1 vs 0	.001	.002
	0 vs 1	.006	.025

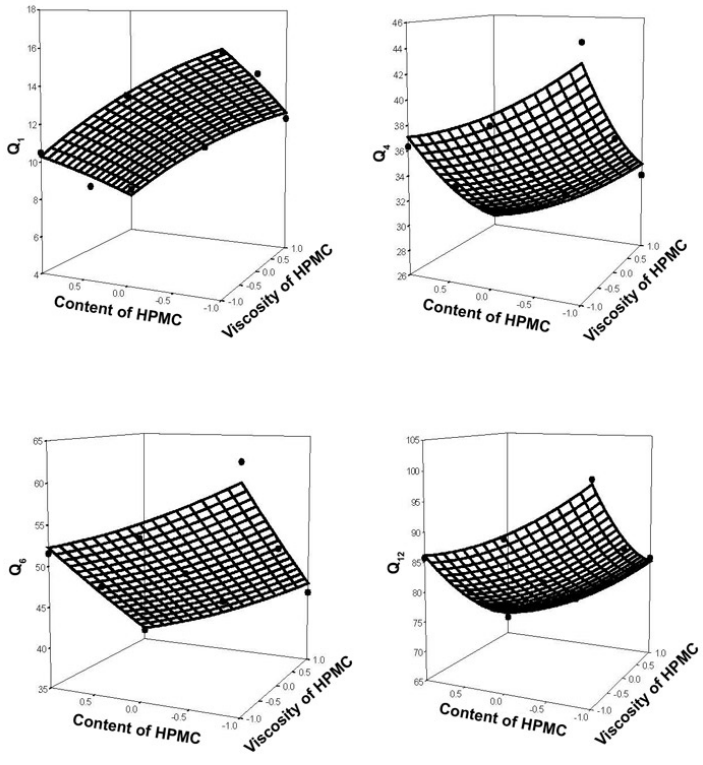

Figure 2. Response surface plot for influence of viscosity and content of HPMC on percentage drug release at 1 hour (Q_1), 4 hours (Q_4), 6 hours (Q_6), and 12 hours (Q_{12}). HPMC indicates hydroxypropyl methylcellulose.

CONCLUSION

The present investigation described the influence of viscosity and content of HPMC on dipyridamole release using 3^2 full factorial design. All formulations had desired floating lag time (<2 minutes) regardless of viscosity and content of polymeric matrices. Results of multiple regression analysis indicate that both factors significantly affect the diffusion exponent (n), release rate constant (k), and percentage drug release at 1 hour, 4 hours, 6 hours, and 12 hour, ($P < .05$). Mechanism of drug release was found to be anomalous type to case-II transport depending upon the viscosity and content of polymer. It was found that content of HPMC had a dominant role in the initial phase of drug release, while in the later phase viscosity of HPMC predominated.

ACKNOWLEDGMENTS

Authors are thankful to Sun Pharmaceutical Ltd (Vadodara, India) for providing gift sample of dipyridamole, Colorcon Asia Pvt, Ltd (Goa, India), and Meggle GmbH (Wasserberg, Germany) for providing HPMC and Tablettose 80, respectively.

REFERENCES

1. Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. *Int J Pharm.* 2000;195:125–135.

2. Yeole PG, Khan S, Patel VF. Floating drug delivery systems: need and development. *Indian J Pharm Sci.* 2005;67:265–272.

3. Kohri N, Miyata N, Takechi S, Nomura A. Evaluation of pH independent sustained release granules of dipyridamole by using gastric acidity controlled rabbits and human subjects. *Int J Pharm.* 1992;81:49–58.

4. He X, Kadomura S, Takekuma Y, Sugawara M, Miyazaki K. A new system for the prediction of drug absorption using a pH controlled Caco-2 model: evaluation of pH dependent soluble drug absorption and pH related changes in absorption. *J Pharm Sci.* 2004;93:71–77.

5. Vazquez MJ, Perez-Marcos B, Gomez-Amoza JL, Matinez-Pacheco R, Souto C, Concheiro A. Influence of technological variables on drug release of drug from hydrophilic matrices. *Drug Dev Ind Pharm.* 1992;18:1355–1375.

6. Ford JL, Rubinstein MH, Hogan JE. Formulation of sustained release promethazine hydrochloride tablet using HPMC matrices. *Int J Pharm.* 1985;24:327–337.

7. Campos-Aldrete ME, Villafuerte-Robles L. Influence of the viscosity grade and particle size of HPMC on metronidazole release matrix tablets. *Eur J Pharm Biopharm.* 1997;43:173–178.

8. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. *Pharm Acta Helv.* 1985;60:110–111.