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Statistical Evaluation of Influence of Xanthan Gum and Guar Gum Blends on Dipyridamole Release from Floating Matrix Tablets

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ABSTRACT The present investigation explored the use of xanthan gum and guar gum for development of floating drug delivery system of dipyridamole using factorial design approach. The content of polymer blends (X_1) and ratio of xanthan gum to guar gum (X_2) were selected as independent variables. The diffusion exponent (n), release rate constant (k), percentage drug release at 1 hr (Q_1) and 6 hr (Q_6) were selected as dependent variables. Tablets of all batches had desired buoyancy characteristics. Multiple regression analysis with two way ANOVA revealed that both the factors had statistically significant influence on the response studied ($p < 0.05$). Results of Tukey test showed the relative contribution of each level of different factors for the response studied. It was concluded that the ratio of xanthan to gaur gum had equal or dominant role as controlling factor on kinetics of drug release compared to content of polymer blends.

KEYWORDS Xanthan gum, Guar gum, Dipyridamole, Factorial design

INTRODUCTION

In recent years, the value of hydrophilic polymer based matrix tablets as vehicles for controlled release delivery has been increasingly demonstrated with the publication of numerous patents and research papers and their utilization in new products in the market place. The widespread and successful use of such polymeric systems could be attributed to their ease of manufacturing, relatively low cost, favorable in vivo performance and versatility in controlling the release of drugs with a wide range of physicochemical properties (Durig & Fassihi, 2002). The use of biopolymeric devices to control the release of a variety of drugs has become important in the development of modified release dosage forms (Talukdar et al., 1998). Absorption windows in the proximal gut can limit the bioavailability of orally administered compounds and can be a major obstacle to the development of controlled release formulations for important drugs. The transit of a drug formulation through the gastrointestinal

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(GI) tract will determine how long a compound will be in contact with its preferred absorptive site (Davis, 2005).

Dipyridamole, a poorly soluble weak base with pKa of 6.4, exhibits pH dependent solubility in digestive fluid (Kohri et al., 1992; Sugawara et al., 2005; Zhou et al., 2005). It was reported that the extent of absorption of dipyridamole is remarkably lowered with increase in gastric pH (He et al., 2004). Requirement of low pH for optimum absorption of dipyridamole reflects its ideal candidature for development of floating drug delivery system (Soppimath et al., 2001; Derendorf et al., 2005). This might be because of the contribution of precipitation potential of drug when pH changes from acidic to neutral region (Kostewicz et al., 2004; Gu et al., 2005). Based on above reports it was decided to prepare a floating dosage form containing dipyridamole which may increase the gastric residence time and release drug in proximal GI tract (Yeole et al., 2005).

Xanthan gum is a hydrophilic polymer, secreted from *Xanthomonas campestris*. This polymer is studied for the fabrication of matrices with constant drug release characteristics (Talukdar & Plaizier-Vercammen, 1993; Talukdar et al., 1998; Cox et al., 1999; Billa & Yuen, 2000; Munday & Cox, 2000). It was observed that fickian diffusion is dominant during the fist half of the dissolution period of diclofenac sodium minimatrices with xanthan gum of different levels, while erosion predominates during the latter half; facilitating an approach toward zero-order release (Sujjaareevath et al., 1998). Recently the potential of guar gum, as an inexpensive and flexible carrier for oral extended release drug delivery has been highlighted. In vitro and in vivo release of a highly soluble drug (diltiazem) from guar matrix tablets was found to be similar to that of a commercial reference product (Dilacor X®) (Altaf et al., 1998). Combination of xanthan and galactomannan was recently explored for formulation of matrix tablets for oral controlled delivery of theophylline and these matrices were able to produce constant drug release profile with combination of diffusion and relaxation. They reported decrease in drug release with increase in content of polymer blend (Vendruscolo et al., 2005). In present investigation, the influence of the content of polymer blend with different ratio of xanthan gum and guar gum on dipyridamole release from floating matrix tablets was statistically evaluated using 3^2 full factorial design.

MATERIALS AND METHODS

Materials

Dipyridamole was received as a gift sample from Sun Pharmaceutical Ltd., Vadodara (India). Xanthan gum (Xantural® 75) was received as a gift sample from CP Kelco, San Diego, CA. Guar gum was obtained from Lesar chemicals, Vadodara (India). Lactose (Tablettose 80) was received as a gift sample from Meggle GMBH, Wasserberg (Germany). All other ingredients used were of analytical grade and met USP 24 specifications, procured from Lesar chemicals, Vadodara (India).

Methods

Full Factorial Design

The content of polymer blends (X_1) and ratio of xanthan gum to guar gum (X_2) were selected as independent variables. Content of polymer blend was evaluated at 10, 15, and 20% of total tablet weight and ratio of xanthan gum to guar gum was evaluated at 70:30, 50:50 and 30:70 of total polymer content. The diffusion exponent (n), release rate constant (k), percentage drug release at 1 hr (Q_1) and 6 hr (i_6) were selected as dependent variables. The experimental design with corresponding formulations is outlined in Table 1.

A statistical model, $Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$, incorporating interactive and polynomial terms was used to evaluate the response. Where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine 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 one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when two factors are changed simultaneously. The polynomial terms (X_1^2, X_2^2) are included to investigate nonlinearity.

Preparation of Dipyridamole Floating Tablets

Dipyridamole (37.5%) was mixed with the required quantity of polymer blend containing different ratio of xanthan gum to guar gum, sodium bicarbonate (10%) and lactose in a laboratory cube blender for 15 min. The powder blend was then lubricated with magnesium stearate (1%) for additional 3 min and compressed

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)	Percentage drug release	
	X_1	X_2			Q_1	Q_6
M1	−1	−1	0.654	0.209	20.78	66.28
M2	−1	0	0.617	0.229	23.42	67.84
M3	−1	1	0.543	0.270	29.22	69.44
M4	0	−1	0.715	0.149	14.17	56.87
M5	0	0	0.741	0.158	15.18	60.10
M6	0	1	0.581	0.239	24.44	66.31
M7	1	−1	0.766	0.123	11.32	47.70
M8	1	0	0.751	0.136	12.54	55.20
M9	1	1	0.578	0.212	20.27	60.31

	Actual values	
Coded values	X_1	X_2
−1	10	70:30
0	15	50:50
1	20	30:70

X_1 is content of polymer blend (%) and X_2 is ratio of xanthan gum to guar gum. Each batch contains 37.5% of dipyridamole, 10% of sodium bicarbonate, 1% of magnesium stearate and quantity sufficient of filler.

into tablets with average weight 400 ± 2 mg manually on 10 station rotary tablet machine (Rimek, Ahmedabad, India) using 10 mm standard flat faced tools. Compression force was adjusted to obtain tablets with hardness in the range of 5–6 kg/cm^2. The average diameter of tablets was 10 ± 0.1 mm and thickness 4 ± 0.2 mm.

In Vitro Buoyancy Study

The in vitro buoyancy was characterized by floating lag time and total floating time. The test was performed using USP 24 type II apparatus at 100 rpm in 900 mL of 0.1*N* HCl maintained at 37 ± 0.5°C. The time required for tablet to rise to the surface of dissolution medium and duration of time the tablet constantly float on dissolution medium were noted as floating lag time and total floating time, respectively ($n = 3$) (Patel and Patel, 2006).

In Vitro Drug Release Study

The in vitro drug release was performed using USP 24 type II apparatus at 100 rpm in 900 mL of 0.1*N* HCl maintained at 37 ± 0.5°C. The samples were withdrawn at predetermined time intervals for period of 12 hr and replaced with the fresh medium. The samples were filtered through 0.45 μm membrane filter, suitably diluted and analysed at 283 nm using double beam UV-Vis spectrophotometer (Shimadzu Corporation, UV-1601, Japan). The content of drug was calculated using equation generated from calibration curve. The test was performed in triplicate. High reproducibility of data was obtained (SD < 3%), hence only average values were considered.

Statistical Analysis

The statistical analysis of the factorial design batches were performed by multiple regression analysis using Microsoft Excel®. To evaluate contribution of each factor with different levels on responses, two way analysis of variance (ANOVA) followed by Tukey test was performed using Sigma Stat software (Sigma Stat 2.03, SPSS, Chicago, Illinois, USA). To graphically demonstrate the influence of each factor on responses, the response surface plots were generated using sigma plot software (Sigma Plot Software 8.0, SPSS, Chicago, Illinois, USA).

RESULTS AND DISCUSSION

In current study, floating system is developed by incorporation of xanthan gum and guar gum at variable ratio and change in content of its polymer blends using 3^2 full factorial design.

Tablets of all formulations had desired floating lag time (<3 min) regardless of ratio of xanthan gum to guar gum and content of polymer blend incorporated,

which might be because of the evolution of carbon dioxide resulting from interaction between sodium bicarbonate and dissolution medium (0.1 N HCl, pH 1.2). The evolved gas entrapped inside the hydrated matrices leads to lowering of density of polymeric matrices enabling the dosage form to float on surface of dissolution medium. The floating lag time was not differed vastly with change in ratio of xanthan gum to guar gum and content of polymer blend, as both the polymers used for the preparation of matrices had high and rapid swelling tendency (Krishnaiah et al., 2002), leading to quick formation of outer gel layer, which entraps gas formed into the matrix. Also the content of polymer blend used was 10–20% of total tablet weight, which was sufficient to form intimate contact between particles of polymeric materials. Vendruscolo and co-workers (Vendruscolo et al., 2005) also reported similar observation. They reported formulation prepared using xanthan gum and galactomannan derived from *M. Scabrella* (Mannan to Galactose ratio of 1.1 : 1), showed rapid swelling properties and form quick outer gel layer, resulting in formation of gel mass, responsible for controlled release of diclofenac sodium in a constant manner.The total floating lag time was found to be more than 8 hr for tablets of all batches, showing good matrix integrity for extended period of time.

It has been reported that drug release from hydrophilic matrices is a complex interaction between swelling, diffusion and erosion of dosage form (Colombo et al., 1995; Reynolds et al., 1998). It is known that the drug release from hydrophilic swellable matrices is controlled by diffusion through the gel layer, for water-soluble drugs or, by erosion of the outer polymer chains, for poorly soluble drugs (Mitchell et al., 1993). The gradual penetration of water produces swelling to form a hydrated gel layer through which the drug has to pass by dissolution and diffusion across the ever-increasing diffusion pathway length. Swelling has been shown to follow either square root of time, anomalous behavior or zero order drug release kinetics depending upon the physicochemical properties of active moiety and other formulation components. It is apparent therefore that other mechanism in addition to diffusion must take place at the interface between the gel and the surrounding medium known as erosion of the outer polymeric chain caused by polymer chain relaxation and gradual disentanglement. To obtain kinetic parameters of dissolution profiles, data were fitted to Korsmeyer and Peppas power law model (Korsmeyer et al., 1983) using sigma stat software.

The results of diffusion exponent (n), release rate constant (k), and percentage drug release at 1 hr (Q_1) and 6 hr (Q_6) are shown in Table 1. From results of multiple regression analysis, it was observed that both the factors had statistically significant influence on all the dependent variables studied ($p < 0.05$, Table 2). The high value of multiple correlation coefficient clearly indicates that the responses are strongly dependent on factors studied ($p < 0.05$, Table 2). The results of two way ANOVA followed by Tukey test are depicted in Table 3 and Table 4, respectively.

The influence of content of polymer blend and ratio of xanthan gum to guar gum on diffusion exponent (n) is shown in Fig. 1. Although both the factors had statistically significant influence ($p < 0.05$, Table 2 and Table 3), the diffusion exponent ranges from 0.543–0.766 indicates anomalous drug release because of the involvement of swelling, diffusion and/or erosion of matrices, which might be caused by poor solubility of dipyridamole and high swelling tendency of polymers used. Results of Tukey test showed that diffusion exponent was more dependent upon ratio of xanthan gum to guar gum compared to content of polymer blend. The effect was also seen from response plot as there is greater curvature on axis of ratio of xanthan gum to guar gum, while little flattening of

TABLE 2 **Summary of Regression Output of the Measured Responses**

	Co-efficient of regression parameters							
Parameters	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}	r^2	p
Diffusion exponent (n)	0.721	0.046	–0.072	–0.019*	–0.028*	–0.064	0.980	0.0239
Release rate constant (k)	0.165	–0.039	0.040	0.007*	0.015*	0.026	0.992	0.0062
Q_1	15.93	–4.881	4.610	0.128*	1.662*	2.987	0.994	0.0035
Q_6	61.02	–6.725	4.202	2.363	0.035*	0.105	0.996	0.0024

*indicate response are insignificant at $p = 0.05$.

TABLE 3 Result of Two Way ANOVA for Dependent Variables

Source of variation	df	SS	MS	*F*	*p*
Diffusion exponent (*n*)					
Content of polymer blend	2	0.0147	0.0073	8.034	0.040
Ratio of xanthan gum to guar gum	2	0.0393	0.0197	21.53	0.007
Residual	4	0.0037	0.0009		
Total	8	0.0576	0.0072		
Release rate constant (*k*)					
Content of polymer blend	2	0.00978	0.00489	37.77	0.003
Ratio of xanthan gum to guar gum	2	0.01100	0.00548	42.29	0.002
Residual	4	0.00052	0.00013		
Total	8	0.02130	0.00266		
Q_1					
Content of polymer blend	2	148.51	74.25	95.11	<0.001
Ratio of xanthan gum to guar gum	2	145.35	72.68	93.09	<0.001
Residual	4	3.12	0.781		
Total	8	296.99	37.12		
Q_6					
Content of polymer blend	2	271.36	135.68	21.25	0.007
Ratio of xanthan gum to guar gum	2	105.95	52.98	8.30	0.038
Residual	4	25.54	639		
Total	8	402.84	50.36		

DF is degree of freedom, SS is sum of square, MS is mean sum of square and *F* is Fischer's ratio.

TABLE 4 Results of Tukey Test Performed Using Two Way ANOVA for Comparison of Levels

		P	
Response	Comparison for levels	Content of polymer blend (X_1)	Ratio of xanthan gum to guar gum (X_2)
Diffusion exponent (*n*)	−1 vs 1	0.041	0.009
	−1 vs 0	0.083	0.935
	0 vs 1	0.732	0.012
Release rate constant (*k*)	−1 vs 1	0.002	0.002
	−1 vs 0	0.010	0.380
	0 vs 1	0.113	0.005
Q_1	−1 vs 1	0.001	0.001
	−1 vs 0	0.002	0.020
	0 vs 1	0.024	0.001
Q_6	−1 vs 1	0.006	0.033
	−1 vs 0	0.065	0.208
	0 vs 1	0.067	0.231

curve was seen for content of polymer blend (Fig. 1a). Also in case of content of polymer blend, the difference was only significant between matrices prepared with either 10 or 20% of polymer content ($p < 0.05$, Table 4). In case of ratio of xanthan gum to guar gum, the difference was not significant ($p > 0.05$, Table 4) between matrices prepared with xanthan gum to guar gum ratio of either 70:30 or 50:50, because at low level of guar gum dominancy of particles of xanthan gum restricts the swelling of particles of guar gum resulting in little change in value of diffusion exponent. Increasingthelevel of guar gum, the value of diffusion exponent tended to decline and gave mechanism of drug release nearer to square root of time profile.

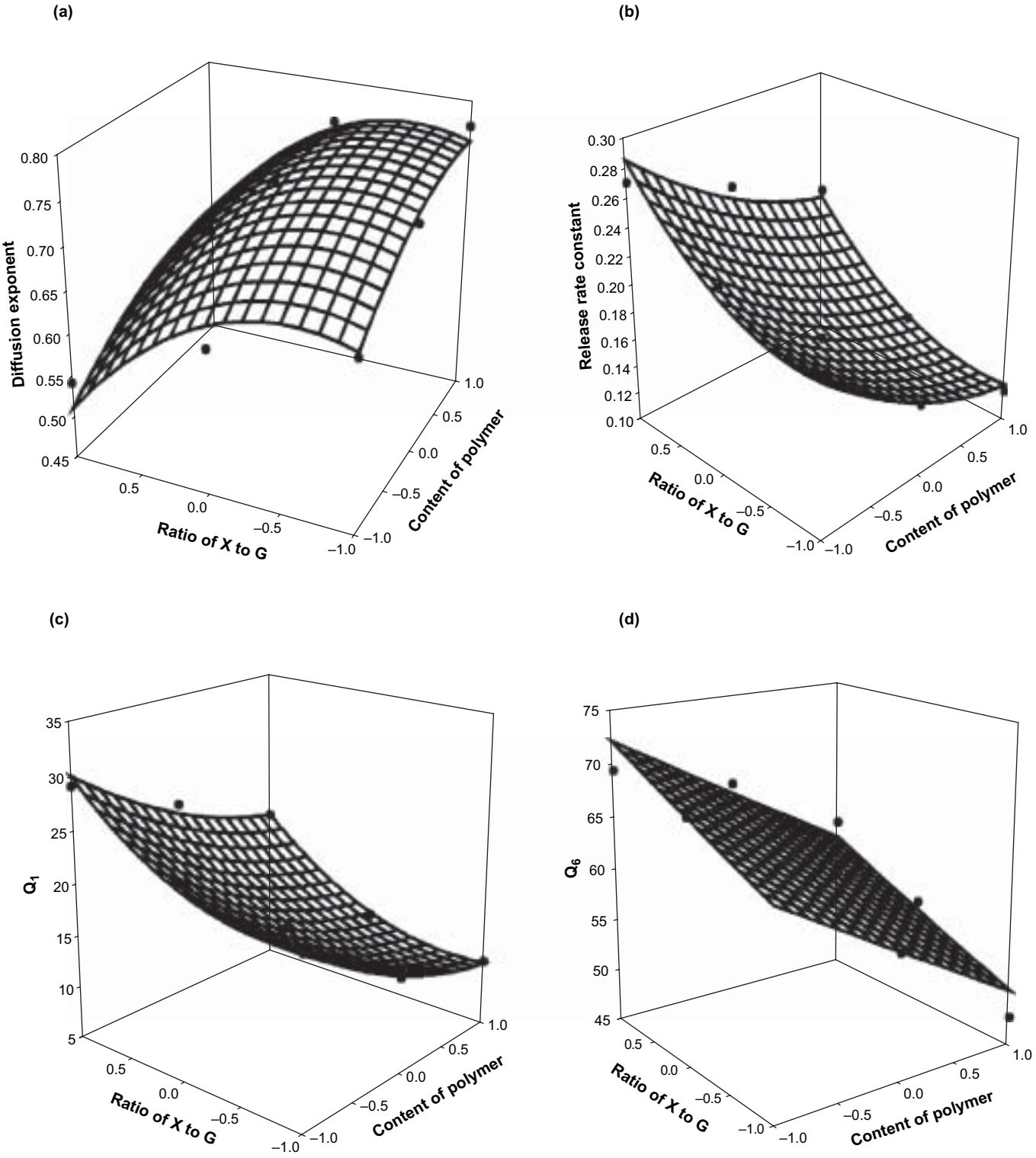

FIGURE 1 **Response Surface Plot for Influence of Content of Polymer Blend and Ratio of Xanthan Gum to Guar Gum on (a) Diffusion Exponent (b) Release Rate Constant (c) Q_1 and (d) Q_6.**

This effect was explained on thebasis that guar gum, being highly swellable polymer allowed faster penetration of dissolution medium creating such an environment that drug dissolved within gel matrix subsequently behaves as soluble component and releases from matrix via diffusion mechanism more promptly rather than anomalous release.

The influence of content of polymer blend with different in ratio of xanthan gum to guar gum on release rate constant (k) is shown in Fig. 1b. From results of

multiple regression analysis and two way ANOVA, it was observed that both the factors significantly contributed on release rate constant ($p < 0.05$, Table 2 and Table 3). Results of Tukey test revealed that both the factors had significant contribution with little dominancy of content of polymer blends. It was observed that the release rate constant tended to decline with an increase in the content of polymer blends ($p < 0.05$), as observed by other authors who used xanthan gum alone or in combination with other gums (Vendruscolo et al., 2005; Billa & Yuen, 2000). It was reasoned that as amount of gums in the matrix increased, there would be a greater degree of gum hydration because of more intimate contact between particles of gums leading to increased tortuosity of matrices and the possibility of interaction of molecules of dipyridamole with swollen gum particles decreased mobility within swollen matrices. In case of ratio of xanthan gum to guar gum, increased drug release from matrix was observed with an increase in the level of guar gum in polymer blend. The observed results were explained on the basis that increased level of guar gum leads to faster penetration of dissolution medium inside the matrices and opens up the channels for drug to get released, resulting in increased drug release rate. Vendruscolo and co-workers (Vendruscolo et al., 2005) reported similar observation. They reported incorporation of galactomennan in xanthan gum matrices produces higher release rate of theophylline compared to plain xanthan gum matrices containing similar proportion of gums.

To describe the dissolution profile, two time level points, i.e., percentage drug release at 1 hr (Q_1) and 6 hr (Q_6) were selected. The influence of content of polymer blends with different ratio of xanthan gum to guar gum on percentage drug release at 1 hr is shown in Fig. 1c. Results of multiple regression analysis and two way ANOVA showed that both factors had statistically significant influence ($p < 0.05$, Table 2 and Table 3). The quadratic term of the factor (ratio of xanthan gum to guar gum) was also found significant ($p < 0.05$, Table 2), indicating that the change in level of guar gum in polymeric blends was relatively more significant on initial burst release. The observed effect was also supported by results of two way ANOVA and Tukey test (Tables 3 and 4), which indicate that each level of the ratio of xanthan gum to guar gum had equal or relatively more contribution for initial burst effects. The higher drug release obtained with increased proportion of guar gum might be attributed to its high and rapid swelling property, which results in rapid influx of dissolution medium inside the matrices before the molecule of xanthan gum particles forms a stiff gel, leading to more solubilization of insoluble drug particles with simultaneous dissolution and diffusion through the channels formed. The observed effect was significant in case of poorly soluble drug because the rate and amount of dissolution medium entering in matrices may significantly contribute to initial phase of drug release until stable gel layer is not formed. Other authors (Xu & Sunada, 1995; Bravo et al., 2002) also have made similar kind of observation. Bravo and coworkers reported increased drug release in initial phase by incorporation of high swellable filler (microcrystalline cellulose) in formulation containing lactose and starch as filler from hydrophilic matrices. Xu and Sunada reported higher drug release rate when lactose was being replaced with microcrystalline cellulose from HPMC matrices. It was observed that release of drug in initial phase declined with an increase in content of polymer blends, which might be due to rapid formation of gel layer resulting from more intimate contact of polymeric particles with one another, giving decreased drug release. The influence of content of polymer blends with different ratio of xanthan gum to guar gum on percentage drug release at 6 hr is shown in Fig. 1d. Results of multiple regression analysis with two way ANOVA revealed significant contribution of both the factors on the response ($p < 0.05$, Tables 2 and 3). Increasing content of polymer blend, the drug release at 6 hr was slow, which was also shown by negative coefficient in front of factor content of polymer blend. At higher level of polymer content in matrices, formation of tightly swollen gel layer retarded the drug release from matrices. For percentage drug release at 6 hr, results of Tukey test revealed that the effect of content of polymer blend was more significant compared to the ratio of xanthan gum to guar gum. The observed effect was also cleared from response surface plot as little decline was seen in response on axis of the ratio of xanthan gum to guar gum. The explanation for the observed effect could be that once the stable gel layer is formed, the change in type of polymeric content had little contribution in drug release although it was affected to some extent.

Overall results explained that the ratio of xanthan gum to gaur gum had equal or dominant role as controlling factor on kinetics of drug release compared to content of polymer blends. Thus, by proper selection of the

ratio of xanthan gum to guar gum and content of polymer blends, desired drug release kinetics was achievable.

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