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Research Article

Fabrication of Modified Release Tablet Formulation of Metoprolol Succinate using Hydroxypropyl Methylcellulose and Xanthan Gum

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Abstract. The present investigation was undertaken to fabricate modified release tablet of metoprolol succinate using hydroxypropyl methylcellulose (HPMC) and xanthan gum as a matrixing agent. A 3^2 full factorial design was employed for the optimization of formulation. The percentage drug released at a given time (Y_{60}, Y_{240} and Y_{720}) and the time required for a given percentage of drug to be released ($t_{50\%}$) were selected as dependent variables. The *in vitro* drug dissolution study was carried out in pH 6.8 phosphate buffer employing paddle rotated at 50 rpm. The similarity factor (f_2) was calculated for selection of best batch considering mean *in vitro* dissolution data of Seloken® XL as a reference profile. It is concluded that the desired drug release pattern can be obtained by using a proper combination of HPMC (high gelling ability) and xanthan gum (quick gelling tendency). The economy of xanthan gum and faster hydration rate favors its use in modified release tablets. The matrix integrity during dissolution testing was maintained by using hydroxypropyl methylcellulose.

KEY WORDS: factorial design; hydroxypropyl methylcellulose; matrix tablet; metoprolol; modified release; xanthan gum.

INTRODUCTION

The concept of regulating drug delivery in the human body has been in existence for many years because of major benefits such as improved patient compliance and decreased side effects. Many innovative methods have been developed in the last few years for obtaining modified drug release. From the practical view point, hydrophilic matrix tablet is one of the least complicated approaches for developing modified release dosage form.

Hydroxypropyl methylcellulose (HPMC) is one of the most commonly used hydrophilic excipient for developing matrix tablet because it works as a pH-independent gelling agent (1). Swelling as well as erosion of the polymer occurs simultaneously and contributes to overall drug release (2). Out of various grades of hydroxypropyl methylcellulose available, Methocel® K, is the fastest to hydrate because of lower amount of the hydrophobic methoxyl substitution and a higher amount of the hydrophilic hydroxypropoxyl substitution (3).

Xanthan gum is a high-molecular-weight extracellular polysaccharide produced by fermentation process from microorganism (*Xanthomonas campestris*). Xanthan gum is known to tolerate high concentration of electrolyte in solution. The viscosity of the xanthan gum solution is nearly independent of pH and temperature. Xanthan gum is biodegradable and biocompatible and forms gel in water. These properties have led to an increase in use of xanthan gum for fabrication of modified release dosage form. The overall compaction behavior of HPMC and xanthan gum is quiet similar. Xanthan gum is readily cheap and more readily flowable than HPMC (4,5).

Metoprolol ((+)-1-(isopropyl amino)-3-[*p*-(2-methoxyethyl)]-2-propanol succinate) is a selective beta-adrenergic receptor blocker useful in treatment of hypertension, angina and heart failure. Metoprolol succinate is a white crystalline powder with high aqueous solubility and high permeability throughout gastrointestinal tract (6). Half-life of metoprolol succinate ranges from 3 to 7 h (7).

Numbers of patents have been granted for modified release metoprolol formulations (8–23). The present research work was undertaken to fabricate low-cost modified release (24 h) tablets of metoprolol succinate without infringing existing patents using Methocel® K100M and xanthan gum as a matrixing agents. Another reason of using combinations of Methocel® K100M and xanthan gum was to overcome the disadvantages of individual matrixing agents. Hydroxypropyl methylcellulose forms firm gel but do not hydrate quickly (24). On the other hand, xanthan gum hydrates very quickly (24). Xanthan gum cannot form a strong gel, causing erosion or dissolution of gel around the tablet, thereby requiring high concentration (24). A 3^2 full factorial design was employed for optimization. The percentage drug released at a given time (Y_{60}, Y_{240} and Y_{720}) and the time required for 50% of drug to be released ($t_{50\%}$) were selected as dependent variables (25–27). The similarity factor f_2 was used to compare dissolution profiles of a test and a market formulation (28–30).

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MATERIALS AND METHODS

Materials

Metoprolol succinate was obtained as a gift sample from Lupin Pharma Pvt. Ltd., Pune, India. Hydroxypropyl methylcellulose (Methocel® K100M, Colorcon Asia Pvt. Ltd., Goa, India) and xanthan gum (Lupin Pharma Pvt. Ltd, Pune, India) were received as gift. Dibasic calcium phosphate (DCP) and magnesium stearate were procured from Laser Chemicals, Ahmedabad, India. Cab-O-Sil M5 was received as gift from Cabot Sanmar, Chennai, India. Seloken® XL tablets (AstraZeneca, India) was procured from local pharmacy.

Method

Preparation of Hydrophilic Matrix Tablets

The drug-filler blend was mixed with various concentrations of hydrophilic polymers such as HPMC (Methocel® K100M), xanthan gum, and combination of both the matrixing agents. The powder blend was granulated by using a vehicle blend consisting of 1:9 ratio of water to isopropyl alcohol. The wet mass was passed through 20# mesh screen (850-μm opening) and the resultant granules were dried at 55°C. The granules of 20/40# mesh cut were used for preparation of modified release metoprolol succinate tablets. Magnesium stearate and Cab-O-Sil M5, each at 1% *w*/*w*, were uniformly mixed with the granules and the tablets with crushing strength of 9±5 kPa were prepared on a single station tablet press (Cadmach Machinery, Ahmedabad, India). The total weight of the tablet was 500 mg. The tablets were evaluated for percentage friability and *in vitro* drug dissolution study. The composition of various formulations is given in Table I.

Evaluations

1. Percentage Friability

Twenty tablets were rotated in a friabilator (Model EF2, Electrolab, Mumbai, India) at 25 rpm for 4 min. The tablets were then dedusted, and the loss in weight due to fracture or abrasion was recorded as percentage weight loss (percent friability).

2. *In Vitro* Drug Dissolution Study

The *in vitro* dissolution study (n=3) of marketed product (Seloken® XL) and the formulated metoprolol succinate matrix tablets was carried out according to USP in 500 ml of phosphate buffer solution (pH 6.8) maintained at 37±0.5°C. The paddle was rotated at a speed of 50 rpm (31). The samples of dissolution medium (10 ml) were withdrawn up to 24 h and analyzed spectrophotometrically at 275.7 nm by using Shimadzu-1700 UV/Visible spectrophotometer (Japan). An equal volume of fresh dissolution medium, maintained at the same temperature, was added after withdrawing each sample to maintain the volume. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally (r=0.99).

Analysis of In Vitro Dissolution Data

The method of Bamba *et al*. was adopted to ascertain kinetics of drug release (32). The mean *in vitro* drug release data from 0% to 60% and 0% to 100% were fitted to different kinetic models (zero order, first order, Higuchi, Hixon-Crowell, Korsmeyer-Peppas and Weibull) to evaluate the kinetics of drug release from the matrices (33–38). A FORTRAN software, developed in-house, was used. The least Fischer (F) value was used to establish superior fit of the release models out of the tested formulations. The results are displayed in Table II.

The mean dissolution time (MDT), measure of the rate of the dissolution process, was calculated using Eq. 1.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M} \quad (1)$$

Where i is the dissolution sample number; n is the number of observation; t_{mid} is the midpoint time between i and $i-1$ and ΔM is the additional amount of drug dissolved between i and $i-1$ (39). The drug release rate and MDT are inversely related. Linder and Lippold found that application of MDT

Table I. Composition and Results of Metoprolol Succinate Matrix Tablets

Ingredient (milligram per tablet)	Batch code											
	AH_1	AH_2	AH_3	AH_4	AH_5	AX_1	AX_2	AX_3	AX_4	AX_5	AX_6	AX_7
Metoprolol succinate	95	95	95	95	95	95	95	95	95	95	95	95
Methocel® K100M	50	100	150	200	250	–	–	–	–	–	–	-
Xanthan gum	–	–	–	–	–	50	100	150	200	250	300	350
DCP	345	295	245	195	145	345	295	245	195	145	95	45
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Cab-O-Sil M5	5	5	5	5	5	5	5	5	5	5	5	5
Results												
MDT (h)	4.3	5.6	6.9	8.9	9.4	3.7	4.8	5.6	6.7	7.7	8.8	9.5
f_2	31.3	39.4	50.0	84.9	75.7	28.1	32.2	36.3	45.0	57.2	79.8	67.2

DCP dibasic calcium phosphate, *MDT* mean dissolution time (MDT of reference product was 9.0 h), f_2 similarity factor

Table II. Results of Model Fitting from 0% to 60% and 0% to 100% Drug Release for Batches AH_3–AH_5 and AX_5–AX_7

	Zero order		First order		Higuchi		Hixon-Crowell		Korsmeyer-Peppas		Weibull	
Batch code	F^a	F^b	F^a	F^b	F^a	F^b	F^a	F^b	F^a	F^b	F^a	F^b
AH_3	139.4	1.7	3,503	16	13.0	210.4	17.3	166	15.8	251.6	19.1	316.1
AH_4	25.2	16.8	468	9.51	4.52	55.5	11.4	349.5	4.6	34.3	6.9	303
AH_5	43	6.8	163.7	2	14.4	154.6	2.3	195.4	2.3	69.9	4.3	192.9
AX_5	70.1	38.9	544.1	24.2	2.1	6.5	28.5	352	2	9	3.2	310
AX_6	53	21.0	544	10.6	2.8	30.2	13.5	224	2.7	22	4.8	238
AX_7	11.1	18.2	49.7	12.5	9.6	56.7	14.0	129	8.9	36.1	11.1	123.7

[a] Fischer value for 0–100% drug release
[b] Fischer value for 0–60% drug release

provides a more accurate drug release rate than the t_x% approach (40).

The mean dissolution data (n=3) were used for computation of similarity factor (f_2) using Eq. 2 as recommended by Moore and Flanner (28). Ten percentage differences between reference and test products was considered as applicable at all time points (41–42). The mean dissolution data of Seloken® XL were taken as reference profile.

$$f_2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{n=1}^{n}(R_t - T_t)^2\right]^{-0.5}\times 100\right\} \qquad (2)$$

Where n is the number of pull points; R_t is the reference profile at time point t and T_t is the test profile at the same time point. The value of f_2 should be between 50 and 100 (43). The f_2 value of 100 suggests that the test and reference profiles are identical and, as the value becomes smaller, the dissimilarity between releases profiles increases.

RESULT AND DISCUSSION

The reference product, *i.e.*, Seloken® XL, met the criteria laid down in USP (31). The following criteria were chosen for the selection of acceptable batches: $15\% < Y_{60} < 20\%$, $20\% < Y_{240} < 40\%$, $60\% < Y_{720} < 70\%$, $6\text{ h} < t_{50} < 8\text{ h}$, and $8\text{ h} < \text{MDT} < 10\text{ h}$.

For highly soluble drugs like metoprolol succinate, a rapid rate of hydration of matrixing agent is necessary. A slow polymer hydration rate may lead to "dose dumping" due to quick penetration of dissolution fluid into tablet core and subsequent diffusion of drug solution. Hence, a rapidly hydrating hydrophilic matrixing agent was chosen in the present study. DCP, an insoluble filler, was used to improve compressibility and retard initial burst release.

Preliminary Batches for Tablets Containing Methocel® K100M

Figure 1 shows drug release profile of preliminary batches of tablets containing different concentrations of Methocel® K100M (10–50% *w/w*) and the reference product. Figure 1 clearly demonstrates that the release rate is greatly influenced by the formulation factors such as the amount of HPMC and DCP. The drug dissolution can be either controlled by disentanglement or diffusion and it depends on the polymer molecular weight and the thickness of the diffusion boundary layer (44). Slow drug release (Y_{60}=12%) was observed from the tablets containing 50% *w/w* of Methocel® K100M while relatively faster drug release (Y_{60}>20%) was observed of formulations containing 10%, 20% and 30% of Methocel® K100M as compared to the reference product. From the results, it is clearly concluded that the drug release was dramatically retarded when the polymer level was changed from 10% to 50% *w/w*. As the polymer level was increased, the polymer gel formed is more likely to be resistant to drug diffusion and erosion (45). As the release rate-limiting polymer changes from a glassy state to rubbery state, a gel structure is formed around the tablet matrix, which considerably decreases the release of drug since it has to diffuse through this gel barrier into the bulk phase. The strength of gel depends on the chemical structure and molecular size of polymer (45–47). The faster drug release in case of formulation containing low amount of Methocel® K100M may be due to less tortuous diffusion path (radius of conical pile, r). The percentage friability from formulated batches AH_1–AH_5 was within the acceptable limits (<1%).

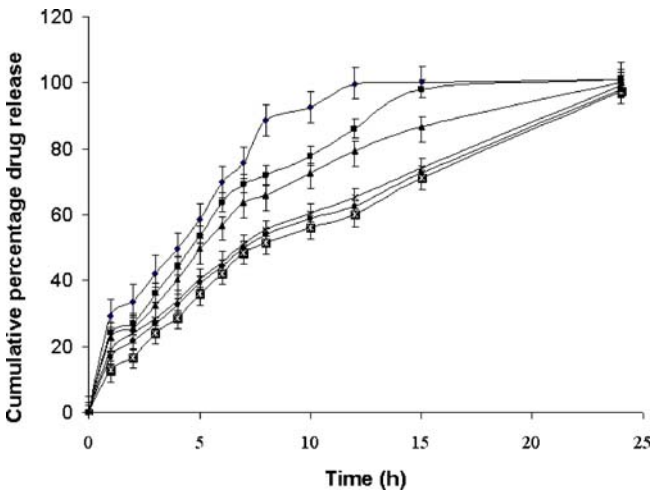

Fig. 1. Comparative dissolution profile of metoprolol succinate from Methocel® K100M formulations to reference product; AH_1 (-◆-), AH_2 (-■-), AH_3 (-▲-), AH_4 (-×-), AH_5 (-⊡-), reference product (-●-)

Preliminary Batches for Tablets Containing Xanthan Gum

Figure 2 shows drug release profile of preliminary batches containing different concentrations of xanthan gum (10% *w/w* to 70% *w/w*) and the reference product. Incomplete and slow drug release was observed from the formulation containing 70% *w/w* xanthan gum. In the early stage of the drug dissolution study, a thick gel layer was formed around the tablets with a dry interior core. The drug release was considerably delayed due to gel formation. The batches containing low concentration of xanthan gum (AX_1–AX_4) exhibited high initial drug release (Y_{60}>20%). Moreover, the tablets of batches AX_1–AX_4 also did not maintain their integrity during the drug dissolution study. The percentage friability of the formulated batches AX_1–AX_7 was within the acceptable limits (<1%).

Optimization of Formulations (Preliminary Batches)

The batches AH_3–AH_5 (Methocel® K100M) and batches AX_5–AX_7 (xanthan gum) showed almost similar drug release profile to that of the reference product. Table I shows the result of MDT and f_2. The mean *in vitro* drug dissolution data from 0% to 60% and 0% to 100% were analyzed for model selection. The method of Bamba *et al.* (32) was adopted for model selection for batches AH_3–AH_5 and AX_5–AX_7. Model fitting was done using an in-house computer program "FORTRAN" developed by the authors. Zero-order, first-order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas and Weibull models were tested (33–38). Considering Fischer (*F*) value in both the cases (0–60% and 0–100% drug release), Korsmeyer-Peppas model showed superior fit over the other models in the batches containing Methocel® K100M and xanthan gum (Table II). The slope and intercept values for 0% to 100% drug release were selected for further studies, *i.e.*, evolving modified Korsmeyer-Peppas equation.

The slopes and intercepts for the formulations containing Methocel® K100M (batches AH_3, AH_4 and AH_5) were 0.522, 0.5421, 0.6665 and −0.6881, −0.7658, −0.9197, respectively. The slopes and intercepts were 0.4922, 0.5234, 0.5593 and −0.6902, −0.7476, −0.8176, respectively, for the formulations containing xanthan gum (batches AX_5–AX_7). The unified equations for slope and intercept were evolved using linear regression analysis using slope/intercept as a dependent variable and polymer concentration as independent variable (48). Equations 3 and 4 represent unified equation of slope and intercept for formulations AH_3, AH_4, and AH_5 containing Methocel® K100M.

$$Equation\ of\ slope = 0.288 + (0.00722 \times polymer\ concentration) \quad (r = 0.923) \tag{3}$$

$$Equation\ of\ intercept = -0.328 - (0.0116 \times polymer\ concentration) \quad (r = 0.982) \tag{4}$$

Similarly, Eqs. 5 and 6 represent unified equation of slope and intercept for formulations AX_5, AX_6, and AX_7 containing xanthan gum.

$$Equation\ of\ slope = 0.324 + (0.00335 \times polymer\ concentration) \quad (r = 0.993) \tag{5}$$

$$Equation\ of\ intercept = -0.370 - (0.00636 \times polymer\ concentration) \quad (r = 0.996) \tag{6}$$

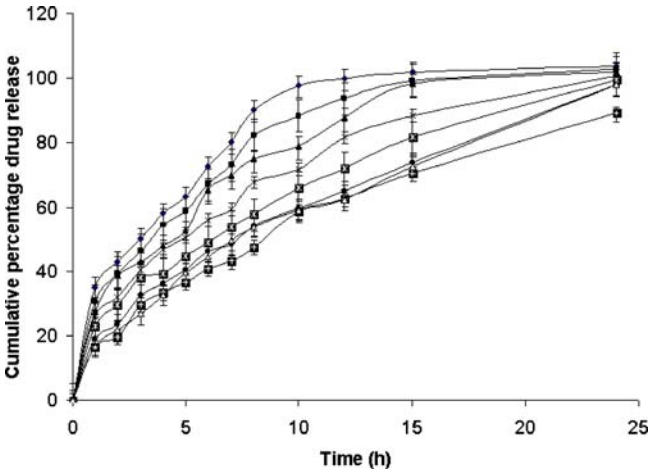

Fig. 2. Comparative dissolution profile of metoprolol succinate from xanthan gum formulations to reference product; AX_1 (-◆-), AX_2 (-■-), AX_3 (-▲-), AX_4 (-×-), AX_5 (-⊠-), AX_6 (-●-), AX_7 (-⊞-), reference product (-△-)

Table III. Observed Responses from a 3^2 Full Factorial Design

Batch code	Variable		Response value					
	X_1	X_2	Y_{60}	Y_{240}	Y_{720}	t_{50} (h)	MDT (h)	f_2
M_1	−1	−1	26.8	47.2	80.2	4	6.5	43.2
M_2	−1	0	24.1	44.7	78.2	5	6.9	48.2
M_3	−1	1	20.1	39.3	68.8	6	8.5	66.1
M_4	0	−1	24.1	42.8	72.5	5	7.5	53.1
M_5	0	0	21.7	40.2	69.6	6	8.2	63.3
M_6	0	1	14.7	30.1	61.7	8	9.5	82.1
M_7	1	−1	21.1	41.9	70.9	6	8.0	59.3
M_8	1	0	16.9	34.3	63.3	7	8.9	89.2
M_9	1	1	13.1	28.3	60.1	8	9.6	76.1

X_1 amount of xanthan gum, X_2 amount of Methocel® K100M, Y_{60} percentage drug release at 60 min, Y_{240} percentage drug release at 240 min, Y_{720} percentage drug release at 720 min, *MDT* mean dissolution time, f_2 similarity factor

Table IV. Design Layout of 3^2 Full Factorial Design

Independent variables	Levels		
	Low	Medium	High
X_1=% of Xanthan gum	20%	30%	40%
X_2=% of Methocel® K100M	10%	20%	30%
Transformed value	−1	0	+1

X_1 amount of xanthan gum, X_2 amount of Methocel®

Table V. Result of Regression Analysis for Dependent Variables

Responses	Intercept	b_1	b_2	b_1b_2	r	p value
Y_{60}	20.0	−3.1	−4.2	–	0.999	<0.05
Y_{240}	39.7	−4.1	4.4	–	0.996	<0.05
Y_{720}	68.9	−4.8	−5.9	–	0.997	<0.05
t_{50}	6.3	0.8	1	–	0.896	<0.05
MDT	8.2	0.7	0.8	–	0.994	<0.05
f_2	64.5	11.1	11.7	−1.5	0.875	<0.05

Y_{60} percentage drug release at 60 min, Y_{240} percentage drug release at 240 min, Y_{720} percentage drug release at 720 min, t_{50} time required for 50% of drug to be released, *MDT* mean dissolution time, f_2 similarity factor

The modified Korsmeyer-Peppas equation (Eq. 7) was evolved individually for formulations containing Methocel® K100M and xanthan gum by combining the unified equations of slope and intercept.

$$\log f = (\textit{equation of slope} \times \log t) + (\textit{equation of intercept}) \quad (r = 0.999) \tag{7}$$

Where, f and t are fraction of drug released and time, respectively. Validation of Eq. 7 was done by formulating checkpoint batches AH_6 and AX_8 containing 43% Methocel® K100M and 63% xanthan gum, respectively. Statistically insignificant difference was observed between theoretical and practical drug release at 5% confidence level for batches AH_6 and AX_8 with $t_{\text{caluclated}} < t_{\text{critical two-tail}}$.

Two or more matrixing agents can be used to overcome the disadvantages of individual matrixing agent or to achieve desired drug release pattern (49,50). Hydroxypropyl methylcellulose forms stiff gel without quick hydration (24). Xanthan gum hydrates very quickly but cannot form a strong gel, causing erosion or dissolution of gel around the tablet (24). Xanthan gum is available at lower cost and readily flowable than HPMC (4–5). A logical reason to use the blend of HPMC and xanthan gum in the matrix tablet of metoprolol succinate was that the drug release is superiorly explained by Korsmeyer-Peppas equation by both the matrixing agents, *i.e.*, the same mechanism of drug release.

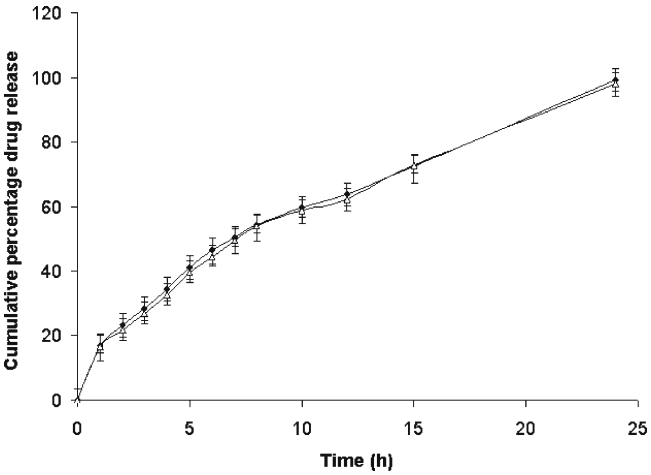

Fig. 3. Cumulative percentage of drug release of batch M_8 with reference product; batch M_8 (—●—) and reference product (—△—)

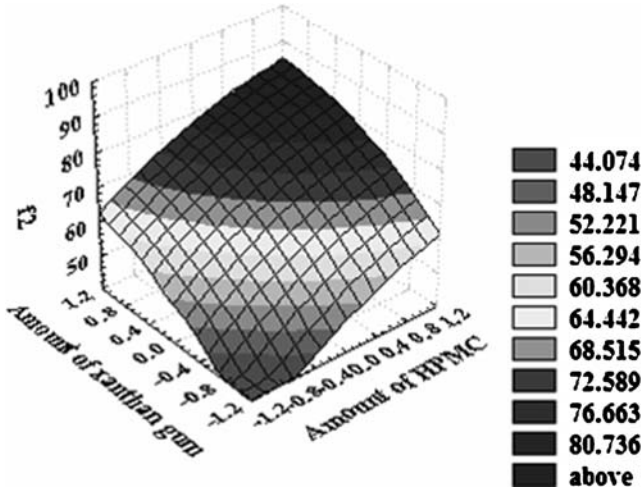

Fig. 4. Response surface plot for similarity factor f_2

Factorial Design

A two-factor three-level full factorial design was used for systemic study of combination of hydrocolloids and cellulose ether. Tables III and IV show the design layout and the ranges of matrixing agents. The linear interactive model is shown in Eq. 8.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 \tag{8}$$

Where Y is the dependent variable; b_0 is the arithmetic mean response of nine runs and b_i is the estimated coefficient for the factor X_i. The main effects (X_1 and X_2) represent the average result of changing one factor from its low to high values. The interaction term (X_1X_2) shows how the response values change when two factors are simultaneously changed. Equation 8 can be used to draw conclusion after considering the magnitude of coefficient and the mathematical sign that the coefficient carries. A high positive or negative value in the equation represent that by making a minor change in the setting of that factor one may obtain a significant change in the dependent variable.

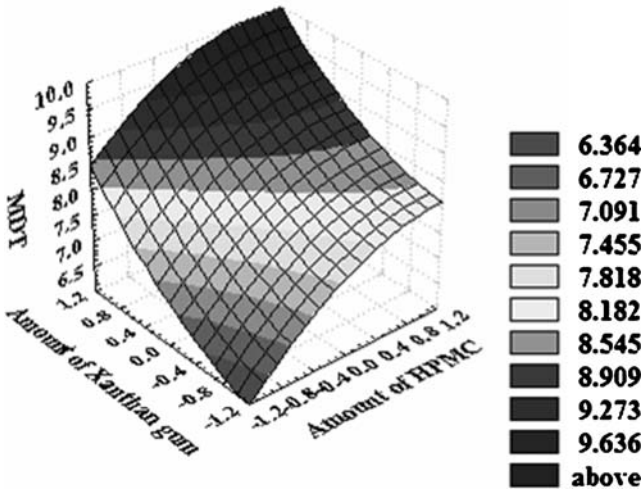

Fig. 5. Response surface plot for mean dissolution time (*MDT*)

The data shown in Tables III and IV reveal that the independent variables (X_1 and X_2) exhibit a great influence on responses. The models relating the selected responses to the transformed factors are shown in Table V. It can be concluded that a good fit was found for all the responses.

Batch Selection

The release profile of the reference product was used for the selection of ideal values of drug release. The ideal values of Y_{60}, Y_{240}, Y_{720}, $t_{50\%}$ and MDT were 17%, 34%, 63%, 7, and 9 h, respectively. The reference product satisfied the dissolution requirement of USP. The batches M_3, M_6, M_8 and M_9 met the set criteria of Y_x, $t_{50\%}$ and MDT. For final screening, similarity factor f_2 was compared for batches M_3, M_6, M_8 or M_9. The batch showing f_2 value nearest to 100 may be ranked as the best batch. Accordingly, batch M_8 was ranked as the best batch (f_2=89). Shah *et al.* suggested that the average difference between two dissolution profiles is 2%, 5%, 10%, 15%, or 20% for calculated f_2 of 83, 65, 50, 41, and 36, respectively (42). The only batch which showed less than 2% is batch M_8. The coefficient of Methocel® K100M and xanthan gum were nearly the same (~11) indicating favorability of combination of both the matrixing agent.

Figure 3 shows dissolution profiles of batch M_8 and reference product. Figures 4 and 5 show the response surface plot for the similarity factor f_2 and MDT, respectively. The plots were drawn using Statistica® software. It is obvious from Figs. 4 and 5 that by varying concentration of Methocel® K100M and xanthan gum one can tailor the selected dependent variables significantly.

CONCLUSION

Important formulation factors were systematically studied for the development of modified release tablets of metoprolol succinate. It is possible to fabricate modified release tablets of metoprolol succinate using hydroxypropyl methylcellulose (Methocel® K100M) and xanthan gum. The combination of matrixing agents namely xanthan gum and Methocel® K100M overcomes disadvantages of each polymer. The initial drug burst release was controlled by quick gelation of xanthan gum whereas subsequent drug release and matrix integrity were maintained by firm gel of Methocel® K100M. The economy of xanthan gum may help the formulator to decrease the cost of the fabricated product. The drug release was found to be dependent on the amount and type of matrixing agent. The drug release was explained by Korsmeyer-Peppas model from Methocel® K100M and xanthan gum matrices.

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