Optimization of sustained release matrix tablet of metoprolol succinate using central composite design

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Abstract: The present study was performed to optimize the formulation of metoprolol succinate (MS) sustained release tablets using hydroxypropyl methylcellulose (HPMC) and sodium alginate (SA) as the matrix combination. After investigating the effects of various parameters on drug release, a 2-factor, 5-level central composite design was employed, using the amount of HPMC K4M (A) and SA (318 cP) (B) as the independent variables and the drug percentage released at 1h, 4h, 8h, 20h (Q_1, Q_4, Q_8, Q_{20}) as the responses. Response surfaces were established to obtain the matrix ranges and the main factors affecting four responses. In order to validate the optimization study, six confirmatory runs were performed; indicating high predictability of response surface methodology for MS sustained release tablets. Data fitting to Peppas equation indicated that the mechanism of drug release could be diffusion along with erosion. This matrix combination can be used as a good alternative to the commercially pellet technology, which was complicated, time-consuming and energy-intensive.

Keywords: Central composite design, sustained release matrix tablet, Metoprolol succinate, HPMC, sodium alginate

INTRODUCTION

As a $beta_1$-selective adrenoceptor blocking agent, orally administered metoprolol succinate is clinically used for the treatment of hypertension, angina pectoris and heart failure (Falkner and Kushner, 2008; Herlitz *et al.,* 2002). Its half-life ranges from 3 to 7 hours (Agewall and Kendall, 1997; Wikstrand *et al.,* 2003). When overdose, it causes a series of adverse reactions, such as bronchospasm, dyspnea and shortness of breath (Abrahamsson *et al.,* 1990). In addition, the solubility of metoprolol succinate is above 270 mg/ml in aqueous solution. Metoprolol succinate has been formulated as once-daily extended release tablet (TOPROL-XL) to provide a sustained release of metoprolol. The tablets consist of a multiple unit system containing metoprolol succinate in a multitude of controlled release pellets. However, the preparation of pellets is complicated and time-consuming.

In order to obtain oral sustained release, matrix tablets are widely accepted because of their simplicity and easy formulation. As the modified release dosage form, it is flexible to obtain a desirable drug release profile and broad regulatory acceptance, especially for water-soluble drugs. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose, chitosan, carbomer, guar gum, xanthan gum and sodium alginate are widely used as the matrix materials (Rajesh *et al.,* 2009; Shoaib *et al.,* 2006; Khan *et al.,* 2009; Iqbal *et al.,* 2011; Petrovic *et al.,* 2009). Among them, sodium alginate (SA), a sodium salt of alginic acid, a natural and non-toxic polysaccharide, can be used to modify the release of highly water-soluble drugs, for its rapid hydration and erosion (Liew *et al.,* 2006).

During formulation screening, it is generally necessary to explore the effect of the independent variables on responses, and then to perform the optimization to obtain the ideal formulations. Selected as the most popular response surface methodology, the central composite design was proved to be suitable for establishing an appropriate model for the responses and variables (Weon et al., 2000; Sun and Zhang, 2004; Hamed and Sakr, 2001; Gil et al., 2006). Besides, the interaction between independent variables can be studied and a few experiments were operated to obtain much information by using response surface methodology (Takayama and Nagai, 1989; Singh *et al.,* 1995; Bouckaert *et al.,* 1996).

In this study, HPMC and SA were employed as the combination matrix and the central composite design was used to optimize the tablet formulation of metoprolol succinate, which could provide sustained drug release for 20 hours.

MATERIALS AND METHODS

Materials

Metoprolol succinate (purity of 98.5 %-100.5 %) was a gift sample from Hisoar Pharmaceutical Co., Ltd. (Taizhou, China). HPMC K100LV (nominal viscosity of 100 cP), HPMC K4M (nominal viscosity of 4000 cP), HPMC K15M (nominal viscosity of 100 cP nominal viscosity of 15000 cP) and HPMC K100M (nominal viscosity of 100000 cP) were provided by Shanghai

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Colorcon Coating Technology Ltd. (Shanghai, China). Five grades of sodium alginate with viscosity of 216 cP, 318 cP, 530 cP, 700 cP and 825 cP were provided by Qingdao Huanghai Biological Pharmaceutical Co., Ltd. (Qingdao, China). Lactose monohydrate was kindly provided by J. Rettenmaier & Söhne (JRS, Germany). Magnesium stearate was purchased from Liaocheng Ahua pharmaceutical Co., Ltd (Liaocheng, China).

Preparation of sustained release matrix tablets

Batches of tablets, with each tablet containing 47.5 mg metoprolol succinate (MS), were prepared by direct compression method. MS, lactose, HPMC, SA and magnesium stearate, sifted through 80-mesh (about 180μm) screen, were thoroughly mixed in a polythene bag and then compacted into 10 mm tablets by tabletting machine (Rimek, Mini PRESS IISF, Ahmedabad, India). All the obtained sustained release tablets were stored in an airtight container at room temperature (provide the temperature) for further studies.

In vitro drug release studies

The release studies (six replicates) of MS sustained release tablets were performed in 500 ml phosphate buffer (pH 6.8) (37.0 ± 0.5ºC) using the USP 32-NF27 dissolution test apparatus 2 (Sotax A7 Dissolution Apparatus: Sotax Ltd, London, UK) with the paddle rotation at 50 rpm. Samples (2 mL) were withdrawn and filtered for analysis at specified time points (1 h, 4 h, 8 h and 20 h), and assessed for MS content by HPLC (Shimadzu Corporation, Japan) according to USP 34-NF 27 monograph of MS extended release tablets. For analysis, a reversed phase Shimadzu-pack VP-ODS C_{18} (4.6×150mm, 5μm particles) column was used and the peak of MS was eluted with mixtures of acetonitrile and phosphate buffer (pH 3.0, 0.065 mol/L) (125:375, v/v). The flow rate of 1.0 ml/min was maintained. The column effluent was monitored at 274 nm. Quantification of the compounds was carried out by measuring the peak areas in relation to those of standards chromatographed under the same conditions ($R^2 > 0.999$).

Influence of individual factors on the release of MS

The effects of polymer viscosities (SA: 216 cP-825 cP; HPMC: 1000 cP-100000 cP) and weight ratios (SA: 10%-40%; HPMC: 10%-60%) were investigated. In all formulations, lactose was used as diluent to control the tablet weight to 310mg.

Effect of HPMC viscosity

The effect of various viscosities of HPMC (K100LV, K4M, K15M, K100M) with the same amount of 50 mg per tablet and the same amount of 160 mg SA (318 cP) on release profile was studied.

Effect of SA viscosity

In order to estimate the effect of viscosity of SA on release profile, SA with similar particle size distribution at the same amount but different viscosities (216 cP, 318 cP, 530 cP, 700 cP, 825 cP) was compared. These tablets contained 50 mg HPMC K4M.

Effect of proportion of HPMCK4M

The influence of the proportion of HPMCK4M (10%-60 %) on drug release was studied by preparing matrix tablets having the same amount of SA (380 cP, 50 mg).

Effect of proportion of SA(380cp)

The effect of the proportion of SA on drug release was performed by preparing matrix tablets containing 0%, 10% to 40% of SA (380 cP) with the same amount of HPMC (K4M, 80 mg).

Central composite design

Central composite design was performed using two factors, the amount of HPMC K4M and SA (318 cP), each at five levels. Lactose was used as a diluent to control the tablet weight to 310mg. All thirteen combinations were presented in table 1. The batch size for each formulation was 200 tablets. The amount of HPMC (A) and sodium alginate (B) were chosen as the independent variables while quantities of drug released in 1h (Q_1), 4h (Q_4), 8h (Q_8) and 20h (Q_{20}) were selected as the responses. The following criteria were adopted: Q_1=not more than 25%; Q_4 =between 20% and 40%; Q_8 =between 40% and 60%; Q_{20}= not less than 80%, based on the provisions of the United States Pharmacopoeia (USP 34-NF 27) on the release of MS sustained release tablets.

Table 1: Factor combinations of the chosen experimental design (α=1.414)

Trial No.	Coded factor levels (actual weight in each tablet)	
	A	B
1	-1 (80mg)	-1(30 mg)
2	1(170 mg)	-1(30 mg)
3	0(125 mg)	0(45 mg)
4	-1(80 mg)	1(60 mg)
5	α(188.64 mg)	0(45 mg)
6	0(125 mg)	0(45 mg)
7	-α(61.36 mg)	0(45 mg)
8	0(125 mg)	0(45 mg)
9	0(125 mg)	0(45 mg)
10	0(125 mg)	0(45 mg)
11	1(170 mg)	1(45 mg)
12	0(125 mg)	-α(23.79 mg)
13	0(125 mg)	α(66.23 mg)

Translation of coded levels in actual levels

Coded level	-α	-1	0	1	α
A:HPMCK4M (mg)	61.36	80	125	170	188.64
B:SA(318cp) (mg)	23.79	30	45	60	66.23

Data analysis

The release profiles were analyzed by one-way ANOVA to examine the statistical difference. The relationships between responses and independent variables of all designed formulations were processed by Design-Expert® software (version8.0, Stat-Ease Inc., Minneapolis, USA). Statistical analysis including multiple regression analysis and response surface analysis were conducted. The developed models were adopted for the multiple correlation coefficient (R^2), the adjusted multiple correlation coefficient (adjusted R^2) and corresponding P value provided by analysis of variance (ANOVA). The greater values of R^2 and adjusted R^2 are preferable. It was considered significant when the corresponding P value was less than 0.05. The effects of the independent variables on responses were shown in three-dimensional contour plots. The overlay plot, optimized formulations and desirability which comprehensively evaluate four responses can be created by setting ranges of independent variables and responses in Design Expert software, therefore formulations were optimized.

In order to validate the optimization study, six formulations were chosen from the optimized formulations. The corresponding P values and predicted error (%) were employed to evaluate the differences between the predicted and the observed values.

RESULTS

Single factor impact

Effect of HPMC viscosity

Different grades of HPMC (E, F, K) are different in their relative proportions of the hydroxypropyl and methoxyl substitutions. With the increase of the hydrophilic hydroxypropyl group, they differ in their rates of hydration, which is shown below: HPMC K>HPMC E>HPMC F (Ishikawa *et al.,* 2000). For drugs with high water solubility like metoprolol succinate, the use of HPMC grade with a rapid hydration is desirable, since an inadequate polymer hydration rate may result in 'burst release' owing to quick penetration of dissolution medium fluids into the tablet core. Hence, the rapidly hydrating HPMC K was chosen for this study.

As shown in fig. 1, the formulations containing the same amount 50 mg HPMC with different viscosities exhibited the discrepant release profiles. The release rates of metoprolol succinate in 4 h and 8 h from the formulations using HPMC with low viscosity (K100LV) were faster than those using HPMC with high viscosities (K4M, K15M and K100M) ($P<0.05$). With the increase of HPMC viscosity, the release rate had a tendency to decrease (Lee *et al.,* 1999). It was probably due to more polymer entanglement, stronger gel strength and also less effective molecular diffusional area at higher viscosity (Ravi *et al.,* 2008). With the increase of the viscosity degree of HPMC, the swelling of its side chains undergoes faster to form a very strong gel, which had more ability to resist the drug diffusion and gel erosion, thus decreasing the drug release rate (Maderuelo *et al.,* 2011).

However, the drug release rates between high viscosities had no significant differences ($P>0.05$). The fastest drug release rate was observed for K100LV formulation. The K4M formulation exhibited a slightly greater drug release rate than the K15M and K100M formulations. The insignificant differences in the drug release profiles for K4M, K15M and K100M formulations suggested that the impact of HPMC viscosity on controlling the release of MS was limited. It was reported that the drug release rate no longer decreased when HPMC viscosity was above 4000 cP (Sung *et al.,* 1996).

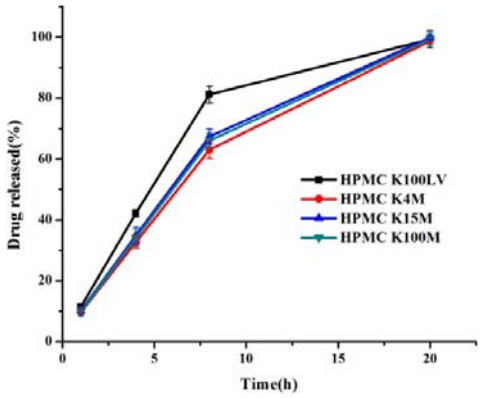

Fig. 1: The effect of HPMC viscosity on release profile of metoprolol succinate sustained release matrix tablet.

Nevertheless, the initial release rate in 1h and final release in 20h had no obvious differences between low viscosities and high viscosities, which might be attributed to the rapid swelling of large amount of 160mg SA(318 cP), offsetting the different viscosities of HPMC. A small amount of 50 mg HPMC with different viscosity and a large amount of 160mg SA (318 cP) ensured no obvious final release in 20 h. The viscosity of HPMC primarily contributed to the release rates in 4h and 8h. Hence, HPMC K4M was chosen as the HPMC type in matrix tablets for subsequent optimization.

Effect of SA viscosity

The release curves of MS sustained tablets containing 160mg SA with different viscosities (216 cP-825 cP) were presented in fig. 2. It was observed that the release in 4 h and 8 h from the formulations using SA with low viscosity (216 cP) was faster than those using SA with high viscosities (318 cP, 530 cP, 700 cP, 825 cP) ($P<0.05$). However, the release rates between formulations with those high viscosities had no significant differences ($P>0.05$). Therefore, lower-viscosity SA tended to show faster drug release compared to higher-viscosity SA

(Efentakis and Koutlis, 2001). Nevertheless, the initial release rate in 1h and final release in 20h had no obvious differences between low viscosities and high viscosities of SA, which might be attributed to high viscosity of HPMC K4M, counteracting the impact of SA viscosities. SA (318 cP) was finally chosen as the type for subsequent optimization study.

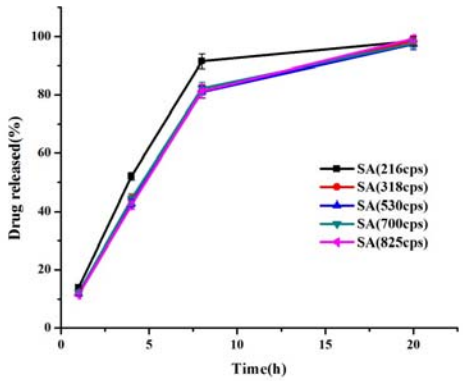

Fig. 2: The effect of SA viscosity on release profile of metoprolol succinate sustained release matrix tablet.

Effect of HPMC proportion

The release amount of MS in 1 h, 4 h, 8 h and 20 h was apparently retarded with the increase of HPMC K4M from10 % to 60 % ($P<0.05$), as shown in fig. 3. The 'burst release' of MS in 1h was relatively retarded with the increase of HPMC K4M. And the increase of HPMC K4M from10% to 60% directly resulted in the decrease of drug release in 4 h and 8 h. When the level of HPMC K4M was less than 50%, the ultimate drug release was approximately 90%. Under the level of 50 % of HPMC K4M, the final release was not affected by the amount of HPMC K4M. However, if HPMC K4M was above 50 %, the final release was evidently inhibited. This can be related to the swelling and erosion of HPMC. When HPMC matrix was immersed in aqueous solutions, it absorbed water and swelled, which made gel layer thicken gradually, the diffusion distance for the drug to pass the gel gets long and thus slows the drug release rate (Tiwari Hardy, 2007). With the increase in polymer percentage in tablets, the percentage of swelling increased and the percentage of erosion decreased (Maderuelo *et al.,* 2011). The thicker gel layer had more power to resist the drug diffusion and gel erosion (Wan *et al.,* 1993), which resulted in the incomplete release. This experiment indicated that formulations with a wide release profiles may be obtained by varying the HPMC K4M level from 10% to 60%.

Effect of sodium alginate proportion

As shown in fig. 4, the amount of SA had a significant effect on the early release (before 8 h) of MS ($P<0.05$). Its release from the matrix decreased with the increase of SA amount in tablets. The mechanism of drug release from alginate-based matrix tablets is swelling along with gradual matrix erosion (Sriamornsak *et al.,* 2007). Higher drug release rates in 1 h and 4 h was due to fewer polymer particles available for the formation of a continuous and effective resistant gel barrier. On the contrary, higher polymer concentration gave rise to a more effective diffusion barrier to a further decrease in the release rate in 1 h and 4 h (Liew *et al.*, 2006).

Different from HPMC, the amount of SA had no significant effect on the later stage of the release course (after 8 h) ($P>0.05$) (Liew *et al.,* 2006). At 8 h and 20 h, it was observed that four release curves almost overlapped and almost all MS was released, owing to the almost complete erosion of sodium alginate (Sriamornsak *et al.,* 2007).

Table 2: The compositions, responses and drug release mechanism of designed formulations of metoprolol succinate sustained release tablets.

Run	A (mg)	B (mg)	Q_1 (mg)	Q_4 (mg)	Q_8 (mg)	Q_{20} (mg)	N	K	r
1	80	30	21.77	50.78	75.10	99.96	0.52	23.19	0.990
2	170	30	19.34	40.82	60.08	90.50	0.52	19.66	0.999
3	125	45	17.71	42.48	65.74	98.70	0.58	18.38	0.997
4	80	60	15.84	43.97	73.81	99.46	0.63	17.01	0.987
5	188.64	45	14.78	35.42	52.21	83.66	0.58	15.22	0.999
6	125	45	16.39	40.02	62.00	95.55	0.60	16.98	0.997
7	61.36	45	18.66	47.51	74.46	100.00	0.57	20.05	0.989
8	125	45	18.5	41.39	62.93	95.64	0.55	18.92	0.998
9	125	45	16.41	39.38	60.32	93.10	0.59	16.95	0.998
10	125	45	16.37	40.09	61.34	92.85	0.59	17.06	0.997
11	170	60	14.29	35.34	55.71	89.99	0.62	14.66	0.999
12	125	23.79	18.87	43.77	64.32	94.29	0.54	19.68	0.996
13	125	66.21	15.72	41.21	67.46	99.60	0.63	16.55	0.995

A: HPMC K4M, B: SA(318cps), Q_i: responses, the drug release percent at 1h (Q_1), 4h (Q_4), 8h (Q_8) and 20h (Q_{20}). Release mechanism was fitted by Peppas equation: n, r and k were diffusional exponent, correlation coefficient and release rate, respectively.

By the single-factor investigation and after comprehensive consideration, HPMC K4M and SA (318 cP) were determined to be the matrix excipients to retard the release of metoprolol succinate, and their weight amount in the sustained release tablets (60-190 mg and 23-67 mg, respectively) were selected to perform the succeeding CCD optimization.

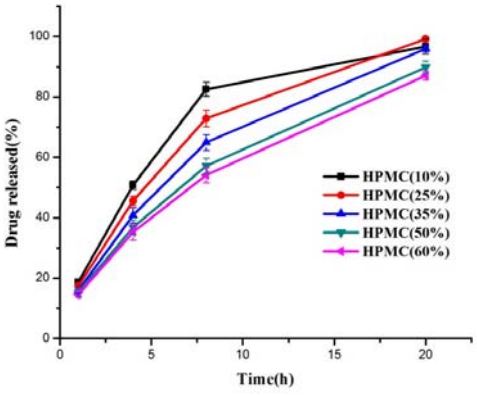

Fig. 3: The effect of HPMC K4M proportion in the sustained release tablets on release profile of metoprolol succinate sustained release matrix tablet.

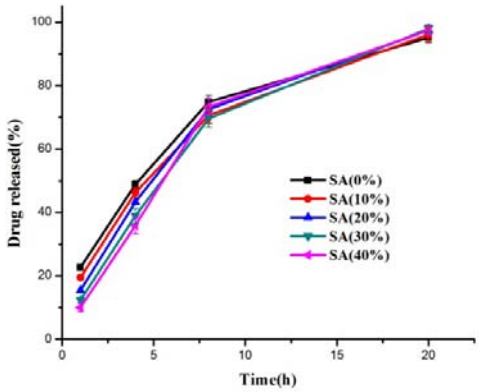

Fig. 4: The effect of sodium alginate (318cP) proportion in the sustained release tablets on release profile of metoprolol succinate sustained release matrix tablet.

Central composite design

Monofactorial experiment had limited ability to make sure the precise value for crucial factors (Ooijkaas *et al.*, 1999; Lotfy *et al.*, 2007). Experimental design is generally a subsequent and requisite method for formulation optimization, such as mixture design (Martinello *et al.*, 2006), factorial design (Beck-

Table 3: The fitting models and corresponding parameters

Models	Responses	Fitting equation	R^2	Adj R^2	P
Linear model	Q_1	Q_1=17.28-1.18A-1.93B	0.7794	0.7352	0.005
	Q_4	Q_4=41.71-4.46A-1.99B	0.8753	0.8503	0.0001
	Q_8	Q_8=64.27-8.07A-0.15B	0.8813	0.8575	0.0001
	Q_{20}	Q_{20}=94.90-5.26A+0.88B	0.7795	0.7354	0.0005
2FI model	Q_1	Q_1=17.28-1.18A-1.93B+0.22AB	0.7831	0.7107	0.0024
	Q_4	Q_4=41.71-4.46A-1.99B+0.33AB	0.8773	0.8364	0.0002
	Q_8	Q_8=64.27-8.07A-0.15B-0.77AB	0.8853	0.8470	0.0001
	Q_{20}	Q_{20}=94.90-5.26A+0.88B+7.500*10^3AB	0.7795	0.7060	0.0026
Quadratic model	Q_1	Q_1=17.08-1.18A-1.93B+0.22AB+0.023A^2+0.31B^2	0.7958	0.7453	0.023
	Q_4	Q_4=40.67-4.46A-1.99B+0.33AB+0.58A^2+1.1B^2	0.9220	0.8662	0.0009
	Q_8	Q_8=62.47-8.07A-0.15B-0.77AB+0.83A^2+2.1B^2	0.9409	0.8986	0.0004
	Q_{20}	Q_{20}=95.17-5.37A+0.88B+0.22AB-1.53A^2+1.28B^2	0.8782	0.7912	0.0042

Table 4: Analysis of variance for quadratic model

Value	DF	Q_1		Q_4		Q_8		Q_{20}	
		SS	P	SS	P	SS	P	SS	P
Model	5	41.85	0.023	201.03	0.0009	556.88	0.0004	256.31	0.0042
A	1	11.20	0.0305	159.20	<0.0001	521.42	<0.0001	221.32	0.0003
B	1	29.78	0.0031	31.64	0.0086	0.19	0.8526	6.17	0.3068
AB	1	0.19	0.7328	0.44	0.6825	2.37	0.5132	2.250	0.9949
A^2	1	3.561	0.9629	2.37	0.3561	4.74	0.3629	16.58	0.1137
B^2	1	0.67	0.5301	8.36	0.1060	30.76	0.0422	8.63	0.2337
Residual	7	10.74		17.02		35.00		35.54	
Lack of fit	3	6.89	0.2092	10.80	0.2174	17.98	0.3634	13.05	0.5664
Pure error	4	3.84		6.22		17.02		22.49	
Cor toal	12	52.58		218.04		591.89		291.85	

Table 5: The comparison of predicted values and observed values of selected formulations

Compositions HPMC:SA	Dependent variables	Predicted values	Observed values	Predicted error (%)	P
159.63:53.55	Q_1	15.27	16.00	-4.78	0.978
	Q_4	36.95	35.43	4.11	
	Q_8	57	56.28	1.26	
	Q_{20}	91.07	90.02	1.15	
159.84:56.24	Q_1	15.03	16.27	-8.25	0.980
	Q_4	36.88	36.04	2.27	
	Q_8	57.32	56.64	1.19	
	Q_{20}	91.45	89.32	2.33	
161.31:60.00	Q_1	14.69	15.02	-2.25	0.976
	Q_4	36.82	36.25	1.55	
	Q_8	57.32	56.48	1.47	
	Q_{20}	91.45	89.65	1.97	
159.82:51.87	Q_1	15.43	15.08	2.27	0.976
	Q_4	37.01	36.42	1.59	
	Q_8	56.81	55.96	1.50	
	Q_{20}	90.81	89.78	1.13	
159.96:51.19	Q_1	15.49	15.27	1.42	0.987
	Q_4	37.03	36.95	0.22	
	Q_8	56.74	56.68	0.11	
	Q_{20}	90.70	89.54	1.28	
160.13:50.60	Q_1	15.55	15.89	-2.19	0.993
	Q_4	37.05	37.56	-1.37	
	Q_8	56.67	55.98	1.22	
	Q_{20}	90.60	91.25	-0.72	

Broichsitter *et al.,* 2012; Bushra *et al.,* 2008) and response surface methodology (Nazzal *et al.*, 2002). Central composite design (CCD), a response surface methodology, can build a second order model for the response variable without the need to perform a complete full-level factorial experiment. After the designed experiments are performed, linear regression is usually used to gain the results.

The responses (Q_1, Q_4, Q_8 and Q_{20}) of all formulations were listed in table 2 and fig. 5. To investigate the effect of two polymers and their potential interaction, the data were submitted to multiple regression analysis using the statistical package in Design Expert® software. The model was performed by the analysis of variance (ANOVA). Proper models consisting of two independent variables include linear, quadratic and 2FI models. The best fitting model was determined by comparing several statistical parameters including the multiple correlation coefficient (R^2), the adjusted multiple correlation coefficient (adjusted R^2) and corresponding P values. The equations and statistical parameters of mathematical models are shown in table 3.

The multiple correlation coefficient (R^2) and the adjusted multiple correlation coefficient (adjusted R^2) of quadratic model were larger than those of linear model and 2FI model. Quadratic model might be the best fitting model. According to its fitting equations, it was concluded that the independent variables (A and B) had significant effects on responses (Q_1, Q_4, Q_8 and Q_{20}) ($P<0.05$). Analysis of variance for response surface quadratic model is shown in table 4. A had a significant influence on Q_1, Q_4, Q_8 and Q_{20} ($P<0.05$), while Q_8 and Q_{20} were slightly affected by B ($P>0.05$). This was in consistent with the view that sodium alginate matrix had the ability to provide a sustained release for highly water-soluble drug even in the presence of a water-soluble excipient (Liew *et al.,* 2006). The interaction AB, A^2 and B^2 had no remarkable effect on responses (Q_1, Q_4, Q_8 and Q_{20}) ($P>0.05$). The response surface plots are shown in fig.6 (a, b, c and d), which illustrated that the reduction of Q_1 and Q_4 resulted from the increase of HPMC K4M and SA (318 cP), while the reduction of Q_8 was primarily attributed to the increase of HPMC K4M. The increase of Q_{20} should be attributed to the reduction of HPMC K4M and SA (318 cP).

Optimum release profile

To achieve a sustained release tablets with optimized release performance, the initial burst release should be controlled and the complete drug release should be ensured. Based on the criteria of release range, the overlay plot is presented in fig. 7, which showed an acceptable region to meet the requirement of these

responses. To further optimize the formulation, the ranges of Q_1, Q_4, Q_8 and Q_{20} were set at 10%-20%, 25%-37%, 45%-57%, 80%-100%. In Design Expert software, eight optimized formulations were generated. The optimum formulations were provided with A and B values of 159-165 mg, 50-60 mg, respectively.

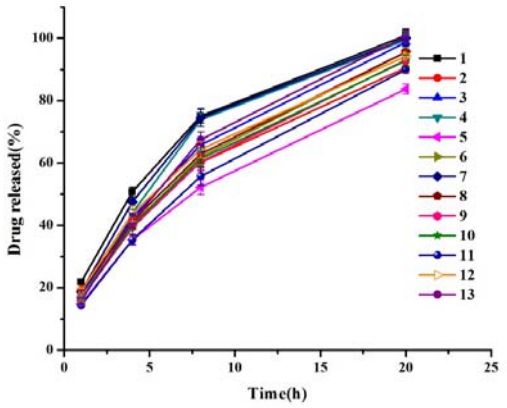

Fig. 5: The drug release profiles of designed formulations (HPMC K4M, sodium alginate (318 cP).

In order to validate the optimization study, six formulations were chosen from the optimized formulations. The corresponding P values and predicted error (%) were employed to evaluate the differences between predicted values and observed values. P-values of six formulations were all above 0.05 (table 5), which demonstrated the high predictability of central composite design.

In order to propose a possible release mechanism, release data from matrix tablets were fitted to the following Peppas equation (Ritger and Peppas, 1987):

$M_t/ M_\infty = kt^n$ Where, M_t is the amount of drug released at time t; M_∞ is the amount of drug released infinitely; M_t /M_∞ is the percentage of released drug at time t; k is a constant indicating the properties of drug delivery system and n is the release exponent indicative of the release mechanism. A value of n =0.45, indicates Case I (Fickian) diffusion, 0.45<n <0.89 indicates anomalous (non-Fickian) diffusion and n = 0.89 indicates Case-II transport (Ritger and Peppas, 1987).

As shown in table 2, the values of exponent constants (n) ranged between 0.52 and 0.63, the intermediate values between 0.45 and 0.89, indicating that diffusion along with erosion could be the release mechanism of MS from sustained release tablets.

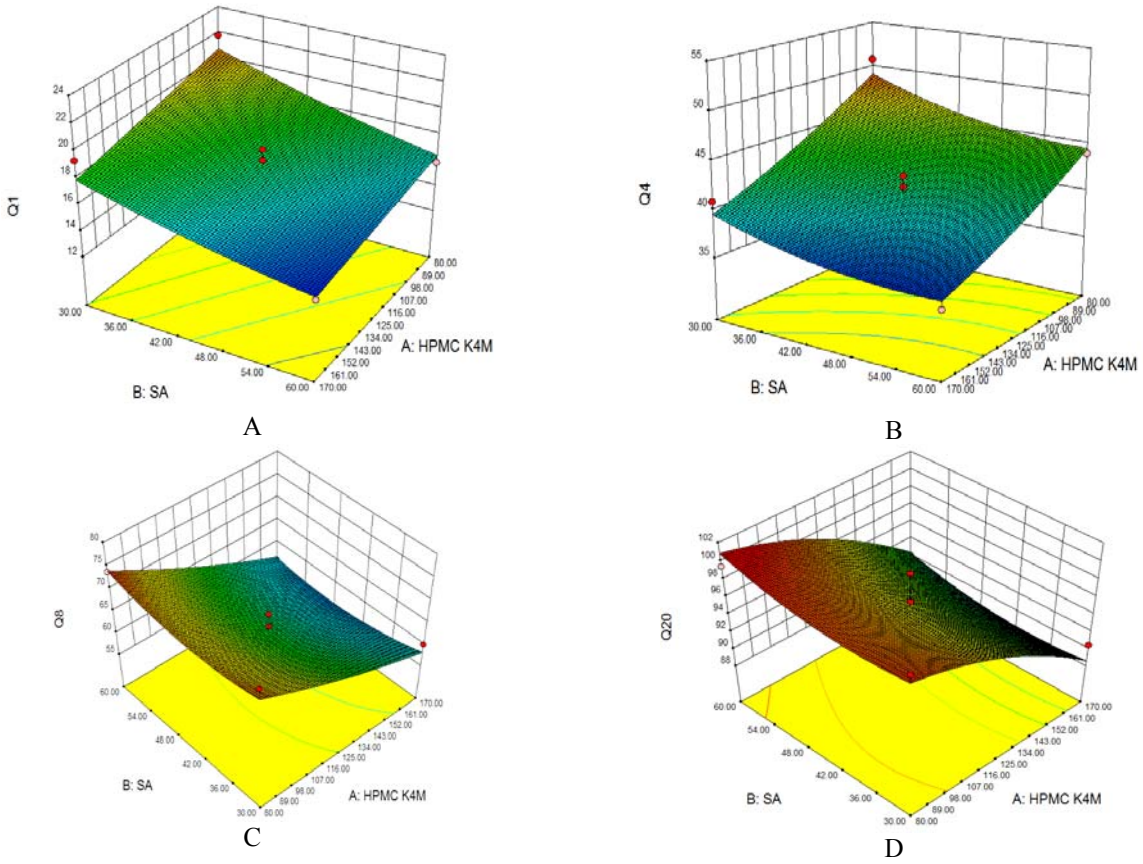

Fig. 6: Response surface plots of Q_1 (a), Q_4 (b), Q_8(c) and Q_{20}(d)

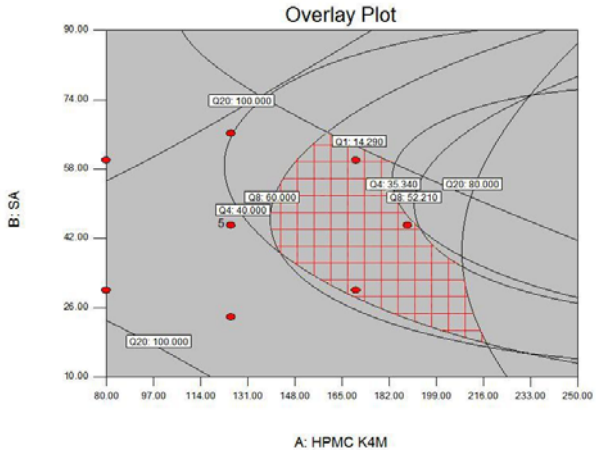

Fig. 7: The overlay plot of optimum release profiles.

DISCUSSION

In the present study, the formulation of MS sustained release tablets was optimized using HPMC and SA as the matrix combination. After investigating the effects of various parameters on drug release, a 2–factor, 5-level central composite design was employed, using the amount of HPMC K4M (A) and SA (318 cP) (B) as the independent variables and the drug percentage released at intervals as the responses. Response surfaces were also established to obtain the matrix ranges and the main factors affecting four responses. Six confirmatory runs were then performed to validate the optimization, which was indicative of the high predictability of response surface methodology for MS sustained release tablets. Data fitting to Peppas equation indicated that the mechanism of drug release could be diffusion along with erosion.

CONCLUSIONS

On the basis of single factor studies, the central composite design was successfully applied for the formulation optimization. It was concluded that not only the viscosity of HPMC and sodium alginate, but also their proportion had significant effects on the release profiles. This matrix combination can be used as a good alternative to the commercially pellet technology, which was complicated, time-consuming and energy-intensive.

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