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Optimization of Extended Zero-order Release Gliclazide Tablets Using D-optimal Mixture Design

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The objective of this study was to develop and optimize the gliclazide extended-release formulations by using simultaneously combination of two hydrophilic polymers: HPMC K 15M and sodium alginate as retardant. D-Optimal mixture design was employed to evaluate the effect of HPMC (X_1), lactose (X_2), and sodium alginate (X_3) concentrations on the release rate of gliclazide from the matrices. The drug release percent at 3, 6, 9 and 12 h were the target responses and were restricted to 20–30, 45–55, 70–80 and 90–100%, respectively. Response surface methodology and multiple response optimization utilizing the polynomial equation were used to search for the optimal formulation with specific release rate at different time intervals. Validation of the optimization study indicated high degree of prognostic ability of response surface methodology. The mechanism of drug release from optimized extended-release matrix tablets was followed by the zero-order release pattern. This study demonstrated that D-optimal mixture experimental design facilitated the formulation and optimization of extended release hydrophilic matrix systems of gliclazide.

Key words——extended-release matrix tablet; D-optimal mixture design; gliclazide; response surface methodology; optimization

INTRODUCTION

Extended-release tablets based on hydrophilic matrices have more advantages than conventional dosage forms. They are widely used in oral controlled drug delivery because of their flexibility in obtaining a desirable drug release profile, cost effectiveness, broad FDA acceptance and favorable *in vivo* performance.[1,2] Numerous polymers can be used for the preparation of hydrophilic polymer matrix system, in view of modulating the kinetic drug release process. Hydroxypropyl methylcellulose (HPMC), a kind of pH-independent hydrophilic material, has been used widely as matrices for oral controlled-release drug delivery systems. It is non-toxic, readily compressible, and able to accommodate high levels of drug loading. Upon hydration, HPMC matrices rapidly form a gel layer of sufficient strength to achieve controlled drug release.[3] Sodium alginate, a water soluble salt of alginic acid, is a natural polysaccharide extracted from marine brown algae. At low pH, hydration of alginic acid forms high-viscosity gel. Under acidic conditions (*e.g.*, in the stomach) the swelling of alginates scarcely occurs. A drug is likely to be released by diffusing through the insoluble matrix. Under neutral conditions, alginates swell and the drug release depends on the swelling and erosion processes.[4] Insufficient drug absorption of controlled release products in the later stage was observed because water penetration and polymer swelling were limited in the colon (small volume of gastrointestinal fluid and viscous colonic content).[5] Therefore, in this study, HPMC and sodium alginate used as retardant were used to modify the drug release and to ensure that most of drug was released in a period of time comparable to the gastrointestinal residence time.

Gliclazide is a second-generation sulphonylurea used worldwide in the treatment of Type 2 diabetes. It is a weak acid with a good lipophilicity and a pH dependent solubility.[6] Gliclazide belongs to the Class II of the biopharmaceutical classification[7] in which the drug dissolution rate is the controlling step in drug absorption. Gliclazide matrix tablet with extended release characteristics was developed in order to obtain a better predictable release of the active principle and to allow a once-daily dosing regimen. This new formulation demonstrated less pH-dependent than those of the existing formulation. Therefore, Gliclazide matrix tablet can significantly improve patient compliance, especially under the situations of prolonged use of drug, and also reduce the total dosage of administered drug and, consequently, the possible

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side effects.[8,9]

Response surface methodology (RSM) is a widely practiced approach to design an optimized pharmaceutical formulation with an appropriate dissolution rate in a short time period and minimum trials. Central composite design (CCD),[10] Box-Behnken,[11] Doehlert and mixture designs[12] are the different types of RSM designs available for statistical optimization of the formulations. The optimization procedures are designed to minimize the number of trails, and to analyze the response surfaces in order to realize the effect of causal factors and to obtain the appropriate formulations with target goals.[13,14] Mixture design is a special type of RSM designs in which the factors are the components of a mixture and the response is a function of the proportions of each ingredient. The mixture components cannot range in an independent way since their sum has to be equal to 100% and specific experimental matrices and mathematic models have to be used.[15] D-optimal mixture design is suitable for pharmaceutical blending problems allowing investigation, with the least number of experiments, of the effects of changes in mixture composition and selection of the optimal composition for achieving the prefixed target.[16]

The purpose of this study was to develop and optimize the formulations of gliclazide matrix tablets with zero-order drug release profiles using D-optimal mixture design and multiple response optimization utilizing superimposed contour diagrams, and to evaluate the usability of D-optimal mixture design in development of the gliclazide matrix tablets.

MATERIALS AND METHODS

Materials The active ingredient gliclazide was kindly offered by Xin Xin Pharmaceutical Manufactory (Tianjin, China). The excipents were as follows: sodium alginate (Shanghai Chemical Regent Corp., China), hydroxypropyl methylcellulose (HPMC) (Methocel K 15M Premium, The Dow Chemical Company, MI, USA), lactose (New Zealand Lactose Co., New Zealand), magnesium stearate (Shinwa Alcohol Industry Co., Tokyo, Japan). All other reagents and solvents used were of analytical grade.

Preparation of Tablets The extended-release tablets were formulated by using wet granulation technique. Drug and the lactose (diluent) were sifted through #80 manually and mixed well to ensure the uniformity of premix blend. Several drug-diluent premixes were then mixed with the selected combination and ratio of hydrophilic polymers (HPMC K 15M and sodium alginate), previously sifted through #60, for 5 min. Premix blend was wet granulated with 90% ethanol and the granules were sized through #18 and were dried at 50°C for 1 h. Dried granules were lubricated with 1% magnesium stearate. Tablets containing 30 mg of gliclazide were compressed using 8 mm diameter flat-faced punches. The upper punch pressure was 135 kg/cm^2.

Experimental Design D-optimal mixture experimental design was used to statistically optimize the formulation and evaluation of the effects of the formulation ingredients on the dissolution rate. The Design-Expert software (version 7.0, Stat-Ease Inc., Minneapolis, USA) selected the D-optimal design points in the experimental domain for the proposed model from a set of candidate points as a base design. Fourteen model formulations including 6 estimate formulations, 4 estimate lack of fit formulation and 4 replicates formulations were randomly arranged by Design-Expert software.

D-optimal mixture design provides an empirical mathematical model to describe the effect of formulation ingredients on the dissolution of matrix formulations. The models are given as follows:

Linear model:

$$Y = b_1X_1 + b_2X_2 + b_3X_3$$

Quadratic model:

$$Y = b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3$$

Special cubic model:

$$Y = b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3$$

Where Y is the measured response, b_1–b_{123} are the coefficients of the respective variables and their interaction terms. Factor evaluated in this study were the content of HPMC (X_1), lactose (X_2) and sodium alginate (X_3). The total amount of the varying ingredients (HPMC, sodium alginate and lactose) was maintained at 100 mg. The dependent and independent variables selected are shown in Table 1, which were selected based on the results of preliminary experimentation. The concentration range of ingredients used to prepare the 14 formulations and the respective observed responses are given in Table 2.

Tablet Assay and Physical Evaluation The tablets were assayed for drug content using methanol as the extracting solvent, and the samples were analyzed spectrophotometrically at 226 nm (Shimadzu

Table 1. Independent and Dependent Variables of the D-optimal Mixture Design[a]

Formulation variables	Levels	
	Low	High
X_1=amount of HPMC (mg)	20	40
X_2=amount of lactose (mg)	40	65
X_3=amount of alginate (mg)	5	25
Response variables	Constraints	
$Y_{3\,h}$=percent dissolved in 3 h	$20\% \leqslant Y_{3\,h} \leqslant 30\%$	
$Y_{6\,h}$=percent dissolved in 6 h	$45\% \leqslant Y_{6\,h} \leqslant 55\%$	
$Y_{9\,h}$=percent dissolved in 9 h	$70\% \leqslant Y_{9\,h} \leqslant 80\%$	
$Y_{12\,h}$=percent dissolved in 12 h	$95\% \leqslant Y_{12\,h} \leqslant 100\%$	

[a] The amount of gliclazide was fixed at 30 mg. The amount of total excipients was fixed at 100 mg ($X_1+X_2+X_3=100$).

Table 2. The Composition, Responses and Drug Release Mechanism of Model Formulations of Gliclazide Extended-release Tablets[a]

Run	X_1 (mg)	X_2 (mg)	X_3 (mg)	$Y_{3\,h}$	$Y_{6\,h}$	$Y_{9\,h}$	$Y_{12\,h}$	n	k	r
1	20.00	65.00	15.00	33.16	73.27	94.33	100.00	0.77	16.50	0.9746
2	40.00	40.00	20.00	18.35	45.84	72.01	99.37	1.20	5.25	0.9983
3	30.83	53.33	15.83	23.17	53.28	80.55	98.56	1.01	8.47	0.9950
4	40.00	55.00	5.00	20.68	46.00	65.40	80.28	0.93	8.29	0.9946
5	20.00	55.00	25.00	30.35	71.81	97.34	100.00	0.80	15.58	0.9685
6	30.00	65.00	5.00	27.05	59.42	80.42	97.57	0.87	11.59	0.9925
7	30.00	45.00	25.00	22.27	56.80	93.51	100.00	1.02	8.92	0.9826
8	40.00	47.50	12.50	19.53	49.21	74.47	93.26	1.06	7.03	0.9945
9	25.42	59.17	15.42	28.74	62.88	92.68	100.00	0.87	12.62	0.9841
10	34.17	46.67	19.17	20.69	49.22	84.09	99.13	1.13	6.52	0.9922
11	30.00	65.00	5.00	24.63	55.31	78.93	95.65	0.95	9.51	0.9928
12	20.00	55.00	25.00	32.06	70.56	96.76	100.00	0.80	15.48	0.9681
13	40.00	40.00	20.00	18.34	46.02	68.13	98.70	1.19	5.26	0.9978
14	40.00	55.00	5.00	19.92	45.17	67.66	83.79	1.00	7.20	0.9948

[a] X_1: HPMC K 15M, X_2: lactose, X_3: sodium alginate. Y_i: responses, the drug release percent at 3 h ($Y_{3\,h}$), 6 h ($Y_{6\,h}$), 9 h ($Y_{9\,h}$) and 12 h ($Y_{12\,h}$). Release mechanism fitted by power model ($M_t/M_\infty=kt^n$), r, k and n are correlation coefficient, release rate and release exponent, respectively.

2450 UV-VIS Spectrophotometer, Japan). Tablets were also evaluated for the hardness ($n=6$) (YPJ-2000 A hardness tester, China), friability ($n=6$) (CJY-300B friability tester, 100 rpm), weight variation ($n=20$) and thickness ($n=10$) (Shanhe digital vernier caliper, China).

***In Vitro* Release Kinetics** Dissolution studies were carried out using the USP XXVIII, basket apparatus (ZRS-8G dissolution tester, Tianjin, China) at 37℃±0.5℃ and 50 rpm using 0.1 N HCl (2 h) and phosphate buffered solution, pH 7.4 (PBS) (10 h), as the dissolution media. Dissolution studies were carried out in triplicate, maintaining the sink conditions for all the formulations. A 5 ml aliquot of sample was withdrawn hourly for 12 h, filtered and assayed spectrophotometrically at 226 nm (Shimadzu 2450 UV-VIS Spectrophotometer, Japan). At least 6 tablets of each formulation were determined. The mean and SD of dissolved percent were calculated. The cumulative percentage of drug release was calculated for the formulations using MS-Excel software after correcting the values for the drug loss occurred during sampling. The drug release data were curve fitted using Origin v7.0 Software to study the possible mechanism of drug release from hydrophilic swollen matrices.

The drug release from HPMC matrix tablets was fitted to the following power model in order to study the possible release mechanism.

$$M_t/M_\infty=kt^n$$

Where, M_t is the amount of drug released at time t, M_∞ is the amount of drug released after infinite time, M_t/M_∞ is the fractional drug release percentage at

time t, k is a constant incorporating the structural and geometric characteristics of the matrix tablets, and n is the release exponent indicative of the drug release mechanism. For the particular case of cylindrical tablets, $n \leq 0.45$ corresponds to a Fickian diffusion release (case I diffusion), $0.45 < n < 0.89$ to an anomalous (non-Fickian) transport, $n = 0.89$ to a zero-order release kinetics (case II transport), and $n > 0.89$ to a super case II transport.[17–19]

Optimization Data Analysis and Optimization-model Validation The released drug percent at 3, 6, 9 and 12 h (responses) of all model formulations were treated by Design-Expert software. Suitable models for mixture designs consisting of three components include linear, quadratic and special cubic models. The best fitting mathematical model was selected based on the comparisons of several statistical parameters including the standard deviation (SD), the multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2), predicted multiple correlation coefficient (predicted R^2) and the predicted residual sum of square (PRESS) proved by Design-Expert software. The models were evaluated in terms of statistically significant coefficients and R^2 values. Subsequently, the feasibility and grid searches were performed to locate the composition of optimum formulations.

Eight optimum checkpoints were selected based on the criteria from optimum formulation described earlier by intensive grid search, performed over the entire experimental domain, to validate the chosen experimental design and polynomial equations. The formulations corresponding to these checkpoints were prepared and evaluated for various response properties. Subsequently, the resultant experimental data of response properties were quantitatively compared with that of their predicted values to calculate the percentage prediction error.

RESULTS AND DISCUSSION

Drug Content and Physical Evaluation The assayed content of drug in various formulations varied between 97.40% and 99.66% (average 98.53%). Tablet weights varied between 128.23 and 130.79 mg (average 129.51 mg), hardness between 3.3 and 4.1 kg/cm^2 (average 3.7 kg/cm^2), thickness between 2.12 and 2.20 mm and friability ranged from 0.27% and 0.53% (average 0.40%). Thus all the physical parameters of the compressed matrices were found to be practically within controls.

***In Vitro* Release Kinetics** The dissolution profiles of all model formulations required by the mixture experimental design are shown in Fig. 1. The responses of these formulations are summarized in Table 2. The wide variation of responses indicated that the factor combinations resulted in different drug release rates. The drug release rate and burst effect decreased with the increase in the tablet content of HPMC. It was also noted that the drug released at later stage was incomplete, while the added amount of HPMC was at high level. Incorporated lactose into the HPMC matrix could increase the drug release rate. Sodium alginate can swell in acidic solution but

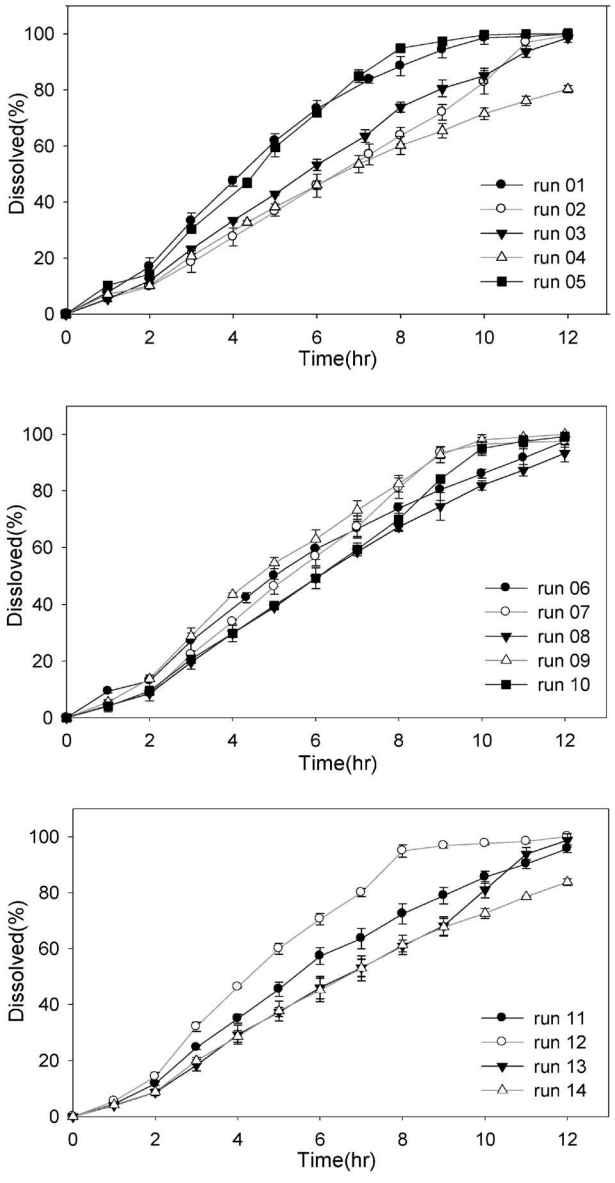

Fig. 1. Dissolution Profiles of All Model Formulations

does not dissolve, and is soluble in alkali solution, so it was chosen as a copolymer to modify the dissolution pattern. It was found that the drug release rate decreased in pH 1.2 medium and increased in pH 7.4 medium as the content of sodium alginate increased.

The 12-hourly cumulative percentages of drug release were treated according to the power model in order to know the mechanism of drug release from the trial formulations. In our experiments the *in vitro* release profiles of drug from all the formulations could be best expressed by the power model, the correlation coefficients (r) were above 0.9681 as shown in Table 2. The values of exponent constants (n) were from 0.77 to 1.20 indicting that the mechanism of drug release from matrix tablets was from non-Fickian transport to zero-order release kinetics and super Case II transport. This is further supported by the fact that the combinations of polymer swelling, drug dissolution and matrix erosion determine the drug release from matrices. Water-soluble drugs are released primarily by diffusion of dissolved drug molecules across the hydrated gel layer, while poorly soluble drugs are primarily released by polymer erosion mechanism.[20)]

Fitting of Data to the Model The primary objective of this study was to develop a hydrophilic matrix with the zero-order constant release. The RSM utilizing polynomial equation and systemic formulations design such as D-optimal mixture experimental design were applied in this study. The optimal extended-release matrix tablets must have a minimal burst effect and complete drug release in a 12-hour time period. Therefore, the ranges of the responses, Y_{3h}–Y_{12h} (drug release percent in 3, 6, 9 and 12 h, respectively) were 20–30, 45–55, 70–80 and 95–100%, respectively. According to the response requirement and the preliminary experimental, the levels of excipients were set at HPMC (X_1) from 20 to 40, lactose (X_2) from 40 to 65, and sodium alginate (X_3) from 5 to 25. All the responses observed for 14 formulations were simultaneously fitted to linear, quadratic and special cubic model by Design-Expert software. The best fitting mathematical model was selected based on the comparisons of several statistical parameters including R^2 and S.D. proved in Table 3. Responses $Y_{3\,h}$–$Y_{12\,h}$ were found to follow quadratic, special cubic, special cubic and quadratic model, respectively. Only statistically significant ($p<0.05$)

Table 3. Summary of Results of Regression Analysis for Responses $Y_{3\,h}$, $Y_{6\,h}$, $Y_{9\,h}$ and $Y_{12\,h}$

Models	R^2	Adjusted R^2	Predicted R^2	S.D.	PRESS	Remarks
Response ($Y_{3\,h}$)						
Linear model	0.9555	0.9475	0.9272	1.18	25.26	—
Quadratic model	0.9837	0.9735	0.9484	0.84	17.89	Suggested
Special Cubic model	0.9838	0.9699	0.9437	0.90	19.53	—
Response ($Y_{6\,h}$)						
Linear model	0.9544	0.9461	0.9324	2.36	90.52	—
Quadratic model	0.9798	0.9671	0.9426	1.84	76.89	—
Special Cubic model	0.9897	0.9808	0.9582	1.41	55.95	Suggested
Response ($Y_{9\,h}$)						
Linear model	0.9207	0.9063	0.8739	3.50	214.39	—
Quadratic model	0.9466	0.9132	0.8260	3.37	295.74	—
Special Cubic model	0.9735	0.9507	0.9036	2.54	163.92	Suggested
Response ($Y_{12\,h}$)						
Linear model	0.5878	0.5128	0.2830	4.42	373.48	—
Quadratic model	0.9371	0.8979	0.7448	2.02	132.92	Suggested
Special Cubic model	0.9374	0.8838	0.4060	2.16	309.44	—

Regression equations of the fitted model[a]

$Y_{3\,h}=0.725X_1+0.691X_2+0.378X_3-0.021X_1X_2-0.016X_1X_3$

$Y_{6\,h}=6.784X_1+3.356X_2+12.574X_3-0.180X_1X_2-0.455X_1X_3-0.252X_2X_3-0.007X_1X_2X_3$

$Y_{9\,h}=7.695X_1+4.119X_2+21.373X_3-0.210X_1X_2-0.742X_1X_3-0.438X_2X_3+0.014X_1X_2X_3$

$Y_{12\,h}=-0.135X_1+1.394X_2-0.443X_3+0.072X_1X_3$

[a] Only the terms with statistical significance are included.

coefficients were included in the equations.

In the present study, HPMC (X_1), lactose (X_2) and sodium alginate (X_3) had significant effects on gliclazide release rate. Sodium alginate was known to form a physical gel by hydrogen bonding at low pH, swelling of alginates scarcely occurred in the early stage of dissolution. The effect of combination of HPMC and sodium alginate (X_1X_3) used as retardant had a negative effect on the drug release from matrix tablets. Lactose was the water-soluble material, which facilitated formation of channels within the polymeric matrix. Channel formation enhanced water penetration and drug release by diffusing through the insoluble matrix, which explained the positive main effect of lactose at the early stage. Therefore, the interaction effects (X_2X_3 and $X_1X_2X_3$) were not significant on $Y_{3\,h}$, and response $Y_{3\,h}$ followed quadratic model. Under neutral conditions, sodium alginate was more hydrophilic than HPMC, which rapidly hydrated and swelled to form a gel layer over the tablet surface. Lactose could be regarded as filler that could modify the internal geometry of polymeric matrices during dissolution, resulted in polymer chain relaxation with volume expansion, and enhanced the swelling and erosion rate of HPMC and sodium alginate. There were the complicated interaction effect of factors (X_1, X_2 and X_3) on the responses ($Y_{6\,h}$ and $Y_{9\,h}$), and the drug release mainly depended on the swelling and erosion processes during the intermediate stage. Therefore, responses $Y_{6\,h}$ and $Y_{9\,h}$ followed special cubic model. Swelling process of HPMC and sodium alginate had basically completed during the final stage of dissolution, erosion process of polymers played the leading role in the drug release. Sodium alginate dissolved faster than HPMC, which could speed up the dissolution of HPMC. Moreover, the interaction effects of lactose and polymers (X_2X_3, X_1X_2 and $X_1X_2X_3$) were not significant. Consequently, response $Y_{12\,h}$ followed quadratic model. As shown in Table 3, the value of positive coefficient of X_2 was larger, which showed that the effect of lactose was the increasing influence factor on the drug release from extended-release matrix tablets. The results showed that sodium alginate (X_3) could increase the release rate during the final stage. The coefficient of X_1X_3 indicated that combination of HPMC and alginate had the pronounced retardant effect on the drug release in the whole stage of dissolution.

Standardized Main Effects and Reliability of the Models Standardized Main Effects (SME), presented in Table 4, were calculated by dividing the main effects with the standard error of the main effects.[21] Only statistically significant ($p<0.05$) values are given. The larger SME value of X_2 suggested the paramount importance of lactose on drug release. R^2-value denotes the percentage of variability in responses that are fitted to the models. In the present study, the high R^2-value represents the reliability of the design. Additionally, the p-values of lack of fit were greater than 0.05, which further strengthened the reliability of the models.

Optimization and Validation of Response Surface Methodology The triangular-dimensional contour plots were constructed based on the model polynomial functions using Design-Expert software in Fig. 2(A)-(D). These plots are very useful to illustrate the interaction effects of the factors on the responses. These four responses were then combined to determine an all over optimum region. The overlay plot provided by the Design-Expert software showed that an acceptable region met the requirement of these responses in Fig. 2(E).

By intensive grid search performed over the whole experimental region, eight optimum checkpoint formulations were selected to validate the chosen experimental domain and polynomial equations. For all of the eight checkpoint formulations, the results of the physical evaluation and tablet assay were found to be within limits. Table 5 shows the composition of optimum checkpoint formulations, their predicted and experimental values for all the response variables, and the percentage error in prognosis. Percentage

Table 4. Standardized Main Effects of the Factors on the Responses[a]

	Standardized main effects (SME)			
	$Y_{3\,h}$	$Y_{6\,h}$	$Y_{9\,h}$	$Y_{12\,h}$
X_1	23.94	3.25	7.18	46.49
X_2	25.18	4.41	10.30	71.34
X_3	23.22	2.85	2.80	34.26
$X_1 * X_2$	3.68	3.29	3.56	—
$X_1 * X_3$	3.10	2.78	3.25	7.30
$X_2 * X_3$	—	2.63	2.79	—
$X_1 * X_2 * X_3$	—	2.59	2.66	—
R^2	98.34%	98.97%	96.57%	93.48%
p-Value of lack of fit	0.9534	0.6528	0.1085	0.2489

[a] Only the terms with statistical significance are included.

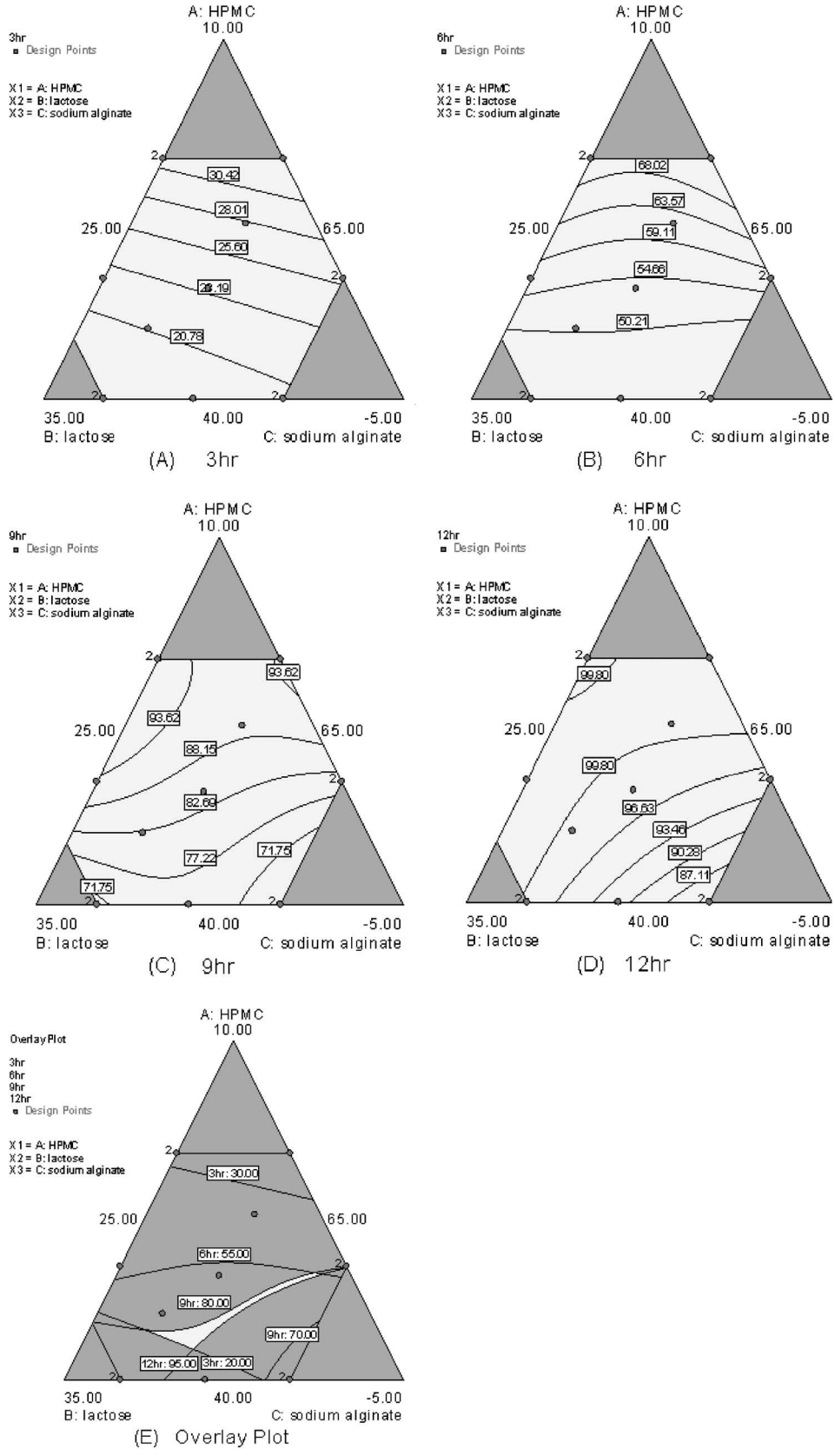

Fig. 2. The Triangular-dimensional Contour Diagrams

The effect of HPMC (X_1), lactose (X_2) and sodium alginate (X_3) on the release of gliclazide from matrix tablets are illustrated. (A) 3 h drug release percent, (B) 6 h drug release percent, (C) 9 h drug release percent, (D) 12 h drug release percent, (E) overlay plot.

Table 5. Composition of Optimum Checkpoint Formulations, the Predicted and Experimental Values of Response Variables and Percentage Prediction Error

Optimized formulation composition ($X_1 : X_2 : X_3$)	Response variable	Experimental value (%)	Predicted value (%)	Percentage prediction error (%)
35.02 : 49.99 : 14.99	$Y_{3\,h}$	22.27	21.06	1.21
	$Y_{6\,h}$	50.81	49.73	1.08
	$Y_{9\,h}$	77.43	79.91	−2.48
	$Y_{12\,h}$	97.77	96.08	1.69
34.66 : 51.79 : 13.54	$Y_{3\,h}$	20.43	21.47	−1.04
	$Y_{6\,h}$	48.34	49.86	−1.52
	$Y_{9\,h}$	78.58	79.38	−0.80
	$Y_{12\,h}$	98.14	95.29	2.85
35.32 : 49.45 : 15.23	$Y_{3\,h}$	20.89	20.87	0.02
	$Y_{6\,h}$	50.38	49.56	0.82
	$Y_{9\,h}$	79.69	79.72	−0.03
	$Y_{12\,h}$	96.23	96.11	0.12
36.09 : 47.45 : 16.46	$Y_{3\,h}$	21.21	20.31	0.90
	$Y_{6\,h}$	48.56	49.12	−0.56
	$Y_{9\,h}$	81.60	79.27	2.33
	$Y_{12\,h}$	97.63	96.71	0.92
35.47 : 48.15 : 16.39	$Y_{3\,h}$	21.89	20.62	1.27
	$Y_{6\,h}$	51.22	49.49	1.73
	$Y_{9\,h}$	76.20	79.99	−3.79
	$Y_{12\,h}$	98.00	96.88	1.12
35.01 : 50.67 : 14.32	$Y_{3\,h}$	21.55	21.17	0.38
	$Y_{6\,h}$	50.79	49.70	1.09
	$Y_{9\,h}$	80.75	79.56	1.19
	$Y_{12\,h}$	96.37	95.63	0.74
34.52 : 52.46 : 13.02	$Y_{3\,h}$	22.12	21.63	0.49
	$Y_{6\,h}$	53.35	49.91	3.44
	$Y_{9\,h}$	77.56	79.13	−1.57
	$Y_{12\,h}$	97.60	95.02	2.58
36.59 : 47.62 : 15.79	$Y_{3\,h}$	21.11	20.18	0.93
	$Y_{6\,h}$	51.99	48.90	3.09
	$Y_{9\,h}$	76.92	78.58	−1.66
	$Y_{12\,h}$	97.65	96.01	1.64

prediction error is helpful in establishing the validity of generated equations and describing the domain of applicability of RSM model. For validation of RSM results, the experimental values of the responses were compared with the anticipated values and the prediction error was found to vary between −3.79% and + 3.44%. Thus the low magnitudes of error in the present investigation prove the high prognostic ability of the RSM.

In this study, the ideal zero-order release profile was treated as the reference curve and was used to calculate its similarity (f_2) to the dissolution profiles of the eight optimum checkpoint formulations. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent dissolution between the test and reference curves.[22] The similarity factor was calculated using the following equation.

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

Where n is the number of time points, R_t and T_t are the percentage dissolved at time t for the reference and test products, respectively. W_t (an optional weight factor) is applied to the value or values that are deemed more important than others. It was taken as one, since all the dissolution time points were treated equally. Generally, f_2 values greater than 50 (50–

100) ensure similarity or equivalence of the two curves. Eight optimum checkpoint formulations had an f_2 value that ranged between 71.10 and 82.20. The values of f_2 indicated the equivalence to the release profile of the optimum formulation and zero-order release profile. To further illustrate the mechanism of drug release from the optimized formulation, the exponent constants (n) was estimated from the power model. The estimated n mean value of the optimized formulation was found to be 0.92, which indicates zero-order release kinetics and corroborates the measured f_2 values.

CONCLUSION

Hydrophilic matrix tablets of gliclazide with HPMC K 15M, lactose and sodium alginate were prepared and optimized using D-optimal mixture experimental design and multiple response optimizations. The quantitative effect of these factors on the release rate could be predicted by using polynomial equations. The model was found to be satisfactory for describing the relationships between formulation variables and individual response variables. The experimental values of the response variables obtained from the optimized formulation were very close to the predicted values. The results of optimization-model validation demonstrated the reliability of the assumed model in the preparation of extended-release matrix tablets having zero-order drug release. Thus, D-optimal mixture experimental design and optimization technique can be successfully used in the development of gliclazide extended-release tablets with the zero-order drug release properties.

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