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Original Article

FORMULATION AND CHARACTERIZATION OF SUSTAINED RELEASE MATRIX TABLETS OF IVABRADINE USING 3^2 FULL FACTORIAL DESIGN

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ABSTRACT

Objective: Ivabradine (IB) is anti-Ischemic drug and used for the symptomatic management of stable angina pectoris. IB acts by reducing the heart rate in a mechanism different from beta blockers and calcium channel blockers, two commonly prescribed anti-anginal drugs. IB has a short biological half-life and the dose of 5/7.5 mg twice a day. In this present study, an attempt has been made to prepare sustained release tablet of IB to achieve the desired drug release.

Methods: The sustained release polymers, hydroxypropyl methylcellulose K100M (HPMC K100M), guar gum (GG) and xanthan gum (XG) were taken for the preliminary trail from which guar gum and xanthan gum had shown better drug release. Initially, drug-excipients compatibility studies were carried out by using Fourier transformed infrared spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) which showed no interaction between drug and excipients. Tablets were prepared by wet granulation technique and evaluated for pre-compression and post-compression parameters.

Results: 3^2 full factorial design was applied to achieve controlled drug release up to 24 h. The concentration of GG (X_1) and XG (X_2) were selected as independent variables and the % CDR at 2 h. (Y_1) and 18 h. (Y_2) were taken as dependent variables. *In vitro* drug release study revealed that as the amount of polymers increased, % CDR decreased.

Conclusion: Contour as well as response surface plots were constructed to show the effect of X_1 and X_2 on % CDR and predicted at the concentration of independent variables X_1 (10 mg) and X_2 (10 mg) for a maximized response. The optimized batch (O1) was kept for stability study at 40±2 °C/75±5 %RH for a period of 6mo according to ICH guidelines and found to be stable.

Keywords: Sustained release matrix tablet, IB, Guar gum, Xanthan gum, 3^2 full factorial design

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INTRODUCTION

To formulate an API in an extended drug delivery system is related to its pharmacokinetics parameters. An appropriate formulation can make the absorption, distribution, metabolism and elimination (ADME) profile of a drug much more favorable. It is designed to maintain constant levels of a drug in the patient's bloodstream by releasing the drug over an extended period. Maintaining constant blood levels of the drug in the bloodstream increases the therapeutic effectiveness of the drug. The sustained release drug delivery system provides the sustained and continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that targets the delivery of a drug to a specific region within the GI tract for either a local or systemic effect. The change of the ADME can have a profound impact on many aspects of the clinical use of the drug from patient compliance and convenience to its very efficacy, tolerance and safety parameters [1].

IB is If channel antagonist used in the treatment of angina pectoris which is an underlying cause of heart attack when beta blockers are not responding. IB is rapidly and almost completely absorbed after oral administration with a peak plasma level reached in about 1 h under fasting condition. It has a plasma half-life about (2 h) and bioavailability is 40% orally, due to the first-pass effect in the gut and liver. The short biological half-life and dosing frequency of IB make it an ideal candidate for sustained release tablet [2].

The objective of the present study was to prepare and evaluate IB sustained release tablet, in order to improve its reducing dose frequency, bioavailability and efficacy.

MATERIALS AND METHODS

IB was gifted from Torrent Pharmaceuticals, Ahmedabad. XG, lactose, GG, starch, magnesium stearate and talc were purchased from SD Fine Chemicals, Mumbai, India. All other chemicals and solvents used were of the pharmaceutical and analytical grade. Double distilled water was used throughout the study for experimental work.

Drug-excipient compatibility studies by DSC

The possibility of drug–excipient interaction was investigated by DSC. It allows the fast evaluation of possible incompatibilities because it shows changes in appearance, shift or disappearance of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction. The DSC thermograms of pure drug, a mixture of the drug with GG and XG, starch and lactose were recorded. The samples were separately sealed in aluminium cells and set in a DSC-60 instrument (Shimadzu Corporation, Tokyo, Japan). The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 20 °C/min over a temperature range of 50 to 300 °C [3-4].

3^2 full factorial design

A 3^2 full factorial design was employed to systematically study the joint influence of the effect of independent variable concentration of GG (X_1) and XG (X_2) on the dependent variable, i.e. % CDR at 2 h (Y_1) and % CDR at 18 h (Y_2) (table 1). In this design, 2 factors were evaluated, each at 3 levels, and experimental trials are performed in all 9 possible combinations. A statistical model incorporating interactive and polynomial terms is used to evaluate the response. Polynomial equation generated by this design is as follows:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_1 to b_2 are the regression coefficients. The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms

(X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity.

The response values are subjected to MLRA (Multiple linear regression analysis) to find out the relationship between the factors used and response values obtained. After application of full factorial design and with the help of produced polynomial terms, amount of formulation variable was optimized [5-7].

Preparation of sustained-release tablets

The matrix tablets, with a theoretical weight of 200 mg, containing IB together with other excipients were prepared by wet granulation technique. IB and other excipients are weighed accurately, transferred in mortar and pestle and thoroughly mixed for 15 min. The powder mixture was granulated with 10%w/v starch paste. The wet mass was passed through 10# sieve and granules were dried at 50 °C for 30 min in a hot air oven. The dried granules were passed through a 20# sieve and lubricated with talc and magnesium stearate which was previously passed through an 80# sieve. Tablets were compressed using 6 mm punch on 10 stations rotary tablet punching machine (Karnavati Engineering).

The hardness of the tablets was maintained between 5.0 to 6.0 kg/cm^2. The detailed compositions of the prepared sustained release tablet formulations are given in table 2 [8].

Table 1: Selection of levels for independent variables and coding of variable

Levels	Coded value	Independent variables	
		Concentration of GG (mg) X_1	Concentration of XG (mg) X_2
Low	-1	10	10
Intermediate	0	20	20
High	+1	30	30

GG–guar gum, XG–xanthan gum

Table 2: Composition of factorial design batches

Ingredients (mg)	O1	O2	O3	O4	O5	O6	O7	O8	O9
IB	15	15	15	15	15	15	15	15	15
GG	10	20	30	10	20	30	10	20	30
XG	10	10	10	20	20	20	30	30	30
Lactose	160	150	140	150	140	130	140	130	120
MS	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2
Total weight (mg/tablet)	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

IB–ivabradine, GG–guar gum, XG–xanthan gum, MS–magnesium stearate

Evaluation parameters of sustained-release tablets

Pre-compression evaluations

Bulk density (BD)

Weigh accurately 10 g of powder, which was previously passed through a 20# sieve and transferred into 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in g/cm^3 by the following formula [9].

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Bulk Volume}}$$

Tapped density (TD)

Weigh accurately 10 g of powder, which was previously passed through a 20# sieve and transfer in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14±2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V_1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume (V_2) to the nearest graduated units. If the difference between the two volumes is less than 2%, then final the volume (V_2). Calculate the tapped density in g/cm^3 by the following formula [9].

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped Volume}}$$

Carr's index

Compressibility index is used as an important parameter to determine the flow behaviour of the granules. It is indirectly related to the relative flow property rate, cohesiveness and particle size. It is simple, fast and popular method for predicting flow characteristics. Carr's index can be represented by the equation [10]:

$$Carr's\ Index = \frac{tapped\ density - bulk\ density}{tapped\ density} X\ 100$$

Hausner's ratio

Hausner's ratio is used to predict the flowability of the granules. This method is similar to compressibility index. Hausner's ratio can be represented by an equation as shown below [10]:

$$Hausner's\ ratio = \frac{tapped\ density}{bulk\ density}$$

Angle of repose

The angle of repose of powder was determined by the funnel method. The accurately weight powder blend was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation [10].

$$\theta = \tan^{-1} h/r$$

Post-compression evaluations

Weight variation

Uniformity of weight as described in the United States Pharmacopeia (USP) was followed. Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight. The percentage deviation was calculated and checked for weight variation. Using this procedure weight variation range of all batches of formulations were determined and recorded [11].

$$Percentage\ Deviation = \frac{Individual\ Weight - Average\ Weight}{Individual\ Weight}$$

Thickness

The thickness of three tablets was measured using vernier callipers. The extent to which the thickness of each tablet deviated from±5% of the standard value was determined [11].

Hardness

The hardness of the tablet was determined by Monsanto hardness tester. Three tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded [11].

Friability

Friability of tablets was performed in a Roche friabilator. Five tablets were weighed together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and re-weighed [11].

$$F = \frac{Winitial - Wfinal}{Winitial} X\ 100$$

Drug content

The drug content was carried out by weighing ten tablets from each batch and calculated the average weight. Then the tablets were triturated to get a fine powder. From the resulting triturate, the powder was weighed accurately which was equivalent to the specified weight of IB and dissolved in 100 ml volumetric flask containing 100 ml of pH 6.8 phosphate buffer and volume was made up to 100 ml with phosphate buffer. The volumetric flask was shaken using a sonicator for 1 h and after suitable dilution with pH 6.8 phosphate buffer, the drug content was determined using UV-visible spectrophotometer at 277.60 nm [12].

***In vitro* drug release study**

The release of the prepared tablets was determined using U. S. P-type II paddle type dissolution rate test apparatus (TDT-06P, Electrolab) using 900 ml of pH 6.8 phosphate buffer as dissolution medium. The paddle was adjusted at 50 RPM and the temperature of 37±1 °C was maintained throughout the experiment. Withdrawn not less than 5 ml of the dissolution medium at 1, 2, 4, 8, 12, 18, 20, 24 h time interval up to 24 h and were replaced with the same volume of fresh dissolution media after each withdrawal. Filtered each sample through a membrane filter with a pore size of not more than 0.45 mm. The samples were analysed after appropriate dilution by UV spectrophotometer at λ max 277.60 nm [13-14].

Statistical analysis

Statistical analysis of the 3^2 factorial design batches was performed by MLRA using Microsoft excel. In this design 2 factors are evaluated, each at 3 levels, and experimental trials are performed at all 9 possible combinations. To evaluate the contribution of each factor with different levels to the response, the two-way analysis of variance (ANOVA) was performed using the design expert 10.0.6.0 (STAT–EASE) demo version software. To graphically demonstrate the influence of each factor on the response, the response surface plots, the normal plot of residual, two-dimensional counterplot, 3-D graph, and overlay plot, were generated using the design expert 10.0.6.0 (STAT–EASE) demo version software [3, 15-16].

Checkpoint analysis

A checkpoint analysis was performed to confirm the role of the derived polynomial equation and contour plots in predicting the responses. Values of independent variables were taken at 3 points and the theoretical values of % CDR at 2 h and %CDR at 18 h were calculated by substituting the values in the polynomial equation [3, 15-16].

Optimization of formulation

The computation for optimized formulation was carried using design expert 10.0.6.0 (STAT–EASE) software. The optimized formulation was obtained by applying constraints (goals) on the dependent (response) and independent variables (factors). The models were evaluated in terms of statistically significant coefficients and R2 values. Various feasibility and grid searches were conducted to find the optimum parameters. Various 3D response surface graphs were provided by the design expert software. The optimized formulation factors were evaluated for various response properties [3, 17-18].

Kinetics of drug release

In order to describe the kinetics of drug release from sustained release formulation, various mathematical equations have been proposed, namely zero order, first order, higuchi model and hixson–crowell cube root law. To authenticate the release model, dissolution data can further be analyzed by Korsmeyer Peppas equation. The criteria for the selection of most suitable model were the value of regression coefficient (R^2) nearer to 1, smallest values of Residual Sum of Squares (SSR) and Akaike Information Criteria (AIC) [3, 14].

Stability study

Stability studies of the optimized formulation were carried out to determine the effect of the presence of formulation additives on the stability of the drug and also to determine the physical stability of the formulation under accelerated storage conditions. The tablets were stored in an aluminium foil and subjected to elevated temperature and humidity conditions of 40±2 °C/75±5 % RH for a time period of six mo [3, 5].

RESULTS AND DISCUSSION

Drug excipients compatibility study by DSC

The DSC thermogram (fig. 1) of pure IB exhibited a sharp endothermic peak at 198.42 °C which corresponds to its melting and decomposition. Basically, IB endothermic peak was evident in all the thermograms of its physical mixtures with the mentioned excipients which might indicate compatibility. In conclusion, the observed DSC results ruled out the incidence of any incompatibility between IB and the investigated excipients.

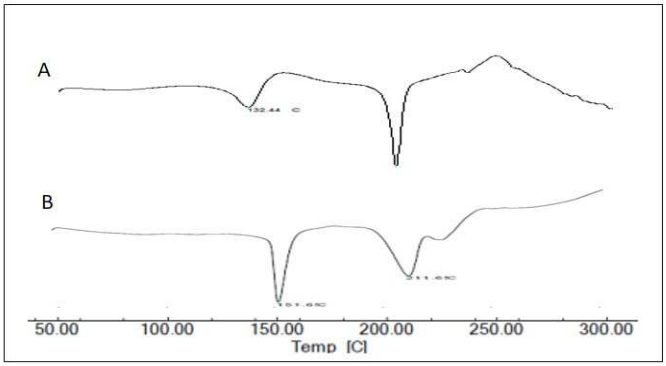

Fig. 1: DSC thermogram of (A) IB and (B) mixture of IB with all excipients

Evaluation parameters of full factorial design batches O1 to O9

Pre-compression evaluations

All the precompression parameters were evaluated i.e. bulk density, tapped density, carr's index, hausner's ratio, the angle of repose. Bulk density ranged from 0.513±0.31 to 0.654±0.45 g/cm^3, tapped density ranged from 0.602±0.28 to 0.773±0.42 g/cm^3, carr's index ranged from 12.32±1.2 % to 15.39±1.25 %, hausner's ratio ranged from 1.14±0.005 to 1.18±0.07 whereas angle of repose ranged from 23.25±2.28 to 27.30±1.25.

All these results as shown in table 3 indicated that, the powder blend possesses good to passable flowability and compressibility properties.

Table 3: Pre-compression evaluations of batches O1 to O9

Batch Code	Bulk density (g/cm^3)*	Tapped density (g/cm^3)*	Compressibility index (%)*	Hausner's ratio*	Angle of repose (Θ)*
O1	0.513±0.31	0.602±0.28	14.78±1.34	1.17±0.071	23.25±2.28
O2	0.597±0.39	0.696±0.31	14.22±1.31	1.16±0.025	26.15±1.43
O3	0.548±0.32	0.639±0.28	14.24±1.18	1.16±0.025	25.26±1.31
O4	0.603±0.44	0.708±0. 38	14.83±1. 85	1.17±0.011	24.15±2.27
O5	0.559±0.53	0.654±0.49	14.52±1.27	1.16±0.05	27.30±1.25
O6	0.654±0.45	0.773±0.42	15.39±1.25	1.18±0.07	25.32±1.25
O7	0.612±0.32	0.698±0.28	12.32±1.2	1.14±0.015	25.30±2.15
O8	0.632±0.25	0.726±0.21	12.94±1.26	1.14±0.005	24.30±1.15
O9	0.579±0.41	0.668±0. 36	13.32±1.27	1.15±0.035	24.64±2.52

*n = 3. (mean±SD)

Table 4: Post-compression evaluation of batches O9 to O17

Batch code	Weight variation*	Thickness (mm)#	Hardness (kg/cm^2)#	% Friability $	% Drug content @
O1	Pass	3.41±0.095	5.94±0.036	0.41±0.017	99.26±1.32
O2	Pass	3.42±0.02	5.69±0.015	0.47±0.02	98.60±1.87
O3	Pass	3.47±0.015	5.11±0.023	0.57±0.45	99.00±0.71
O4	Pass	3.53±0.32	5.73±0.208	0.61±0.45	99.50±1.47
O5	Pass	3.30±0.05	5.81±0.098	0.50±0.015	99.33±1.52
O6	Pass	3.28±0.075	5.83±0.055	0.53±0.03	98.13±2.23
O7	Pass	3.45±0.047	5.61±0.0 58	0.43±0.15	99.45±1.18
O8	Pass	3.60±0.041	5.48±0.03	0.63±0.04	99.86±1.52
O9	Pass	3.20±0.037	5.48±0.018	0.61±0.03	99.40±0.36

*n = 20, # = 3, $ = 5 and @ = 10. (mean±SD)

Post-compression evaluations

The tablets from all the batches were evaluated for various physical parameters before proceeding further and results are listed in table 4.

Weight variation

All the formulated batches passed the weight variation test as the % weight variation was within the pharmacopoeia limits of ±5% of the weight.

Thickness

The thickness of all tablets was in the range between 3.20±0.037 mm to 3.60±0.041 mm.

Hardness and friability

The hardness of tablets was in the range between 5.11±0.023 to 5.94±0.036 kg/cm^2. Friability was in the range between 0.41±0.017 to 0.63±0.4 %. Friability values were less than 1 % in all cases which shows good mechanical strength at the time of handling and transports.

Drug content

Drug content of all tablets was found in the range between 98.13±2.23 to 99.86±1.52 %. This ensured the uniformity of the drug content in the tablets.

***In vitro* drug release study**

All the formulated sustained release tablets of IB (Batches O1 to O9) were developed using different concentrations of GG and XG (10, 20 and 30 mg) each and subjected to *in vitro* drug release study using pH 6.8 phosphate buffer for 24 h. Results of % CDR values are shown in fig. 2. From the fig., it was observed that as the concentration of both the polymers GG and XG increases, the amount of drug release decreases. The results also revealed that batch O1 containing less concentration of GG and XG has shown better drug release (99.82 %). Therefore, it was considered as optimized batch among all formulated batches.

Statistical analysis

Preliminary investigations of the process parameters revealed that factors concentration of GG (X_1) and concentration of XG (X_2) highly influenced the rate of *in vitro* dissolution and, hence, were used for further systematic studies.

Effect of polymers on % CDR at 2 h

Mathematical relationships generated for the studied response variables concentration of GG (X_1) and concentration of XG (X_2) for %CDR at 2 h (Y_1) is as follows:

$$Y_1 = 30.16 - 3.98X_1 - 1.42X_2 + 0.27X_1X_2 - 2.40X_1^2 + 0.14X_2^2,\ R^2 = 0.9920$$

Higher values of correlation coefficients for %CDR at 2 h indicate a good fit. The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries, i.e. positive or negative. MLRA revealed that coefficient b_1 and b_2 is negative. This indicates that on decreasing X_1 and X_2, % CDR increases.

The lower level of X_1 and of X_2 was found to be favorable conditions for obtaining better dissolution. Table 5 shows the results of ANOVA, which was performed to identify insignificant factors. The coefficients b_1, b_2, and b_1^2 were found to be significant at P is less than 0.05 and thus, were retained in the reduced model equation [18].

$$Y_1 = 30.16 - 3.98X_1 - 1.42X_2 - 2.40\ X_1^2,\ R^2 = 0.9893$$

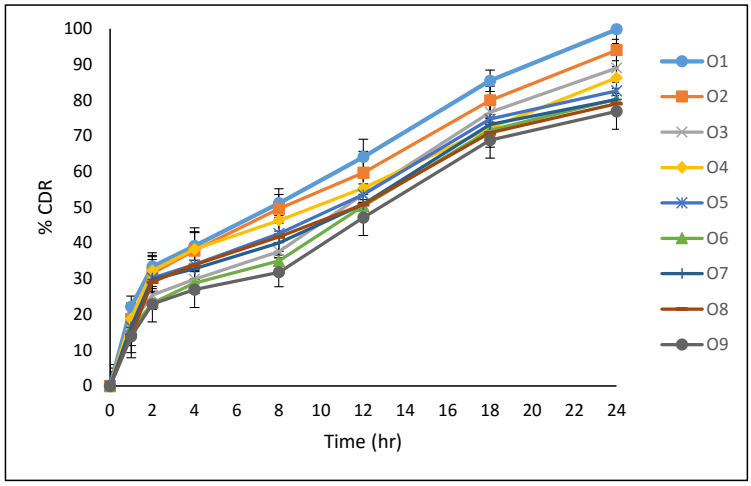

Fig. 2: % cumulative drug release study of batches O1 to O9 (n = 6)

Table 5: ANOVA response surface quadratic model for Y_1

Source	SS	Df	MS	F Value	p-value prob>F
Model	119.14	5	23.83	74.59	0.0024
X_1	95.20	1	95.20	298.02	0.0004
X_2	12.13	1	12.13	37.96	0.0086
X_1X_2	0.29	1	0.29	0.90	0.4137
X_1^2	11.49	1	11.49	35.96	0.0093
X_2^2	0.038	1	0.038	0.12	0.7521
Residual	0.96	3	0.32	-	-
Cor Total	120.10	8	-	-	-

*ANOVA-analysis of variance, Df-degrees of freedom, SS-sum of squares, MS-mean of squares, F-Fischer's ratio.

The change in % CDR at 2 h as a function of X_1 and X_2 is depicted in the form of response surface plot {fig. 3(a), 3(b)} based on full factorial design.

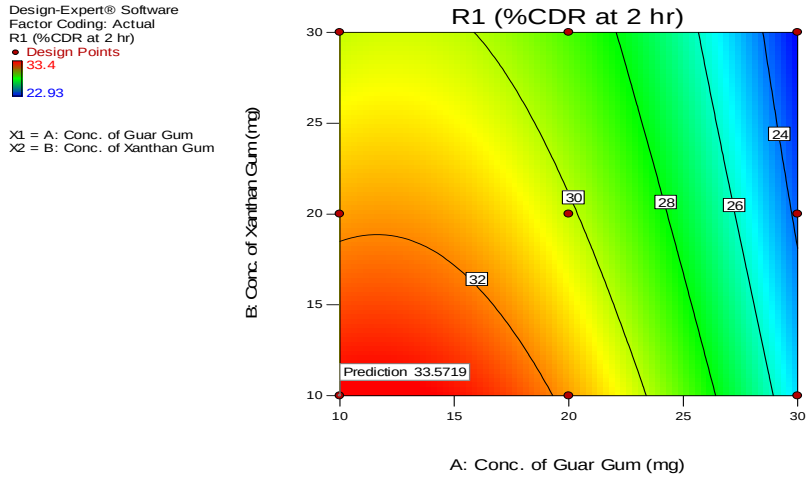

Fig. 3(a): Two-dimensional contour curve of GG (X_1) and XG (X_2) for %CDR at 2 h (Y_1)

Effect of polymers on % CDR at 18 h

Mathematical relationships generated for the studied response variables concentration of GG (X_1) and concentration of XG (X_2) for %CDR at 18 h (Y_2) is as follows:

$$Y_2 = 74.69 - 3.97X_1 - 4.53X_2 + 0.61X_1X_2 + 1.17X_1^2 + 0.66X_2^2,\ R^2 = 0.9983$$

Higher values of correlation coefficients for %CDR at 18 h indicate a good fit. The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries, i.e. positive or negative. MLRA revealed that coefficient b_1 and b_2 is negative. This indicates that on decreasing X_1 and X_2, % CDR increases. The lower level of X_1 and of X_2 was found to be favorable conditions for obtaining better dissolution. Table 6 shows the results of ANOVA, which was performed to identify insignificant factors. The coefficients b_1, b_2, b_{12}, and b_1^2 were found to be significant at P is less than 0.05 and thus, were retained in the reduced model equation [18].

$$Y_2 = 75.12 - 3.97X_1 - 4.53X_2 + 0.61X_1X_2 + 1.165X_1^2,\ R^2 = 0.994$$

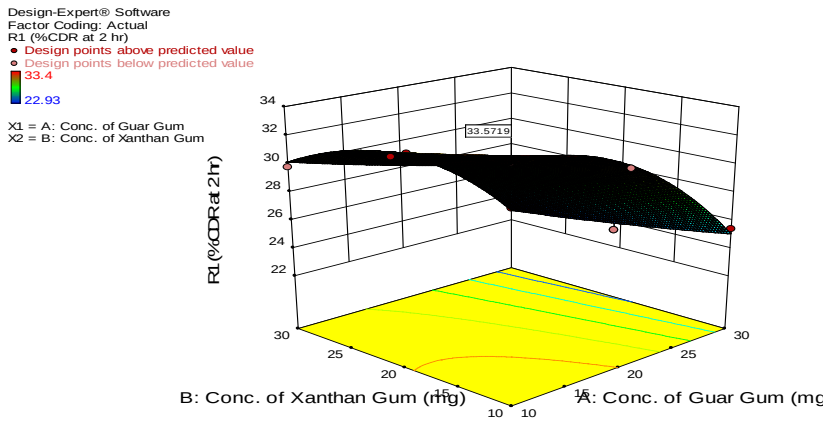

Fig. 3(b): 3-D graph showing the effect of GG (X_1) and XG (X_2) for % CDR at 2 h (Y_1)

Table 6: ANOVA response surface quadratic model for Y_2

Source	SS	Df	MS	F Value	p-value prob>F
Model	223.17	5	44.63	371.43	0.0002
X_1	94.80	1	94.80	788.92	<0.0001
X_2	123.31	1	123.31	1026.11	<0.0001
X_1X_2	1.48	1	1.48	12.28	0.0393
X_1^2	2.71	1	2.71	22.59	0.0177
X_2^2	0.87	1	0.87	7.25	0.0743
Residual	0.36	3	0.12	-	-
Cor Total	223.53	8	-	-	-

SS-sum of squares, Df-degrees of freedom, MS-mean of squares, F-Fischer's ratio.

The change in % CDR at 18 h as a function of X_1 and X_2 is depicted in the form of response surface plot {fig. 4(a), 4(b)} based on full factorial design.

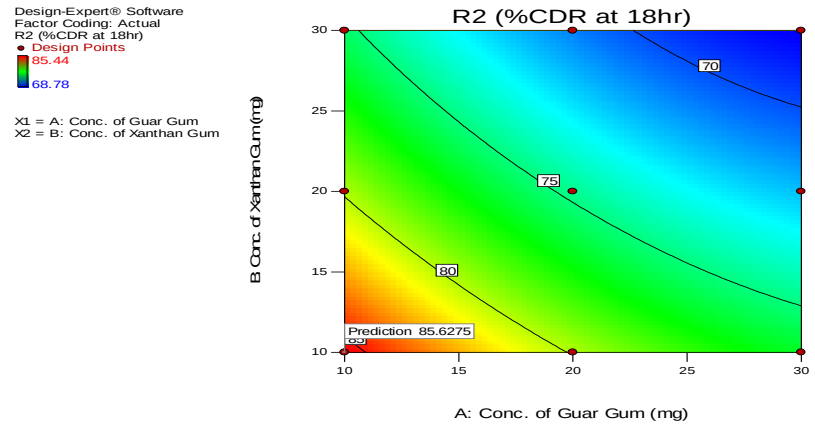

Fig. 4(a): Two-dimensional contour curve of GG (X_1) and XG (X_2) for %CDR at 18 h (Y_2)

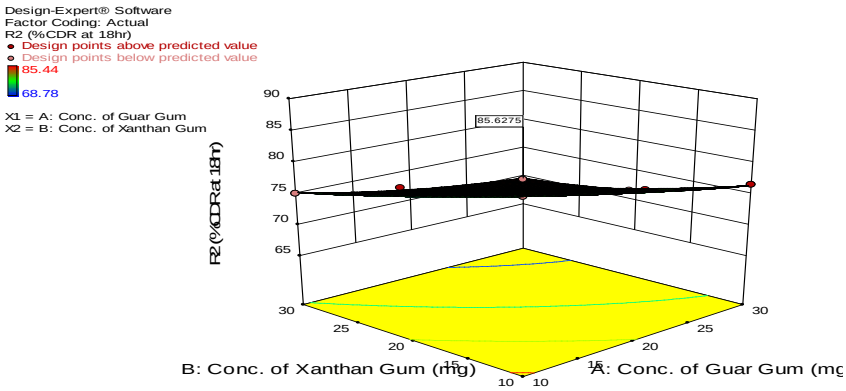

Fig. 4(b): 3-D graph showing the effect of GG (X_1) and XG (X_2) for % CDR at 18 h (Y_2)

Checkpoint analysis

Three checkpoint batches were prepared and evaluated for % CDR at 2 h and % CDR at 18 h, as shown in table 7. When measured % CDR values were compared with predicted % CDR, the differences were found to be not significant. Thus, it can be concluded that the obtained mathematical equation is valid for predicted values [18].

Table 7: Checkpoint batches with predicted and measured value of %CDR at 2 h and at 18 h

Batch Code	X_1	X_2	% CDR at 2 h		% CDR at 18 h	
			Measured	Predicted	Measured	Predicted
O10	-1	0.5	34.50	35.73	74.04	75.08
O11	0.5	1	25.22	26.44	68.22	69.43
O12	0	0.5	24.12	23.24	69.05	70.10

Optimization of formulation

The overlay plot of responses, generates an optimized area as per desired criteria as shown in fig. 5. This was the most important part of the response surface methodology. After studying the effect of the independent variables on the responses, the levels of these variables that give the optimum response were determined. The optimum formulation was selected based on the criteria of attaining complete and controlled drug release. Batch O1 having 10 mg of GG and 10 mg of XG fulfilled maximum requisites of an optimum formulation because of better regulation of release rate. The said formulation released 33.57 % of the drug in 2 h and 85.62 % in 18 h, however, the drug completely got released, i.e. 99.82 % in 24 h, which were in close agreement with the theoretical values [18].

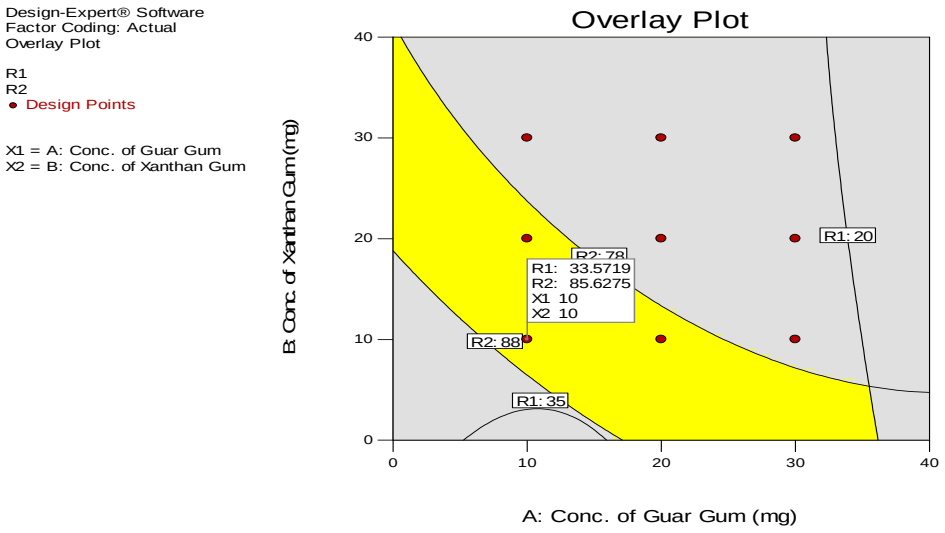

Fig. 5: Overlay plot of optimized batch

Drug release kinetic study

In order to examine the kinetics of drug release from prepared sustained release matrix tablets, the dissolution data of optimized formulation O1 were fitted into different kinetic models, i.e. zero order, first order, higuchi, hixson-crowell and korsemeyer-peppas model. The criteria for the selection of most suitable model were the value of regression coefficient (R^2) nearer to 1, smallest values of SSR and AIC. Table 7 shows the data obtained. The optimized formulation fitted well into korsemeyer-peppas, it was confirmed the desired release profile. The calculated R^2 value for korsemeyer-peppas was 0.9882. According to korsemeyer-peppas equation, the release exponent "n" value is between 0.45<n<0.89, which indicates that the drug release is non-fickian diffusion type and states that release followed the diffusion controlled mechanism [18].

Table 8: Fitting of release profile of optimized formulation to kinetic models

Batch	Model	Parameters used				
		R^2	R	K	SSR	AIC
O1	Zero-order	0.7756	0.9672	4.745	1705.6322	61.5335
	First-order	0.9307	0.9738	0.109	526.9088	52.1362
	Higuchi	0.9882	0.9943	19.794	89.5076	37.9546
	Korsemeyer–Peppas	0.9882	0.9942	19.881 n=0.498	89.4736	39.9515
	Hixson Crowell	0.9149	0.9761	0.029	646.5765	53.7735

Stability study

Stability study of the sustained release matrix tablet of IB was carried out for 6 mo at specified conditions. The stability studies of the optimized formulation (O1) shown no significant changes in the physical parameters, % drug content and % drug release in 24 h

when stored at 40±2 °C/75±5 % RH. So, it was considered that formulation having good stability.

CONCLUSION

The matrix types of tablets are potential to be an effective sustained release drug delivery system over a prolong period of time. The type and level of polymer used are important factors that can affect the drug release and also the physicochemical properties of this sustained release matrix tablets. 3^2 full factorial design was applied to achieve controlled drug release up to 24 h. Among all the developed formulations, an O1 formulation which contains the mixture of two polymers GG and XG in a proportion of 10 mg each gave sustain drug release for 24 h when compared with other formulations. So, O1 was selected as the best formulation. The drug release kinetics follows korsemeyer-peppas. So, the mechanism was found to be non fickian and shows continuous and uniform drug release for an extended period of time, an attribute highly desirable for any sustained release formulation. The stability studies were carried out according to ICH guideline which indicates that the selected formulation was stable. From the economical point of view, it may be beneficial for the local pharmaceutical firms to adopt such simple technologies for the preparation of sustained release product.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declare none

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