Research Paper

Development and Evaluation of a Chronomodulated Delivery System of Metoclopramide Hydrochloride

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Chronomodulated delivery system of metoclopramide hydrochloride was developed for the treatment of morning sickness and diabetic gastroparesis. Drug-excipient compatibility studies revealed no significant degradation of metoclopramide hydrochloride in presence of selected tabletting and compression coating excipients. Immediate release core tablets of metoclopramide hydrochloride were prepared using direct compression technique and various physicochemical parameters were evaluated. The core tablets were subjected to compression coating with a mixture of glyceryl dibehenate, hydrogenated castor oil and dicalcium phosphate; the levels of which were optimized statistically using face-centred cube design to achieve desired *in vitro* drug release profile of not more than 10 % at 4 h, not less than 50 % at 4.5 h and not less than 85 % at 5 h interval. Increase in the concentration of glyceryl dibehenate and hydrogenated castor oil in the formulation significantly decreased drug release at 4.5 and 5 h time intervals in distilled water as dissolution medium whereas quantity of dicalcium phosphate was found to have no influence on drug release characteristics. A quadratic model was suggested for the release profile at 4 h whereas linear model signified the release at 4.5 and 5 h. Formulation containing 100, 92 and 150 mg of glyceryl dibehenate, hydrogenated castor oil and dicalcium phosphate respectively per tablet was considered optimum since it showed the desired release profile. As the formulation showed the desired lag time during *in vitro* drug release, night time administration of the formulation could be expected to prevent the symptoms of morning sickness among pregnant women and hypoglycaemia upon administration of antidiabetic medication in gastroparetic patients.

Key words: Chronomodulated delivery, metoclopramide hydrochloride, optimization, glyceryl dibehenate, hydrogenated castor oil, gastric paresis, morning sickness

Certain diseases like arthritis, asthma, myocardial infarction, congestive heart failure, stroke and peptic ulcer exhibit a peak time of activity within a circadian rhythm. The drug therapy of such diseases therefore needs to be optimized by tailoring the dosing schedule based on chronobiological pattern of these diseases. There have been a number of reports in the literature where chronomodulated delivery systems have been developed for the treatment of asthma, hypertension and arthritis in a way that the medication when administered at bed time would release the drug at once, after a lag time of 5-6 h to elicit the therapeutic response early in the morning at which time the disease symptoms are at the peak[1-6]. Such a therapy would improve patient compliance and reduces the necessity of mid-night administering the medication to achieve optimum response early in the morning. Almost 80 % of pregnant women suffer from morning sickness in the first trimester of pregnancy[7]. They have to deal with severe nausea and bouts of vomiting early in the morning, which affects the appetite and eating, resulting in weakness and malnutrition. Thus, morning sickness is a chronological symptom, the treatment or prevention of which, could be handled more efficiently with a chronomodulated delivery system of a drug. Diabetic gastroparesis is a chronic gastrointestinal

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disorder seen among type I and II diabetic patients in which the gastric contents are emptied at a slower rate than usual. Administration of antidiabetic medicines in such a situation where there is inadequate glucose level in the blood can create serious concerns of hypoglycaemia[8]. Fluctuation in blood glucose levels among diabetic patients with gastroparesis is also a typical chronological event happening mostly early in the morning. Chronomodulated therapy with a gastric prokinetic agent therefore would be most justified in such a situation.

Metoclopramide hydrochloride (MH), a dopamine receptor antagonist is indicated in the treatment of gastro oesophageal reflux disease, nausea and vomiting[9]. Oral therapy with MH is proven safe in relieving the symptoms of morning sickness[10]. It is the only approved drug in USA for managing diabetic gastroparesis by improving gastric emptying rate to allow faster and better systemic absorption of glucose for preventing hypoglycaemia that could result with antidiabetic drugs.

MH is available commercially as immediate release tablets, orally disintegrating tablets, solution, as well as controlled release formulations, but not as a chronomodulated delivery system. There have been no reports related to the development of such a delivery system, though extensive work on sustained release formulations, controlled release matrix tablets, flash release films, melt in mouth tablets, buccoadhesive tablets, gastro-retentive delivery of MH has been reported[11-19]. All these formulations could result in optimum therapeutic effect only after 1 to 2 h of oral administration or in a sustained manner depending on the type of dosage form. This would render the medication almost ineffective in curbing the early morning nausea and vomiting in pregnant women or in preventing blood glucose fluctuations in gastroparetic diabetic patients, typically occurring after taking antidiabetic medication in the morning. To overcome this problem, authors have earlier attempted to develop a chronomodulated delivery system for MH that can be administered at bedtime and which would elicit maximum therapeutic effect early in the morning after a lag time of 6-7 h[20]. Development of such a formulation involved optimization using one-variable-at-a-time (OVAT) approach wherein the quantities of glyceryl dibehenate as a release modulator and dicalcium phosphate as a diluent were optimized to obtain the desired *in vitro* release profile. Design of experiments (DOE) is a comprehensive multivariate approach for fruitful appraisal and optimization of the formulations allowing extraction of maximal information out of a few well-designed experiments. The current study was aimed at optimizing the chronomodulated formulation of MH using face-centred cubic design (FCCD), a technique under the umbrella of DOE, wherein the quantities of glyceryl dibehenate, dicalcium phosphate and hydrogenated castor oil, an additional release modifier were optimized to achieve the desired release profile.

MATERIALS AND METHODS

MH was procured from Ipca Laboratories Pvt., Ltd. Microcrystalline cellulose (Avicel PH 102), magnesium stearate and dicalcium phosphate (Di-tab) were procured from Signet Chemicals Ltd. Glyceryl dibehenate (Compritol 888 ATO), hydrogenated castor oil (Kolliwax HCO) were gift samples from Gattefosse Pvt., Ltd., and BASF Ltd., respectively. Lactose spray-dried (Supertab) was obtained from DFE Pharma Ltd., and crospovidone (Polyplasdone XL 10) from Ashland Specialties Ltd. All these suppliers were based in Mumbai, India.

Drug-excipient compatibility studies:

Binary mixtures of MH and tabletting excipients were prepared as per the ratios given in Table 1. Glass vials filled with mixtures were closed with rubber closures, sealed with aluminium caps and stored at 25±2° as a control. Those glass vials filled with mixtures and stored at 40±2°/75±5 % RH were covered with perforated aluminium foil. The study was carried out for 4 w. The samples were analysed for single maximum impurity and total impurity content using following method.

Each binary mixture equivalent to 50 mg MH was dissolved in the solvent system composed of acetonitrile and water in 9:1 ratio, diluted suitably and 10 µl of the sample solution was subjected to analysis using high performance liquid chromatography (HPLC) of

TABLE 1: RATIOS OF MH AND EXCIPIENT BINARY MIXTURES FOR COMPATIBILITY STUDIES

Binary mixture	Ratio
MH:lactose	1:1
MH:microcrystalline cellulose	1:1
MH:dicalcium phosphate	1:10
MH:colloidal silicon dioxide	1:0.5
MH:crospovidone	1:0.5
MH:magnesium Stearate	1:0.5
MH:glyceryl dibehenate	1:10
MH:hydrogenated castor oil	1:10

MH: metoclopramide hydrochloride

the make Agilent Technologies 1260 Infinity. Reverse phase, C18 column (4.6×250 mm) with 5 µ silica packing was employed at 30° for impurity separation, which were quantified using ultraviolet detector at 276 nm. Gradient analysis was performed using two mobile phases, one of which consisted of a mixture of 5.4 g anhydrous sodium acetate in 1000 ml of water, acetonitrile and tetramethyl ammonium hydroxide 25 % (87:12.8:0.2) and the other one contained a mixture of water and acetonitrile in the ratio of 75:25. The flow rate was maintained at 1.5 ml/min.

Preparation and evaluation of core tablets of MH:

Immediate release core tablets of MH were prepared using the compositions given in Table 2. The blend of MH, microcrystalline cellulose, spray-dried lactose, silicon dioxide and crospovidone XL 10 was passed through 40# sieve and mixed well for 5 min in a container blender (RP Products) at 15 rpm. Magnesium stearate was added to the blend and mixed for 3 min. The final blend was compressed into tablets using a Cadmach CMD4 single rotary machine fitted with 4.7 mm standard concave circular plain punches. Average weight, weight variation, hardness using Dr. Schleuniger hardness tester (Model 8M) and thickness using Vernier caliper (Mitutoyo, 500-197-30) of the prepared tablets were evaluated. Disintegration time of the tablets was determined using a disintegration test apparatus (Electrolab, ED2L) containing 900 ml of distilled water maintained at 37±0.5°.

Tablets (n=10) were crushed and powdered using a pestle and mortar. Powder equivalent to 11.82 mg MH was dissolved in a mixture of water and acetonitrile (75:25). After suitable dilution of the solution, a sample volume of 5 µl was injected onto C18 column. A mobile phase consisting of buffer solution (5.4 g/l of sodium acetate in water):acetonitrile:tetramethyl ammonium hydroxide (70:30:0.2) was run at 1 ml/min to quantify MH using a UV detector at the wavelength of 276 nm.

TABLE 2: COMPOSITION OF IMMEDIATE RELEASE TABLETS OF MH

Ingredients	Quantity mg/tablet
MH (equivalent to 10 mg of base)	11.82
Microcrystalline cellulose	22.43
Lactose spray-dried	12
Crospovidone XL 10	2.5
Colloidal silicon dioxide	0.5
Magnesium stearate	0.75
Total weight/tablet	50

MH: metoclopramide hydrochloride

***In vitro* release study:**

Tablets (n=6) were subjected to *in vitro* drug release study using USP type 2 dissolution test apparatus (Electrolab) employing 900 ml distilled water as a medium maintained at 37±0.5° and stirred continuously at 50 rpm[21]. The aliquots were withdrawn at the end of 30 min and analysed for MH by HPLC using the same method as employed for the assay.

Preparation of chronomodulated tablets:

Specified quantities of glyceryl dibehenate, hydrogenated castor oil and dicalcium phosphate were passed through 30# sieve and mixed in container blender for 15 min. The blend was transferred to the hopper of Cadmach press coater CPC 900 machine. Compression was done using 9.8 mm circular biconvex punches. The coating blend was fed into the 2 hoppers of the compression machine. The first hopper fed the powder into the die and was pre-compressed to form the lower layer. The core tablets were fed into a vibratory hopper, which were then guided into a rotating wheel. The wheel was synchronized to drop the core tablet accurately at the centre of the pre-compressed lower layer. This was followed by filling the upper layer of coating blend into the die and final compression. Vertical adjustment allowed for centralizing the tablet core to give equal thickness above and below the core. Inspection system allowed for core detection at the point of entry and automatic rejection of a tablet without a core.

Optimization of chronomodulated formulations using DOE:

FCCD was used in the optimization of chronomodulated formulation of MH. Design Expert software 8.05 (Stat-Ease Inc., Minneapolis, MN, USA) was employed for this purpose. Glyceryl dibehenate (X_1), dicalcium phosphate (X_2) and hydrogenated castor oil (X_3) were selected as factors (independent variables). Each factor was studied at 3 different levels (–1, 0 and +1) *viz*. X_1 and X_2 each at 50, 100, 150 mg/tablet whereas X_3 at 42, 92 and 142 mg/tablet. Table 3 gives an account of the 17 formulation runs studied with their factor combinations. *In vitro* drug release at 4 h (Y_1), 4.5 h (Y_2) and 5 h (Y_3) were selected as response variables (dependent variables). The targets set for response variables were not more than 10 % drug release in 4 h, not less than 50 % drug release in 4.5 h and not less than 85 % release in 5 h.

TABLE 3: FORMULATION TRIALS AS PER EXPERIMENTAL DESIGN

Std.	Run	Space type	X_1: glyceryl dibehenate(mg)	X_2: dicalcium phosphate (mg)	X_3: hydrogenated castor oil (mg)
16	1	Center	100	100	92
12	2	Axial	100	150	92
13	3	Axial	100	100	42
10	4	Axial	150	100	92
14	5	Axial	100	100	142
5	6	Factorial	50	50	142
9	7	Axial	50	100	92
8	8	Factorial	150	150	142
7	9	Factorial	50	150	142
15	10	Center	100	100	92
4	11	Factorial	150	150	42
1	12	Factorial	50	50	42
11	13	Axial	100	50	92
3	14	Factorial	50	150	42
2	15	Factorial	150	50	42
6	16	Factorial	150	50	142
17	17	Center	100	100	92
Verification of design space by repeating the statistically optimized formulation					
18	18	Verification	100	150	92

Evaluation of chronomodulated tablets:

The compression-coated tablets prepared using formulae listed in Table 3 were subjected to determination of average weight, hardness, assay and *in vitro* release in the manner similar to that described for the evaluation of core tablets.

Dissolution studies in various media:

Chronomodulated tablets were prepared using optimized conditions suggested by Design Expert software (run 18) and 6 tablets were subjected to *in vitro* drug release studies separately in various dissolution media, pH 1.2 hydrochloric acid (0.1 N), pH 4.5 acetate buffer and pH 6.8 phosphate buffer. The test was conducted for 5 h using 900 ml of each medium maintained at 37±0.5° stirred continuously at 50 rpm. The aliquots were withdrawn at 4, 4.5 and 5 h and replaced with fresh medium. Concentration of MH in aliquots was analysed by HPLC using the same method that was used for the assay. One way ANOVA at $\alpha \leq 0.05$ was applied to the *in vitro* release values in all the media to identify any difference in the release profiles.

Accelerated stability studies:

The chronomodulated tablets of run 18 were strip packed using aluminium foil and subjected to accelerated stability studies at 40±2°/75±5 % RH for 3 mo. The samples were evaluated for average weight, hardness, assay and *in vitro* drug release studies at 1, 2 and 3 mo intervals.

RESULTS AND DISCUSSION

Earlier work by the authors involved development of a chronomodulated delivery system of MH using OVAT approach[20]. This work employed glyceryl dibehenate as a compression coating agent to achieve the desired lag time. Glyceryl dibehenate has a melting range of 69-74°. Prolonged exposure of the tablets to higher temperatures during stability studies resulted in uneven surfaces. As a result, a need arose to develop a product with better thermal stability, which is needed in a tropical country like India. Based on the evaluation of several fatty materials, hydrogenated castor oil was chosen as a release retardant along with glyceryl dibehenate for its inert properties and a higher melting range of 83-88°.

In order to ascertain any interactions between MH and the excipients, compatibility study was carried out by admixing MH and various excipients in a fixed proportion and subjecting the binary mixtures to accelerated conditions of temperature and humidity. Excipients used for preparing core tablets as well as the ones intended for compression coating were chosen for the study. Impurity analysis at the end indicated absence of incompatibility between MH and any of the excipients thus proving them suitable for the formulation development (Table 4).

Core tablets of MH were prepared by direct compression using the formula optimized earlier by the authors[20]. The evaluation parameters of the tablets were given in Table 5. Preliminary trials of the compression-coated tablets of MH were taken with glyceryl dibehenate,

TABLE 4: IMPURITY ANALYSIS OF MH-EXCIPIENT BINARY MIXTURES

Binary mixture	Impurities	Initial	Control 25°	40°/75 % RH
MH+lactose	Single maximum	0.04	0.04	0.05
	Total	0.08	0.09	0.11
MH+microcrystalline cellulose	Single maximum	0.03	0.03	0.05
	Total	0.06	0.08	0.08
MH+dicalcium phosphate	Single maximum	0.03	0.04	0.04
	Total	0.05	0.06	0.08
MH+colloidal silicon dioxide	Single maximum	0.04	0.04	0.05
	Total	0.07	0.08	0.09
MH+crospovidone	Single maximum	0.05	0.05	0.07
	Total	0.11	0.12	0.13
MH+magnesium stearate	Single maximum	0.05	0.05	0.05
	Total	0.07	0.08	0.09
MH+glyceryl dibehenate	Single maximum	0.03	0.04	0.05
	Total	0.08	0.08	0.08
MH+hydrogenated castor oil	Single maximum	0.04	0.05	0.05
	Total	0.08	0.08	0.09

MH: metoclopramide hydrochloride

TABLE 5: EVALUATION OF CORE TABLETS OF MH

Evaluation parameter	Result
Average weight (mg)	50.8±1.7
Thickness (mm)	2.1-2.2
Hardness (kp)	2-4
Disintegration time (min)	2-3
Assay (%)	100.4±1.3
In vitro drug release at 30 min (%)	94.3±2.3

Values of assay and % drug release are represented as mean±standard deviation, n=3, n=6, respectively

dicalcium phosphate and hydrogenated castor oil. The release profile targeted was achieved with a formulation containing 100 mg of glyceryl dibehenate, 100 mg dicalcium phosphate and 92 mg hydrogenated castor oil. Hence, this composition was chosen for further optimization using DOE. FCCD was chosen as an experimental design wherein run nos. 6, 8, 9, 11, 12, 14, 15 and 16 were factorial points to detect the main effects of the factors. Axial points (run nos. 2, 3, 4, 5, 7 and 13) were chosen to optimize the response. Run nos. 1, 10 and 17 (Table 3) were taken as centre point in order to detect the curvature of the response and the replicate trials of the centre point ensured minimization of experimental error. The formulations prepared as per the trial runs given in Table 3 showed average weight in ±5 % range of the theoretical weight, hardness in the range of 4-7 kp and assay in the range of 98 to 102 %. *In vitro* drug release data on tablets (n=6) has been furnished in Table 6.

The aim of the work was to develop a formulation that would elicit the therapeutic effect of MH after 5-6 h of administration of the formulation. To achieve this goal, no drug release was desired up to 4 h of administration following which the tablets were expected to release the drug completely in a conventional manner over the period of 1 h. Hence the constraints put for the responses Y_1, Y_2 and Y_3 were not more than 10 % release (at 4 h), not less than 50 % release (at 4.5 h) and not less than 85 % release (at 5 h), respectively. The responses of *in vitro* drug release of trial batches were fed into Design Expert software. Polynomial equation generated by the software for the response Y_1 as a function of independent variables was as follows: $Y_1 = 2.22–10.4X_1–0.89X_2–6.1X_3+4.7X_1X_3+7.2X_1^2+2.7X_3^2$.

X_1 and X_3 represent the main effects, X_1^2 and X_3^2 indicate quadratic effects and X_1X_3 interaction effect of factors glyceryl dibehenate and hydrogenated castor oil. The positive value in the regression equation indicates direct relationship and a negative value an inverse relationship between the factor and the response. Quadratic model was suggested for drug release at 4 h. For estimation of the significance of the model, ANOVA was applied as per the provision of the Design Expert software (Table 7). The model F-value of 179.77 implied that

TABLE 6: RESPONSE PARAMETERS OF DOE STUDIES

Run	Y_1: drug release at 4 h (%)	Y_2: drug release at 4.5 h (%)	Y_3: drug release at 5 h (%)
1	5	60	90
2	4	60	90
3	6	61	91
4	1	38	72
5	2	40	75
6	7	60	90
7	20	85	98
8	1	38	68
9	2	60	90
10	4	62	94
11	3	55	85
12	35	90	92
13	5	63	89
14	32	86	90
15	3	55	86
16	1	37	70
17	6	65	96

Values of % drug release are represented as mean of n=6

the model was significant and there was only a 0.01 % chance that the F-value this large could occur due to noise. All the model terms shown in the above equation except X_2 were found to be significant as indicted by the p values <0.05 (Table 7). Equation for the response Y_2 (*in vitro* release at 4.5 h) generated by the software is as follows. $Y_2 = 60.94–17.3X_1–1.4X_2–10.3X_3$.

Linear model was suggested for the drug release at 4.5 h. Application of ANOVA indicated that the model and main effects X_1 and X_3were significant whereas X_2 was not significant since the p value of its coefficient was more than 0.05 (Table 8). Model reduction was implemented to remove interaction terms and quadratic terms from the regression equation since they were statistically not significant.

$Y_3 = 88.47–10.9X_1–0.2X_2–5.5X_3$ was the polynomial linear equation generated by the software for the response Y_3 (*in vitro* drug release at 5 h). As per ANOVA, the model and the model terms X_1 and X_3 were significant. However, X_2 in this case also was not significant (Table 8). Statistical treatment during optimization studies thus indicated that all the three responses were influenced by only two factors X_1 and X_3 and/or their interactions, whereas factor X_2 did not have any significant impact on the responses. Hence the response surface plots and contour plots were

TABLE 7: ANOVA FOR RESPONSE SURFACE REDUCED QUADRATIC MODEL FOR *IN VITRO* DRUG RELEASE AT 4 H

Source	Sum of squares	Df	Mean square	F value	p-value	Statistical significance
Model	1960.9	5	392.2	179.77	0.000001	Significant
X_1	1081.6	1	1081.6	495.77	0.000001	Significant
X_2	10.0	1	10.0	13.21	0.221012	Non-significant
X_3	362.1	1	362.1	170.56	0.000000	Significant
$X_1 X_3$	180.5	1	180.50	82.74	0.000002	Significant
X_1^2	157.3	1	22.2	72.12	0.000004	Significant
X_3^2	22.2	1	22.2	10.18	0.008605	Significant
Residual	24.0	11	2.2			
Lack of fit	23.3	9	2.6	7.78	0.119072	Non-significant
Pure error	0.7	2	0.03			
Core total	1984.9	16				

TABLE 8: ANOVA FOR RESPONSE SURFACE REDUCED LINEAR MODEL FOR *IN VITRO* DRUG RELEASE AT 4.5 AND 5 H

In vitro drug release at 4.5 h						
Source	Sum of squares	Df	Mean square	F value	p-value	Statistical significance
Model	4053.80	2	2026.90	97.47	0.00001	Significant
X_1	2811.50	1	2811.50	143.92	0.00001	Significant
X_2	181.40	1	181.40	2.87	0.32456	Non-significant
X_3	1060.90	1	1060.90	51.02	0.00000	Significant
Residual	291.14	14	20.80			
Lack of fit	278.47	12	23.21	3.66	0.23421	Non-significant
Pure error	12.67	2	6.33			
Core total	4344.94	16				
In vitro drug release at 5 h						
Source	Sum of squares	Df	Mean square	F value	p-value	Statistical significance
Model	1490.60	2	745.30	25.85	0.00002	Significant
X_1	1116.70	1	1116.70	14.21	0.00002	Significant
X_2	71.40	1	71.40	1.18	0.27041	Non-significant
X_3	302.50	1	302.50	10.49	0.00594	Significant
Residual	403.50	14	28.83			
Lack of fit	384.97	12	32.08	3.44	0.24731	Non-significant
Pure error	18.67	2	9.33			
Core total	1894.24	16				

generated considering only two variables *viz.* X_1 and X_3 (fig. 1).

The first response surface plot in fig. 1 indicated that the *in vitro* release at 4 h was inversely proportional to the quantities of factors X_1 and X_3 i.e. as the concentration of glyceryl dibehenate and hydrogenated castor oil increases the drug release decreases. The curvature of the lines on the contour plot showed quadratic relationship between the response and the factors. *In vitro* drug release at 4.5 and 5 h also indicated inverse impact of concentrations of glyceryl dibehenate and hydrogenated castor oil on the amount of drug release. The straight lines on the contour plots of these responses indicated linear relationship between the response and the variables.

After generating the response surface plots, optimization process was undertaken with desirable characteristics of responses to probe the optimal solution. An overlay plot was obtained by overlapping the contour plots for the three responses. Yellow zone in the fig. 2 indicated the design space fulfilling the criteria of <10 % release at 4 h, >50 % and >85 % drug release at 4.5 and 5 h, respectively. The optimized formulation (red point circled in yellow zone of the overlay plot) suggested by the software was prepared (run 18) and subjected to *in vitro* release studies. For all the responses, the relative error was found to be less than 5 % between the observed values and the predicted values thus verifying the predictability of the model (Table 9). Hence the formulation of run18 suggested by the model

TABLE 9: COMPARISON OF PREDICTED AND OBSERVED RESPONSES OF OPTIMIZED RUN 18

Response	Predicted results	Actual results	Relative error (%)
% Drug release at 4 h	3.85	4.10	3.75
% Drug release at 4.5 h	59.10	62.04	4.67
% Drug release at 5 h	85.83	89.11	3.56

TABLE 10: *IN VITRO* RELEASE OF MH FROM OPTIMIZED CHRONOMODULATED FORMULATION IN VARIOUS MEDIA

Time point	Distilled water	pH 1.2 (0.1 N HCl)	pH 4.5 buffer	pH 6.8 buffer
4 h	4.10±2.6	0	2.8±0.8	0
4.5 h	62.04±1.4	72.3±2.3	63.9±2.6	67.1±4.1
5 h	89.11±2.7	95.5±1.9	90.4±3.5	93.1±3.4

Values of % drug release are represented as mean±standard deviation of n=6

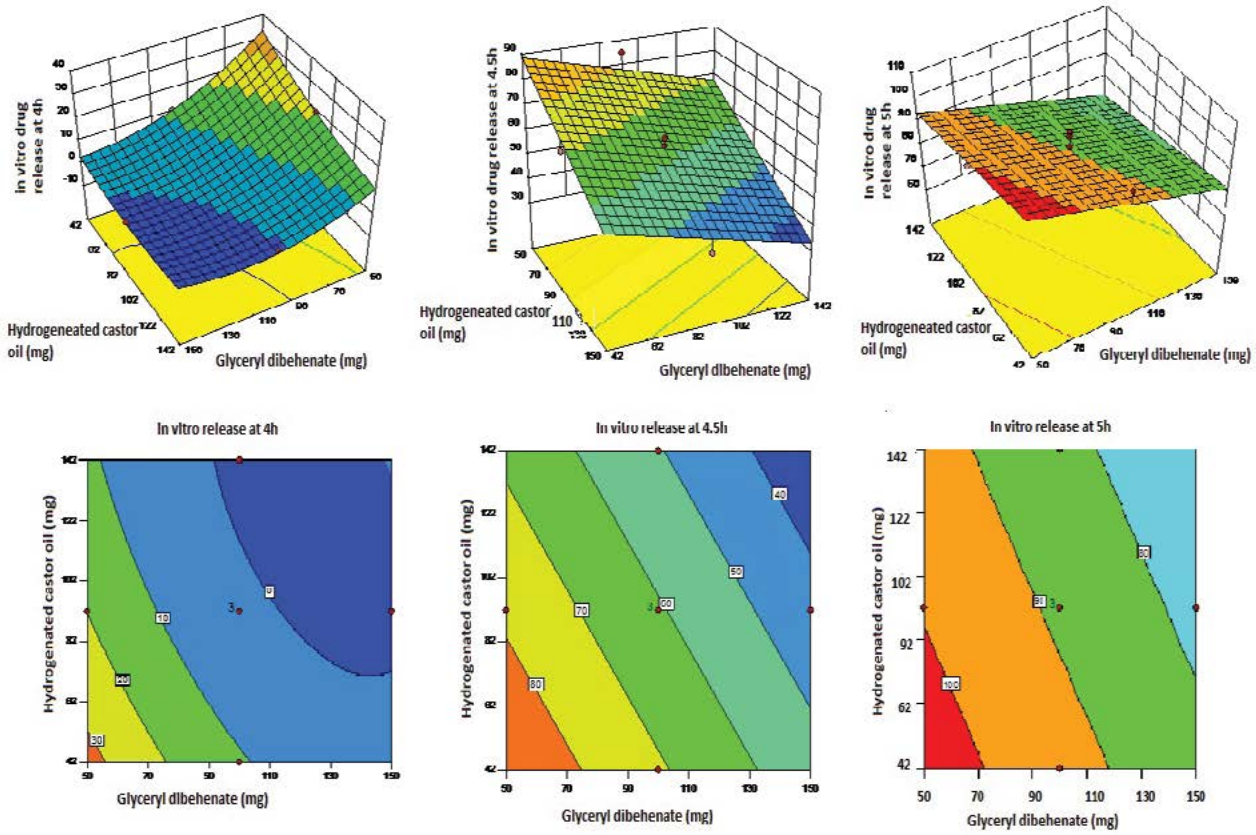

Fig. 1: Response surface and contour plots

Response surface plots (upper row) and contour plots (lower row) for the effect of concentration of glyceryl dibehenate and hydrogenated castor oil on *in vitro* drug release at 4, 4.5 and 5 h

TABLE 11: ACCELERATED STABILITY STUDIES OF OPTIMIZED CHRONOMODULATED FORMULAION OF MH

Test	Specification	Initial	1 month	2 months	3 months
Description	White to off-white, circular, biconvex tablets	White to off-white, circular, biconvex tablets	White to off-white, circular, biconvex tablets	White to off-white, circular, biconvex tablets	White to off-white, circular, biconvex tablets
Average weight	392 mg±3 %	complies	Complies	Complies	Complies
Hardness	4-7 kp	5-7 kp	4-7 kp	4-6 kp	4-6 kp
Assay	90-110 %	99.5 %±0.8	99.3 %±1.8	98.9 %±1.3	99.1 %±1.7
In vitro drug release	4 h:NMT 10 %	4.1 %±2.6	0 %	1.5 %±2.3	2.6 %±3.1
	4.5 h:NLT 50 %	62 %±1.4	67.1 %±2.7	65.4 %±3.5	68.9 %±3.8
	5 h:NLT 85 %	89.1 %±2.7	87.7 %±2.5	92.2 %±3.2	91.4 %±2.7

Values of assay and drug release are represented as mean±standard deviation, n=3, n=6, respectively

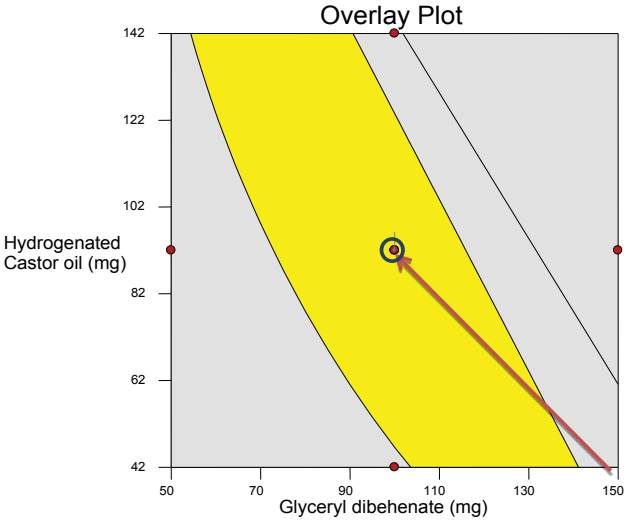

Fig. 2: Overlay plot
Overlay plot depicting the yellow zone where all the responses meet predefined criteria and also the solution (circled red point) indicating optimized conditions

containing 100 mg of glyceryl dibehenate, 150 mg of dicalcium phosphate and 92 mg of hydrogenated castor oil was considered as optimum.

Formulation of run18 was subjected to dissolution studies in various media to compare the effect of pH on the *in vitro* drug release as against that of distilled water which was earlier used as the dissolution medium (Table 10). Drug release profiles from the optimized formulation in different media when compared using one way ANOVA test confirmed no significant difference thus indicating the robustness of the formulation in terms of response parameters.

Tablets of run 18 when subjected to accelerated conditions of temperature and humidity did not show any remarkable changes in the parameters like appearance, hardness, assay or *in vitro* release profile over the storage period of 3 mo (Table 11). Application of one way ANOVA at $\alpha \leq 0.05$ showed no significant difference among the assay values and *in vitro* release profiles thus indicating good stability of the formulation.

In conclusion, chronomodulated formulation of MH was developed and optimized statistically using FCCD as a DOE approach. The formulation comprised of fast disintegrating core tablets of MH, compression coated with mixture of glyceryl dibehenate, hydrogenated castor oil and dicalcium phosphate. Glyceryl dibehenate and hydrogenated castor oil were the key factors that controlled the *in vitro* drug release at all the time points. Night-time administration of the optimized formulation could curb the early morning symptoms of nausea and vomiting in pregnant women and also prevent hypoglycaemia among the diabetic patients with gastroparesis.

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Conflict of interest:

We declare that we have no conflict of interest.

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