International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.2, No.2, pp 1105-1111, April-June 2010

Preparation and Evaluation of Immediate Release tablet of Metoclopramide HCl using Simplex Centroid Mixture Design

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ABSTRACT: Metoclopramide HCl is mainly used as an anti-emetic agent in the cancer chemotherapy. It also stimulates the upper GI tract and is used in the management of some forms of nausea, vomiting and pain associated with migraine as well as in gastric stasis where quick onset of action is required. Conventional tablet may give delayed onset of action (probably 1.5-2 hrs) which may be over come by administering immediate release tablets. The development of immediate release tablet formulations is based on the use of super disintegrants separately or in combination. Seven formulations were prepared using simplex centroid mixture design where sodium starch glycolate (X_1), cross carmellose sodium (X_2) and pregelatinised starch (X_3) were selected as independent variables and dependent variables were disintegration time (Y_1) and release at 15 minutes (Y_2). Response surface plots were drawn, and optimum formulations were selected by grid search method. X_1, X_2 and X_3 when used individually gave satisfactory results but when used in combination gave better results. The results showed a good relationship between the experimental and predicted values, which confirms the predictability of the model.

KEY WORDS: Metoclopramide, immediate release tablets, simplex centroid mixture design,response surface method.

INTRODUCTION

Fast disintegrating or dissolving drug delivery system is a novel system which has advantages such as administration without water anytime and anywhere specially for geriatric and pediatric patients. It is suitable for mentally ill and bedridden patients. The benefits in terms of patients compliance, rapid onset of action, increased bioavailability and good stability make these tablets popular as a dosage form of choice in the current market.[1-3] The basic approach used in the development of the fast disintegrating tablets is the use of various superdisintegrants like sodium starch glycolate (SSG), cross carmellose sodium (CCS) and pregelatinized starch (PGS). These agents bring about fast disintegration due to increased water uptake which causes explosion of tablet matrix[4]. These agents are used separately or in combination to produce a desirable effect.

Metoclopramide HCl [4-amino-5-chloro-N-(2-diethyl amino ethyl-2-methoxybenzamide) hydrochloride monohydrate] is a dopamine receptor antagonist. It is mainly used as an anti-emetic agent in the cancer chemotherapy. It also stimulates the motility of upper GI-tract and is used in the management of some forms of nausea and vomiting. It is also used in gastro-esophageal reflux and gastric stasis [5, 6] . It is reported that metoclopramide HCl is effective in the management of pain and nausea associated with migraine. Studies have reported that metoclopramide is useful in the treatment of migraine for about 60-75% patients[7, 8].

In design of experiment (DOE) approach, process variables are first 'screened' to determine which are important to the outcome (excipients type, percentage, disintegration time (DT), etc. Next step is the 'optimization', when the best settings for the important variables are determined. It involves the use of 'mixture designs' for changing mixture composition and exploring how such changes will affect the properties of the mixture[9, 10].

The aim of the current study was to develop and optimize fast disintegrating tablets of metoclopramide HCl with low friability and minimum DT, prepared by wet granulation technique for oral delivery. A computer aided optimization process[11, 12] using a simplex centroid mixture design was employed to investigate the effect of three independent variable (factors) i.e.; amount of superdisintegrants: SSG, CCS and PGS. The DT and release after 15 min (rel_{15min}) were taken as the response variables.

MATERIALS AND METHODS

Materials:

Metoclopramide HCl was provided as gift samples by M/s Modi Mundi Pharm. Ltd. (Modipuram , India). Superdisintegrants such as SSG, CCS, and PGS were received as a gift sample by M/s Ferro Signet (Mumbai, India). All other chemicals and reagents were of analytical grade.

Method:

Simplex Centroid Mixture Design

A simplex centroid mixture design was selected for this experiment. It consists of 7 design points. This design generally involves independent variable X and dependent variables Y. The independent variables selected for this study were SSG (X_1), CCS (X_2) and PGS (X_3) and dependent variables include DT (Y_1), rel_{15min} (Y_2).

The raw materials were weighed (Table 1) and passed through 85# screen prior to mixing. Alcoholic solution of PVP (5 % w/v) was prepared and added to the mixture of metoclopramide HCl, sodium lauryl sulphate (SLS), intragranular fraction of superdisintegrants (SSG,CCS,PGS) and microcrystalline cellulose. The granules were obtained by passing the mass from 16 # sieve. These granules were dried at room temperature for 2-3 hrs and were again passed through 18 # sieve. The dried granules were mixed with the extra granular fraction of superdisintegrants and were then lubricated with required amount of magnesium sterate.[13, 14] The granules equivalent to 100 mg were compressed using a multistation tablet compression machine (Rimek MINI, India) of 8 mm die. Hardness was kept at 2 -3 kg/cm².

Drug content and Physical Evaluation

Tablet Thickness:

Thickness of tablets was important for uniformity of tablet size. Thickness was measured using digital vernier calipers.

Tablet Hardness:

The resistance of tablets to shipping or breakage, under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tablet tester. The hardness was measured in terms of kg/cm^2.

Friability:

Friability is the measure of tablet strength. Friabilator was used for testing the friability using the following procedure.

Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

Uniformity of mass of single dose preparation:

Twenty tablets were weighed individually and average weight of one unit of tablet was determined.

Not more than two of the individual masses deviate from the average mass by more than the percentage deviations shown and none deviates by more than twice that percentage.

Uniformity of content:

This test is applicable to tablets that contain less than 10 mg or less than 10 % w/w of active ingredient. Content of active ingredient in tablets and capsules, taken at random, was determined. Tablets were crushed and powdered. Powder equivalent to tablet weight and dissolved in 0.1N HCl. Drug content was calculated by measuring absorbance at wavelength 272 nm.

Wetting time:

Rawas-Qalagi MM et al.[15] measured the wetting time of tablets using a simple procedure. A piece of tissue paper folded twice was placed in a small petri dish containing 10 ml of distilled water. A tablet having amaranth powder on the upper surface is placed on the filter paper .Time required to develop red color on the upper surface of tablet is recorded as wetting time.

Disintegration time:

The DT was measured using a disintegration method (n =3). For this purpose, a petri dish 10 cm (in diameter) was filled with 10ml of water. The tablet was carefully put in the centre of the Petri dish and the time for the tablet to completely disintegrate into fine packets was noted.

In vitro dissolution study:
In vitro release studies (n=3) were conducted for all the formulations using USP type II dissolution test apparatus (paddle). 900ml of 0.1N HCl was taken as dissolution medium and the apparatus was operated at 50 rpm and 37± 2ºC.Aliquots of 10 ml were periodically withdrawn and the sample volume replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically (JASCO V-530 UV/VIS Spectrophotometer) at 272 nm.

Statistical analysis:
Design-Expert software[16] version 7 was used to optimize the quantity of superdisintegrants. The best-fitting mathematical model was selected based on the comparisons of several statistical parameters including the determination coefficient (R^2), the adjusted determination coefficient (adj-R^2) and the *F*-value provided by analysis of variance (ANOVA). Subsequently, grid search was performed to locate the composition of optimum formulations. Also, three-dimensional response surface graphs were drawn in MS-Excel using the output files generated by the Design Expert Software.

Validation of Optimization Model:
Seven optimum formulations were selected by grid search, performed over the entire experimental domain, to validate the chosen experimental design and polynomial equations. The criterion for selection of formulation was primarily based on the highest possible values of DT and rel_{15min}. The formulation corresponding to these optimized quantities were prepared and evaluated for various responses. The resultant experimental data of responses were subsequently compared quantitatively with the predicted values. Also, linear regression plots between observed and predicted values of the responses were attempted using MS- Excel, forcing the line through the origin.

RESULTS AND DISCUSSION
The fast disintegrating tablets of metoclopramide HCl are beneficial in case of nausea and pain associated with migraine. Also it reduces the gastric stasis problem during migraine which may result into poor absorption of other drugs .These tablets bring about rapid disintegration within a minute and thus have a rapid onset of action .The fast disintegration was brought about by use of superdisintegrants and also due to the high porosity of tablets. Preliminary studies carried out prior to experimental design involved the use of various superdisintegrants separate or in combination and accordingly, a suitable range for each was selected

The time of disintegration ranged from 9 to 22 sec and the results met the BP[17] specification which states the limit for uncoated fast dissolving tablets as 1 min.
The maximum official weight variation for tablets heavier than 100 mg is 5 %, therefore, all formulations met the USP 28th ed. specifications[18] .The results are shown in Table 2.
Metoclopramide Immediate release tablet content ranged from 87.05 to 98.31%**,** and hardness was between 2-3 kg / sq.cm[17].
Wetting time: The wetting time gives the significance of time required for the tablet to absorb moisture and also the minimum volume of liquid required. The tablets with combination of SSG and CCS have shown minimum time to acquire moisture while the tablet with PGS singly took longest time to wet.

RSM Optimization:
According to Eriksson et al., [10] screening is used in the beginning of the experimental procedure for investigating large numbers of factors aiming to reveal the most important among them. Optimization is applied for finding a factor combination matching an optimal response profile. The design supporting special cubic model is found to be relevant for optimization. (Table 3)
The coordinate system for the mixture problem is called a simplex coordinate system. With three components the coordinate can be plotted on a triangular graph[12].

Mathematical Modeling:
Mathematical relationships generated using ANOVA for the studied response variables are expressed as equation 1 and 2
DT = 11.52A+15.52B+ 22.52C-18.76AB-4.76AC-4.76BC …….. (1)

rel_{15min}= 95.84A+92.00B+86.23C+18.79AB+ 1.66AC+ 3.45BC-6.04ABC …….. (2)

All the polynomial equations were found to be statistically significant ($P<0.01$), as determined using ANOVA. The polynomial equation comprises the coefficient for intercept. (eq 1 and 2) The sign and magnitude of the main effects signify the relative influence of each factor on the response.
The values obtained for main effects of each factor in equation 1 and 2 i.e. concentration of superdisintegrants SSG (X_1), CCS (X_2) and PGS (X_3) used separately or in combination signify more pronounced effect on DT (Y_1) as well as rel_{15min} (Y2). The use of X_1 and X_2 in combination gives prominent results for the factors Y_1 and Y_2. At a given set of factor levels however, these higher-order polynomials

yield results as the net effect of all the coefficient terms contained in the polynomial.

Response Surface Analysis:

Response surface diagrams illustrating model equations and showing the effects of superdisintegrants on metoclopramide tablets to DT and rel_{15min} were created to interpret the mixture region fig 1**.** In the response surface, each factor (pure and mixture component) is represented at the apex of an equilateral triangle; each point within this triangle refers to a different proportion of components in the mixture. The maximum percentage of each ingredient considered by the regression is placed at the corresponding corner while the minimum is positioned at the middle of the opposite side of the triangle.

The figure1shows that the DT was less for X_1 and X_2 as compared to X_3; the triangle point for X_3 goes upward denoting increased DT. On the other hand, the use of these parameters in combinations as X_1X_2, X_2X_3, and X_1X_3 also showed different DT. The lowest value was obtained for the combination of X_1X_2. The inclination of curve in Fig.1 shows that in the formulation containing a combination of X_1 and X_2, the effect of X_1 in decreasing the DT was more pronounced than X_3. The other diagram showing the release of drug after 15 min shows maximum release of 98.31% from the formulation containing combination of X_1X_2, while the minimum release value as obtained for X_3.(Figs 2 and 3)

Optimization:

The process was optimized for the response Y_1 and Y_2. For selection of optimum formulations the following maximizing criteria was adopted: rel_{15min}>95% and DT<10 sec. Upon exhaustive grid searches, the formulation with combination of superdisintegrants SSG (7.5mg) and CCS (4.5mg) fulfilled maximum requisites of an optimum formulation due to better regulation of release rate and minimum DT. The formulations showed rel_{8h} as 98.97% and DT as 8.85 sec.

Validation of RSM results:

For all 6 checkpoint formulations, the results of the physical evaluation and tablet assay were found to be within limits. Table 4 lists the composition of the checkpoints, the predicted and experimental values of all the response variables, and the percentage error in prognosis. Figure 4 shows linear correlation plots between the observed and predicted response variables, the residual plots showing the scatter of the residuals versus observed values. The linear correlation plots drawn between the predicted and observed responses demonstrated higher values of r^2 (ranging between 0.8103 and 0.961), indicating excellent to good fitting of model (P<0.001). Upon validation, the optimum formulations exhibited percentage error for various response variables, varying from -0.803 to 6.86 % (DT) and -0.153 to 0.212 % ($rel_{15\ min}$). Thus, the low magnitudes of error as well as the significant values of r^2 in the current study indicate a high prognostic ability of RSM

An optimized formulation of immediate release tablets was found to give minimum disintegration time (8.85 sec) and higher drug release at 15 min (98.97 %) which may give quick onset of action. The higher value of SSG in combination with CCS gave better result. Design and analysis of experiments were used as good tools to obtain the optimal formulation, which showed minimum friability, no lamination and that also met all official compendial specifications.

The above study shows that, the combination of SSG with CCS in the appropriate proportion gives the tablet with minimum DT and higher percent of drug release. Use of mixture design gives the appropriate quantity of superdisintegrants for the optimized formulation. The formulation was found to be satisfactory for all evaluation parameters.

TABLE.1 PREPARATION OF METOCLOPRAMIDE HCL IMMEDIATE RELEASE TABLETS (DESIGN MIXTURE)

Formulation	Independent Variables*		
	A	B	C
M1	1	0	0
M2	0	1	0
M3	0	0	1
M4	0.5	0.5	0
M5	0.5	0	0.5
M6	0	0.5	0.5
M7	0.33	0.33	0.33
Coded Level	**Actual Values†**		
	A	**B**	**C**
0	0	0	0
0.33	4	4	4
0.5	6	6	6
1	12	12	12

*A is sodium starch glycolate (SSG), B is cross carmellose sodium (CCS) and C is pre gelatinized starch (PGS). †All quantities in milligrams. Each tablet contains metoclopramide HCl 15 mg, superdisintegrant(s) 12 mg, sodium lauryl sulphate 3 mg, microcrystalline cellulose 68 mg and magnesium stearate 2 mg.

TABLE.2 EVALUATION OF METOCLOPRAMIDE IMMEDIATE RELEASE FORMULATIONS (n=5) PREPARED AS PER SIMPLEX CENTROID DESIGN.

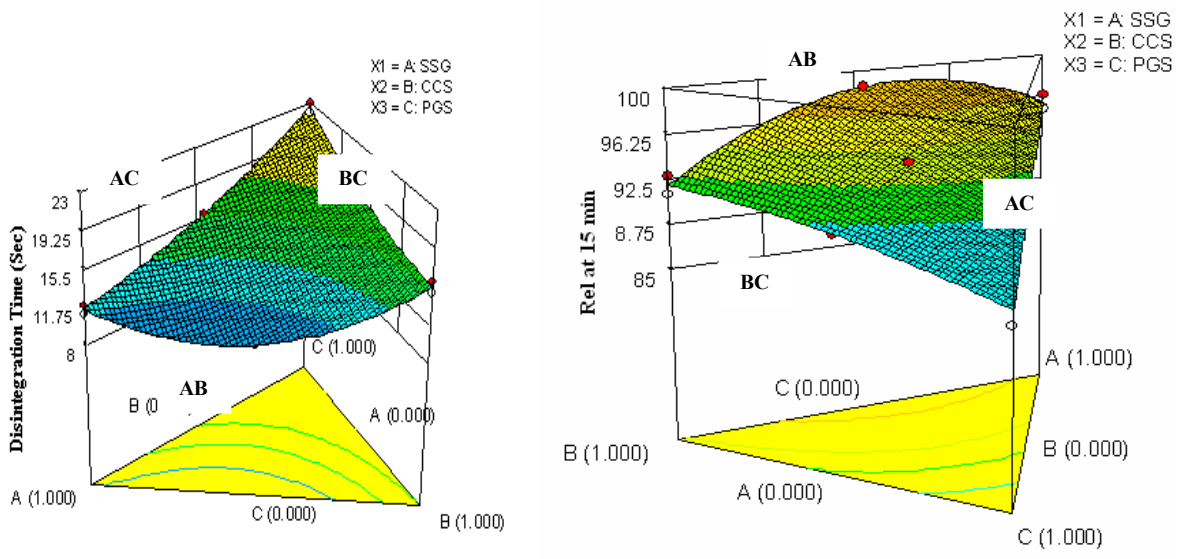
Formulation	Wetting time (sec)	Friability (%)	Disintegration Time (seconds) (Y_1)	% rel_{15min} (Y_2)
M1	3.17	0.198	12	95.22 ± 0.02
M2	3.42	0.176	15	92.758 ± 0.04
M3	4.89	0.2	22	87.050 ± 1.02
M4	3.04	0.261	9	98.311 ± 0.07
M5	4.56	0.148	18	89.845 ± 0.05
M6	4.08	0.211	16	91.246 ± 0.03
M7	3.97	0.357	13	93.892 ±0.02

TABLE.3 ANALYSIS OF VARIANCE OF THE SUPER CUBIC MODEL FOR THE RESPONSES

Model	Disintegration time	% rel_{15min}
Super cubic	Significant	Significant
R^2	0.9907	0.9676
Adj-R^2	0.9791	0.9029
F value	85.35	38.55

TABLE.4 VALIDATION OF OPTIMIZED FORMULATION

Composition		Dependent variable	Experimental value	Predicted value	Percentage error
X_1 mg	X_2 mg				
4.8	7.2	DT	9.78	9.417	3.71
		rel_{15min}	98.13	98.01	0.122
7.2	4.8	DT	8.85	9	-1.69
		rel_{15min}	98.97	98.78	0.191
9.6	2.4	DT	9.75	9.31	4.51
		rel_{15min}	98.21	98.07	0.142
8.4	3.6	DT	8.71	8.78	-0.803
		rel_{15min}	98.5	98.62	-0.121
9.9	2.1	DT	10.2	9.5	6.86
		rel_{15min}	97.72	97.87	-0.153
8.7	2.3	DT	8.84	8.79	0.565
		rel_{15min}	98.71	98.50	0.212



(A) **(B)**

Fig 1 . Triangular-dimensional contour diagrams illustrating effects of superdisintegrants on Metoclopramide immediate release tablets. (A) DT (B) Rel at 15 min

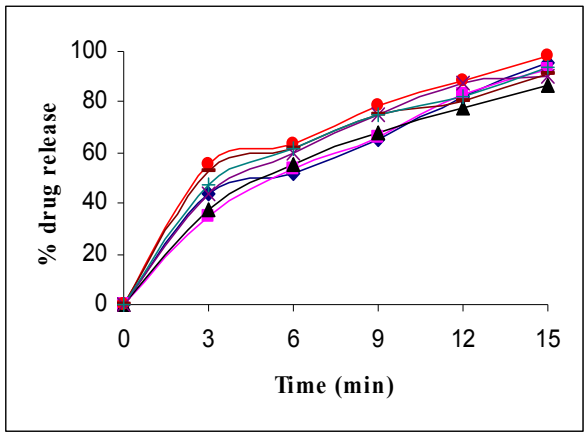


Fig.2. % drug rel $_{15min}$ of M1-M7
♦ **M1,** ■ **M2 ,** ▲ **M3,** ● **M4 ,** x **M5,** - **M6 ,** + **M7**

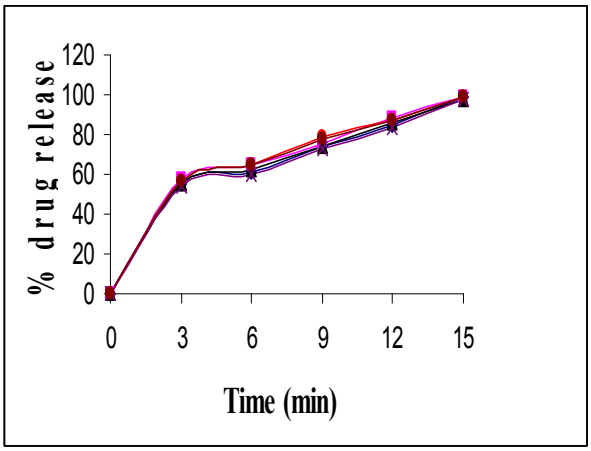
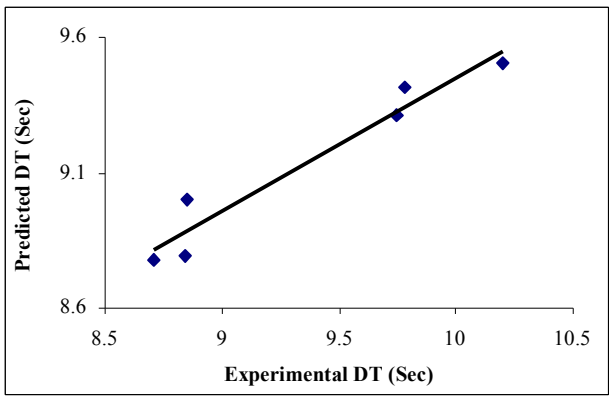
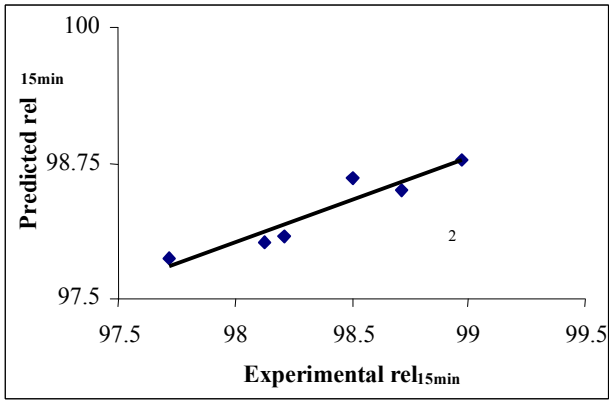


Fig.3. % drug rel $_{15min}$ of optimized formulation
♦ **A1,** ■ **A2,** ▲ **A3,** ● **A4,** x **A5,** ♦ **A6**



(A)



(B)

Fig 4 . Linear correlation plots between Observed and predicted variables A: DT; B: rel $_{15\ min}$

ACKNOWLEDGEMENT

The authors wish to acknowledge the support and counsel extended by Dr.K.G.Bothara Principal of AISSMS College of Pharmacy, Pune, Maharashtra, India.

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