Research Article

Formulation and evaluation of natural gum based fast dissolving tablet of Meclizine hydrochloride by using 3^2 factorial design

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Abstract

Objective: Current research is focused on formulation and evaluation of natural gum based fast dissolving tablet of Meclizine Hydrochloride by applying 3^2 factorial design for the improvement of the drug absorption. **Material and methods:** Direct compression method was used. Two factors as independent variable (x_1) Fenugreek mucilage(x_2) sodium saccharin glycolate were taken with three level (+1, 0, -1). The level two factors were selected on basis of preliminary experiments conducted and their effect on dependent variable (disintegration time) was estimated. **Results and conclusion:** Formulated tablets were evaluated for parameters in which the values were found to be in the range of hardness 2.1-2.6 kg/cm², thickness 2.227-2.296 mm, weight variance 182-196 mg, wetting time 58-68 seconds, water absorption ratio 0.1628-0.2439, disintegration time 56 sec – 9 min, friability 0.53-0.68 % and % cumulative drug release 88.79 – 99.87 %). The software design expert (11.0) was used for getting experimental design, modeling the response surface and calculating the static evaluation. The tablet parameters tests of formulation (F1 to F10) were observed within prescribe limit. Disintegration time observed 56 seconds, % cumulative drug release 88.79 % to 98.90 %. Batch F6 was observed as promising batch.

Keywords: Meclizine hydrochloride, fenugreek mucilage powder, fast dissolving tablets, pharmaceutical excipients

Introduction

A tablet is a pharmaceutical dosage form. Tablets could also be defined because the solid unit dose style of medicine or medicaments with or without appropriate excipients and prepared either by molding or by compression (Sharma, 2019). Quick dissolving tablet is that the most generally used dosage type due to its convenience in terms of self- administration, compactness, and ease in producing. It can be beneficial in cases like nausea, sudden episodes of allergic attack or coughing, wherever an extremely fast onset of action needed. An enhanced bioavailability notably in cases of insoluble and hydrophobic medicine, because of fast disintegration and dissolution of these tablets occurs. Stability for extended length of time, since the drug remains in solid dose kind until it's consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability (Tiwari et al.,

2018; Gupta et al., 2012). Meclizine hydrochloride (MCZ) is a first-generation antihistamine of the piperazine class. MCZ is a H1 receptor antagonist and practically insoluble in water (Vemula and Katkum, 2014). Fenugreek Mucilage are used as thickeners and flavoring for different foods. These polysaccharides, when extracted in water, can result in a highly viscous solution with slimy appearance (Saini et al., 2012; Alamri, 2014).

Material and methods

Meclizine hydrochloride was procured from Yarrow Chem, Mumbai, Fenugreek Seeds were procured from the local market, Sodium starch glycolate Magnesium Stearate, Mannitol, Talc was procured from S.D. Fine Pvt.Ltd, Mumbai, Vanillin and Micro Crystalline Cellulose was procured from, Rankem, Mumbai. All other chemicals used were of analytical grade.

Method of extraction

Fenugreek seeds were collected from local market. Collected seeds were carefully washed and dried under shade for 24 h, further dried at 30– 40°C until constant weight was obtained. Size was reduced through grinder. Powdered seeds were

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Table 1. Preparation of fast dissolving tablet

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Meclizine Hydrochloride	20	20	20	20	20	20	20	20	20	20
Gum	1	2	3	4	5	6	7	8	9	10
Sodium Starch Glycolate	10	9	8	7	6	5	4	3	2	1
Magnesium Stearate	5	5	5	5	5	5	5	5	5	5
Mannitol	25	25	25	25	25	25	25	25	25	25
Talc	5	5	5	5	5	5	5	5	5	5
Meglumine	2	2	2	2	2	2	2	2	2	2
MCC	67	67	67	67	67	67	67	67	67	67
Total Weight	135	135	135	135	135	135	135	135	135	135

passed through sieve no. #22 and stored it in air tight container for further use. Extraction of mucilage includes two steps (de Alvarenga et al., 2016).

Step1: Extraction of mucilage: Powdered seeds kept in 500ml of distilled water. Heated with continuous stirring at 60°C for approximately 4h. Concentrated solution was filtrated through muslin cloth and cool at 4°C-6°C.

Step2: Isolation of Mucilage: Extracted mucilage was isolated in acetone. This allows filtration through muslin cloth. Washed with acetone and the mucilage filtrated through muslin cloth. Processed mucilage was further dried to constant weight at 35–45°C in hot air oven. Hard mucilage cake was grinded and sieved through sieve # 22, stored in desiccators for further used (Nayak et al., 2004; Kaur et al 2011; Zhao, 2005).

Characterization of fenugreek mucilage

Swelling ratio

One gram of mucilage was placed into a 25ml glass stopper measuring cylinder. 25 ml of water was added into the cylinder containing mucilage and mixture was shaken thoroughly at intervals of every 10 min for 1 h. The sample was allowed to stand for 3 hr at room temperature and volume occupied by mucilage was measured. The mean value was calculated, related to 1 g of mucilage (Malviya et al., 2019).

Standard calibration curve: The standard calibration curve of Meclizine Hydrochloride was carried out on UV

spectrophotometer by using phosphate buffer of pH 7.4 as the solvent. From solution having concentration 100 µg/ml samples of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 and 5 ml were pipette out into 10ml volumetric flasks. The volume was made up to the mark with Phosphate buffer 7.4 to get the final concentration of 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 µg/ml respectively. The absorbance of concentration was measured at 272.00nm (Malviya et al., 2019).

Preparation of fast dissolving tablet using drug Meclizine Hydrochloride:

The superdisintegrant and gum in different ratios were used to prepare the tablets. All the ingredients were shown in table 1 were passed through sieve no. 60. The total 10 formulations (F1–F10) were prepared using different concentrations of Fenugreek mucilage and sodium starch Glycol ate to study its effect on disintegration time (Vijaya et al., 2006). Preparation of Factorial formulation with the corresponding formulation is outlined in table 2 and 3. The effect of the independent variables, viz., Fenugreek mucilage (X_1) and SSG (X_2) on the dependent variable (Swamy et al., 2008; Gohel et al., 2004; Shahi et al., 2014).

Preparation of Factorial formulation with the corresponding formulation is outlined here. The effect of the independent variables, viz., Fenugreek mucilage(X_1) and SSG (X_2) on the dependent variable, disintegration time range 11 to 58sec (Nandare et al., 2011).

Data analysis by design expert Software a 3² full factorial design was used. In this design 2 factors were evaluated, each at 3 levels and experimental trials were performed at all 9 possible combinations. The amount of Fenugreek mucilage (X_1) and the amount of SSG (X_2) was selected as independent variables. The disintegration time was selected as dependent variable. A polynomial term was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1X_1 + b_{22}X_2X_2 + b_{12}X_1X_2$$

Where, y is the dependent variable, b_0 is the arithmetic mean

Table 2. Variable with coded value in factorial design

Coded factor	Level	Factor	
		Factor (x_1) (%w/w)	Factor (x_2) (%w/w)
-1	Low	3	0.5
0	Intermediate	4	1.5
+1	High	15	2.5

Table 3. Preparation of factorial formulation

Ingredients (mg)	A1	A2	A3	A4	A5	A6	A7	A8	A9
Meclizine Hydrochloride	25	25	25	25	25	25	25	25	25
Gum	6	6	6	8	8	8	10	10	10
Sodium Starch Glycolate	1	3	5	1	3	5	1	3	5
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Mannitol	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Meglumine	2	2	2	2	2	2	2	2	2
MCC	71	69	67	69	67	65	67	65	63
Total Weight	125	125	125	125	125	125	125	125	125

response of the 9 runs, and b1 is the estimated coefficient for the factor X_1 . The main effects (X_1 and X_2) the common results of dynamical one factor at a time from its low to high price. The interaction terms (X_1X_2) show however the response changes once 2 factors are at the same time modified.

The polynomial terms (X_1X_1 and X_2X_2) are included to investigate nonlinearity (Swamy et al., 2008).

Final equations in terms of coded factors

$$DT = -0.00111 + 0.148333 X_1 - 0.19833 X_2 - 0.255(X_1X_2) + 0.351667(X_1)^2 + 0.361667(X_2)^2$$

Final equations in terms of actual factors

$$DT = -0.00111 + 0.148333 \text{ Gum} - 0.19833 \text{ SSG} - 0.255 \text{ Gum} * \text{SSG} + 0.351667(\text{Gum})^2 + 0.361667(\text{SSG})^2$$

The above equation revealed the effect of independent variables on the desired response. The regression coefficient values are the estimates of the model fitting. The r^2 was high indicating the adequate fitting of the quadratic model. The polynomial equations can also be used to draw conclusions considering the magnitude of co-efficient and the mathematical sign it carries; i.e. positive or negative

The positive coefficient of variable X_1 i.e. Fenugreek mucilage, the response of disintegration time showed an increase in the A1 and A9 value with the increase in the gum concentration.

The second variable X_2 i.e. SSG, responses showed positive coefficient for response A1 and A2, respectively.

ANOVA for the dependent variables A1 and A9, respectively are shown in table 3. ANOVA and Multiple regression analysis were done using Stat-Ease Design Expert 11.0 software. The response surface plot of the Fenugreek mucilage and SSG are shown in figure 4.

The main effect of A and B represents the average result of changing variables at a time from its low level to high level. The interaction terms (AB , A^2 , B^2) reveal the A1 and A10 changes when the two variable are simultaneously changed. The negative coefficient for the independent variable (B , B^2), (B , AB , A^2 , B^2) and (B , B^2), (B , AB) indicate unfavorable effects on the Fast

Dissolving Tablet (A1 and A9), respectively. The independent variables exhibit positive interaction which indicates the favorable effect on the Fast Dissolving Tablet (A1 and A9), respectively.

The variance Inflation Factor (VIF) measures how much the variance of that model coefficient is inflated by the lack of orthogonality in the design and calculated for fast dissolving tablet (A1 and A9) respectively, which is found to be 1 indicating good estimation of coefficients. Similarly, Ri-squared is near to zero which is leading to good model. The model F value calculated for fast dissolving tablet (A1 and A9) respectively, are found to be 2.53, and there are only 5-10% chance of large lack of fit F value which could be due to noise and non significant lack of fit F value is good fit of model. In all cases "Pred R-squared" values are in reasonable agreement with the "Adj R-squared" values. The Adeq-Precision is the measures of the signal to noise ratio. A ratio > 4 is desirable. In the case of Fast Dissolving Tablet, the Adeq-Precision value is in range of 5.3670 which indicates an adequate signal.

Direct compression

Direct compression technique is that the easiest method to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. The ingredients were weighted and passed through #60 mesh separately in these method drug with other excipient is mixed in mortal pestle geometrically and the mixture thus obtained is compressed into tablets through 6mm flat faced punch on pilot pressed 10 station machine tablet. The total weight of the formulation was maintained 200 mg (Kalyankar et al., 2015; Sukhavasi et al., 2012).

Factorial Design

A 3^2 full factorial design was used. In this style 2 factors were evaluated, each at 3 levels and experimental trials were performed at all 9 possible combinations. The amount

of Fenugreek mucilage (X1) and the amount of SSG (X2) was selected as independent variables. The disintegration time was selected as dependent variable. A polynomial term was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1X_1 + b_{22}X_2X_2 + b_{12}X_1X_2$$

Where, y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_1 is the estimated coefficient for the factor X_1 . The main effects (X_1 and X_2) represent the typical results of dynamic one factor at a time from its low to high price. The interaction terms (X_1X_2) show however the response changes once a pair of factors are simultaneously modified. The polynomial terms (X_1X_1 and X_2X_2) are included to investigate nonlinearity (Jain et al., 2012).

Evaluation of prepared tablets

Hardness

Hardness of tablet is outlined as the force applied across the diameter of the tablet within the order to break the tablet. It is done by using hardness tester like Pfizer hardness tester or Monsanto tablet hardness tester.

Thickness

Thickness of tablets is determined using vernier caliper. An average value is calculated by using tablets in $n=3$ and then the mean ($\pm$) standard deviation values of thickness are noted.

Weight Variance

According to Indian Pharmacopoeia procedure for the calculation of uniformity of weight, twenty tablets are taken and their weight is recorded individually and collectively on an electronic weighing balance. The mean of the weight of tablet was determined from the total weight.

Wetting Time

A piece of tissue paper is folded twice and is placed in a small Petri dish containing 6ml. of distilled water. A tablet is rigorously placed on the surface of the folded tissue paper and the time required for water to reach the topmost surface of the tablet is noted as the wetting time. Less is the wetting time, indicates more porous the tablet.

Water Absorption Ratio

To measure water absorption ratio of the tablet, a piece of tissue paper is folded twice and was placed in a small petri dish (Internal Diameter is= 6.5 cm) containing 5 ml of distilled water. The tablet is placed on the paper, and the time for complete wetting of the tablet was measured in seconds.

Water absorption ratio was determined using the equation:

$$R = \frac{W_b - W_a}{W_a} \times 100$$

Where,

W_a is weight of tablet before water test and W_b is weight of tablet after the test

Disintegration Time

The test is carried out using the disintegration apparatus. Distilled water is used as a disintegration media and the time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus is measured.

Friability

Friability is measured of mechanical strength of tablets. Roche friabilator is employed to see the crumbliness by following procedure. A reweighed tablet is placed in the friabilator. Friabilator comprises a plastic chamber that revolves at twenty five revolutions per minute, dropping the tablets at a distance of six inches with every revolution. The tablets are revolved within the friabilator for four minutes for one hundred revolutions. At the tip of check, tablets are reweighed; the loss within the weight of tablet is that the measure of crumbliness and is expressed in share as;

$$\% \text{ Friability} = \frac{\text{Loss in weight}}{\text{Initial Weight}} \times 100$$

In vitro drug release studies

In vitro dissolution was carried out in USP XXIV dissolution test apparatus. 900 ml Phosphate buffer of pH 6.8 solution was used as dissolution medium. The stirrer was adjusted to rotate at fifty revolutions per minute. The temperature of dissolution medium was maintained at $37 \pm 0.5^\circ\text{C}$ throughout the experiment. One lozenge was used in each test. Samples of dissolution medium (5ml) were withdrawn by means that of syringe. Solution was filtered with Whatman filter paper. Samples were withdrawn after 5, 10, 15, 20, 25, 30, 35, 45 minute intervals of time and analyzed for drug release by measuring the absorbance at 272 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium to maintain the sink condition (Malviya et al., 2019).

Results and discussion

Evaluation parameters of the prepared tablets

The prepared tablets of Meclizine Hydrochloride by direct compression were evaluated for the various parameters like Hardness in the range of 2.1-2.6 kg/cm², % Friability 0.53 - 0.68, Weight variance 182 - 196 mg, Thickness 2.227-2.296 mm, Wetting time 58-68 seconds, Water absorption ratio 0.1628 - 0.2439, Disintegration time 56 seconds – 9 minutes and % Drug content 79 - 99.87 (Table 4).

Evaluation of tablets prepared by Factorial Design

The prepared tablets of Meclizine Hydrochloride by direct

Table 4. Evaluation of prepared fast dissolving tablet

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Hardness (kg/cm ²)	2.2	2.2	2.6	2.1	2.5	2.1	2.3	2.2	2.4	2.4
Friability (%)	0.61	0.68	0.59	0.53	0.63	0.25	0.64	0.58	0.67	0.56
Weight Variation (mg)	196	186	184	188	183	184	187	182	185	184
Thickness of Tablet(mm)	2.294	2.228	2.295	2.239	2.249	2.227	2.283	2.296	2.285	2.296
Wetting Time (second)	63 sec	64 sec	58 sec	66 sec	68 sec	60 sec	59 sec	58 sec	60 sec	64 sec
Water Absorption ratio	0.2436	0.2433	0.2251	0.2224	0.2223	0.2439	0.2228	0.2224	0.02235	0.1628
Disintegration Time	6 min	8 min	9 min	5 min	7 min	56 sec	3 min	9 min	6 min	59 sec
% Drug Content	98.15	95.47	93.5	97.56	93.58	99.87	93.47	94.53	98.41	97.54

Table 5. Evaluation of factorial formulation

Formulation	A1	A2	A3	A4	A5	A6	A7	A8	A9
Hardness (kg/cm ²)	2.2	2.6	2.1	2.5	2.3	2.2	2.4	2.2	2.1
Friability (%)	0.40	0.35	0.34	0.25	0.35	0.30	0.45	0.24	0.35
Weight Variation (mg)	199.31	195.12	196.53	199.31	196.45	199.32	199.45	197.32	195.11
Thickness of Tablet (mm)	2.229	2.236	2.254	2.244	2.284	2.276	2.214	2.234	2.248
Wetting Time (second)	1.6	0.23	0.52	0.39	0.23	0.26	1.26	0.39	0.51
Water Absorption ratio	0.154	0.123	0.154	0.215	0.184	0.154	0.184	0.153	0.153
Disintegration Time (sec)	0.56	0.19	0.58	0.32	0.29	0.11	1.5	0.22	0.50
% Drug Content	94.51	93.27	96.41	97.55	96.85	99.74	91.68	92.47	94.56

Table 6. Percent cumulative drug release of prepared tablet

Time (min)	Cumulative Drug Release (%) Batch no.									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
5	75.15	72.25	78.96	69.25	67.81	67.88	65.16	63.92	62.67	65.86
10	85.01	83.02	81.05	82.71	79.09	78.16	75.42	74.02	72.99	71.56
15	90.72	87.10	85.19	89.52	87.60	88.68	84.49	82.90	81.11	79.69
20	94.71	91.71	89.13	91.22	91.79	91.72	88.65	87.68	86.20	81.48
25	96.79	94.18	93.00	95.94	94.91	94.93	91.11	89.83	87.86	89.68
30	98.60	98.27	96.86	97.55	95.80	98.90	92.98	90.67	88.79	94.15

compression were evaluated for the various parameters like Hardness in the range of 2.1-2.6 kg/cm², % Friability 0.24-0.40, Weight variation 195.11-199.45 mg, Thickness 2.214-2.284 mm, Wetting time 0.23-1.6 seconds, Wetting absorption ratio 0.123-0.215, Disintegration time 0.11-0.58 seconds and % Drug content 92.47-99.74 (Table 5, table 6 and table 7).

Dissolution study

The prepared tablets were tested for the amount of drug release at a specific period of time for 30 minutes. This study shows that the % drug release of the batch F6 shows maximum drug release of 98.90 % in the 30 minutes of time interval with the maximum drug content. Due to which it is regarded as the optimized formulation (Figure 1).

In the Study of the % drug release of the factorial design the batch A6 shows the maximum amount of drug release in the duration of 30 minutes i.e. 98.44 % (Figure 2).

Discussion

The prepared tablets of Meclizine Hydrochloride with fenugreek mucilage powder as a superdisintegrant shows that the fenugreek mucilage can be a better alternative than the other synthetic disintegrants. The evaluation parameters of the tablets shows the satisfactory values as required in the terms of hardness, weight variation, friability, thickness, wetting time, water absorption ratio, drug content and the most important disintegration time was very low. The % drug

Table 7. Percent cumulative drug release of factorial batches

Time (min)	Batch no.								
	A1	A2	A3	A4	A5	A6	A7	A8	A9
0	0	0	0	0	0	0	0	0	0
5	71.85	71.96	82.15	64.15	69.65	77.47	82.14	71.56	83.5
10	75.15	78.69	85.69	69.47	71.96	84.23	87.63	76.96	87.62
15	81.74	85.51	91.52	75.96	76.93	89.63	89.36	79.63	91.15
20	86.67	88.14	92.36	82.18	84.56	95.16	93.15	86.4	93.44
25	91.52	91.52	94.62	89.36	89.82	96.18	95.33	89.63	96.65
30	94.53	95.52	96.14	91.46	94.15	98.44	97.56	92.47	97.14

Figure 1. Percent cumulative drug release of the prepared tablets **Figure 2.** Percent cumulative drug release of the prepared factorial batches

release study shows that the drug release in the batch F6 was maximum i.e. 98.90 % and more than 50 % of the drug was released within 5 minutes with the maximum amount of drug content i.e. 99.87 with the disintegration time of 56 seconds (Figure 3). All these parameters shows that the batch F6 shows good results when compared to the other batches therefore, it was concluded that the batch F6 was the optimized batch.

Preparation of fast dissolving tablet the superdisintegrant and

Figure 3. Response surface plot of fast dissolving tablet on disintegration time

gum in different ratios were used to prepare the tablets. The total 10 formulations (F1–F10) were prepared using different concentrations of Fenugreek mucilage and sodium starch glycolate to study its effect on, Hardness (kg/cm^2) 2.1 to 2.6, Friability (%) 0.53 to 0.68, Weight variation (mg) 182 to 196, Thickness of tablet (mm) 2.227 to 2.296, Wetting time (second) 58sec to 68sec, Water absorption ratio 0.1628 to 0.2439, Disintegration time range 56sec to 9min. The value of % cumulative drug release range 88.79% to 98.90%.

Conclusion

From the present study, it can be concluded that natural super disintegrates like Fenugreek mucilage powder showed better disintegrating property than the most widely used synthetic super disintegrates like SSG in the formulations of FDTs and may be used as disintegrate in tablet formulations.

The effect of different amount of complex and surfactant is used in different batches and the blending time for powder is also different for every batch. From these parameters the evaluation of tablet batches performed like wetting time,

water absorption ratio, disintegration time, percent drug release.

From the studies made it was found that batch F6 and F10 was having good disintegration time. The factorial design conclusively demonstrated use of response surface design of fast dissolving tablet on disintegration time.

Conflict of interest: None

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