

FORMULATION AND EVALUATION OF MECLIZINE HYDROCHLORIDE FAST DISSOLVING TABLETS USING SOLID DISPERSION METHOD

BHASKAR DARAVATH^{1,2}, RAMA RAO TADIKONDA^{3*}

¹Sri Shivani College of Pharmacy, Mulugu Road, Warangal, AP, India-506007, ²Acharya Nagarjuna University, Nagarjuna Nagar, Guntur, AP, India-522510, ³Avanathi institute of Pharmaceutical sciences, Hyderabad, AP, India-500090
 Email: tadikondarao@yahoo.com

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ABSTRACT

Objective: The present research is aimed to investigate the effect of polyethylene glycol 4000 and 6000 as solid dispersion carriers on the solubility and dissolution rate of Meclizine hydrochloride.

Methods: In this, meclizine hydrochloride solid dispersions were prepared by using solvent evaporation method and evaluated for solubility studies, drug-carrier compatibility studies and *in vitro* dissolution studies. Formulations F4 and F8 were selected to prepare the tablets and compared with control tablets (conventional tablets using pure drug).

Results: From the *in vitro* dissolution studies, tablets containing polyethylene glycol 6000 showed almost complete drug release within the 20 min. The percent drug release in 20 min (Q_{20}) and initial dissolution rate for formulation F8 was $99.26 \pm 1.62\%$, $4.96\%/min$. These were very much higher compared to control tablets ($44.67 \pm 1.48\%$, $2.23\%/min$). The relative dissolution rate was found to be 2.22 and dissolution efficiency was found to be 57.94 and it is increased by 3.0 fold with F8 formulation when compared to control tablets (22.05).

Conclusion: Formulation of the meclizine hydrochloride-polyethylene glycol solid dispersions is a suitable approach to improve the solubility and dissolution rate.

Keywords: Dissolution efficiency, Initial dissolution rate, Polyethylene glycol, Relative dissolution rate, Solubility.

INTRODUCTION

Solid dispersions are drug molecular dispersions in the polymer dispersed phase in solid form and prepared by solvent evaporation method and fusion method [1]. One of the interesting processes to improve the solubility and dissolution rate of drugs can be by using a well-known process of fabricating solid dispersions [2]. This study focuses on the use of solid dispersion technologies to improve the dissolution of poorly water-soluble drugs and in turn their oral bioavailability. Solubility enhancement will increase the drug's acceptability and bioavailability by reducing the dose required and sometimes can result in faster onset of action [3, 4]. Liquisolid compact is another technique to improve the dissolution rate of many poorly soluble drugs[5].

The present study is aimed to formulate and develop Meclizine hydrochloride (MCZ) fast dissolving tablets of using solid dispersion method to improve the solubility and dissolution rate. MCZ is a first-generation antihistamine of the piperazine class drug, used in the treatment of motion sickness. It is acting as H₁ receptor antagonist and practically insoluble in water [6]. Some of the recent research examples on MCZ are meclizine hydro chloride mouth dissolving tablets [7], Cyclodextrin-meclizine HCl inclusion complexes [8], Metabolism and pharmacokinetics of meclizine suspension [9], meclizine HCl orally disintegrating tablets [10], Meclazine-maltodextrin oro-dissolving tablets [11]. In the present study an attempt was made to prepare a solid dispersion of MCZ using PEG 4000 and 6000 by solvent evaporation method. PEG act as continuous phase in the solid dispersion in which MCZ is dispersed as internal phase. Some of the reported drugs as PEGs solid dispersions are nisoldipine [12], simvastatin [13], diclofenac sodium [14], clopidogrel [15], gliclazide [16], paracetamol [17]. From the support of above literature, it was planned to prepare the MCZ-PEG solid dispersions to enhance the dissolution rate.

MATERIALS AND METHODS

Materials: Meclizine hydrochloride was gift sample from Samed labs Ltd, India. PEG 4000 and 6000 were obtained from CDH, Delhi, India and all other reagents used were of analytical grade and obtained from S.D. Fine Chemicals, Mumbai, India.

Preparation of solid dispersions

MCZ- PEG solid dispersions using 4000 and 6000 grades as carriers were prepared by the solvent evaporation method (Table 1). Accurately weighed amount of drug and carriers in various ratios dissolved in ethanol in a round bottom flask and the solvent was evaporated at 45°C temperature. Solid dispersions were subsequently stored in a vacuum oven at room temperature for 48 h to remove the residual solvent. The dried solid dispersions were grinded in a mortar and pestle and passed through sieve # 60 and were stored in desiccators until use.

Table 1 Formulation of MCZ solid dispersions

Formulation Code	Ingredients quantity in mg			MCZ:PEG ratio
	MCZ	PEG 4000	PEG 6000	
F1	25	12.5	-	1:0.5
F2	25	25	-	1:1
F3	25	50	-	1:2
F4	25	100	-	1:4
F5	25	-	12.5	1:0.5
F6	25	-	25	1:1
F7	25	-	50	1:2
F8	25	-	100	1:4

Solubility studies

The solubility studies of prepared solid dispersions were performed in 0.1 N HCl, distilled water and 7.4 pH phosphate buffers. An excess amount of preparation was weighed and transferred into conical flasks which contain 10 ml of media. The content in conical flask were sonicated for 2 h at room temperature, there after the samples were placed on a shaker, agitated at room temperature for 48 h. Finally the suspensions were filtered through a Whatman filter paper, suitably diluted and analyzed spectrophotometrically at 232 nm.

Drug-carrier compatibility studies

The thermograms were recorded for drug, carrier, and physical mixture using differential scanning calorimeter (Shimadzu, Japan). About 2-4 mg sample in an open aluminium standard pan was heated at a scanning rate of 5° C /min from a temperature 0 to 450 °C under a nitrogen gas flow.

Micromeritic properties of blend

The flow properties of powder plays vital role in the manufacturing of tablets. The flow properties were studied through measuring the angle of repose, Carr's index. Powder mixtures of different formulations were evaluated for angle of repose, bulk density, tapped density and compressibility index. The fixed funnel method was employed to measure the angle of repose (θ) and it was calculated using the following formula:

$$\tan \theta = h/r \quad [1]$$

In which, θ is the angle of repose, h is the height of the cone and r is radius of base. To measure the angle of repose, a funnel was fixed to a stand so that the lower tip of funnel was 2.5 cm above the surface. A graph paper was placed on a flat surface. The powder blend was allowed to fall freely on the graph paper through the funnel (6.8 cm diameter), till the tip (8 mm diameter) of heap formed just touches the funnel. The radius of heap was noted and the angle of repose was determined. The bulk density (ρ_b) of a powder was determined by measuring the volume of a known mass of powder sample into a 50 ml graduated cylinder. Tapped density (ρ_{tap}) of powder samples were determined by a tap density apparatus. The apparatus was set for 500 tapings for 5 min at stroke height 20 mm at the rate of 100 strokes/min [18]. The Carr's Index is a measure of the propensity of a powder to be compressed and it is calculated using the following formula:

$$\text{Carr's Index} = [(\rho_{tap} - \rho_b) / \rho_{tap}] \times 100 \quad [2]$$

Preparation of fast dissolving tablets

The fast dissolving tablets (FDTs) were prepared for selected solid dispersion preparations i.e., F4 and F8 formulations (Table 4). Direct compression method was used to prepare the FDTs. The solid dispersion powder equivalent to 25 mg of MCZ, crosspovidone and other excipients were passed through a mesh no 60. The powdered solid dispersion was mixed with crosspovidone. Then spray-dried lactose was added and mixed in a poly bag for 5-10 min. The blend was then lubricated with talc and magnesium stearate for another 5 min. The resultant mixture was directly compressed into tablets using rotary tableting machine.

Table 4 Composition of MCZ tablets using selected solid dispersions

Formulation Code	Ingredients in mg		
	F4	F8	Control
MCZ solid dispersion equivalent to 50 mg MCZ	125	125	-
Pure MCZ	-	-	25
Crosspovidone (5%)	10	10	5
Spry-dried lactose	59	59	67
Magnesium stearate (1%)	2	2	1
Talc (2%)	4	4	2
Total Tablet weight	200	200	100

Physical evaluation of prepared FDTs

The prepared tablets were evaluated for the physical properties like weight variation, hardness and friability [19]. For estimating weight variation, twenty tablets of each formulation were weighed using an electronic weighing balance (Shimadzu). The hardness was measured using Monsanto tablet hardness tester. Friability was determined by taking six tablets in a friabilator (Electrolab).

Drug content

Randomly selected ten tablets were powdered and 100 mg of the powder was transferred to a 100 ml volumetric flask. Initially about 50 ml of 7.4 pH phosphate buffer was added to the volumetric flask and allowed to stand for 6-8 h with intermittent shaking to ensure complete solubility of the drug. Then the volume was made up to

100 ml with buffer. The solution was filtered and analyzed for MCZ content at 232 nm using double beam UV-Visible spectrophotometer.

In vitro Disintegration time

The disintegration time of prepared tablets was estimated using the Gohel procedure [20]. 10 ml of water at room temperature was taken in a petridish of 10 cm in diameter. The tablet was then carefully placed in the centre of petridish and the time required for the tablet to completely disintegrate into fine particles was noted. Measurements were carried out in triplicates.

In vitro Dissolution Study

The MCZ release from prepared tablets was studied using USP XXIV Type II dissolution apparatus (Electro lab) at 50 rpm speed and 37±0.5 °C temperature in 900 mL of 7.4 pH phosphate buffers. An aliquot of 5 ml was collected at predetermined time intervals and replaced with fresh dissolution medium. The samples were filtered by passing through 0.45 µm membrane filters (Millipore, USA) and analyzed spectrophotometrically at 232 nm.

Dissolution parameters

A graph was plotted using cumulative percent drug release as a function of time and percent drug release in 20 min (Q_{20}) was calculated. Initial dissolution rate (IDR) was calculated as percentage dissolved drug over the first 20 min per min. Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (measured by using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. Relative dissolution rate (RDR) was the ratio between amount of drug dissolved from optimized formulation and that dissolved from the control formulation at 20 min [21].

Stability studies

The stability studies of prepared tablets were conducted on F8 formulation tablets according to ICH guidelines [22]. The packed tablets ($n=3$) were stored in the stability chamber maintained at 40±2 °C and 75±5% RH for six months. After six months of storage, the samples were collected and analyzed for assay and *in vitro* dissolution rate. Then the data was analyzed using paired t-test to test the significant variation at 0.05 level of significance (LS). Then the similarity index (F2) was calculated between dissolution rates of tablets before and after storage to prove the stability of tablets [23, 24].

RESULTS

Solubility studies

The solubility studies were conducted in different media for all the prepared solid dispersions and compared with pure drug. From the solubility studies, it was found that as the increase in pH of the media increased the solubility i.e. MCZ showed greater solubility in 7.4 pH phosphate buffer when compared others. The solubility data of different formulations showed in Table 2. From the results given in table, solid dispersions with PEG 6000 showed greater solubility when compared to PEG 4000 and in both carriers, by increasing the carrier concentration the solubility also increased proportionally. From all the above formulations, F8 formulation showed highest solubility in 7.4 pH phosphate buffer.

Table 2 Solubility studies of MCZ-PEG solid dispersions (mg/ml)

Formulation Code	MCZ solubility in mg/ml		
	0.1 N HCl	Distilled Water	7.4 pH Buffer
Pure MCZ	0.334±0.03	0.992±0.12	0.998±0.37
F1	0.398±0.91	1.116±0.25	1.369±0.34
F2	0.441±0.62	1.231±0.74	1.452±0.16
F3	0.492±0.37	1.294±0.29	1.528±0.48
F4	0.514±0.49	1.423±0.57	1.609±0.37
F5	0.407±0.76	1.127±0.82	1.394±0.23

F6	0.478±0.87	1.268±0.38	1.471±0.92
F7	0.516±0.28	1.317±0.45	1.546±0.67
F8	0.549±0.19	1.461±0.61	1.637±0.73

Drug-carrier compatibility studies

The thermograms of the MCZ, PEG 6000 and MCZ with PEG 6000 were shown in Figure 1. The DSC thermograms of MCZ exhibited physical mixture a sharp endothermic peak corresponding to melting point. The thermogram of physical mixture with PEG 6000 showed a short endothermic peak of drug indicating that there were no interactions between drug and carriers.

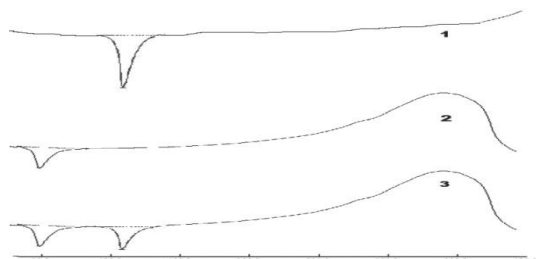


Fig.1: DSC thermograms of A) MCZ B) PEG 6000 C) F8 physical mixture

Micromeritic properties of blend

The powder mixture for tablets were characterized with respect to angle of repose, bulk density, tapped density and Carr's index, (Table 3). Angle of repose was less than 30° and Carr's index values were less than 18 for the powder mixture of all the batches indicating good flowability [25].

Table3: Determination of flow properties (Mean ± SD, n=3)

Formulation	Angle of Repose (°)	Bulk Density (gm/cc ³)	Tapped Density (gm/cc ³)	Carr's Index (%)
F4	29.47±0.62	0.331	0.388	17.22
F8	30.12±0.41	0.338	0.399	18.04
Control	28.14±2.19	0.334	0.395	18.26

Evaluation of fast dissolving tablets

Table 5 showed all the physical parameters determined for MCZ tablets. In weight variation test, the pharmacopoeial limits for the tablets of not more than 5% of the average weight. The tablet hardness and friability were found to be near to 3 kg/cm² and 0.33%, demonstrating the integrity and strength of tablets. The tablets assay was found to be around 99%. From the disintegration test, the prepared tablets were disintegrated rapidly and it was found near to 120 sec.

Dissolution Studies of Fast Dissolving Tablets

From the *in vitro* dissolution studies, tablets made from PEG 6000 showed better results when compared to PEG 4000 and control tablets. The formulation F8 containing PEG 6000 showed fast dissolution than formulation F4 containing PEG 4000 and improved significantly when compared to control tablets. Figure 2 demonstrated the MCZ release patterns by above formulations. The percent drug release in 20 min (Q₂₀) and initial dissolution rate (IDR) for formulation F8 was 99.26±1.62%, 4.96%/min (Table 6). These were very much higher compared to pure drug (44.67±1.48 %, 2.23%/min). The improvement in the dissolution characteristics of a drug described in terms of dissolution efficiency (DE) and relative dissolution rate (RDR). The RDR was found to be 2.22. The DE was found to be 57.94 and it was increased by 3.0 fold with F8 FDT formulation compared to control tablets (22.05).

Table 5: Physical evaluation of MCZ tablets

Formulation	Weight variation* (mg)	Hardness† (Kg/cm ²)	Friability (%)	Disintegration time‡ (sec)
F4	201.68±1.31	3.0±0.42	0.33	122±4
F8	201.92±1.46	3.0±0.64	0.33	121±4
Control	101.82±1.27	3.0±0.26	0.27	119±4

* All values represent mean ± standard deviation, n=20; † n=6; ‡ n=3

Table 6: Dissolution parameters of MCZ F8 and control tablets (Mean ± SD, n=3)

Formulation	(Q ₂₀)	IDR (%/min)	DE	RDR
F8	99.26±1.62	4.96	57.94	2.22
Control	44.67±1.48	2.23	22.05	

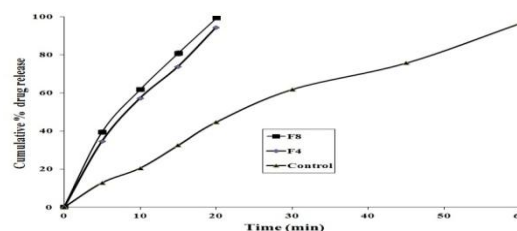


Fig.2: Dissolution studies of MCZ fast dissolving tablets

Stability studies

From the stability studies, after storage of six months, the formulation F8 was subjected to a drug assay and *in vitro* dissolution studies (Table 7) and from the statistical analysis there was no significant difference between before and after storage ($P < 0.05$). The similarity index value between dissolution profiles of optimized formulation before and after storage was found to be 84.07.

Table7: Stability studies of MCZ F8 tablets (n=3)

Time (min)	Before storage	After 6 months storage	t-test at 0.05 LS	Similarity Factor (F2)
0	0.00±0.00	0.00±0.00	Not Significant	84.07
5	39.45±1.68	38.12±1.56		
10	61.78±1.24	59.49±1.73		
15	80.89±1.35	78.76±1.28		
20	99.26±1.62	97.92±1.46		
% Assay	99.12±1.34	98.26±1.38	Not Significant	--

DISCUSSION

In present study, MCZ solid dispersions were prepared by using solvent evaporation method by incorporating PEG 4000 and 6000 as carriers to improve the solubility and dissolution rate. After preparation of solid dispersions, measurement of aqueous solubility was one of the important factors, which govern the dissolution rate. The solubility of MCZ solid dispersion formulations was determined in 0.1 N HCl, distilled water and phosphate buffer pH 7.4. From the solubility studies, it was found that as increase pH of the media, increases the solubility. All the formulations exhibited significant increase in solubility in phosphate buffer pH 7.4. Similar type of results observed in Patel et al study i.e., the solubility of flurbiprofen was measured in four different media and the results showed that the solubility of the flurbiprofen was highest at pH 7.2 [26]. From the solubility studies, all the formulations showed significant increase in solubility when compared to pure drug.

The DSC studies of pure drug, PEG 6000 and physical mixture of both showed that there was no interaction between drug and

carrier. After the completion of solubility studies, then the powder mixtures of solid dispersions were evaluated for physical parameters like angle of repose, tapped density, bulk density and Carr's index. The results of angle of repose ($<30^\circ$) and Carr's index (<18) indicates fair to passable flow properties of the powder mixture. Based on the above results, the prepared solid dispersions of F4 and F8 formulations were converted into tablets and evaluated for physical parameters as well as *in vitro* dissolution rate. The prepared tablets were studied for their physical properties like weight variation, hardness, friability and drug content uniformity and they were complied with pharmacopoeial limits. The average percentage deviation of all tablet formulations was found to be within the mentioned limit. From the physical characterization, all tablet formulations were uniform in hardness, friability and drug content uniformity.

From the dissolution studies, tablets with PEG 6000 were showed increased dissolution rate when compared to PEG 4000. Among the F4, F8 and control tablets, F8 formulation with PEG 6000 as hydrophilic carrier, the dissolution rate of MCZ was increased at a significant level. Similar type of solubility enhancement was observed with PEG 6000 solid dispersions [15]. The probable reasons and mechanisms of increased dissolution rates of solid dispersions have been proposed by Ford. It includes a decrease in crystallite size, solubilization effect of the carrier, absence of aggregation of drug crystallites, enhanced wettability and dispersibility of the drug from the dispersion, dissolution of the drug in the hydrophilic carrier, drug conversion to amorphous state and finally, a combination of the mentioned mechanisms [2]. Overall increase in the dissolution performance of the optimized formulation was described in terms of dissolution parameters (IDR, DE, RDR) and when compared with pure drug, all the above parameters were increased in case of F8 formulation. Similar type of improvement in IDR, DE, RDR was reported in the study of Vemula et al [27]. After storage of six months, the formulation was subjected to a drug assay and *in vitro* dissolution studies and the data showed that there was no significant change. The similarity index value was found as 84.07, which is more than 50 indicates similarity between the dissolution profile before and after storage [20, 21].

CONCLUSION

Present research was intended to enhance the solubility and dissolution rate of MCZ using PEG solid dispersions. From the *in vitro* dissolution studies, tablets made from PEG 6000 showed better results. The percent drug release in 20 min (Q_{20}) and initial dissolution rate (IDR) for formulation F8 was $99.26 \pm 1.62\%$, $4.96\%/min$ (Table 6). These were very much higher compared to pure drug ($44.67 \pm 1.48\%$, $2.23\%/min$). The RDR was found to be 2.22. The DE was found to be 57.94 and it is increased by 3.0 fold with F8 FDT formulation compared to control tablets (22.05). Thus the development of MCZ-PEG solid dispersions can be a promising method to attain the fast dissolution rate.

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