DOI: http://dx.doi.org/10.4314/star.v3i1.9
ISSN: 2226-7522(Print) and 2305-3327 (Online)
Science, Technology and Arts Research Journal
Sci. Technol. Arts Res. J., Jan-March 2014, 3(1): 48-52
Journal Homepage: http://www.starjournal.org/

Original Research

Development and Physical Characterization of Meclizine Hydrochloride Solid Dispersions by using Polyethylene Glycol 8000

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Abstract

Development of the meclizine hydrochloride solid dispersions using polyethylene glycol 8000 is not only to enhance the solubility and dissolution rate but also to produce rapid onset of action. The objectives of present research are to improve the solubility and dissolution rate of meclizine hydrochloride using solid dispersion method. In the present study, the solid dispersions were prepared using solvent evaporation method and evaluated for different physical parameters such as solubility, drug carrier compatibility and powder flow properties. From the results of solubility studies, F4 formulation was selected to prepare the fast dissolving tablets because it showed highest improvement in the solubility among the all formulations and compared with control tablets (conventional tablets using pure drug). The percent drug release in 15 min (Q_{15}) and initial dissolution rate for F4 tablets was 98.52±1.34%, 6.56%/min and these were very much higher compared to control tablets (32.49±1.29 %, 2.17%/min). The relative dissolution rate was found to be 3.03 and dissolution efficiency was found to be 54.45 and it is increased by 3.5 fold with F4 formulation compared to control tablets (16.55). Hence the formulation of polyethylene glycol 8000 solid dispersions is a suitable method to enhance the solubility and dissolution rate of meclizine hydrochloride. Further research warranted to study the efficacy of the developed formulations has to be assessed by pharmacokinetic studies.

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Article Information

Article History:

Received : 30-12-2013

Revised : 10-03-2014

Accepted : 24-03-2014

Keywords:

Dissolution efficiency

Initial dissolution rate

Relative dissolution rate

Solvent evaporation

Solubility studies

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INTRODUCTION

Now days, the pharmaceutical formulation scientists are extensively paying the attention on development of oral dosage forms of poor aqueous solubility drugs through various solubility enhancing approaches (Kaushik *et al.*, 2004). Among those, solid dispersions is one of the widely used approaches to of enhance the solubility and dissolution rate of poorly water-soluble drugs (Patil and Gaikwad, 2009). Solid dispersions are defined as molecular dispersions of drugs in a polymer in solid form. Solvent evaporation method and fusion method are widely used to formulate the solid dispersions (Vippagunta *et al.,* 2002).

Meclizine hydrochloride (MCZ) is a first-generation antihistamine of the piperazine class drug. It is acting as H1 receptor antagonist and practically insoluble in water (Goyani et al., 2012). MCZ is widely used in the treatment of motion sickness, but due to poor water solubility delayed the onset of action. To overcome this problem, this drug is selected for the present study. Nimisha *et al.* (2012) formulated the MCZ mouth dissolving tablets to enhance the dissolution rate as well as the patient compliance. In this study, mouth dissolving tablets were prepared by superdisintegrant addition and sublimation technique and they showed sufficient mechanical integrity to assist patients of any age group for easy administration. George and Vasudevan (2012) were prepared the cyclodextrin-MCZ inclusion complexes to investigate the effect of 2-hydroxypropyl-β-cyclodextrins and β-cyclodextrins on MCZ aqueous solubility and dissolution. The phase solubility profile indicated that the solubility of MCZ was significantly increased in the presence of both 2-hydroxypropyl-β-cyclodextrin and β-cyclodextrin and their in *vitro* dissolution study were showed that, the solubility and dissolution rate of MCZ were significantly improved by complexation with 2-hydroxypropyl-β-cyclodextrin. Vangala *et al.* (2014) developed and prepared the MCZ sublimated fast dissolving tablets to improve the dissolution rate and the tablets containing 10% w/w camphor as sublimating agent showed rapid drug release when compared to other formulations. Gupta *et al.* (2011) developed the MCZ

rapidly dissolving oral films to enhance the dissolution rate and to mask the bitter taste. In this study, the fast dissolving films with suitable appearance, mechanical strength and disintegration time were obtained using Methocel E-5 as a primary film former. MCZ, a poorly water soluble and bitter drug could be successfully incorporated in the fast dissolving films with the help of solubilizers such as β-Cyclodextrine and polyethylene glycol 400. The perusal of the literature showed that there is no literature available on the use of less polymer concentration for the preparation of fast dissolving tablets. Hence, the present research has been undertaken to formulate the MCZ fast dissolving tablets of using solid dispersion method to enhance the solubility and dissolution rate.

MATERIALS AND METHODS

Materials

Meclizine hydrochloride was gift sample from Symed labs Ltd, India. Polyethylene Glycol 8000 and all other reagents used were of analytical grade and obtained from S.D. Fine Chemicals, Mumbai, India.

Preparation of Solid Dispersions

In this study, MCZ solid dispersions were prepared by the solvent evaporation method using PEG 8000 as carrier (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 40°C temperature. Then it was stored in a vacuum oven at room temperature for 48 h to remove the residual solvent. The dried solid dispersions were grinded, passed through sieve # 60 and stored in desiccators until use (Chaitanya *et al.,* 2014).

Table 1: Formulation of MCZ-PEG8000 solid dispersions.

Formulation Code	MCZ HCl	MCZ:PEG 8000 ratio
F1	25	1:0.5
F2	25	1:1
F3	25	1:2
F4	25	1:4
F5	25	1:6
F6	25	1:8

Solubility Studies

The prepared solid dispersions were evaluated for solubility studies in 0.1 N HCl, distilled water and 7.4 pH phosphate buffers. An excess amount of MCZ solid dispersion 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. Subsequently, the suspensions were filtered through a Whatman filter paper. The filtrate was suitably diluted and analyzed spectrophotometrically at a wavelength of 232 nm using a double beam UV-Visible spectrophotometer (Vaskula *et al.,* 2012).

Drug-carrier Interaction 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 5^0 C/min from a temperature 0 to 450 ^{0}C under a nitrogen gas flow (Neduri *et al.,* 2013).

Evaluation of Flow Properties

The flow properties were determined by calculating the angle of repose and Carr's index. Powder mixtures of different formulations were evaluated for angle of repose, bulk density, tapped density and Carr's index. The fixed funnel method was employed to measure the angle of repose (θ) and it was calculated using the following formula:

$$Tan\ \theta = h/r \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots [1]$$

In which, θ is the angle of repose, h is the height of the cone and r is radius of the cone 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 from this angle of repose was determined. The bulk density (ρ_b) of a powder is determined by measuring the volume of a known mass of powder sample that may have been passed through a screen, 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 (Veerareddy and Vemula, 2012). The Carr's Index is a measure of the propensity of a powder to be compressed and it is calculated using the following formula:

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

Preparation of Fast Dissolving Tablets

Formulation F4 was selected to prepare the MCZ fast dissolving tablets (FDTs) based on the results of dissolution and solubility studies (Table 2). The FDTs were prepared by direct compression method. 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 proper portion of crosspovidone. Then excipients other than glidant and lubricant were added and mixed in a poly bag for 5-10 min. The obtained blend was lubricated with talc and magnesium stearate for another 5 min and the resultant mixture was directly compressed into tablets using rotary tabletting machine (Vemula *et al.,* 2010).

Table 2: Composition of MCZ tablets using selected solid dispersions.

Formulation Code	Ingredients in mg	
	F4	Control
MCZ Solid dispersion equivalent to 50 mg MCZ	125	-
Pure MCZ	-	25
Crosspovidone	10	10
Spry-dried lactose	59	159
Magnesium stearate	2	2
Talc	4	4
Total Tablet weight	200	200

Evaluation of Physical Parameters

The prepared tablets were studied for their physical properties like weight variation, hardness, friability and drug content unifrmity. For estimating weight variation, 20 tablets of each formulation were weighed using an

electronic weighing balance (AW 120, Shimadzu Corporation, Japan). The hardness of six tablets was measured using Monsanto tablet hardness tester. Friability was determined on ten tablets in a Roche friabilator (Electrolab, Mumbai, India). For estimation of drug content, ten tablets were crushed, and 100 mg of the powder was accurately weighed and 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, filtered and analyzed for MCZ content at 232 nm. *In vitro* disintegration time of FDT's was estimated using the Gohel procedure. Briefly, 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 (Gohel *et al*., 2004).

In vitro Dissolution Study

The MCZ release from the prepared FDTs was carried out using USP XXIV Type II dissolution apparatus (Electro lab, TDT-08L) at a rotation speed of 50 rpm, and a temperature of 37.0±0.5 °C. The drug release studies were carried out in 7.4 pH phosphate buffer. 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) & analyzed spectrophotometrically at 232 nm. Then a graph was plotted using cumulative percent drug release as a function of time and percent drug release in 15 min (Q15) was calculated. Initial dissolution rate (IDR) was calculated as percentage dissolved of drug over the first 15 min per min. Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (measured 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) is the ratio between amount of drug dissolved from best formulation and from the control formulation at 15 min (vemula *et al.,* 2011).

Stability Studies

The stability studies of prepared tablets were planned on the F4 tablets according to ICH guidelines. The packed samples (n=3) were stored in the stability chamber maintained at 40±2 ^{0}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 (Vemula and Veerareddy, 2013; Vemula and Bontha, 2013).

RESULTS AND DISCUSSION

Solubility Studies of MCZ Solid Dispersions

The aqueous solubility of the solid dispersion formulations of different carriers was determined in different media i.e., 0.1 N HCl, distilled water and phosphate buffer pH 7.4. From the solubility studies of the prepared solid dispersions in different media, it was found that as the increase in pH of the media increased the solubility i.e. MCZ showed superior solubility in 7.4 pH phosphate buffer when compared others. The solubility data of different formulations using different carriers showed in Table 3. From the results given in above tables, solid dispersions with PEG 8000 showed significant improvement in solubility with increasing PEG ratio up to 1:4 ratios, but after no significant improvement in solubility by increasing the ratio of carrier. From all the solid dispersions, formulation F4 showed highest solubility in 7.4 pH phosphate buffer. Similar type of results observed in Patel *et al.,* 2011 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, and decreased as the pH decreases.

Table 3: Solubility studies of MCZ-PEG 8000 solid dispersions (Mean ± SD, n=3)

Formulation Code	MCZ solubility in mg/ml		
	0.1 N HCl	Distilled Water	7.4 pH Buffer
Pure FLB	0.342±0.21	0.961±0.18	0.975±0.23
F1	0.409±0.19	1.127±0.15	1.424±0.46
F2	0.487±0.27	1.292±0.28	1.486±0.12
F3	0.518±0.36	1.343±0.56	1.579±0.28
F4	0.542±0.13	1.471±0.48	1.663±0.53
F5	0.604±0.32	1.481±0.75	1.669±0.37
F6	0.613±0.18	1.489±0.51	1.672±0.72

Drug-carrier Interaction Studies

The thermograms of the MCZ, PEG 8000, physical mixture of MCZ with PEG 8000 were shown in Figure 1. The DSC thermograms of MCZ exhibited a sharp endothermal peak around 206.66^{0}C corresponding to melting point. The DSC thermogram of PEG 8000 exhibited a broad endothermal peak around 69.5^{o}C corresponding to its melting point. The thermogram of physical mixture with PEG 8000 showed a short endothermal peak of drug at 206 ^{0}C indicating that there were no interactions between drug and carrier.

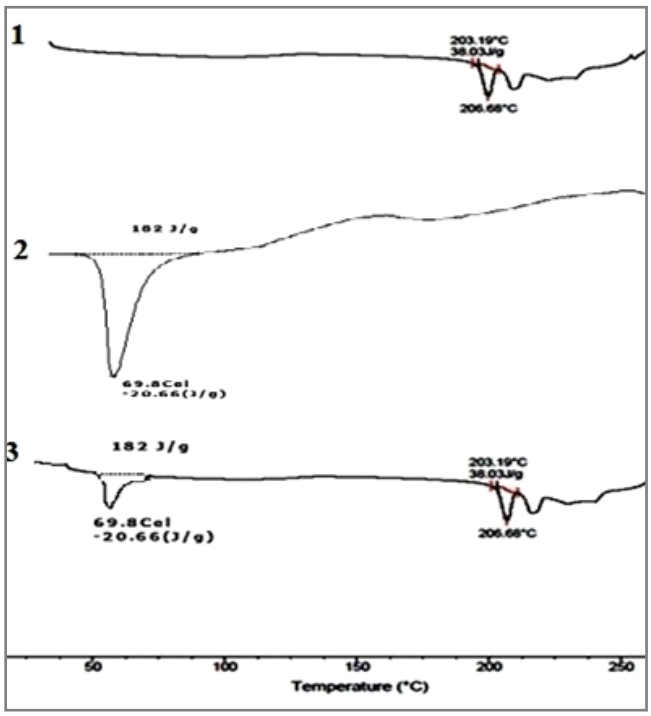

Figure 1: DSC thermograms of 1) MCZ 2) PEG 8000 3) F4 physical mixture.

Evaluation of Flow Properties

The powder mixture for tablets were characterized with respect to angle of repose, bulk density, tapped density and Carr's index (Table 4). Angle of repose was less than 35° and Carr's index values were less than 21 for the powder mixture of all the batches indicating good to fair flowability (Staniforth and Aulton, 2007).

Evaluation of Physical Parameters

Based on the solubility studies, the better solid dispersions were converted into 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 around 3.0 kg/cm^2 and 0.38%, demonstrating the integrity and strength of tablets. The tablets assay was found to contain 98.76±1.43%. From the disintegration test, the prepared tablets were disintegrated rapidly and it was found to be around 120 sec.

***In vitro* Dissolution Study**

From the in vitro dissolution studies, tablets made from 1:4 ratio solid dispersion (F4) showed fast dissolution (98.52±1.34% in 15 min) than other formulations and improved significantly when compared to control tablet (Figure 2). From the *in vitro* dissolution studies, F4 FDTs showed significant increase in dissolution rate when compared to control tablets with pure drug. In the following reported study by Singh et al., similar type of solubility enhancement was observed with PEG 6000 solid dispersions (Singh *et al.,* 2011).

The percent drug release in 15 min (Q_{15}) and initial dissolution rate for formulation F4 was 98.52±1.34%, 6.56%/min. These were very much higher compared to control tablets (32.49±1.29 %, 2.17%/min). The relative dissolution rate was found to be 3.03 and dissolution efficiency was found to be 54.45 and it is increased by 3.5 fold with F4 formulation compared to control tablets (16.55). Overall increase in the dissolution performance of the optimized formulation was described in terms of dissolution parameters (IDR, DE, RDR) and when compared with control tablets and all the above parameters were increased in case of F4 formulation (Table 6). Similar type of improvement in IDR, DE, RDR was reported in the study of Vemula *et al.* (2011).

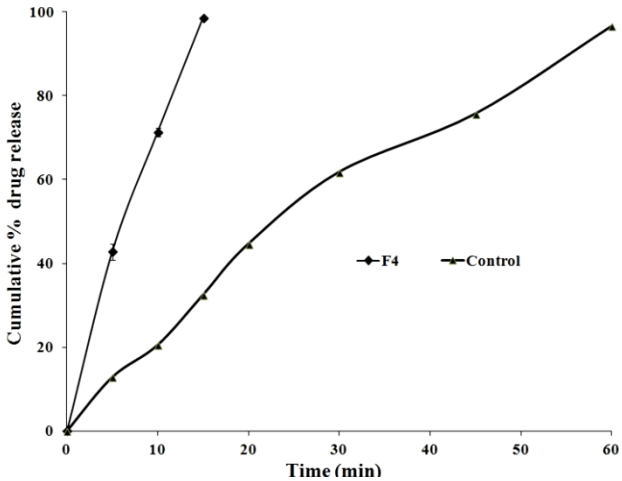

Figure 2: Dissolution studies of MCZ fast dissolving and control tablets

Stability Studies

After storage of six months, the formulation F4 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 85.12, which is more than 50 indicates similarity between the dissolution profile before and after storage (Vemula and Veerareddy, 2013; Vemula and Bontha, 2013).

Table 4: Evaluation of pre-compression parameters (Mean ± SD, n=3).

Formulation	Angle of Repose (^{0})	Bulk Density (gm/cc^3)	Tapped Density (gm/cc^3)	Carr's Index (%)
F4	29.15±1.72	0.345	0.407	15.23
Control	27.36±1.26	0.339	0.397	14.61

Table 5: Physical properties of MCZ tablets.

Formulation	Weight variation* (mg)	Hardness† (Kg/cm^2)	Friability (%)	Disintegration time‡ (sec)	Drug content‡ (%)
F4	201.18±1.72	3.0±0.23	0.38	121±4	98.76±1.43
Control	201.76±1.39	3.0±0.18	0.33	118±4	99.12±1.38

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

Table 6: Dissolution parameters of MCZ F4 and control tablets (Mean ± SD, n=3).

Formulation	(Q_{15})	IDR (%/min)	DE	RDR
F4	98.52±1.34	6.56	54.45	3.03
Control	32.49±1.29	2.17	16.55	

Table 7: Stability Studies of MCZ F4 tablets (Mean ± SD, 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	85.12
5	42.61±1.37	40.23±1.45		
10	71.34±1.45	69.75±1.24		
15	98.52±1.34	96.79±1.19		
% Assay	**98.76±1.43**	**97.14±1.28**	**Not Significant**	**--**

CONCLUSION

Attempts was made to prepare the solid dispersions using various weight ratios of meclizine hydrochloride and PEG 8000 and evaluated for physiochemical properties. *In vitro* dissolution rate of solid dispersion tablets was improved significantly when compared to control tablets due to intermolecular interactions between the polymer and drug. From the results of *in vitro* dissolution study, tablets containing polyethylene glycol 8000 showed almost complete drug release within the 15 min. The percent drug release in 15 min (Q_{15}) and initial dissolution rate for formulation F4 was 98.52±1.34%, 6.56%/min. These were very much higher compared to control tablets (32.49±1.29%, 2.17% /min). The relative dissolution rate was found to be 3.03 and dissolution efficiency was found to be 54.45 and it is increased by 3.5 fold with F4 tablets compared to control tablets (16.55). Thus the development of the PEG solid dispersions can be a promising alternative method to gain the fast dissolution rate.

ACKNOWLEDGEMENT

The authors acknowledge the Symed labs Ltd, India for gift samples. The authors also thank to Management, Chaitanya College of Pharmacy Education and Research for providing facilities.

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