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Development and *in vitro* Characterization of Meclizine Hydrochloride Solid Dispersions

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ABSTRACT

The present research was aimed to develop the meclizine hydrochloride-polyethylene glycol 20000 solid dispersions to enhance the solubility and dissolution rate. They were prepared using solvent evaporation method and evaluated for solubility studies, drug-carrier compatibility studies and *in vitro* dissolution studies. From the solubility studies, formulation F4 was selected to prepare the fast dissolving tablets and compared with control tablets (conventional tablets using pure drug). From the results of *in vitro* dissolution study, tablets containing polyethylene glycol 20000 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 98.46±1.24%, 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 54.44 and it is increased by 3.4 fold with F4 formulation compared to control tablets (16.55). Thus the formulation of polyethylene glycol 20000 solid dispersions is a suitable method to enhance the solubility and dissolution rate of meclizine hydrochloride.

Keywords: Dissolution efficiency, Initial dissolution rate, Relative dissolution rate, Solvent evaporation method, Solubility studies.

INTRODUCTION

From the last few decades, the pharmaceutical formulation scientists are widely focusing on the development of oral dosage forms of poor aqueous solubility drugs by enhancing the solubility using

different approaches[1]. In these, solid dispersions is one of the widely used approaches to of improve the solubility and dissolution rate of poorly water-soluble drugs and in turn their oral bioavailability[2]. Solid dispersions are molecular dispersions of drugs in a polymer in solid form and these can be prepared by various methods. Solvent evaporation method and fusion method are widely used to fabricate the solid dispersions[3].

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 H_1 receptor antagonist and practically insoluble in water[4]. Some of the recent research examples on MCZ are Meclizine hydro chloride mouth dissolving tablets[5], Cyclodextrin-meclizine HCl inclusion complexes[6], Metabolism and pharmaco-kinetics of meclizine suspension[7], Meclizine HCl orally disintegrating tablets[8], Meclazine - maltodextrin oro-dissolving tablets[9]. In the present study an attempt was made to prepare a solid dispersion of MCZ using PEG 20000 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[10], simmvastatin[11], diclofenac sodium[12], clopidrogel[13], gliclazide[14]. From the support of above literature, it was planned to prepare the MCZ-PEG 20000 solid dispersions to enhance the dissolution rate.

MATERIALS AND METHODS

Materials

Meclizine hydrochloride was gift sample from FDC Limited, Mumbai, India. PEG 20000 was 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 by solvent evaporation method

MCZ-PEG 20000 solid dispersions 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.

Solubility studies

The prepared solid dispersions were subjected to 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.

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 5^0 C/min from a

temperature 0 to 450^{0}C under a nitrogen gas flow.

Micromeritic properties of blend

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:

$Tan\ \theta = h/r$ …… [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 (ρb) 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 (ρtap) 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/min15. The Carr's Index is a measure of the propensity of a powder to be compressed and it is calculated using the following formula:

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

Preparation of fast dissolving tablets

From the results of dissolution and solubility studies, the fast dissolving tablets (FDTs) were prepared for selected solid dispersion preparations (Table 4). The FDTs were prepared by direct compression method. The solid dispersion powder equivalent to 25 mg of MCZ, Crospovidone and other tabletting excipients were passed through a mesh no 60. The powdered solid dispersion was mixed with proper portion of Crospovidone. 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.

Evaluation of physical parameters

The designed formulations were studied for their physical properties like weight variation, hardness and friability. 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

In vitro disintegration time of FDT's was determined by following the procedure described by Gohel *et al*. 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. Measurements were carried out in triplicates[16].

In vitro Dissolution Study

The release of MCZ from 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±0.5 °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) and 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 optimized formulation and that dissolved from the control formulation at 15 min.

Stability studies

The stability studies of prepared tablets were planned on the best formulation 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[17,18].

RESULTS AND DISCUSSION

Solubility studies of MCZ solid dispersions

The solubility studies were conducted in different media for all the prepared solid dispersions and compared with pure drug. 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, 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 using different carriers showed in Table 2. From the results given in above tables, solid dispersions with PEG 20000 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* 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[19].

Drug-carrier compatibility studies

The thermograms of the MCZ, PEG 20000, of MCZ with PEG 20000 were shown in Figure 1. The DSC thermograms of MCZ exhibited physical mixture a sharp endothermal peak around 206.66 ^{0}C corresponding to melting point. The DSC thermogram of PEG 20000 exhibited a broad endothermal peak around 69.8^{o}C corresponding to its melting point. The thermogram of physical mixture with PEG 20000 showed a short endothermal peak of

drug at 206^{0}C indicating that there were no interactions between drug and carrier.

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 35° and Carr's index values were less than 21 for the powder mixture of all the batches indicating good to fair flowability[20].

Evaluation of Fast Dissolving Tablets

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 99.14±1.32%. From the disintegration test, the prepared tablets were disintegrated rapidly and it was found to be around 120 sec.

Dissolution Studies of Fast Dissolving Tablets

From the *in vitro* dissolution studies, tablets made from 1:4 ratio solid dispersion (F4) showed fast dissolution (98.46±1.24% in 15 min) than other formulations and improved significantly when compared to control tablet (32.49±1.29 in 15 min). Figure 2 demonstrated the MCZ release patterns by above formulations. From the *in vitro* dissolution studies, MCZ in the form of solid dispersion (F4 formulation i.e., 1:4 ratio) showed significant increase in dissolution rate when compared to tablets with pure MCZ. In the following reported study by Singh *et al*., similar type of solubility enhancement was observed with PEG 6000 solid dispersions[13]. 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].

The percent drug release in 15 min (Q_{15}) and initial dissolution rate for formulation F4 was 98.46±1.24%, 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 54.44 and it is increased by 3.4 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 pure drug, 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*[21].

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 85.11, which is more than 50 indicates similarity between the dissolution profile before and after storage[17,18].

CONCLUSION

In the present study, various weight ratios of meclizine hydrochloride and carriers used to prepare the solid dispersions and evaluated for physiochemical properties. 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 20000 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 98.46±1.24%, 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 54.44 and it is increased by 3.4 fold with F4 formulation compared to control tablets (16.55). In conclusion, development of the solid dispersions can be a promising alternative method to attain the fast dissolution rate and absorption for water-insoluble drugs like meclizine hydrochloride and it was achieved with PEG 20000 as carrier. Further the pharmacokinetic evaluation is needed to prove the capability of PEG 20000 solid dispersions to improve the bioavailability of meclizine hydrochloride.

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Table 1. Formulation of MCZ-PEG20000 solid dispersions

Formulation Code	MCZ HCl	MCZ: PEG 20000 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

Table 2. Solubility studies of MCZ-PEG 20000 solid dispersions (mg/ml)

Formulation Code	MCZ solubility in mg/ml		
	0.1 N HCl	Distilled Water	7.4 pH Buffer
Pure FLB	0.334±0.03	0.992±0.12	0.998±0.37
F1	0.416±0.57	1.138±0.26	1.412±0.76
F2	0.491±0.34	1.284±0.34	1.498±0.81
F3	0.532±0.54	1.324±0.57	1.572±0.25
F4	0.563±0.72	1.476±0.61	1.651±0.48
F5	0.557±0.48	1.462±0.72	1.634±0.92
F6	0.439±0.22	1.342±0.45	1.447±0.92

Table 3. 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	29.37±1.28	0.341	0.402	15.17
Control	28.14±2.19	0.334	0.395	15.44

Table 4. Composition of MCZ tablets using selected solid dispersions

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

Table 5. Physical Properties of MCZ Tablets

Formulation	Weight variation* (mg)	Hardness† (Kg/cm^2)	Friability (%)	Disintegration time‡ (sec)	Drug content‡ (%)
F4	201.47±1.34	3.0±0.48	0.33	122±4	98.92±1.58
Control	101.82±1.27	3.0±0.26	0.27	119±4	99.58±1.13

* 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	98.46±1.24	6.56	54.44	3.03
Control	32.49±1.29	2.17	16.55	

Table 7. Stability Studies of MCZ F4 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	85.11
5	42.81±1.75	40.24±1.69		
10	71.29±1.18	69.71±1.32		
15	98.46±1.24	96.83±1.18		
% Assay	98.92±1.58	97.28±1.43	Not Significant	--

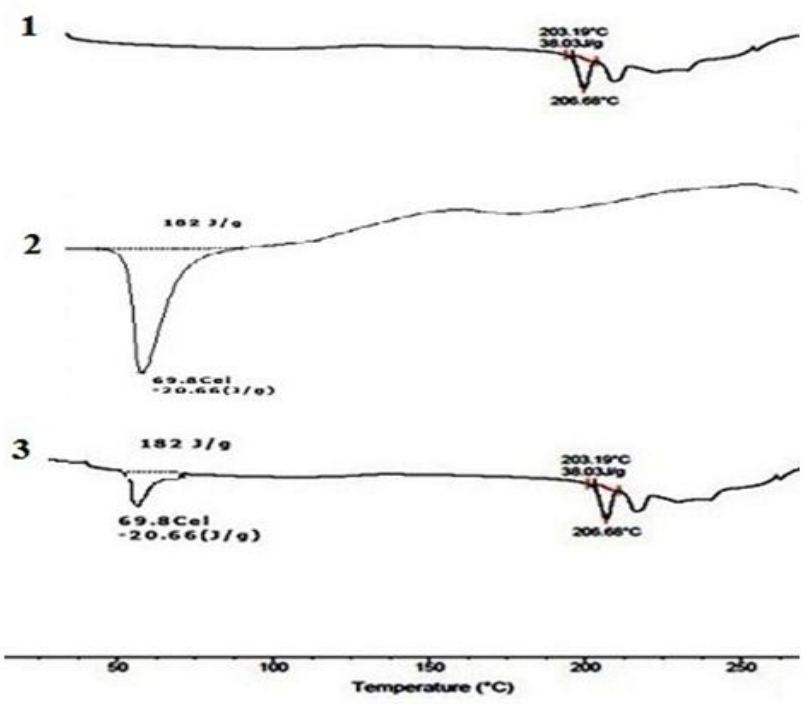

Figure 1. DSC thermograms of A) MCZ B) PEG 20000 C) F4 physical mixture

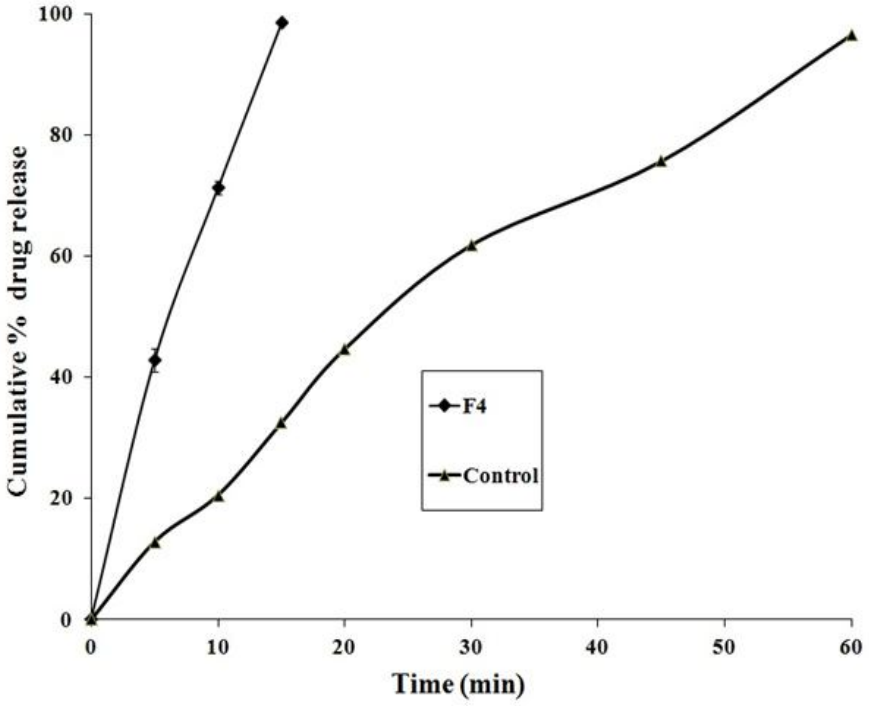

Figure 2. Dissolution studies of MCZ fast dissolving and control tablets