American Journal of Advanced Drug Delivery

www.ajadd.co.uk

Original Article

Meclizine Hydrochloride Fast Dissolving Tablets by Sublimation Method: Formulation and Evaluation

Mohan Vangala, Prabhakar Reddy Veerareddy, Venkat Ratnam Devadasu and Sateesh Kumar Vemula*

Department of Pharmaceutics, Chaitanya College of Pharmacy Education and Research, Kishanpura, Hanamkonda, Warangal, Andhra Pradesh, India-506001.

Date of Receipt- 28/01/2014
Date of Revision- 12/02/2014
Date of Acceptance- 13/02/2014

Address for Correspondence
Department of Pharmaceutics, Chaitanya College of Pharmacy Education and Research, Kishanpura, Hanamkonda, Warangal, Andhra Pradesh, India-506001.

E-mail:
vemulasatish15@gmail.com

ABSTRACT

The current study was aimed to develop the meclizine hydrochloride sublimated fast dissolving tablets using different sublimated agents to enhance the dissolution rate. The prepared fast dissolving tablets were subjected to pre-compression properties and characterized for hardness, weight variation, friability, wetting time, water absorption ratio, and disintegration time. From *In vitro* dissolution studies, the formulation F3 containing camphor (10%w/w) as the sublimating agent showed rapid dissolution of about 98.61% in 30 min, and disintegration time 43 sec when compared with other sublimating agents. The percent drug release in 30 min (Q_{30}) and initial dissolution rate for formulation F3 was 98.61±0.25%, 3.29%/min. These were very much higher compared to marketed tablets (65.43±0.57%, 2.18%/min). The dissolution efficiency was found to be 63.37 and it is increased by 1.4 fold with F3 FDT tablets compared to marketed tablets. Differential scanning calorimetry and Fourier transform infrared spectroscopy studies revealed that there was no possibility of interactions. In conclusion, development of meclizine hydrochloride fast dissolving tablets by sublimation method is an appropriate method to enhance the dissolution rate.

Keywords: Camphor, Dissolution efficiency, *In vitro* dissolution studies, Initial dissolution rate, Sublimating agents.

INTRODUCTION

Poor water soluble drugs are associated to slower rate of absorption from oral route; therefore, it is required to enhance the dissolution of these drugs to ensure maximum therapeutic utility of these drugs[1]. To improve the dissolution rate various techniques have been introduced to enhance the dissolution rate and solubility of the drug[2]. One of the dissolution enhancement methods is the sublimation technique, which is most widely used and industry feasible method to formulate fast dissolving tablets. Sublimation has been used to produce fast dissolving tablets with high porosity. A porous matrix is formed by compressing the volatile ingredients along with other excipients into tablets, which are finally subjected to a process of sublimation[3]. Some of the recent research examples on sublimation method are ondansetron[4], lovastatin[5], clonazepam[6].

The intention of this study is to develop fast dissolving tablets of Meclizine hydrochloride (MCZ) using sublimation method with the aid of incorporation of sublimating agents. MCZ is a first-generation antihistamine of the piperazine class drug, used in the treatment of motion sickness. MCZ is a H_1 receptor antagonist and practically insoluble in water[7]. In the present study, fast dissolving tablets were prepared by sublimation and studied the effect of various sublimating agents and their concentration on the dissolution rate of MCZ. Some of the recent research examples on MCZ are meclizine hydro chloride mouth dissolving tablets[8], cyclodextrin-meclizine HCl inclusion complexes[9], metabolism and pharmacokinetics of meclizine suspension[10], meclizine HCl orally disintegrating tablets[11] and meclizine-maltodextrin oro-dissolving tablets[12].

MATERIALS AND METHODS

Materials

Meclizine hydrochloride is obtained as a gift sample from Symed labs Ltd, India. Crosspovidone was gift samples from Matrix laboratories, Hyderabad, India. All other chemicals used were of analytical grade.

Powder characterization

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:

$$\tan \theta = h/r \quad \ldots\ldots (1)$$

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 the funnel is 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, till the tip of the heap formed just touches the funnel. The radius of the heap was noted and from this angle of repose was determined. Angle of repose less than 30° suggests free flowing properties of the material.

The bulk density 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 densities of powder samples were determined by a tap density apparatus (Intelli, Kshitij Innovations, India). The apparatus was set for 500 tappings for 5 min at a stroke height of 20 mm[13]. The compressibility index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk

and tapped densities and is calculated using the following formulas:

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

In which, ρ_b is bulk density and ρ_{tap} is tapped density.

Preparation of sublimated fast dissolving tablets (FDTs)

Accurately weighed quantity of drug, crosspovidone and sublimating agents were passed through # 60 mesh and carefully added to spray dried lactose and mixed in a poly bag for 15 min. Then the powder mixture was lubricated with talc and magnesium stearate by blending for another 5 min. The resultant mixture was directly compressed into tablets with 6 mm round flat punches using 8-station rotary tabletting machine (Riddhi Pvt Ltd, India). Then these tablets were subjected to sublimation, by placing in a hot air oven at 60°C for 2 h to generate a porous matrix, due to removal of volatilizable component. The final weight of the tablet was adjusted to 100 mg and the compositions of the tablets were given in Table 1.

Evaluation of sublimated fast dissolving tablets

The prepared tablets 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 strength of tablet is expressed by measuring hardness and friability. 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 4 min at 25 rpm. For estimation of drug content, ten tablets were crushed, and the aliquot of powder equivalent to 50 mg of drug was dissolved in suitable quantity of methanol/0.1 N HCl solution. Solution was filtered and diluted and drug content determined by UV-Visible spectrophotometer (Systronics 2202, Ahmedabad, India) at 232 nm. The drug concentration was calculated from the calibration curve.

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[14].

Wetting Time and Water Absorption Ratio (R)

Wetting time was determined as described in the literature elsewhere. Briefly, two circular tissue papers were placed in a Petri dish of 10 cm diameter. Ten milliliter of water containing 0.5 (% w/v) of phenol red was added to the petridish. The dye solution was used to identify the complete wetting of the tablet surface. A tablet was carefully placed on the surface of the paper in the petridish at room temperature. The time required for water to reach the upper surface of tablet and to completely wet them was noted as wetting time. Wetting time was recorded using stop watch and the measurements were carried out in triplicates. The weight of the tablet prior to placement in the petridish was noted (W_b) using digital balance (Shimadzu, Japan). The wetted tablet was removed and reweighed (W_a). Water absorption ratio (R), was then calculated according to the following equation. W_b and W_a were weights before and after water absorption.

$$R = \frac{W_a - W_b}{W_b} \times 100 \ldots\ldots\ldots\ldots (3)$$

In vitro Dissolution Study

The release of MCZ from FDT's was carried out using USP XXIV Type II (paddle method) dissolution apparatus (Lab India) at a rotation speed of 100 rpm, and a temperature of 37±0.5 °C. The drug release studies were carried out in 0.1N HCl 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.

Calculation of dissolution parameters

Cumulative percent drug release was plotted as a function of time and percent drug release in 30 min (Q_{30}) was calculated. Initial dissolution rate (IDR) was calculated as percentage dissolved of drug over the first 30 min per minute. 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 30 min. Relative dissolution rate (RDR) is the ratio between amount of drug dissolved from best formulation and that dissolved from the marketed tablets at 30 min[15].

Drug-Polymer Interaction Studies

To study the possible interaction between MCZ and excipients, DSC study was carried out on pure MCZ, camphor and best formulation. Differential thermal analysis thermograms were obtained using DSC (Perkin-Elmer, Shelton, U.S). The analyses were performed under nitrogen (nitrogen flow rate 50 ml/min) in order to eliminate oxidative and pyrrolytic effects at a standard heating rate of 15ºC/minute over a temperature range of 50ºC - 350ºC. The FTIR spectra of MCZ, camphor and best formulation recorded between 400 to 4000 cm^{-1} on FTIR to detect the drug-excipients interactions. The FTIR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer (Perkin Elmer FT-IR, Perkin Elmer Inst. USA). The resultant spectra were compared for any possible changes in the peaks of the spectra.

Stability studies

To assess the drug and formulation stability, stability studies were done according to ICH guidelines. Best formulation was sealed in aluminum packaging coated inside with polyethylene, and three replicates were kept in the humidity chamber maintained at 40±2 ^{o}C and 75±5% RH for six months[16]. Samples were collected after six months of storage and analyzed for the drug content and *In vitro* dissolution rate and they were subjected to statistical analysis using paired *t*-test to test the significance of difference at 0.05 level of significance (LS). Then the similarity index was calculated between dissolution rates of optimized tablets before and after storage to prove the stability of the dosage form.

RESULTS AND DISCUSSION

Powder characterization

The results of angle of repose and compressibility index (%) ranged from 27.05±2.86 to 31.13±0.93 and 13.21 to 17.35 respectively. Bulk density and tapped density values ranged from 0.324 to 0.336 and 0.382 to 0.401 respectively. The results of angle of repose (<30) and compressibility index (<22) indicates fair to passable flow properties of the powder mixture. The powder mixtures of different formulations were evaluated for angle of repose, bulk density, tapped density and compressibility index and their values were shown in Table 2.

Evaluation of fast dissolving tablets

The physical evaluation parameters of MCZ fast dissolving tablets were shown in

Table 3. In weight variation test, the pharmacopoeial limit for the tablets of not more than 7.5% of the average weight. The hardness of the tablets was found to be in the range of 3.2 to 3.5 kg/cm^2. Another measure of tablets strength is friability. Conventional compressed tablets that loss less than 1% of their weight are generally considered acceptable. The percentage friability for all formulations was below 1% i.e., 0.40 to 0.67, indicating that the friability is within the prescribed limits. The tablets were found to contain above 97 % of the labeled amount indicating uniformity of drug content. The disintegration time of all formulations was found in the range of 43±1.5 to 61±2.5 sec. The wetting time of formulated tablets was found in the range of 121±2.0 to 145±4.0 sec and water absorption ratio was133±4.3 to 156±1.3. From the results it has been found that FDTs containing camphor as sublimating agent showed better results than the others. The formulation F3 containing 10% w/w camphor showed the fastest disintegration (43 sec) and less wetting time (121 sec) as compared to other formulations. In a study, i.e., formulation of ondansetron fast dissolving tablet by camphor sublimation[4], similar type of results was showed.

In vitro Dissolution Study

From the preliminary studies to optimize the suitable super disintegrating agent and concentration used in the fast dissolving tablets, different formulations were prepared and evaluated for drug release using different sublimating agents in various proportions. From the dissolution studies, the formulation containing 6%w/w of crosspovidone showed fast disintegration less wetting time than others (data is not presented). Similar type of results showed in a study i.e., piroxicam fast disintegrating tablets[18]. From the *in vitro* dissolution studies, tablets made from camphor showed fast dissolution rate than other sublimating agents. Among all the formulations, F3 tablets showed complete drug release within 30 min and rapid dissolution when compared to other formulations i.e., 98.61±0.25% in 30 min. Where as in the similar conditions, the marketed tablets of same dose showed 96.09±0.59% drug release in 60 min. The possible reasons and mechanisms for increased dissolution rates are formation of porous structure on the surface of tablet due to sublimation and the presence of superdisintegrants enhance the water permeation (wicking action) in to the tablet leads to fasten the wetting action, disintegration time and finally causes the fast dissolution rate[18]. Figure 1 demonstrated the MCZ release patterns from F1-F9 formulations and Figure 2 represents the comparison between F3 and marketed tablets.

Calculation of dissolution parameters

The percent drug release in 30 min (Q_{30}) and initial dissolution rate (IDR) for formulation F3 was 98.61±0.25%, 3.29%/min. These were very much higher compared to marketed tablets (65.43±0.57%, 2.18%/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 1.51. The DE was found to be 63.37 and it is increased by 1.4 fold with F3 FDT tablets compared to marketed tablets i.e., 45.53 (Table 4). Similar type of improvement in IDR, DE, RDR was reported in the study of Vemula *et al* i.e., flurbiprofen fast disintegrating tablets[15].

Drug polymer interaction studies

DSC thermograms obtained for pure drug, camphor and F3 formulations were showed in Figure 3. The DSC thermogram of MCZ showed endothermic peak at 206.66 ^{0}C and camphor showed at 171.90 ^{0}C, where as thermogram of the F3 formulation did not show any significant shift in the endothermic

peak of drug. Thermogram of the F19 formulation did not show any significant shift in the endothermic peak when compared to pure drug, indicating that there was no change in MCZ in the sublimated tablet. The FTIR spectrum of pure drug, camphor and F3 formulations were compared in Figure 4. The interpretation of FTIR spectra was explained in Table 5. From the FTIR spectral analysis all the principal peaks observed in pure drug were present in the FTIR spectra of the F3 sublimated fast dissolving tablets and some additional peaks were observed, which could be due to the presence of camphor and other excipients. These results suggest that there is no interaction between the drug and excipients used in the present formulation study.

Stability studies

To manifest the prospective utility of the formulation, stability studies were carried out at 40±2°C and 75±5% RH for six months. After storage of six months, the formulation F3 was subjected to a drug assay and *In vitro* dissolution studies (Table 6) 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 79.16, which is more than 50 indicates similarity between the dissolution profile before and after storage[19].

CONCLUSION

An attempt was made to develop the fast dissolving tablets of meclizine hydrochloride by sublimation method to improve the dissolution rate. Meclizine hydrochloride fast dissolving tablets were successfully formulated and evaluated for different parameters, which were found in the acceptable range. From the dissolution studies of all formulations, F3 formulation showed rapid disintegration time as well as fast dissolution rate. The percent drug release in 30 min (Q_{30}) and initial dissolution rate (IDR) for formulation F3 was 98.61±0.25%, 3.29%/min. These were very much higher compared to marketed tablets (65.43±0.57%, 2.18%/min). The DE was found to be 63.37 and it is increased by 1.4 fold with F3 FDT tablets compared to marketed tablets. In conclusion, development of fast dissolving tablets using sublimation method is able to enhance the dissolution rate of meclizine hydrochloride.

ACKNOWLEDGEMENT

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

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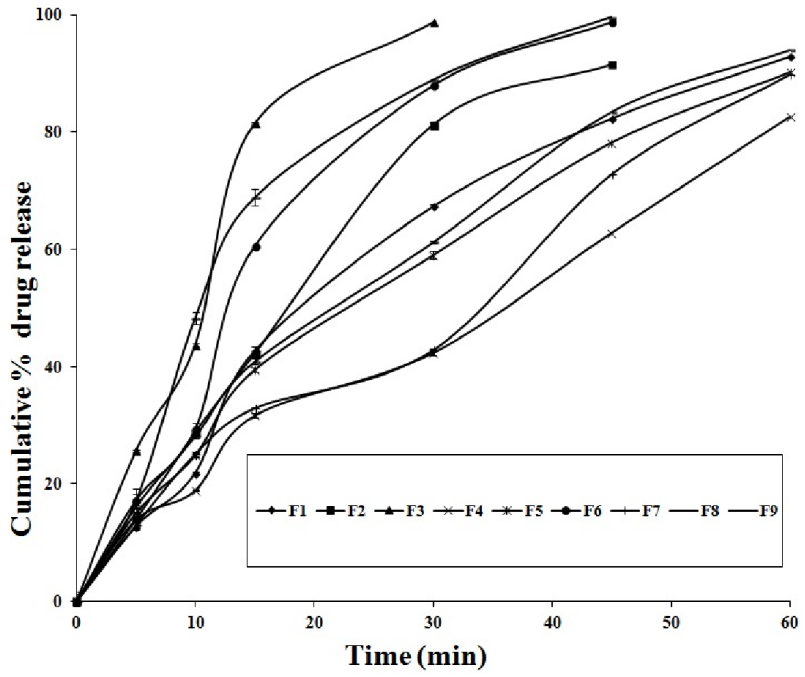

Figure 1. Release profile of MCZ from sublimated fast dissolving tablets (n=3)

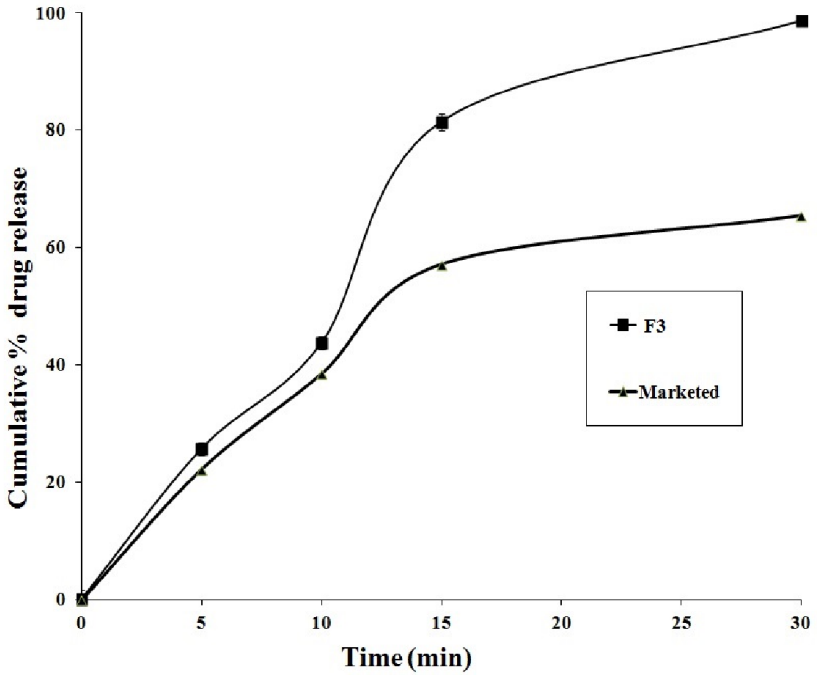

Figure 2. Comparison of MCZ release from F3 sublimated fast dissolving tablets and marketed tablets (n=3)

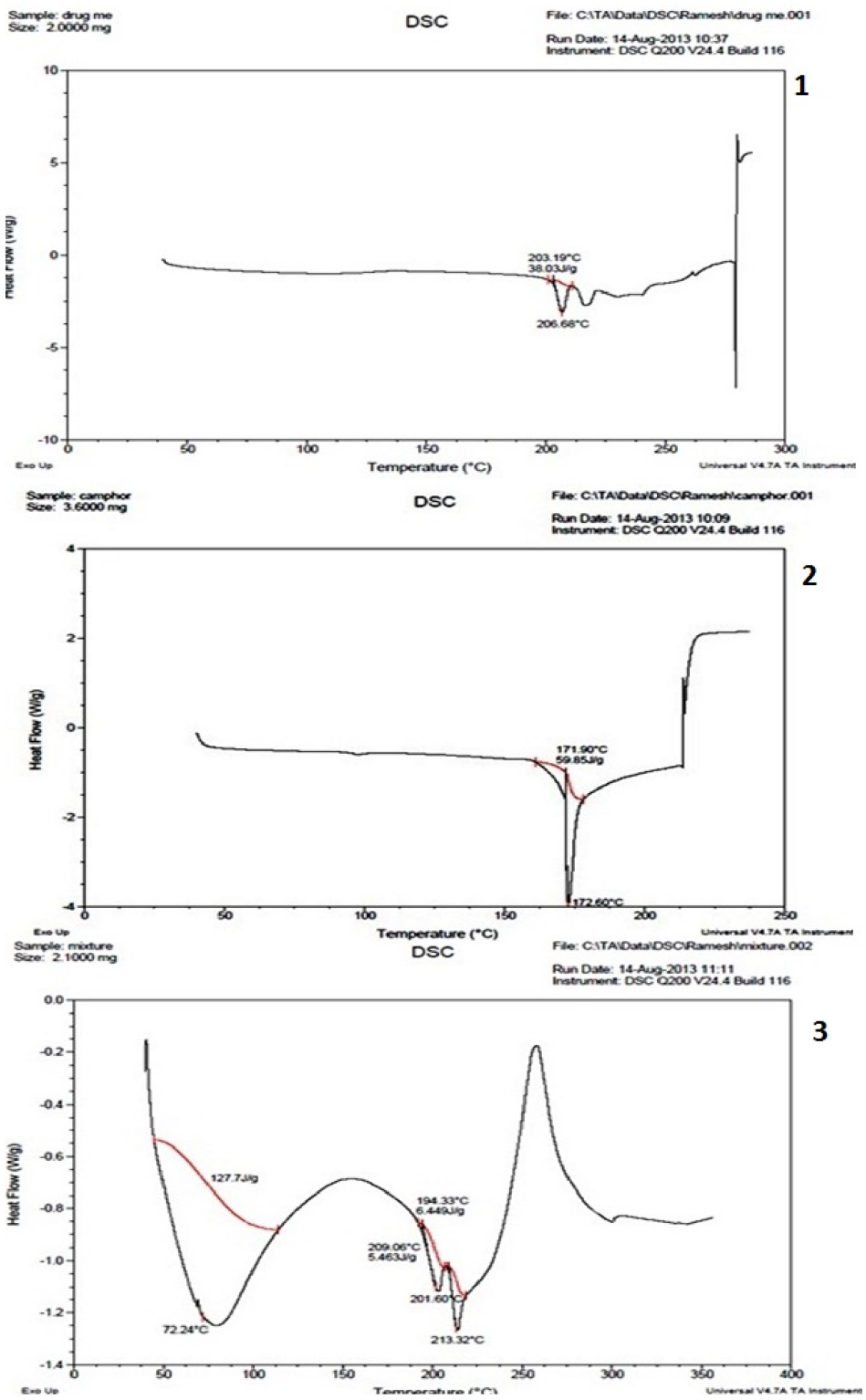

Figure 3. DSC thermograms of MCZ, camphor and F3 formulation

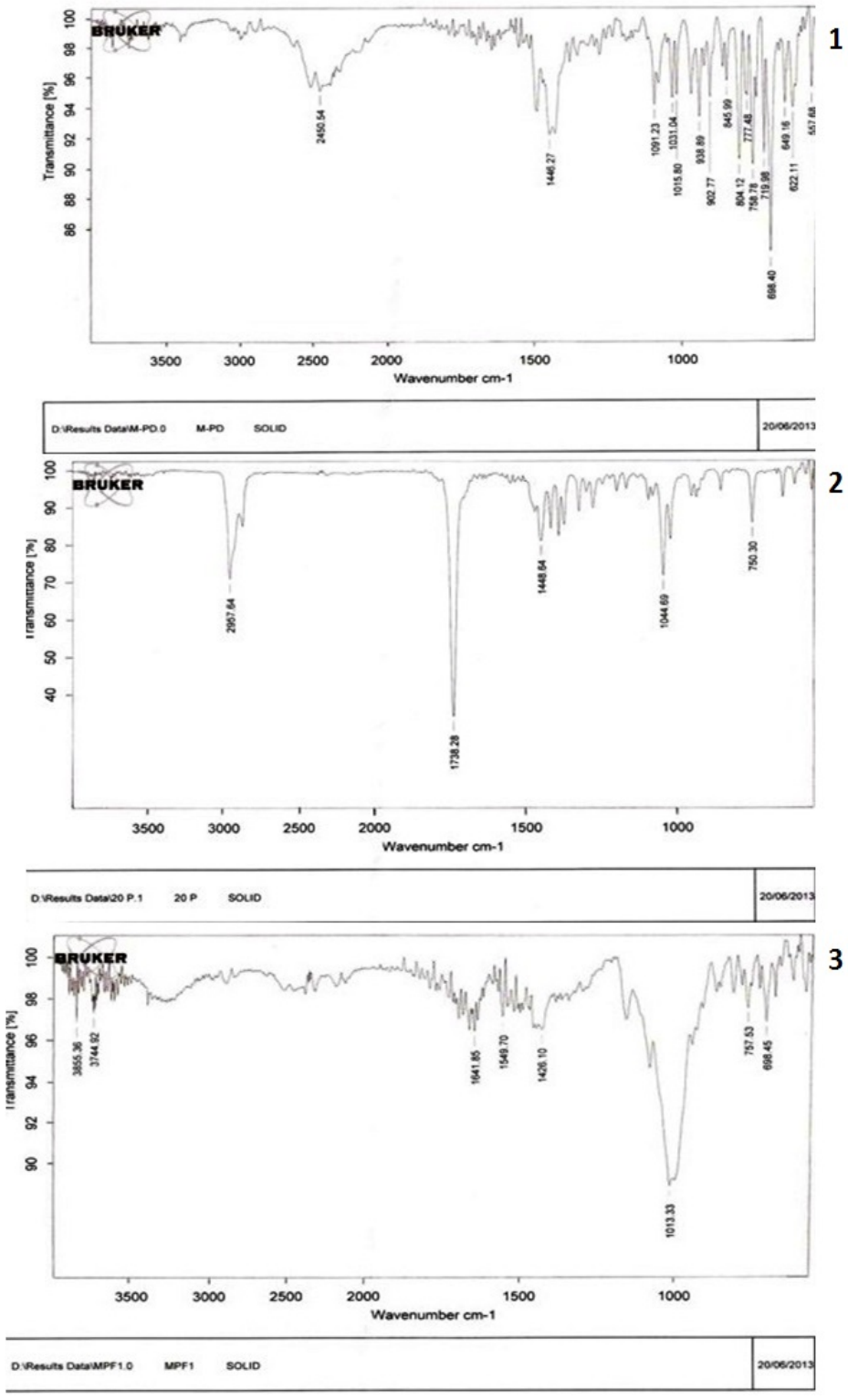

Figure 4. Fourier transform infrared spectra of of MCZ, camphor and F3

Table 1. Formulations of meclizine hydrochloride FDTs by sublimation method

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Meclizine HCl	25	25	25	25	25	25	25	25	25
Camphor	2.5	5	10	-	-	-	-	-	-
Ammonium carbonate	-	-	-	2.5	5	10	-	-	-
Benzoic acid	-	-	-	-	-	-	2.5	5	10
Crosspovidone	6	6	6	6	6	6	6	6	6
Spray dried lactose	62.5	60	55	62.5	60	55	62.5	60	55
Aspartame	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2
Magnesium stearate	1	1	1	1	1	1	1	1	1
Total weight	100	100	100	100	100	100	100	100	100

Table 2. Powder characterization of formulation blend

Formulation	Angle of repose*(^{0})	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)
F1	29.43±1.00	0.335	0.390	14.08
F2	28.45±3.22	0.331	0.401	17.35
F3	27.05±2.86	0.324	0.382	15.14
F4	29.35±4.05	0.336	0.392	14.43
F5	28.17±1.21	0.336	0.387	13.21
F6	30.00±3.38	0.331	0.401	17.35
F7	31.13±0.93	0.324	0.382	15.32
F8	29.02±3.79	0.336	0.387	13.21
F9	30.07±0.92	0.327	0.394	16.99

Table 3. Evaluation of fast dissolving tablets prepared by sublimation method

Formulation	Weight Variation (mg)*	Hardness (kg/cm^2)**	Friability (%)	Disintegration time (sec)***	Water absorption ratio***	Wetting time (sec)***
F1	101±0.92	3.4±0.37	0.46	52±2.0	138±2.0	132±2.5
F2	99±0.99	3.3±0.29	0.42	48±3.0	137±4.1	134±3.5
F3	101±0.84	3.2±0.42	0.40	43±1.5	133±4.3	121±2.0
F4	100±1.10	3.5±0.57	0.43	54±2.5	156±1.3	142±2.5
F5	98±1.12	3.5±0.71	0.54	57±2.0	133±3.2	131±1.5
F6	100±1.15	3.3±0.18	0.63	52±3.0	146±2.6	133±2.5
F7	98±0.68	3.2±0.37	0.67	61±2.5	140±2.0	145±4.0
F8	102±0.56	3.4±0.89	0.51	59±1.5	146±2.6	140±2.5
F9	101±1.43	3.2±0.56	0.63	53±2.5	140±2.0	132±2.0

*All values represent mean ± standard deviation, n=20: **All values represent mean ± standard deviation, n=6: ***All values represent mean ± standard deviation, n=3

Table 4. Dissolution parameters of MCZ F3 and marketed tablets (Mean ± SD, n=3)

Formulation	(Q_{30})	IDR (%/min)	DE	RDR
F3 tablet	98.61±0.25	3.29	63.37	1.51
Marketed tablet	65.43±0.57	2.18	45.53	

Table 5. FTIR graph interpretation of pure MCZ and camphor

Pure MCZ FTIR graph interpretation			Camphor FTIR graph interpretation		
Region in cm^{-1}	Type of vibration	Functional group present	Region in cm^{-1}	Type of vibration	Functional group present
~2400-2500	NH_3 stretch	Ammonium ion	2957	CH_3 stretch	Methyl
1475	C=C stretch	Aromatic (unsaturated)	1448	CH_3 bending	Methyl
1450	CH_3 stretch	Methyl	1738	C=O stretch	Ketone
1901	C-N stretch	Nitrile			
698	C-Cl stretch	Carbon-chlorine			

Table 6. Stability studies of MCZ F3 fast dissolving 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	79.16
5	25.67±0.41	23.18±0.93		
10	43.71±0.52	41.63±0.18		
15	81.45±0.32	78.36±0.75		
30	98.61±0.25	96.82±0.34		
% Assay	99.94±1.24	98.64±1.18	Not Significant	--