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FORMULATION AND EVALUATION OF MECLIZINE HYDROCHLORDE FASTDISSOLVING TABLETS

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ABSTRACT

Meclizine hydrochloride is an antiemetic drug belonging to BCS class II with sedative and histamine (H1) antagonist properties. In the present study an attempt was made to develop fast dissolving tablets of Meclizine hydrochloride and investigate the effect of surfactants on release profile of drug from the tablets. Tablets were prepared using different ratios of super-disintegrants and surfactants. Compatibility study ofdrug and excipients was performed by FTIR Spectroscopy. Tablets were prepared by direct compression technique. The powder of Meclizine hydrochloride and other ingredients were evaluated for pre- compression properties. The tablets were evaluated for Wetting time, Water Weight Variation, Absorptionratio, In-Vitro Disintegration time, In-vitro Dispersion time, *In-Vitro* Dissolution studies. Of all the formulations, F8 (with 12mg crosspovidone and 0.2mg sodium lauryl sulphate) is found to be the promising formulation which is evident from the data obtained from evaluation tests, like pre-compression parameters and post-compression parameters with respect to wetting time (25 ± 0.2), *in-vitro* water absorption ratio (71.6 ± 0.3), *in-vitro* disintegration time (90 ± 05), in-vitro dispersion time (58 ± 0.4), and *in-vitro* dissolution (98.76% at 30min).

INTRODUCTION

Meclizine hydrochloride, 1- [(4-chlorophenyl) (phenyl) methyl]-4-[(3-methyl phenyl) methyl] piperazine hydrate hydrochloride. Meclizine is a histamine (H1) antagonist with anti-emetic and anti-vertigo properties. It is used in the symptomatic treatment of motion sickness and control of vertigo associated with vestibular system diseases. It also exhibits anti-cholinergic, central nervous system depressant, and local anesthetic effects. Meclizine hydrochloride is practically insoluble in water and peak plasma concentration is attained at 1.5 to 6 hours after oral administration. Poorly water-soluble drugs are absorbed slowly from oral route due to poor dissolution Rate or low availability. So, it is necessary to enhance the dissolution of these drugs to ensure maximum therapeutic efficacy of the drugs.[1]Various techniques developed to increase the dissolution rate of those drugs include particle size reduction, incorporation of surfactants, complexation, polymorphism, salt formation, molecular encapsulation, nano suspensions etc. Number of drugs has shown improvement in their dissolution profile when formulated as solid dispersions. Several researchers have demonstrated that surfactants increase the dissolution rate of drugs through improved wettability. [3] Tablets are mostly prepared using freeze drying, tablet molding and direct compression. Of all these methods, direct compression is best option for preparing

tablet due to its advantages like low manufacturing cost and high mechanical integrity of tablets. Thus, an attempt is made in present investigation to enhance the drug release and bioavailability of Meclizine hydrochloride by improving the solubility through formulation of solid dispersion. Water soluble polymers like PEG-6000 used to develop fast dissolving tablets with the addition of surfactant like sodium lauryl sulphate, super- disintegrants like crosspovidone, sodium starch glycolate and croscaramellose.

Materals and Methods

Meclizine hydrochloride is procured from KP Labs, Crosspovidone and sodium starch glycolate from Sanofi Aventis Pvt. Ltd., Goa. All other materials were of analytical grades.

Methods

Method Preparation of Solid Dispersion: Solid dispersion were prepared using Meclizine HCl (drug) and PEG-6000 (hydrophilic carrier) by using kneading method. The carrier is accurately weighed i.e., according to formulation ratio 1:4 (drug: carrier) then wetted with small addition of purified water and finely kneaded in motor and pestle. The drug is added to the above portion and kneaded continuously till satisfactory paste is obtained.

The formed paste triturated with lactose and then dried in hot air oven at 50°c for 1hr and screened through sieve #16 and collected on butter paper. Product is stored in desiccator to carry out further analysis. Method for Preparation of fast dissolving tablets: Formulation of fast dissolving tablets of Meclizine hydrochloride was carried out by direct compression technique.

Eight formulations (f1, f2, f3, f4, f5, f6, f6, f7, f8) of Meclizine hydrochloride are prepared using crosspovidone, croscarmellose and sodium starch glycolate as superdisintegrants in varied amount for different formulations. Sodium lauryl sulphate was used in constant proportions for first six formulations as shown in table no 4. Required quantity of solid dispersion (drug: polymer, 1:4 ratio) was weighed and sifted through sieve #20 and then taken in a polybag. Super-disintegrants and surfactant were weighed and sifted through sieve #20 and added to the above and mixed for 5 minutes. Other excipients such as lactose (diluent), were weighed and passed through sieve #20 separately and added to the above mixture one after the other. The lubricant magnesium stearate and talc (anti-caking agent) were weighed and sieved through sieve # 40, added and mixed for 5 minutes. The final blend was directly compressed to obtain a tablet weighing approx. 200mg.

Compatibility Studies

Fourier Transform Infrared Spectroscopy (FTIR) Studies FTIR spectra for pure drug Meclizine hydrochloride and F8 Optimized formulation were recorded in infrared spectrophotometer with KBr pellets. IR spectrums were depicted in Figures 1,2.

Pre-Copmpression Parameters:

Bulk density, tapped density, carr's index and flow properties, the results were shown in table no. 4.

Post-Compression Parameters:

The prepared tablets were evaluated for weight variation, hardness, friability, thickness; the results were shown in Table no. 5.

Drug content uniformity:

One tablet was weighed and powdered. The whole amount of powdered tablet was transferred into a 100ml volumetric flask. Add 0.1N HCl up to the mark. After few minutes the solution was filtered discarding the first few ml of the filtrate. 2ml of filtrate was taken in a 25ml volumetric flask and diluted up to the mark with 0.1N HCl and analyzed spectrophotometrically at 209nm. The concentration of Meclizine hydrochloride (in gm/ml) was calculated by using the standard calibration curve of Meclizine hydrochloride. Drug content in mg was calculatedby using formula

Concentration in gm/ml x 100 x 25 ÷2×1000.

Wetting time [4,5]

A piece of tissue paper (12cm x 10.75cm) folded twice was placed in a small Petri-dish (internal diameter 6.5 cm) containing 6 mL of Sorenson's buffer pH 6.8 having small volume of dye orange red. A tablet was put on the paper, and the time for complete wetting was measured. Test was conducted using three tablets from each

formulation. An average and standard deviation was calculated.

Water absorption ratio[6]

A piece of tissue paper folded twice was placed in a small Petri-dish containing 6ml of distilled water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio (R) was determined using equation

$R = 100 \times W_a - W_b \div W_b$

Where,

W_b = weight of the tablet before water absorption

W_a = weight of the tablet after water absorption

Three trails for each formulation were performed and standard deviation was also determined.

***In vitro* dispersion time**

It was measured by dropping a tablet in a measuring cylinder containing 6ml of pH 6.8 (simulated saliva fluid). Three tablets from each formulation were randomly selected and In-vitro dispersion time was performed. Standard deviation was also determined and In-vitro dispersion time is expressed in seconds.

***In vitro* disintegration test [7]:**

The In-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 simulated saliva fluid and maintained at 37˚±2˚C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute.

The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

***In-vitro* drug release studies [8]:**

Study is carried out using USP XXIII Dissolution apparatus (Paddle type) at 50 rpm. The drug release profile was studied in 900 mL phosphate buffer of pH 6.8 by maintaining at 37±0.5°C. Aliquots (5mL) of dissolution medium were withdrawn at specific time intervals, filtered and the amount of drug released was determined spectrophotometrically.

Three trials for each batch were performed and average percentage drug release with standard deviation was calculated and recorded.

RESULTS AND DISCUSSION

In the present study, FTIR spectra of pure drug and its formulation with various polymer (F8) is taken to establish the physical characterization of drug and its formulation (Figure 1,2). The drug-excipient study was done by Fourier transform infrared (FTIR) spectroscopy study, the prominent peaks of pure drug were shown at 3441.52cm^{-1} (due to N-H), 2917.95cm^{-1} (due to O- H), 2849.99cm^{-1} (due to C-H), 1736.21cm^{-1} (due to C=O) and 1468.16cm^{-1} (due to aromatic ring). These prominent peaks of Drug were also present in the IR spectrum of formulation F8. From this it clearly indicates that, the drug was not interacted with the polymers used in the formulations.

The values of pre-compression parameters were within prescribed limits and indicated good free flowing property (table 2). All the post-compression parameters are evaluated and results were within IP acceptable limits. Results were shown in table 3, 4. In all the formulations, hardness test indicated good mechanical strength ranges from 2.5kg/cm^2 to 3.2kg/cm^2.The friability range is 0.42 to 0.49% to be well within the approved range (<1%) indicated that tablet had good mechanical hard enough. All the tablets passed weight variation test as the average percentage weight variation was within 7.5% i.e., in the pharmacopoeia limits. The thickness was uniform in all the formulations and values ranged from 4.51mm to 4.60mm. The standard deviation values indicated that all the formulations were within the range. The water absorption ratios were found between 32.6 to 74.5% and wetting time is between 18 to 129 sec. The results of water absorption ration and wetting time were tabulated in table 4. Rapid disintegration within several minutes was observed in all the formulations. The in-vitro disintegration data is provided in table 4. The in-vitro disintegration time of fast dissolving tablets were found to be 30sec to 528sec which is in the range of fulfilling the official requirements.

Table 1 Formulation of 200mg Meclizine hydrochloride fast dissolving tablets

S.NO	Ingredients	Formulation code								
		F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
1	Meclizine HCL	125	125	125	125	125	125	125	125	125
2	Crosspovidone	5	10	-	-	5	-	-	12	-
3	Croscarmellose	-	-	5	10	10	-	-	-	-
4	Sodium starch glycolate	-	-	-	-	-	5	10	-	12
5	Sodium lauryl sulphate	0.2	0.2	0.2	0.2	0.2	0.3	0.4	0.2	0.2
6	Lactose	63.8	58.8	63.8	58.8	53.8	60.7	58.6	56.8	56.8
7	Talc	4	4	4	4	4	4	4	4	4
8	Magnesium Stearate	2	2	2	2	2	2	2	2	2
	Total weight	200	200	200	200	200	200	200	200	200

Table 2 Pre-compression parameter F1-F9 formulations

Formulation	Angle of repose(°) ± S.D	Bulk Density (gm/ml) ± S.D	Tapped Density (gm/ml) ± S.D	CompressibilityIndex (%) ± S.D	Hausner's ratio ± S.D
F1	22.52±0.02	0.68±0.02	0.72±0.01	9.50±0.01	1.0±0.04
F2	26.06±0.04	0.68±0.04	0.76±0.01	13.1±0.03	1.11±0.04
F3	28.00±0.03	0.67 ± 0.03	0.78 ± 0.02	12.8 ± 0.01	1.16±0.03
F4	27.03±0.11	0.62 ± 0.01	0.70 ± 0.02	11.4 ± 0.03	1.12±0.02
F5	23.36±0.12	0.57 ± 0.01	0.63 ± 0.03	9.2 ± 0.04	1.10±0.01
F6	24.52±0.02	0.66 ± 0.02	0.73 ± 0.01	9.5 ±0.01	1.10±0.04
F7	25.01±0.01	0.59 ± 0.04	0.66 ± 0.04	10.6 ± 0.02	1.11±0.03
F8	24.52±0.02	0.66±0.02	0.73±0.01	9.5±0.01	1.10±0.04
F9	25.30±0.23	0.58±0.02	0.79±0.02	26.5±0.03	1.36±0.04

Table 3: Post compression parameters of F1-F9 formulations

Formulation	Hardness (kg/cm2) ±S.D	Thickness(mm) ± S.D	Average weight (mg) ± S.D	Friability(%) ± S.D	Wetting time (sec) ±S.D
F1	3.20±0.21	4.51±0.3	200±1	0.47±0.1	129±0.4
F2	3.20±0.18	4.53±0.4	201±0.5	0.45±0.3	109±0.6
F3	2.90±0.12	4.55±0.7	198±1	0.44±0.1	20±0.3
F4	3.00±0.16	4.57±0.1	199±1	0.44±0.1	57±0.4
F5	2.90±0.20	4.52±0.6	201±0.5	0.48±0.9	68±0.3
F6	3.00±0.18	4.60±0.3	200±0.5	0.45±0.6	59±0.2
F7	2.80±0.12	4.57±0.4	203±0.4	0.42±0.1	53±0.1
F8	2.50±0.14	4.54±0.4	200±0.08	0.46±0.3	25±0.2
F9	2.90±0.08	4.50±0.6	198±0.3	0.49±0.2	62±0.1

Table 4: Post-compression parameters of F1-F9 formulations

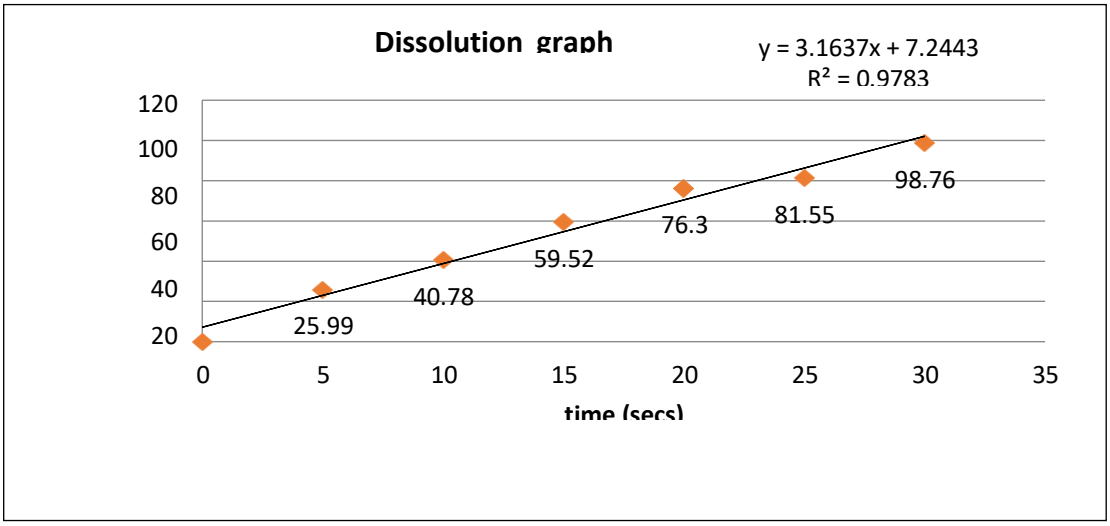
Formulation	Water absorptionratio ± S.D	*In-vitro* Dispersion time(sec) ± S.D	Drug content (%) ± S.D	Disintegration time(sec)
F1	55.9±0.2	340±0.1	97.9±0.05	240±0.2
F2	32.6±0.6	270±0.2	98.7±0.07	290±0.3
F3	74.5±0.2	43±0.3	99.8±0.05	335±0.4
F4	69.3±0.4	171±0.6	99.3±0.1	240±0.7
F5	65.6±0.1	184±0.2	99.0±0.2	380±0.5
F6	67.5±0.2	163±0.1	98.9±0.07	420±0.7
F7	64.8±0.1	150±0.7	98.6±0.3	240±0.3
F8	71.6±0.3	58±0.4	99.9±0.02	90±0.5
F9	53.8±0.3	283±0.4	99.1±0.4	176±0.5

Table 5: *In Vitro* dissolution rate for the formulations

Time in mins	% Drug release (F8)
0	0
5	25.99
10	40.78
15	59.52
20	76.30
25	81.55
30	98.76

Table 6: *In-Vitro* Dissolution Studies of F8 Formulation

Parameters	Conditions
Dissolution medium	900ml pH 6.8 phosphate buffer
Temperature	37°C±1°C
RPM	50
Tablet taken	1 tablet (known drug content)
Volume with drawn	5ml every 5 mins
λ-max	209 nm



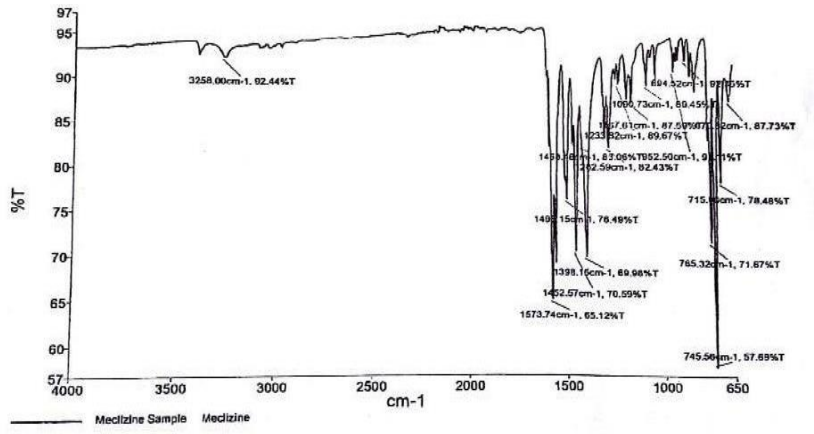


Fig 1: FTIR Study of pure drug

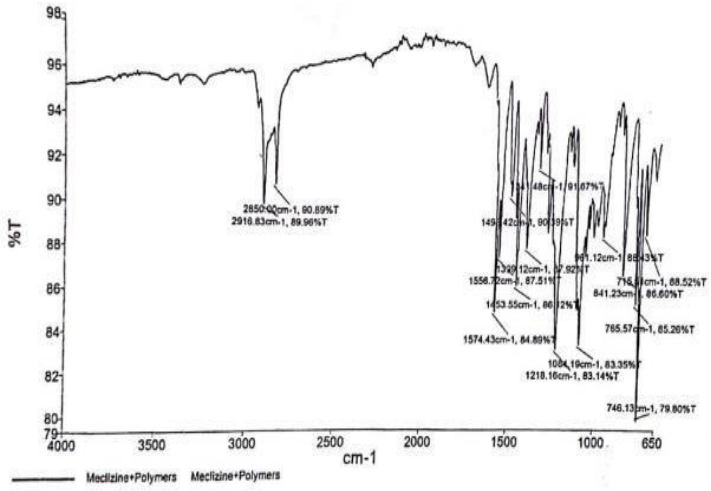


Fig 2: FTIR Study of optimized formulation

Based on the *in-vitro* disintegration time, formulation F8 (12 mg of CPV and 0.2 mg SLS) were found to be promising and showed a disintegration time of 90 secs. In-vitro dissolution studies (Figure 3) of F8 formulation was carried out in pH 6.8 buffer as dissolution medium. The release study results are shown in table 6. The rapid increase in dissolution of Meclizine hydrochloride may be due to rapid swelling and disintegrating tablets rapidly into apparently primary particles.

CONCLUSION

The formulation F8 with superdisintegrant 12mg Crosspovidone and surfactant 0.2mg sodium lauryl sulphate exhibit good flow and compression characteristics. Overall results indicates that formulation F8) was better one and satisfies all the criteria as fast dissolving tablet. Meclizine hydrochloride showing enhanced dissolution may result in improved Bioavailability and effectiveness and hence better patient compliance.

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