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DEVELOPMENT AND EVALUATION OF ORODISPERSIBLE TABLETS OF MECLIZINE HYDROCHLORIDE

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ABSTRACT

In the present study, an attempt has been made to formulate and evaluate orodispersible tablets of meclizine hydrochloride by using direct compression via employing different excipients in different ratio including: superdisintegrants {sodium starch glycolate (SSG), crosscarmellose sodium (CCS), crosspovidone (CP), and microcrystalline cellulose (MCC)} which were used alone and in combination**,** solid dispersion of MHCl in microcrystalline cellulose, diluents: lactose, granulated lactose, and mannitol, along with lubricant and glidants. The prepared formulas were evaluated for pre and post compression parameters including bulk density, tapped density, Carr's index, angle of repose, weight variation, thickness, friability, hardness, in vitro disintegration and dispersion time, wetting time, and water absorption ratio. The formulas containing granulated lactose (as diluent) showed good flow properties. Increasing concentration of three superdisintegrants (CP, SSG, and CCS) was accompanied with an increase in disintegration time (DT) while the disintegration time was decreased with an increase in concentration of MCC. Depending on the obtained results, formula 11 (F11) which contains 4% W/W CP, 10% W/W MCC was selected as an optimum formula and evaluated for further studies including in vitro drug release, content uniformity, drug assay by HPLC technique, drug-excipient compatibility, and accelerated stability tests. The assay studies of the chosen formula F11 was confirmed the uniformity of the drug dose within the dosage form. It released 80% of its content within 6.28 min. No drug-excipient interaction was observed and no significant change in the tablet properties was appeared after the period of stability tests.

INTRODUCTION: United States Food and Drug Administration (FDA) defined orodispersible tablet as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." [1]. European pharmacopoeia also adopted the term "orodispersible tablet" as a tablet that is to be placed in the mouth where it disperses, rapidly before swallowing [2]. The characteristic advantages of oro-dispersible tablets such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden and patients who do not have easy access to water. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current pharmaceutical market [3, 4].

Meclizine hydrochloride (MHCl) is an antihistaminic drug which is used in the prevention and treatment of nausea and vomiting associated with a variety of conditions including motion sickness and for the symptomatic treatment of vertigo caused by ménière's disease and hypersensitivity reactions [5]. Therefore meclizine hydrochloride is a candidate drug to be formulated as orodispersible tablets.

The aim of this study is to develop meclizine hydrochloride as orodispersible tablet with a short disintegration time, sufficient mechanical strength, better patient compliance, and acceptable stability profile by employing different methods of preparation and studying different variables affecting pre and post-compression parameters of formulas of meclizine hydrochloride.

MATERIALS AND METHODS:

Materials: Meclizine hydrochloride (MHCl) was purchased from Oceanic Pharmachem. PVT Ltd. India. Sodium starch glycolate (SSG), microcrystalline cellulose (MCC), croscarmellose sodium (CCS), and Cab-O-Sil were generous gifts from Awamedica drug company, Erbil (Iraq). All the other chemicals used were of analytical reagent grade.

Methods

Preparation of Granulated Lactose: An amount of lactose was placed in a mortar then 5% w/v starch solution was added drop-wise until ball test satisfied .The moisten lactose was sieved through mesh No. 14, weighed and dried at 50 ˚C .Finally the granules were sieved through mesh No. 18 .

Preparation of Solid Dispersion of MHCl in MCC: Three grams of MHCl was dissolved in 10 ml of ethanol, and then three grams of MCC was added and stirred continuously at 78^{o}C until slurry formed. The slurry was dried at 78^{o}C for about 6 hours .The solid dispersion was collected and ground using mortar and pestle and then sieved through mesh No. 18 [6].

Formulation of MHCl Orodispersible Tablets: MHCl orodispersible tablets (formulas F1-F15) were prepared by direct compression method according to the formulas given in (**table 1**).

The procedure is as follows: All the ingredients (except lubricants and glidant) were passed through sieve mesh No.44 meshes separately. Then weighed and mixed in geometrical order for about 10 min. Then lubricants and glidant were added to the mixture and mixed for about 2 min. Finally an accurate weight of the blend was compressed into tablets of 200 mg using 8mm punch tablet compressing machine.

TABLE 1: COMPOSITION OF DIFFERENT FORMULAS OF PREPARED MHCl ODTS.

Ingredients(mg)	Formula Codes														
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
MHCl	25	25	25	25	25	25	25	25	25	26	25	25	25	25	25
SSG		8	16									8			
CCS				8	16								8		
MCC						8	20			20	20			20	
CP								8	16	8	8	8	8	8	
Solid dispersion (MHCl in MCC)															50
Mg Stearate	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Cab-O-Sil	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Lactose up to	200	200	200	200		200	200	200	200	200					
Granulated lactose up to					200						200	200	200		200
Mannitol up to														200	

Determination of Flowability of Formulation Powder Blends:

Angle of Repose: The funnel method was used to determine the angle of repose of the prepared granules. The granules were allowed to pass through a funnel and poured on to a horizontal plane, fixed base diameter (D), free of vibration Petri dish to form a cone. The funnel height was maintained at approximately 2-4 cm from the tip of the granules pile in order to minimize the impact of the falling granules on the tip of the cone. The angle of repose (θ) was measured by measuring the height (H) of the cone of the granules and calculating the angle of repose (θ) from the equation (1) [7].

$$\text{Tan}(\theta) = \frac{H}{0.5 \times D} \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Carr's index: Carr's index (CI) is calculated by using equation (2) [6].

$$CI (\%) = (V\text{-}Vf/V) \times 100 \quad \ldots\ldots\ldots\ldots\ldots (2)$$

where, V (in ml) is the bulk volume and Vf (in ml) is tapped volume of the blend.

Hausner's ratio: Hausner's ratio (HR) is an indirect index of ease of powder flow, can be calculated by the equation (3) [8].

$$HR = TD/BD \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

where TD (in g/ml) is tapped density and BD (g/ml) is bulk density, lower Hausner's ratio below 1.2 indicates better flow properties of the blend.

Evaluation of the prepared Orodispersible Tablets:

Weight variation: Twenty tablets were selected randomly from each formulation and weighed individually. The individual weights were compared with the average weight for the weight variation [9].

Thickness variation: Ten tablets from each formulation were taken randomly and their thickness was measured with a digital vernier caliper [9].

Tablet hardness: The test is done using hardness tester (Erweka TBH 320) and the hardness was expressed in kg/cm^2 as a force required to crush the tablets. The mean of six determinations was used ± SD [10].

Tablet friability: Twenty tablets were weighed and placed in a Roche friabilator and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out, dedusted and reweighed. The percentage friability of the tablets was calculated using equation (4) [9].

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \ldots (4)$$

***In vitro* Disintegration Test:** The *in vitro* disintegration test was done for all formula at 37°C using artificial saliva solution (ASS) as a disintegration medium. Disintegration apparatus (10 ST+ G.B Caleva Ltd.) with a basket rack assembly containing six open ended tubes and 10-mesh screen on the bottom was used. A tablet was placed in each tube of the basket and the time required for complete disintegration of the tablets with no palpable mass remaining in the apparatus was measured [11]. ASS was composed of 0.426 g disodium hydrogen orthophosohate, 1.680 g Sodium bicarbonate, 0.147 g calcium chloride, 1N hydrochloric acid to adjust pH to 6.8, and distilled water up to 1L [12].

Wetting Time and Water Absorption Ratio: The method was reported by Schmid P., *et al.,* (The method was slightly modified by using artificial saliva solution instead of water). A piece of tissue paper folded twice was placed in a small Petri-dish (internal diameter = 6.5 cm) containing 10 ml of ASS and 0.05% w/v amaranth solution (coloring agent). A tablet was placed on the tissue paper and the time required for complete wetting of the tablets was recorded as wetting time. The mean of three determinations was used ± SD [13]. The same procedure of wetting time test was followed for determining the water absorption ratio (WAR) and it was determined according to the equation (5):

$$WAR = [(Wa - Wb)/Wb] \times 100 \quad \ldots\ldots\ldots\ldots\ldots (5)$$

where, Wb and Wa were the weights of the tablets before and after the test.

***In vitro* Dispersion Time:** *In vitro* dispersion time was measured by dropping a tablet in a small beaker containing 6ml of ASS (pH 6.8) [14] and agitated mildly. The time required for complete dispersion of tablets as fine particles was noted as dispersion time [15, 16] .

Variables affecting pre and post-compression parameters of the prepared MHCl formulations

Effect of type and concentration of the Superdisintegrants: Formulas F1- F9 (table 1) were designed to study the effect of the superdisintegrant type (SSG, CCS, MCC and CP) at different concentration on the flowability of the prepared blends and the physical properties of the prepared ODTs.

Effect of combination of Superdisintegrants: Formulas F11, F12, F13 were utilized to study the effect of combination of superdisintegrants on the flowability of the prepared blends and the physical properties of the prepared ODTs.

Effect of type of Diluents: Formulas F10, F11, and F14 were utilized to study the effect of different diluents (lactose, granulated lactose, and mannitol) on the flowability of the prepared blends and the physical properties of the prepared ODTs.

Effect of incorporation of Solid Dispersion: Formulas F7 and F15 were utilized to study the effect of incorporation of solid dispersion of MHCl in MCC on the physical properties of the prepared ODTs.

Drug Content Uniformity: One tablet of the optimum formula (F11) was placed in 100ml volumetric flask, 50ml of 0.01N HCL was added, shaked by mechanical means for 30 min., 0.01N HCl added to volume, filtered, diluted suitably, and finally the quantity of meclizine hydrochloride in the tablet was measured spectrophotometrically at λ_{max} of 232 nm [7].The test repeated in triplicate.

***In vitro* Dissolution Studies:** *In vitro* dissolution studies were performed only for the optimum formula (before and after stability tests) and meclizine (conventional tablet, 25mg) by using type I (Basket) dissolution apparatus (DIST2, G.B Caleva) at 100 rpm, and 900 ml of 0.01N HCL was used as a dissolution medium. Temperature of dissolution medium was maintained at 37±0.5°C. Five ml aliquot of the dissolution medium was withdrawn at specific time intervals and replaced by fresh 0.01N HCl solution. The aliquot was filtered and diluted suitably and then analyzed spectrophotometrically at the λ_{max} of 232nm [7].The mean of three determinations was used.

To analyze the in vitro release data, various kinetic models including (zero order, first order, Higuchi, Korsmeyer-Peppas model, and Hixson-Crowell cube root law) were used to describe the release kinetics. The time required for 80% of drug to be released ($t_{80\%}$) and percent drug dissolved in 2 minutes (D_{2min}) were considered for comparing the dissolution results.

Drug assay by HPLC: High-performance liquid chromatography (HPLC) technique was used to determine the amount of meclizine hydrochloride in the dosage form (optimum formula F20). Separation was performed on C18 column (octylsilane chemically bonded to totally porous silica particles of 5 µm particle size). Detection was achieved using UV–Visible detector at wavelength of 232 nm. The mobile phase was composed of a mixture of methanol and water(65: 35) containing 0.69 gm of monobasic sodium phosphate in each 100ml which was adjusted to the pH of 4 with phosphoric acid [7]. The analysis was performed in isocratic mode with mobile phase at a flow rate of 1.6 ml/min. A volume of 100 µl of each sample was injected into the analytical column.

Twenty tablets of optimized formula were finely powdered. Amount equivalent to 25 mg meclizine hydrochloride was accurately weighed and transferred into a volumetric flask. About 350 ml of the solvent mixture was added, sonicated for 10 min, then shaked by mechanical means for 30 min. and completed to 500 ml with solvent mixture. Sonication, filtration and dilution were performed. The drug content was determined using the above mentioned HPLC technique. The test was repeated in triplicates.

Drug – Excipients Compatibility Studies:

Fourier Transform Infrared (FTIR) Spectroscopy: This study was done for pure MHCl and the optimum formula (F11) using fourier transform infrared (FTIR) spectroscopic analysis (FTIR-8400 Shimadzu) to rule out any drug – excipients interaction that may occur

during the formulation. FTIR were implemented using KBr disk method in the range of 4000-400 cm^{-1} for each of drug alone and optimum formula (as a tablet) [17].

Differential Scanning Calorimetry (DSC): Thermal analysis of powdered sample of MHCl and solid dispersion of (MHCl in MCC) were recorded using DSC (DSC-60 Shimadzu). The thermograms were obtained by heating from 25-300^{o}C at heating rate of 10ºC/min [18].

Accelerated Stability Studies:

Effect of Humidity and Temperature: Stability studies were carried out on optimum formula (F11). The tablets were stored at 40^{o}C/75 ±5 %RH using saturated sodium chloride solution desiccator for duration of one month. Samples were withdrawn at interval of 15 days and tested for various evaluation parameters (hardness, disintegration tests, drug content uniformity, and drug release study) [19].

Effect of Temperature alone (determination of expiration date): The effect of temperature on the degradation of MHCl in the selected optimum formula (F11) was studied. The study was done by storing the tablets in ovens at different temperatures of 40^{o}C, 50^{o}C and 60^{o}C for one month. Samples were withdrawn at certain time intervals to determine the content of MHCl by measuring their UV absorbance [20].

Statistical Analysis: The results of experiments were expressed as mean ± standard deviation. Analysis of variance (ANOVA) test has been performed to determine statistical significant difference using (smith's statistical package version 2.8). The difference is considered as statistically significant if p value < 0.05.

RESULTS AND DISCUSSION:

Variables affecting pre and post-compression parameters of the prepared MHCl Formulations:

Effect of type and concentration of the Superdisintegrant: Formulas F1-F9 were investigated to declare the influence of superdisintegrant types (MCC, CP, SSG and CCS) and their concentration on the properties of the prepared formulation powder blend and ODTs of MHCl.

All batches of prepared tablets were evaluated for the different parameters and results are shown in **tables** (**2 and 3**. Weight variation for prepared tablets was found within accepted specifications of (USP30-NF25). Hardness and friability of all formulations were within acceptable limits (>3Kg/cm^2). The formulas which contain superdisintegrant possessed acceptable values of water absorption ratio (WAR) and in vitro dispersion time (IDT).

TABLE 2: FLOW CHARACTERS AND COMPRESSIBILITY OF THE PREPARED FORMULATION POWDER BLENDS

Formula codes	Angle of repose	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index	Huasner's ratio
F1	41.88 ± 0.54	0.44	0.8	45	1.81
F2	37.79 ± 0.60	0.45	0.72	36.66	1.57
F3	37.34 ± 1.07	0.49	0.76	35.71	1.55
F4	40.70 ± 0.57	0.44	0.77	42.3	1.73
F5	36.91 ± 0.63	0.53	0.74	27.77	1.38
F6	38.22 ± 0.60	0.47	0.76	37.93	1.61
F7	36.46± 0.63	0.49	0.72	31.57	1.46
F8	41.88 ± 0.54	0.46	0.71	35.29	1.54
F9	41.88± 0.54	0.44	0.76	41.93	1.72
F10	41.09±0.96	0.44	0.77	42.3	1.73
F11	24.72 ± 0.81	0.52	0.63	16.66	1.20
F12	25.86 ± 0.79	0.52	0.64	19.23	1.23
F13	27.52 ± 0.76	0.53	0.63	16.66	1.2
F14	38.22 ± 0.60	0.62	0.91	31.81	1.46
F15	28.06 ± 0.76	0.47	0.57	16.66	1.20

TABLE 3: POST-COMPRESSION PARAMETERS OF MHCl ODTS PREPARED BY DIRECT COMPRESSION (EXPRESSED AS MEAN ± SD)

Code	Wt. (mg)	Th. (mm)	Hardness Kg/cm^2	F (%)	DT (sec.)	WT (sec.)	WAR (%)	IDT (sec.)
F1	***199***.45±1.61	3.68±0.021	4.74±0.53	0.2	133.66±8.65	365±5.6	20±3.7	388.33±2.86
F2	199.55±0.001	3.8±0.014	3.7±0.18	0.48	17.8±0.63	30.25±1.9	56.6±12.86	23.43±1.78
F3	198.8±0.001	3.79±0.012	3.49±0.2	0.52	21.41±0.74	28.19±0.37	90±11.92	32.93±1.87
F4	199.41±0.001	3.87±0.014	3.46±0.2	***0***.5	19.5±0.51	32.7±2.64	66.18±8.08	31.37±0.68
F5	199.89±1.171	3.87±0.018	3.56±0.1	0.45	27.74±0.83	35.73±1.75	94.49±1.86	35.29±3.36
F6	199.24±1.529	3.81±0.011	3.49±0.29	0.2	18.23±0.69	59.49±4.63	39.61±2.48	21.61±1.8
F7	200.35±1.179	3.81±0.021	3.92±0.35	0.25	15.02±0.46	48.95±3.41	38.69±1.27	15.49±1.04
F8	199.59±1.39	3.73±0.01	3.65±0.08	0.38	13.72±0.88	20.73±0.22	81.85±8.14	37.63±1.4
F9	199.74±1.36	3.82±0.011	3.63±0.16	0.6	17.94±0.46	55.66±5.62	125.79±1.3	46.6±12.68
F10	***199***.88±1.77	3.74±0.048	6.2±0.47	0.5	22.33±0.5	20.35±0.95	81.94±7.89	32.57±1.16
F11	200.01±1.29	3.89±0.014	3.72±0.07	0.3	9.7±0.29	22.46±1.10	92.54±9.32	15.10±0.53
F12	199.03±1.2	3.76±0.017	3.61±0.23	0.45	19.18±0.58	33.99±2.92	103.17±7.35	28.94±0.35
F13	198.9±1.47	3.87±0.01	3.66±0.17	0.3	17.09±0.55	37.78±0.6	95.5±7.53	27.06±2.89
F14	199.91±1.67	3.22±0.01	4.7±0.23	0.19	348.33±6.23	478.33±49.21	21.48±1.19	418.28±4.65
F15	199.30±1.95	3.81±0.011	3.54±0.34	0.2	21.29±2.12	98.74±4.46	53.83±2.38	39.55±3.01

Th.: Thickness, F: Friability.

The results show that CP is the strongest among other superdisintegrants in term of producing fastest disintegration followed by MCC, SSG, and then CCS (**figure 1**). The probable reason may be high gelling tendency of CCS and SSG than CP and MCC which causes swelling of tablet mass with subsequent retardation of disintegration. Also the results reveal that there is a significant difference (P<0.05) between the DT of formula F1 (control formula: Does not contain superdisintegrant) and those of (F2-F9).

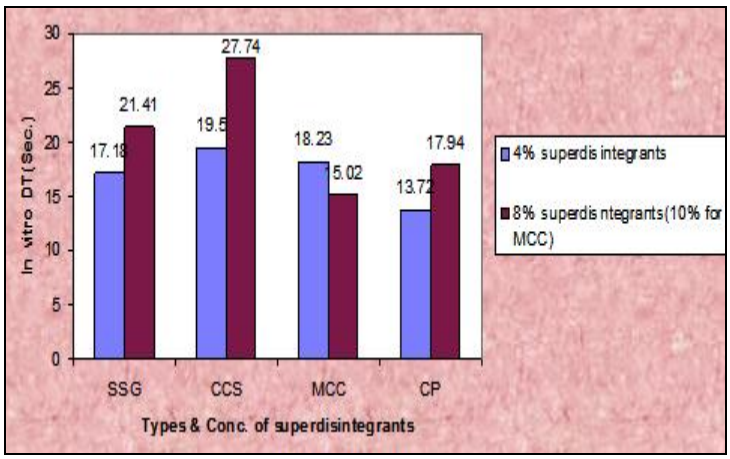

FIGURE (1): *IN VITRO* DT OF FORMULA CONTAINING VARIOUS SUPERDISINTEGRANTS (F2-F9).

Wetting time is closely related to the inner structure of tablets and hydrophilicity of the excipients. According to equation (6) which was proposed by washburn E.W [21], the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders.

$$dl / dt = r \gamma \cos\theta / (4 \eta l) \quad \ldots\ldots\ldots\ldots\ldots (6)$$

where, l is length of penetration, r is capillary radius, γ is surface tension, η is liquid viscosity, t is time, θ is contact angle.

From the equation (6) it is obvious that by increasing the pore size, the wetting time decreases and this can be achieved by compressing the powder at low compression force, addition of superdisintegrants, and utilizing subliming agents. The wetting time was shortest for formula contains (4% CP).

Effect of combination of Superdisintegrants: It was observed that the DT significantly decreases (P=0.0037) by utilizing combination of 10% MCC with 4% CP (F11). Fastest disintegration of tablets of F11 is due to synergistic effect of MCC and CP due to strong wicking or capillary action of these two superdisintegrants. The result is similar to the result of Vijaykumar *et al.,* [22]. While in other combination protocols (MCC with SSG and CCS), (CP with SSG), (CP with CCS), and (SSG with CCS) the DT did not change markedly, even a slight increasing in DT was observed and this may be to the blockade of capillary pores by the coexisting superdisintegrants [23] and interference with action of each other because they posses different mode of action.

Effect of type of Diluents: The results showed that using manually prepared granulated lactose as a diluent resulted in a significant (p<0.05) decrease in angle of repose and Carr's index of the formulation

powder blends (i.e. marked improvement of powder flow) as compared to lactose and mannitol and this is due to the spherical shape and greater particle size of the former diluent that render it to be free flowing.

Formula F14 (contains mannitol as diluent) disintegrates much more slower than F11 (contains manually prepared granulated lactose) and possesses a longer WT as compared to formula containing lactose filler, which could be attributed to slower dissolution characteristics of mannitol [24], small size of mannitol particles and their irregular shape.

Effect of Incorporation of Solid Dispersion: It was observed that by incorporation of solid dispersion of MHCl in MCC, the value of DT and WT increased which may be due to that MCC acts as a carrier for drug as solid dispersion consequently decreases the free superdisintegrant and increases the bonded (H-bonded) superdisintegrant and this may lead to decrease water uptake and ultimately DT and WT increase [6].

Thermograms of pure drug (MHCl) and the solid dispersion of MHCl in MCC (**Figures 2 and 3**) revealed that the pure drug has a sharp endothermic peak with an onset at 222.31°C which matches with melting point of the drug. In case of solid dispersion, the nature of thermogram is totally changed and the sharp peak of the drug shifted to lower range with an onset at 206.96°C and the peak of pure drug have change to a broader peak with reduction of the height of the peak. These changes indicate that the dehydration of pure drug and change in the particle size giving more amorphous type of the product and this suggests that the drug molecularly dispersed in the carrier.

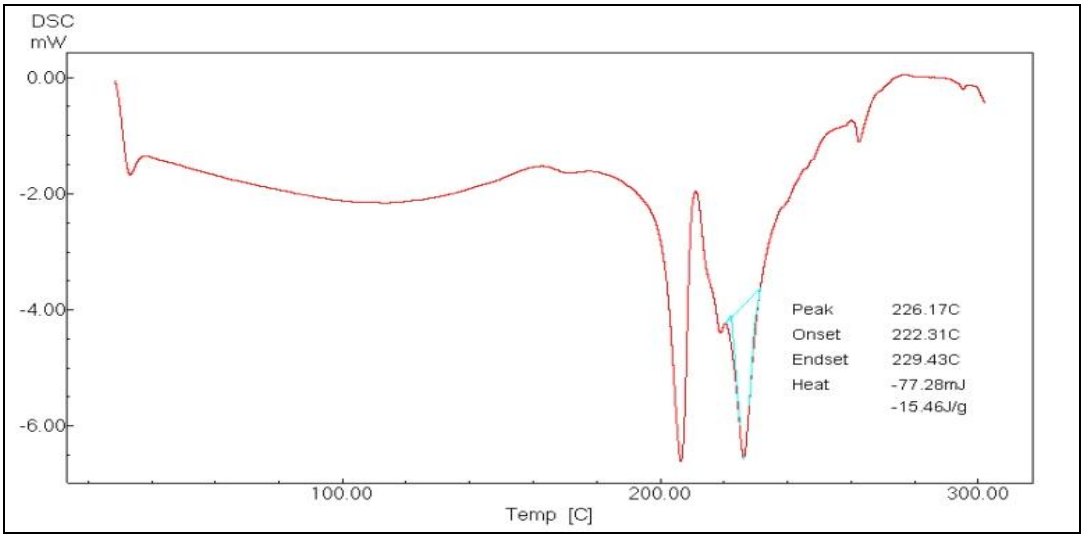

FIGURE 2: DSC THERMOGRAM OF PURE MHCl

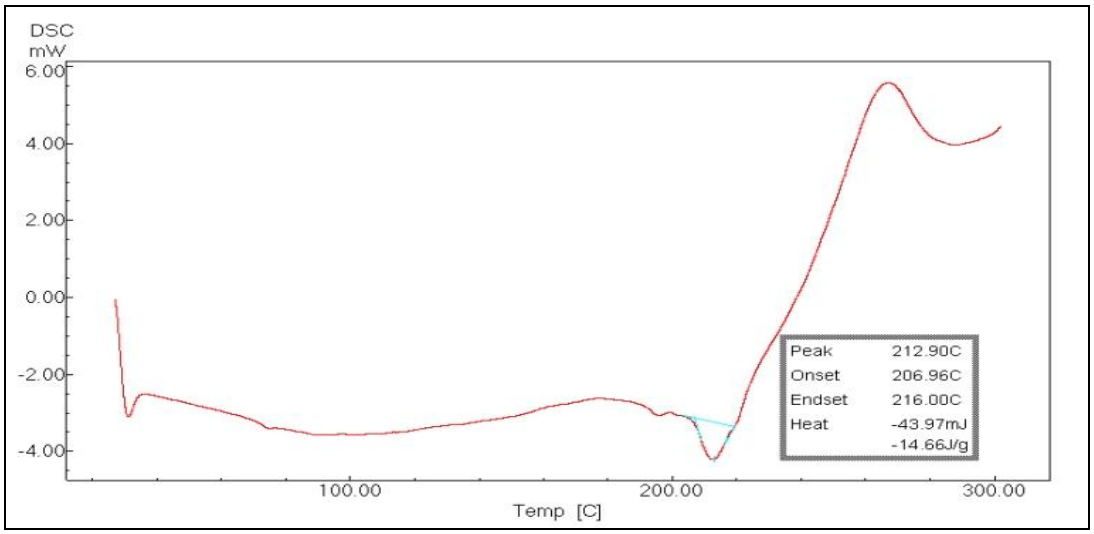

FIGURE 3: DSC THERMOGRAM OF SOLID DISPERSION OF MHCl IN MCC

Drug Content Uniformity: The content uniformity of the prepared MHCl orodispersible tablet was complied with specifications of (USP30-NF25). No tablet lies out of the range of 90-110% of the labeled claimed amount. This result indicates that the dosage form has a uniform distribution and proper dose of the active ingredient [7].

***In vitro* Dissolution Studies:** The linear fitting of the release data of formula F11 and conventional tablet according to various kinetic models indicates that the release of the drug from F11 follows Higuchi model, while from conventional tablet follows first order model. Therefore The time required for 80% of drug to be released ($t_{80\%}$) and percent drug dissolved in 2 minutes (D_{2min}) of F11 and conventional tablet were determined using Higuchi's equation plot and first order equation plot and utilized for comparing the dissolution results. F11 released about 80% of the drug within 6.28 min while conventional MHCl tablet released that amount within 38.82 min (**figure 4**).

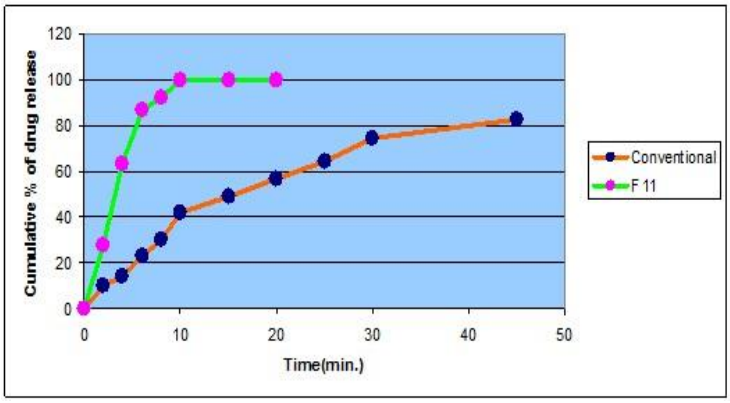

FIGURE (4): DISSOLUTION PROFILE OF MHCl OPTIMUM FORMULA (F11) AND CONVENTIONAL TABLET IN 0.01 N HCl AT 37 ± 0.5 °C AND 100 RPM

Drug assay by HPLC: MHCl elutes with a characteristic sharp peak at retention time of 12.22 minutes (**figure 5**). The percentage of MHCl in powder equivalent to 25mg MHCl was (97±0.20 % W/W). The result of the assay denotes that the tablets contain permitted amount of the drug and the drug is uniformly distributed in each individual unit [7].

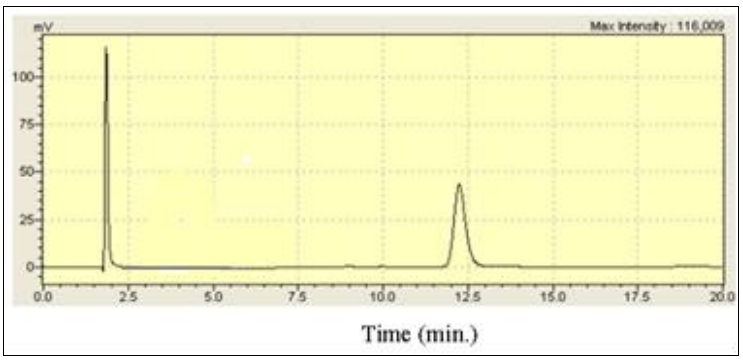

FIGURE 5: HPLC CHROMATOGRAM OF MHCl USING MOBILE PHASE (METHANOL: WATER 65:35)

Drug-Excipients Compatibility Studies: The FTIR spectra for pure drug (MHCl) and the optimum formula showed the main characteristic absorption bands of functional groups of C-CL, C-N amine and C=C stretching. As shown in **figures 6 and 7**, the characteristic absorption peaks of MHCl appear almost at the same region.

These results indicated that there is no chemical interaction between the drug and the excipients and this confirms the compatibility of the drug with the excipients of the optimum formula.

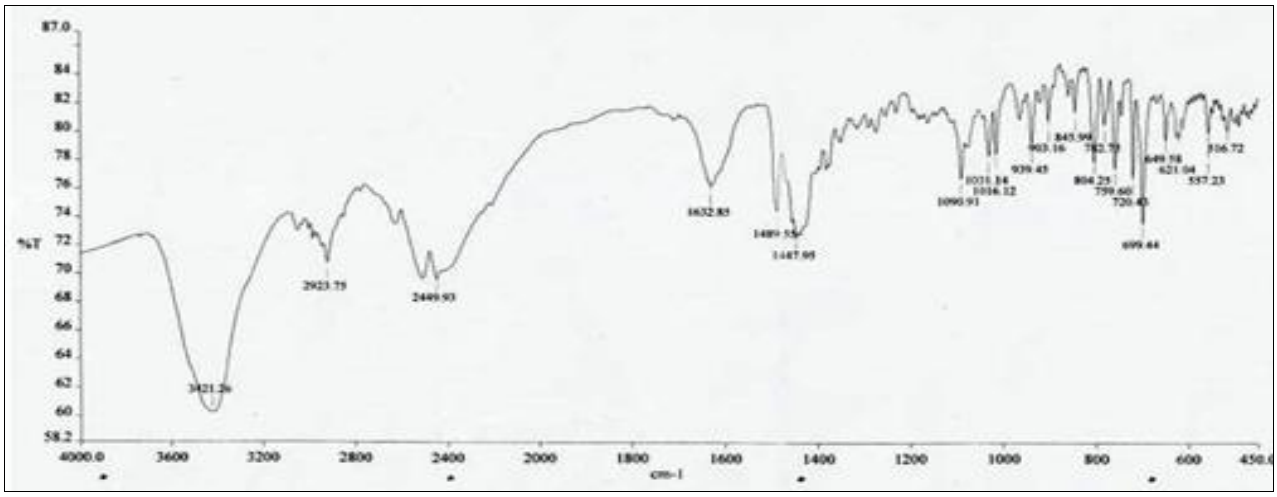

FIGURE 6: FTIR SPECTRA OF PURE MECLIZINE HYDROCHLORIDE POWDER

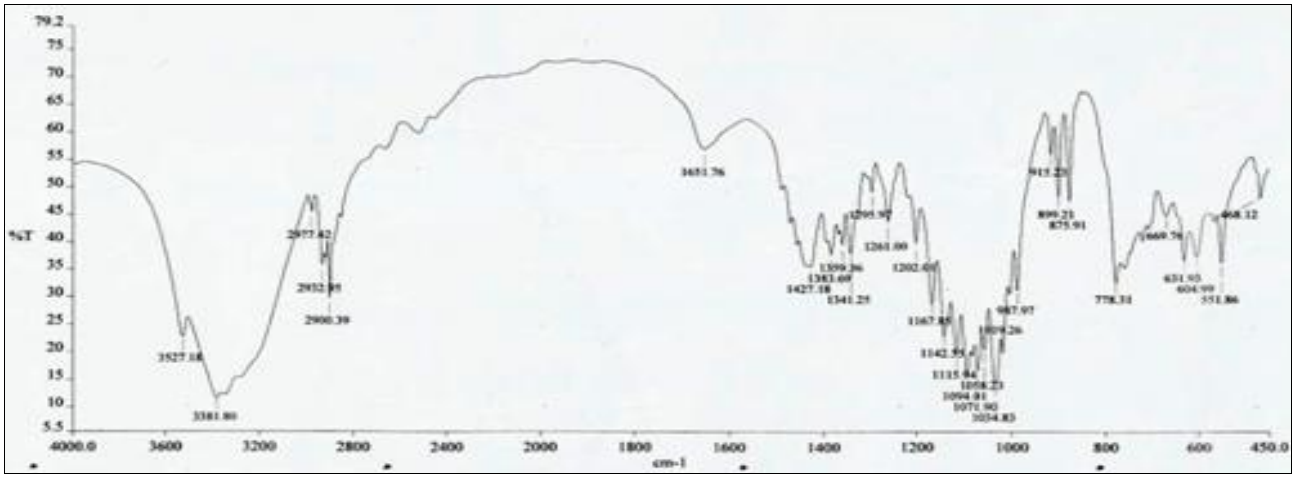

FIGURE 7: FTIR SPECTRA OF OPTIMUM FORMULA OF PREPARED MECLIZINE HYDROCHLORIDE ODTS

Accelerated Stability Studies: Accelerated stability studies of the selected formula (F11) showed no significant changes ($p<0.05$) in tablet hardness, drug content, disintegration times and release profile after storage at 40°C/75 ±5 % RH for duration of one month.

Effect of Temperature alone (determination of Expiration Date): The stability of the selected formula (F11) was studied at three different temperatures; 40°C, 50°C, and 60°C for one month. The degradation of MHCl followed first-order kinetics because straight lines were obtained when the logarithm of percent drug remaining was plotted versus time. The date of expiration for MHCl was determined through constructing Arrhenius plot as shown in **figure 8** in order to estimate the degradation rate constant at 25°C (K_{25}) which was equal to 1.2×10^{-4} day^{-1}. Equation (7) is used for calculating the shelf-life [20]:

$$t_{90\%} = 0.105/K_{25} \quad \ldots\ldots\ldots\ldots\ldots\ldots (7)$$

Where $t_{90\%}$ is the time required for a drug to lose 10% of its potency and it was found to be 875 days or about 2.39 years for MHCl.

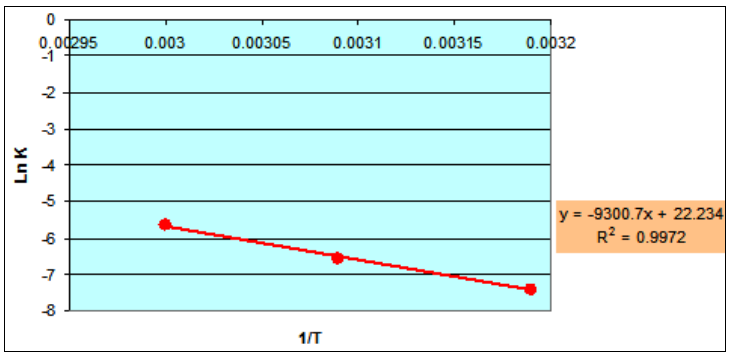

FIGURE 8: ARRHENIUS PLOT OF MHCl IN FORMULA F11 FOR THE ESTIMATION OF THE EXPIRATION DATE

CONCLUSIONS: From the present study, it can be concluded that combination of 4% crospovidone and 10% microcrystalline cellulose as superdisintegrants and granulated lactose as filler is a rational approach for preparation of orodispersible tablets of meclizine hydrochloride.

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