Research Article

Formulation and Evaluation of Oro-Dispersible Tablets Containing Meclizine Hydrochloride

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ABSTRACT

A dosage forms that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention and hence Fast disintegrating oral drug delivery system was developed. The present study was aimed at formulation and evaluation of Meclizine Hydrochloride Oro-Dispersible Tablets. Meclizine HCl is a first generation antihistamine of the piperazine class. It has been used in the treatment of motion sickness (H1 receptor antagonist). Meclizine Hydrochloride is a poor water soluble drug and allied to slower rate of absorption from oral route, so, there is a necessity to enhance the dissolution of this drug to ensure maximum therapeutic utility of it. Oro-dispersible tablets of Meclizine Hydrochloride were prepared by direct compression method. All the batches of ODTS were evaluated for appearance, thickness, weight variation, hardness, friability, *in-vitro* disintegration time, *in-vitro* dispersion time, wetting time, content uniformity, *in-vitro* dissolution study. The stability studies for optimized formulation (F10) were performed for 3 Months and then tablets were evaluated. The results obtained were satisfactory and complies with the pharmacopeial specifications.

Keywords: Meclizine hydrochloride, Oro-Dispersible Tablets (ODT), fast disintegrating tablet, superdisintegrant, PEG 6000.

INTRODUCTION

Fast disintegrating drug delivery system are those when put on tongue disintegrate instantaneously and releasing the drug which dissolve or disperses in the saliva without the need of water.[1] The fast disintegrating tablet (FDT) is also termed as fast melting, fast dispersing, Oro-dispersible, rapid dissolve, rapid melt, and quick disintegrating tablet. All FDTs approved by the Food and Drug Administration (FDA) are classified as orally disintegrating tablets. Recently, the European Pharmacopeia adopted the term Oro-dispersible / fast disintegrating tablet for a tablet that disperses or disintegrates in less than 3 minutes in the mouth before swallowing. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients. The disintegration time for good FDTs varies from several seconds to about a minute. Recent technological developments in the dosage form designing the ODTs fulfill the requirement of patient needs without compromising its efficacy. The ODTs satisfies the patient's requirements that are difficulty in swallowing of the conventional tablets or capsules. Another benefit of ODTs it does not require water or chewing before swallowing. Other ODTs containing some agents which will increase the rate of disintegration in the oral cavity (Superdisintegrants) are simply called as oral disintegrating tablets, which may take up to a minute for complete disintegration in the mouth.[2] The target of these new oral dissolving/disintegrating dosage forms have generally been pediatric, geriatric, bedridden and developmentally disabled patients and also patients with persistent nausea, who are in travelling, or who have little or no access to water are also good candidates for ODTs .[3]

MATERIALS AND METHODS

Meclizine Hydrochloride is purchased from Symed Laboratories Ltd., India. All other chemicals used were of analytical grade.

Manufacturing process of Meclizine HCl ODT (Method I)

Accurately weighed quantity of drug, camphor, and superdisintegrant were passed through number 60 mesh and carefully added to microcrystalline cellulose and mixed in a poly bag for 15 min. Then the powder mixture was lubricated with talc and magnesium stearate by blending for another 5min. The resultant mixture was directly compressed into tablets. Then these tablets were subjected to sublimation, by placing in a hot air oven at 60°C for 2 hr to generate a porous matrix, due to removal of volatilizable component. Composition of formulations was given in Table 1.

Manufacturing process of Meclizine HCl ODT (Method II)

Meclizine HCl and Polyethylene glycol solid dispersions were prepared by the solvent evaporation method. 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 granulated along with diluents using PVP K 30 as a binder. The wet mass was screened through sieve no. 16 and dried at 60°C for 30min.

Table 1: Composition of formulations of Meclizine HCl ODT (Method I)

Sr.No.	Name of ingredient	F1	F2	F3	F4	F5
1	Meclizine HCl	25	25	25	25	25
2	Camphor	05	08	10	10	10
3	Mannitol	15	15	15	15	15
4	Microcrystalline Cellulose	16	16	14	15	13
5	Lactose	25	20	18	15	15
6	Poly Vinyl Pyrrolidone	5	5	5	5	5
7	Sodium Starch Glycolate	2	4	6	8	10
8	Saccharin Sodium	2	2	2	2	2
9	Strawberry	1	1	1	1	1
10	Magnesium stearate	3	3	3	3	3
11	Colloidal silicon dioxide	1	1	1	1	1
	Total Weight	100	100	100	100	100

The granules were prepared using direct compression method after incorporating excipients. Finally these granules were compressed on tablet compression machine using standard punches. Composition of formulations was given in Table II.

Table 2: Composition of formulations of Meclizine HCl ODT (Method II)

Sr.no.	Name of ingredient	F6	F7	F8	F9	F10
1	Meclizine HCl	25	25	25	25	25
2	Polyethylene glycol 6000	10	20	25	30	40
3	Mannitol	15	15	15	15	08
4	Microcrystalline Cellulose	15	10	05	05	05
5	Lactose	20	13	10	05	05
6	Poly Vinyl Pyrrolidone	3	5	8	8	5
7	Sodium Starch Glycolate	5	5	5	5	5
8	Saccharin Sodium	2	2	2	2	2
9	Strawberry	1	1	1	1	1
10	Magnesium stearate	3	3	3	3	3
11	Colloidal silicon dioxide	1	1	1	1	1
	Total Weight	100	100	100	100	100

Evaluation of Oro-Dispersible Tablets of Meclizine Hydrochloride [4-6]

Evaluation of Pre-Compression Parameters

The results of precompression parameters were given in table III.

Bulk density

Bulk density is a characteristic of a powder rather than individual particles and is given by the mass, M, of the powder occupying a known volume, V_o. It is expressed in g/ml. An accurately weighed quantity of granules was transferred into a 50 ml measuring cylinder with the aid of the funnel. The unsettled apparent volume, to the nearest graduated unit occupied by the granules was measured. Bulk density was determined using the formula,

$$\rho_{bulk} = m/V_o$$

where, ρ_{bulk} = Bulk density; m = Mass of the blend and V_o = Untapped Volume.

Tapped density

The measuring cylinder containing a weighed quantity of granules (after measurement of bulk density) was subjected to 500 taps in tapped density tester (Electro Lab USP II). The tapped density was calculated by using the formula,

$$\rho_t = m/V_t$$

where, ρ_t = Tapped density; m = Mass of the granules and V_t = Final tapped volume.

Carr's compressibility index

Compressibility indices are a measure of the tendency for arch formation and the ease with which the arches will fail. It is calculated by using the formula,

$$CI = \rho_t - \rho_{bulk} / \rho_t \times 100$$

where, CI = Compressibility index; ρ_{bulk} = Bulk density and ρ_t = Tapped density.

Hausner's ratio

Hausner found that the ratio ρ_t / ρ_{bulk} was related to inter particle friction and, as such could be used to predict powder flow properties. He showed that powders with low inter particle friction, such as coarse spheres, had ratios of approximately 1.2; whereas more cohesive, less free flowing powders such as flakes have values greater than 1.6. It is calculated using the formula,

$$\text{Hausner's Ratio} = \rho_t / \rho_{bulk}$$

Where, ρ_{bulk} = Bulk density and ρ_t = Tapped density.

Angle of repose

Angle of Repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by fixed funnel method and is the measure the flowability of powder/granules**.** Weighed

quantity of granules was passed through a funnel kept at a height of 2 cm for the base. The powder is passed till it forms heap and touches the tip of the funnel. The height of the heap formed and radius of the base of the heap was measured. Angle of repose was calculated by using the formula,

$$\theta = \tan^{-1}(h/r)$$

where, θ = Angle of repose; h = height of the heap of pile and r = radius of base of pile.

S.No	Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Bulk density (gm/ml)	0.740±0.30	0.720±0.32	0.740±0.29	0.740±0.31	0.750±0.30	0.760±0.29	0.805±0.21	0.702±0.31	0.780±0.22	0.790±0.21
2	Tapped density (gm/ml)	0.930±0.19	0.910±0.21	0.930±0.19	0.910±0.21	0.912±0.22	0.912±0.23	0.940±0.18	0.905±0.20	0.920±0.26	0.944±0.18
3	%Carr's index	20.34±0.25	20.46±0.23	20.54±0.21	20.65±0.20	17.56±0.30	17.11±0.34	14.79±0.48	22.70±0.20	15.65±0.32	16.35±0.24
4	Hausner's Ratio	1.260±0.12	1.260±0.14	1.260±0.13	1.260±0.15	1.213±0.13	1.214±0.12	1.172±0.13	1.290±0.15	1.190±0.16	1.202±0.19
5	Angle of Repose	21.05±0.22	22.40±0.20	20.88±0.20	22.15±0.21	21.92±0.23	20.20±0.28	24.01±0.26	25.03±0.24	24.15±0.25	20.12±0.24

Table 3: Evaluation of precompression parameters (Meclizine HCl)

EVALUATION OF POST-COMPRESSION PARAMETERS [7-13]

All formulations were evaluated for post-compression parameters. Results are shown in table IV.

(i) Weight variation: 20 tablets were selected randomly from the lot and weighted individually to check for weight variation.

(ii) Thickness: Tablet thickness is an important parameter to be controlled to facilitate packaging. Tablet thickness must be controlled within a ±5% variation of a standard value. Any variation within a particular lot should not be apparent to the unaided eye of the consumer. Thickness of all the formulations was measured using a Vernier calliper. It is expressed in mm. Results were shown in table IV.

(iii) Hardness: Tablets require a certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packaging, and shipping. Tablet hardness of all the formulations was measured using a Monsanto hardness tester. It is expressed in kg/cm^2. Results were shown in table IV.

(i) **Friability:** Friability is a measure of the resistance of the tablet to abrasion. The laboratory friability tester is known as the Roche friabilator. This device subjects the tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that rotates at 25 rpm, dropping the tablets form a height of 6 inches with each revolution. Twenty tablets were weighed accurately and placed in the friabilator and was operated for 100 revolutions or 4 minutes. The tablets were then deducted and weighed. The weight loss of 0.5 to 1% is considered as acceptable limits for conventional uncoated tablets. The weight loss was calculated using the formula,

Friability, F (%) = (Weight loss/Initial weight)*100

The friability of the all the formulations was determined as per the above procedure.

(ii) **Wetting time:** The tablet was placed in a petridish of 6.5cm in diameter, containing 10ml of water at room temperature, and time for complete wetting was recorded. To check for reproducibility, the measurements were carried out 3 times and the mean value calculated.

(iii) **In-vitro Disintegration time:** Tablet disintegration study was performed for oral dispersible tablets containing Meclizine HCl. Disintegration time was determined using USP tablet disintegration tester in distilled water at 37˚C±2˚C. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds. The results were shown in table IV.

(iv) Uniformity of Dispersion Test: The fineness of dispersion test was done by place 2 tablets in 100 ml of water and stir until completely dispersed. A smooth dispersion is produced, which passes through a sieve no. #25.

(v) Content Uniformity: Ten tablets were accurately weighed and powder-crushed in a glass pestle mortar. An accurately weighed amount equivalent to 10 mg of pure drug was taken dissolved in suitable quantity of 0.1N HCl. Solution was filtered, diluted and the assay was performed spectrophotometrically at 232 nm in triplicates.

Evaluation of taste by panel (Mouth feel): The taste evaluation was done by panel testing. For this purpose, 6 human volunteers were selected to taste all the

formulation by keeping in the mouth till they disintegrated and ranked on a scale of perception

(vi) ***In-Vitro* Drug Release Studies:**

The dissolution test has been carried out for all the formulations. The in vitro drug release is performed using USP dissolution apparatus- II, 24 type paddle apparatus using 500 ml of 0.1N HCL at paddle rotation of 50 rpm at 37±0.5°C. 5 ml of the samples were withdrawn at predetermined time intervals of 0, 5, 10, 15, 30, 60, 180, 300, 600 and 900 seconds and replaced with the fresh medium of 0.1 N HCL. The samples were filtered through 0.45 mm membrane filter, suitably diluted and analyzed at 232 nm using double beam UV/Visible spectrophotometer. Cumulative amount of drug released was calculated for different sampling time intervals. The results obtained in the *in-vitro* dissolution studies for different formulations were recorded in Table V and graphs for all formulations were plotted as shown in fig I and II.

The data obtained in the *in-vitro* dissolution study has been grouped according to one mode of data treatment as follows:

Cumulative percent drug released vs. time in hours

Comparative *in-vitro* Drug Release Profile:

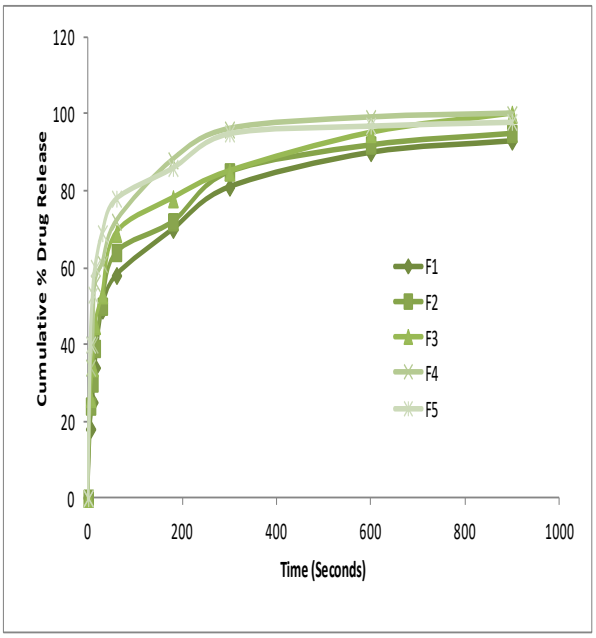

Figure 1: In-vitro drug release profile for all formulations of Meclizine HCl ODT (method I) (F1-F5)

(xi) Stability studies

Drug content of an optimized batch was performed at different stability storage conditions, as per ICH guidelines. The drug release profile of batch F10 met the dissolution acceptance criteria to pass the amount of drug release test according to USP requirements. Therefore batch F10 was selected as optimised batch and subjected to further studies.

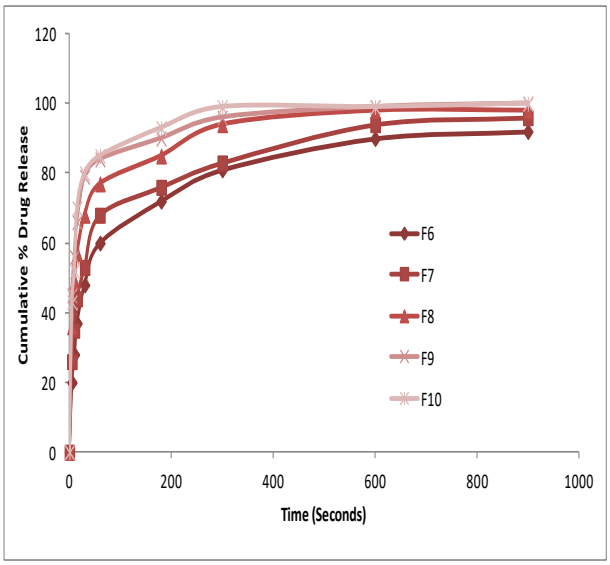

Figure 2: In-vitro drug release profile for all formulations of Meclizine HCl ODT (method II) (F6-F10)

The optimised batch F10 was charged for stability at 40°C and 75% RH for 3 months. Tablets were evaluated for physical appearance, color, hardness, friability, disintegration and dissolution studies. Oral dispersible Meclizine HCl tablets have not shown any significant change at the time of storage. The results shows optimized tablets have the good stability. From the results, it can be concluded that fast disintegrating Meclizine HCl tablets successfully prepared with enhanced dissolution of the drug and good taste masking product. The results obtained have shown in the Table VI.

RESULTS AND DISCUSSION

Oral dispersible tablets were prepared by direct compression. All the batches of ODTS were evaluated for appearance, thickness, weight variation, hardness, friability, *in-vitro* disintegration time, *in-vitro* dispersion time, wetting time, content uniformity, *in-vitro* dissolution study.

The drug release profile of batch F10 met the dissolution acceptance criteria to pass the amount of drug release test according to **USP** requirements. Oro-dispersible tablets from F10 batch showed 98.91% drug release at the end of 10 min. In vitro dissolution profile indicated faster and maximum drug release from formulation F10 (as shown in fig II). Therefore batch F10 was selected as optimised batch and subjected to further studies. The optimised batch F10 was charged for stability at 40°C and 75% RH for 3 months. Tablets were evaluated for physical appearance, color, hardness, friability, disintegration and dissolution studies. Oro-dispersible Meclizine HCl tablets have not shown any significant change at the time of storage.

Table 4: Evaluation of Post-Compression Parameters for all formulations of Meclizine HCl ODT

S. No.	Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Average Weight (mg)	102±2	101±3	103±2	102±2.5	103±2.8	103±2.5	102±3	101±4.5	102±3.5	103±2.5
2	Thickness (mm)	3.4±0.11	3.3±0.15	3.6±0.11	3.3±0.15	3.4±0.17	3.2±0.22	3.3±0.16	3.4±0.16	3.1±0.25	3.3±0.17
3	Hardness (Kg/Cm^2)	7.0±0.21	6.5±0.32	6.8±0.20	6.2±0.32	7.2±0.10	7.0±0.15	6.2±0.24	5.8±0.28	6.2±0.25	6.8±0.21
4	Friability (%)	0.48±0.07	0.65±0.05	0.70±0.04	0.60±0.09	0.73±0.02	0.62±0.07	0.59±0.08	0.53±0.09	0.60±0.04	0.71±0.03
5	Wetting time (sec)	101±1	99±2	97±3	100±1	102±4	100±2	104±5	118±3	100±4	120±2
6	Disintegration Time (Secs)	92±0.32	96±0.23	99±0.15	88±0.32	100±0.13	72±0.32	87±0.24	79±0.36	93±0.38	99±0.36
7	*Invitro* dispersion	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
8	Assay of Drug (%)	98.45	95.72	99.57	97.65	95.64	98.50	97.61	99.42	98.45	98.91
9	Taste Masking	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good

ranging from 0 – 4. 0 – Good 1 – Tasteless 2 – Slightly bitter 3– Bitter 4– Very bitter

Table 5: In-Vitro Drug release profile of all formulations Of Meclizine HCl ODT

Sl.No.	TIME (SECONDS)	(% of Drug release)									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	0	0	0	0	0	0	0	0	0	0	0
2	5	18	24	26	34	40	20	26	36	45	43
3	10	25	30	34	40	53	28	35	49	56	52
4	15	34	39	45	56	60	37	44	57	66	70
5	30	49	50	53	61	69	48	53	68	79	80
6	60	58	64	69	72	78	60	68	77	84	85
7	180	70	72	78	88	86	72	76	85	90	93
8	300	81	85	85	96	95	81	83	94	96	99
9	600	90	92	95	99	97	90	94	98	99	99
10	900	93	95	100	100	98	92	96	98	100	100

Table 6: Results of Stability studies for optimized formulations of Meclizine HCl ODT (F10)

Characteristics	Initial	1st month	2nd month	3rd month
Hardness	6.3	6.5	6.0	6.2
% Friability	0.60	0.64	0.65	0.70
Disintegration	85 sec	84 sec	88 sec	85 sec
Assay (LIMIT-90-110%)	99.08%	99.5%	98.84%	98.20%
Dissolution (NLT 70%)	100 %	101.04%	98.98%	99.68%
Moisture content (NMT-5.0%)	1.826%	1.953%	1.987%	2.028%
Description (Round shaped white colored Tablet)	Comply	Comply	Comply	Comply

CONCLUSION

Oral dispersible tablets of Meclizine Hydrochloride was successfully prepared by using direct compression method using polyethylene glycol 6000 as taste masking agent and microcrystalline cellulose and sodium starch glycolate as disintegrant, will surely enhance the patient compliance, low dosing, rapid onset of action, increased bioavailability, low side effect, good stability, and its popularity in the near future. From the study, it can be concluded that polyethylene glycol 6000 act as better taste masking agent and combination of microcrystalline cellulose and sodium starch glycolate showed better disintegration and drug release. The prepared tablets disintegrate within few seconds without need of water; thereby enhance the absorption leading to its increased bioavailability.

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