FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF PHENIRAMINE MALEATE

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Summary

The objective of the present investigation was to prepare orodispersible tablets of pheniramine maleate by direct compression method using three super disintegrants, viz., croscarmellose sodium, crospovidone and sodium starch glycolate at different concentrations with microcrystalline cellulose were used along with sodium bicarbonate and citric acid as effervescent agent. Orodispersible tablet is the fast growing and highly accepted drug delivery system, convenience of self administration, compactness and easy manufacturing. Pheniramine maleate is a member of alkylamine class of H_1 receptor antagonists. It is an antihistamine used in the treatment of allergic conditions including urticaria and angioedema. It is completely absorb after oral administration. The bland were examined for angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. The prepared tablets were evaluated for thickness, hardness, friability, and weight variation, content uniformity, wetting time, Water absorption ratio, *in-vitro* dispersion time, dissolution studies and FTIR studies. Twelve formulations F1 to F12 were prepared with three super disintegrants with different concentration. The optimum formulation was chosen and their optimum results were found to be in close agreement with experimental finding. Among three super disintegrants crospovidone F5 emerged as overall best formulation. Short-term stability studies on the formulations indicated no significant changes in the drug content and *in vitro* dispersion time ($p < 0.05$).

Keywords: Orodispersible tablets, super disintegrants, pheniramine maleate, direct compression.

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Introduction

Most of the oral pharmaceutical dosage form like conventional tablets and capsules are formulated but it was difficult to swallow for elderly and children. This problem is also applicable to active working or travelling people who do not have ready access to water[1]. Recent advances in novel drug delivery system aims to provide rational drug therapy by enhanced safety and efficacy of drug molecule by formulating convenient dosage form to administration[2]. One such approach is orodispersible tablets (ODTs). An orodispersible tablet is a solid dosage form that disintegrates and dissolves in mouth without water within 60 seconds or less[3]. The various technologies used to prepare ODTs include freeze drying and sublimation[4]. The commonly used super disintegrants are croscarmellose sodium, crospovidone and sodium starch glycolate[5]. In many orally disintegrating tablet technologies based on direct compression, the addition of super disintegrants principally affects the rate of disintegration and hence dissolution and also effervescent agent also further hastens the process of disintegration.

Pheniramine maleate is a member of alkylamine class of H_1 receptor antagonists. It is an antihistamine used in the treatment of allergic conditions including urticaria and angioedema. It was selected as drug candidate, since it is not available in such dosage form. Aim of the present study was to develop orodispersible tablets of pheniramine maleate by simple and cost effective direct compression method using three super disintegrants, croscarmellose sodium, crospovidone and sodium starch glycolate at different concentrations with microcrystalline cellulose were used along with sodium bicarbonate ant citric acid as effervescent agent. The blend and prepared tablets were evaluated and compared with three super disintegrants, effect on the *in vitro* dispersion time, *in vitro* drug release and FTIR studies were observed. From the twelve formulations, the optimum formulations were selected.

Material and Method

Pheniramine maleate was gift sample from Aventis Pharma, Gujarat. Sodium starch glycolate, croscarmellose sodium and crospovidone were obtained as gift sample from AET Laboratories Hyderabad. Microcrystalline cellulose and sodium bicarbonate were gift sample from LOBA Chemical Pvt. Ltd., Mumbai. All other chemicals used were of analytical reagent grade.

Method

Preparation of pheniramine maleate tablets

Pheniramine maleate tablets were prepared by direct compression method. All the ingredients were passed through sieve No. 44 separately. Then the ingredients were weighed and mixed in geometrical order. The blend thus obtained was directly compressed using 8 mm round flat punch by rotary tablet compression machine. Twelve batches F1 to F12 were prepared with various proportions of super disintegrants (croscarmellose sodium, crospovidone and sodium starch glycolate) and microcrystalline cellulose was used along with sodium bicarbonate and citric acid as effervescent agents were shown in Table 1.

Tablet 1 Formulation of Pheniramine Maleate Tablets

Ingredients (mg)*	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Pheniramine Maleate	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Sodium bicarbonate	16	16	16	16	16	16	16	16	16	16	16	16
Citric acid	16	16	16	16	16	16	16	16	16	16	16	16
Croscarmellose sodium	6	9	12	15	_	_	_	_	_	_	_	_
Crospovidone	−	_	_	_	6	9	12	15	_	_	_	_
Sodium starch glycolate	_	_	_	_	_	_	_	_	6	9	12	15
Microcrystalline cellulose 102	30	30	30	30	30	30	30	30	30	30	30	30
Mannitol (pearlitol SD200)	63	60	57	54	63	60	57	54	63	60	57	54
Aspartame	4	4	4	4	4	4	4	4	4	4	4	4
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	150	150	150	150	150	150	150	150	150	150	150	150

*All the quantities expressed are in mg/tablet.

Characterization of orodispersible tablets

Evaluation of blends

Angle of repose

Angle of repose was determined by using funnel method[6]. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and the angle of repose (Θ) was calculated using the formula.

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

Bulk density

Apparent bulk density (p_b) was determined by pouring the blend in to a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was calculated using the formula[6].

$$p_b = M / V_b$$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (p_t) was calculated by using formula.

$$p_t = M / V_t$$

Compressibility index

The simplest way for measuring of free flow of powder was compressibility, a indication of the ease with which a material can be induced to flow was given by compressibility index (I).[6]

$$I = (V_0 - V_t / V_0) 100$$

Where, vo is the bulk volume and vt is tapped volume.

Hausner's ratio

Hausner's ratio was an indirect index of ease of powder flow. It was calculated by the following method

$$\text{Hausner ratio} = p_t / p_d$$

Where, p_t is tapped density and p_d is bulk density lower hausner's ratio (< 1.25) indicates better flow properties than higher ones (> 1.25).[8]

Evaluation of tablets

Weight variation

Twenty tablets were selected at random and weighted individually. The individual weights were compared with average weight for determination of weight variation.

Friability

Friability of the tablets was determined by using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were deducted using a soft muslin cloth and reweighed. The friability (f) was given by the formula.

$$F = (1-W_0 / W) 100$$

Where, W_0 is weight of the tablets before and W is weight of the tablets after test.

Hardness

Hardness was measured by using Monsanto hardness tester.[6]

Thickness

Thickness was measured by using digital Vernier calipers.

Wetting time and water absorption ratio

The method reported by Yunixia et al [9] was following to measure the tablet wetting time. A piece of tissue paper (12 cm × 10.75 cm) folded twice was placed in a petridish containing 6 mL of simulated saliva pH 10, a tablet was put on the paper ,the time required for complete wetting was measured. The wetted tablet was taken and weighed. Water absorption ratio (R) was determined by using following equation

$$R = 100 \times (W_a - W_b) / W_b$$

Where W_b is weight of tablet before water absorption and W_a is weight of tablet after water absorption.

Content uniformity

Ten tablets were weighed and powdered. The powder equivalent to 12.5 mg of pheniramine maleate content was determined by measuring the absorbance at 265 nm after appropriate dilution with methanol. The drug content was calculated as an average of three determinations.

***In vitro* dispersion time**

One tablet was placed in a beaker containing 10 mL of pH 6.8 phosphate buffer at 37 ± 0.5^0C and time required for complete dispersion was determined.

***In vitro* dissolution study**

In vitro dissolution of pheniramine maleate orodispersible tablets was studied in USP XXIII type-2 dissolution apparatus (Electrolab, Model- TDT- 08L) employing a paddle stirrer at 50 rpm using 900 mL of pH 6.8 phosphate buffer at 37 ± 0.5^0C as dissolution medium. One tablet was used in each test. Aliquots of dissolution medium (5 mL) were withdrawn at specific intervals of time and analyzed for drug content by measuring the absorbance at 265 nm. The volume withdrawn at each time interval was replaced with fresh quantity of the dissolution medium. Cumulative percent of drug released was calculated and plotted against time.

IR spectral analysis

Infrared spectra of drug and its inclusion complexes were recorded by KBr pellet method using Fourier Transform Infrared Spectrophotometer. A base line correction was made using dried potassium bromide and then spectra of dried mixtures of drug and inclusion complexes with potassium bromide were recorded.

Short term stability studies

Short-term stability studies on the promising formulations F5 were carried out by storing the tablets at 40±2^{0}C and 75±5% RH over a 3 month period. At intervals of 1month, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time.

Results and Discussion

Twelve formulations of Pheniramine maleate were prepared by direct compression method with varying concentration of three super disintegrants, sodium starch glycolate, crospovidone and croscarmellose sodium with microcrystalline cellulose were used along with sodium bicarbonate ant citric acid as effervescent agent and directly compressible mannitol was used as diluents to enhance mouth feel. The slight bitter taste of the drug has been masked by using aspartame. A total of twelve formulations were designed. The powder blend was evaluated the physical properties such as angle of repose, bulk density, tapped density, compressibility index and hausner's ratio were tabulated in Table 2. The angle of repose between 30 and 32, this indicates passable flowability, the percentage compressibility index and hausner's ratio were within the limits (< 15%).

The prepared tablets were evaluated for hardness, friability, thickness, weight variation, content uniformity were shown in Table 3. The drug content was found to be in the range of 98 to 100 (acceptable limits) and the hardness of the tablets was found to be 2.8 to 3.2 kg / cm^2 were tabulated in Table 3. Friability below 1% was indicating good mechanical resistance of tablets. Water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in the precence of little amount of water were also found within the limits.

Table 2 Evaluation of Pheniramine Maleate Orodispersible Tablet Blend

Formulations	Angle of repose	Bulk density	Tapped density	Percent compressibility index	Hausner Ratio
F1	31^0 62"	0.49	0.65	16.0	1.22
F2	32^0 28"	0.30	0.36	15.6	1.20
F3	32^0 62"	0.25	0.31	18.3	1.24
F4	30^0 20"	0.21	0.25	15.0	1.19
F5	31^0 74"	0.22	0.25	12.0	1.13
F6	30^0 90"	0.37	0.43	13.9	1.16
F7	32^0 12"	0.37	0.42	11.9	1.13

F8	32^0 54”	0.33	0.37	10.8	1.12
F9	31^0 62”	0.25	0.30	16.6	1.20
F10	30^0 94”	0.25	0.30	15.6	1.21
F11	31^0 22”	0.37	0.45	16.7	1.21
F12	31^0 30”	0.21	0.25	16.0	1.19

In vitro dispersion test was done for all the formulation. Tablet disintegration was affected by the wicking and swelling of the disintegrants from the 12 formulations F5 (crospovidone) shown less disintegration time, 24 seconds when compared with others super disintegrants. Water absorption ratio for F5 was 84% it shows good water absorption capacity.

In vitro drug release studies of pheniramine maleate prepared tablets F1 to F12 using different super disintegrating agents by different concentrations. The maximum drug release for the formulation F1, F2, F3and F4 using different concentration of croscarmellose sodium, at the end of the 15 minutes are 96%, 96%, 97% and 96% were shown in Table 4 and Figure 1 respectively for the formulations F5, F6, F7 and F8 using crospovidone at different concentrations. The drug release was found to be 97%, 96%, 95% and 96% at the end of 15 minutes. It concluded that F5 formulation gives maximum drug release within 10 minutes respectively for the formulation F9, F10, F11 and F12 using sodium starch glycolate at different concentrations. The drug release was found to 84%, 87%, 84% and 81% at end of 15 minutes were shown in Table 4 and Figure 1 from these three different super disintegrating agent 4% W/W crospovidone formulation F5 show good drug release.

Table 3 Evaluation of Pheniramine Maleate Orodispersible Tablet

Formulations	**Hardness Kg/cm^2 ± SD**	**Friability (%)**	**Thickness (mm)**	**Content uniformity (%) ±SD**	**Wetting time (s)**	***In vitro* dispersion time (s) ±SD**	**Water absorption ratio (%)**
F1	2.86±0.02	0.90	2.48±0.02	98.46±0.6	92±0.81	54±1.24	66.3± 0.54
F2	3.26±0.07	0.79	2.44±0.02	98.86±0.6	63±0.21	40 ±1.34	71.3± 0.56
F3	3.10±0.11	0.69	2.51±0.04	99.47±1.8	42±0.24	38 ±1.32	77.4± 0.45
F4	2.98±0.05	0.94	2.49±0.02	99.75±1.6	55±0.25	53 ±1.26	74.6± 0.64
F5	2.88±0.01	0.64	2.55±0.06	99.86±0.9	30±0.85	24 ±1.26	84.1 ±0.88

F6	3.10±0.12	0.64	2.48±0.05	100.46±0.9	34±0.92	46 ±1.04	78.3± 0.78
F7	2.80±0.15	0.73	2.49±0.08	98.46±0.7	63±1.12	53 ±1.25	77.3± 0.24
F8	2.96±0.01	0.89	2.58±0.06	98.46±1.5	35±0.13	58 ±1.24	72.0± 0.45
F9	2.80±0.03	0.78	2.55±0.03	99.25±1.2	68±1.24	45± 0.98	62.6± 0.65
F10	2.94±0.02	0.84	2.51±0.02	100.46±0.9	71±0.25	58 ±1.12	59.6± 0.48
F11	2.83±0.05	0.74	2.50±0.08	100.70±1.6	69±0.87	56 ±1.54	53.8± 0.95
F12	3.12±0.05	0.89	2.57±0.06	98.46±0.8	53±1.00	54 ±1.25	49.0± 0.35

*Average of three determinations

Table 4 *In Vitro* Drug Release Studies of Pheniramine Maleate Orodispersible Tablet

Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
0	0	0	0	0	0	0	0	0	0	0	0	0
2	51.84	52.30	56.35	52.74	63.44	60.54	60.24	58.44	50.62	50.72	49.64	48.70
5	59.72	75.52	68.25	60.34	77.68	72.34	73.14	72.53	53.54	54.83	53.34	53.84
7	76.60	87.83	79.30	75.93	89.40	87.60	84.83	85.86	63.63	62.74	66.74	62.92
10	87.83	92.42	85.90	89.10	97.36	96.90	94.64	93.36	74.90	71.88	69.74	73.92
15	95.90	96.15	97.48	96.38	96.82	96.16	95.34	95.64	83.70	86.88	83.92	81.44
30	95.26	92.76	96.35	95.80	95.42	94.24	95.15	94.82	95.84	96.10	92.44	88.80
45	93.80	91.14	95.74	95.16	93.80	93.85	93.64	92.32	93.72	94.20	94.52	92.56

The graph were plotted cubic root of 100 cubic root of drug remained vs. time, the drug release for the optimized formulation F5 according to Hixon and Crowell equation. From the results drug release of F5 formulation shows Hixons and Crowell mechanisms. It indicates a change in the surface area and diameter of the tablet with the progressive dissolution of tablet as the function time. IR spectroscopic studies indicated that the drug was compatible with all the

excipients. The IR spectrum of F5 showed all the characteristic peaks of pheniramine maleate pure drug, thus confirming that no interaction of drug occurred with the components of the formulation. Short term stability studies of the above formulations indicated that there were no significant changes in drug content and *in vitro* dispersion time at the end of 3 month period ($p < 0.05$).

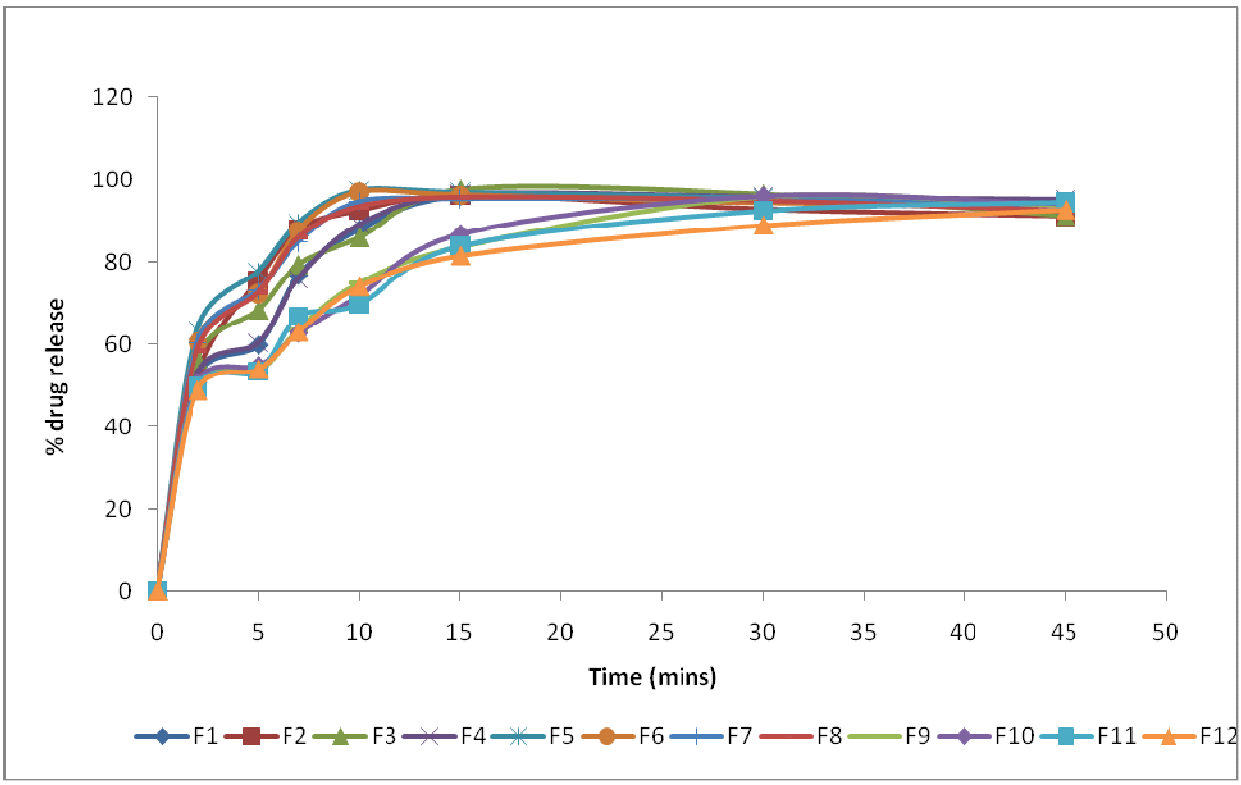

Figure 1 *In Vitro* Drug Released Studies of Pheniramine Maleate Orodispersible Tablet

Conclusion

The orodispersible tablets of pheniramine maleate were prepared by direct compression method using three super disintegrants, viz., croscarmellose sodium, crospovidone and sodium starch glycolate at different concentrations with microcrystalline cellulose were used along with sodium bicarbonate and citric acid as effervescent agent. A total of 12 formulations were designed (F1 to F12). Among these formulations tablets containing 4% crospovidone F5 formulation were optimized due to its fast *in vitro* dispersion when compare to other formulations and 97% drug release with in 15 min.

References

1. Shirwaikar. Fast disintegrating tablet of atenolol by dry granulation method. *Ind J Pharm Sci* 2004; 66: 422-426.
2. Banker BS and Anderson GR, Lachman L, Leon Liberman HA and Kanig JL. *The theory and practice of industrial pharmacy.* Edition 3, Varghese publishing house 1987; 293-345.
3. Sunada H and Bi YX. Preparation evaluation and optimization of rapidly disintegrating tablets. *Powder Technologies* 2002; 122: 188-198.
4. Shin SC, Oh IJ, Lee YB, Choi HK, and Choi JS. Enhanced dissolution of furosemide by Co-precipitating or Cori dining with cross povidone. *Int J Pharm Sci* 1998; 24: 175-177.
5. Marshall, Lachaman L, Leon Liberman HA and Kanig JL. *The theory and practice of industrial pharmacy.* Edition 3, Varghese publishing house. 1987; 67-85.
6. Marshall K, Lachaman L, Leon Liberman HA and Kanig JL, *The theory and practice of industrial pharmacy.* Edition 3, Varghese publishing house 1987; 66-99.
7. Lindberg N, Palsson M pihl A, Freeman R, Freeman J, Zetezener H and Enstand G. Flowability Measurement of pharmaceutical powder mixture with poor flow using five different techniques. *Drug Dev Ind Pharm* 2004; 30(7): 785-791.
8. Levis SR and Deasy PB. Pharmaceutical application of reduced grades of surfactants co-processed Micro crystalline cellulose. *Int J pharm* 2001; 230: 25-33.
9. Akihikol and Masayasn S. Development of oral dosage form for elderly patient. *chem Pharm Bull* 1996; 44(11): 2132-2136.
10. Peh KK and Wong CF. Polymeric films as Vehicle for buccal delivery swelling Mechanical and bio adhesive properties. *J pharm pharma Sci* 1999; 2(2): 53-61
11. Dandagi PM, Sreenivas SA, Manvi FV, Patil MB, Mastiholimath VS and Gadad AP. Taste masked Ofloxacin mouth disintegrating tablets. *Ind Drugs* 2005; 42(1): 52-55.