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FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF PHENIRAMINE MALEATE

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ABSTRACT: In the present study an attempt has been made to formulate Pheniramine maleate a selective H_1 receptor antagonist into Orodispersible tablet. The tablets were prepared by direct compression method using super disintegrants like croscarmellose sodium, crospovidone, sodium starch glycollate, low hydroxyl propyl cellulose and pre gelatinized starch in different ratios.The blend was examined for various pre compression parameters. Tablets were evaluated by measuring hardness, friability, content uniformity, weight variation and drug release pattern. All the tablets met the pharmacopoeial requirements for physical tests. Almost in all the formulations with increase in concentration of superdisintegrants, the drug release was rapid. Stability studies were also perfomed. Dissolution studies indicated that the tablets containing crospovidone and croscarmellose sodium showed rapid dissolution compared to other disintegrants releasing almost 100% of the drug in six minutes.

Key words: Pheniramine maleate, Orodispersible tablets, Super disintegrating agents, Direct compression.

INTRODUCTION

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Among that solid dosage forms are popular because of its various advantages. But many patients express difficulty in swallowing tablets and capsules and thus do not comply with prescription , which results in high incidence of non compliance and ineffective therapy.[1] Convenience of administration and patient compliance are gaining significant importance in the design of dosage forms. Recently more stress is laid down on the development of organoleptically elegant and patient friendly drug delivery systems for pediatric and geriatric patients. [2, 3] Fast disintegrating tablets are gaining prominence as new drug –delivery systems. These dosage forms dissolve or disintegrate in the oral cavity within a minute without the need of water or chewing.[4]

Pheniramine Maleate is H_1 receptor antagonist. It inhibits the effect of histamine on capillary permeability and on vascular, bronchial and many other types of smooth muscle. It is used in allergic conditions, itching and mainly to prevent motion sickness, nausea, vomiting and vertigo.[5]

The objective of this study was to enhance safety and efficacy of drug molecule, achieve better compliance, solve the problem of difficulty in swallowing, enhance onset of action, and provide stable dosage form. Orodispersible tablets of Pheniramine Maleate were formulated by direct compression method using various super disintegrants. Influence of these super disintegrants was studied by evaluating the formulated tablets.

MATERIALS AND METHODS

Pheniramine maleate was obtained as gift sample from sanofi-Avents, super disintegrants such as crospovidone, croscarmellose sodium, sodium starch glycolate, low substituted hydroxy propyl cellulose were from signet chemicals and all other chemicals used were of analytical grade.

Pre formulation studies

The solubility of drug was determined in water chloroform, ethanol and ether, pH of the drug was determined in 1% w/v solution. The Micrometric properties of drug such as angle of repose bulk density, tapped bulk density were determined. The results are depicted in Table 1

Preparation of tablets

Pheniramine maleate orodispersible tablets were prepared by direct compression method using superdisintegrants (croscarmellose sodium, crospovidone, sodium starch glycollate, low substituted hydroxyl propyl cellulose, and pre gelatinized starch) in varying concentration. All the ingredients depicted in Table 2 (except talc and magnesium stearate) were mixed homogenously and co ground in a mortar and pestle. Finally talc and magnesium stearate were added and mixed for 5 min. The mixed blend of drug and excipients were compressed using a Cad mach single punch tablet punching machine with 9mm flat face punch to produce convex shaped tablets weighing 170 mg.

Evaluation of powder blend

All micrometric properties of powder blend like Angle of repose, Tapped Density, Bulk Density, % compressibility, Hausner ratio, porosity were determined.

Physico chemical characterization of Tablets

The thickness, diameter of the tablets was determined using vernier calipers. The hardness of the tablets (n = 6) was determined by using Monsanto hardness tester. The friability (%) of the tablets was determined using Roche friabilitor. Weight variation test of the tablets was carried out as per the official method.

Drug content

Three tablets were crushed and quantity equivalent to 45mg was taken and determined using 0.1M Hcl with UV spectrophotometer at 265 nm. [6]

Wetting time

It was determined by placing a double folded tissue paper in a Petri plate with 6ml of water or buffer (simulating pH of saliva) and the tablet was placed on the paper. The time taken for complete wetting of tablets was measured by maintaining water at 37°C.[7]

In vitro dispersion time

Tablet was added to 10 ml of phosphate buffer solution pH 6.8 (pH of saliva) at 37+/- 0.5°C. Time required for complete dispersion of tablet was measured.[8]

Invitro disintegration time

The time required for disintegration of six tablets, placed in each tube of disintegration test apparatus was measured at 37+/-2°C using 900 ml distilled water.[9]

In vitro Dissolution studies[10]

The in vitro dissolution study was carried out USP type 2 dissolution apparatus carried out in 900 ml of 0.1M Hcl at 50 rpm. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37± 0.5°c. At predetermined time intervals, 5ml aliquot was withdrawn filtered through Whatman filter paper and assayed spectrophotometricly at 265.6nm using UV-visible spectrophotometer. The dissolution experiments were conducted in triplicate.

Stability studies

Selected formulation were subjected to stability studies as per ICH guidelines at 30°C/ 65 % RH and 40°C / 75% RH for 1 month. Sample were taken and analyzed at time interval of 10 days.

Comparison of formulated tablet with marketed tablet

Selected formulations were compared with marketed tablet (Avil) for different tests like hardness, friability, thickness, uniform of drug content, in vitro disintegration, weight variation, in-vitro dissolution and dispersion studies.

RESULTS AND DISCUSSION

Results of pre formulation studies are shown in Table 1.Micrometric properties of the drug complied with I.P. The results of physiochemical evaluation of blend are tabulated in Table 3. The blend of different formulations (F1 – F10) was free flowing with Angle of repose ranging from 25 – 27° except LHPC - > 30°. (The flow is excellent if the angle of repose value is < 20; passable, if between 30-34; very poor if the value is > 34). BulkDensity, Tapped Density, porosity, Carr's Index, and Hausner's ratio were also complied with Indian Pharmacopoeia. Values are expressed as mean ± SD. (n = 3)

The results of physicochemical evaluation of tablets are given in Table 4 .Weight variation of different batches of tablets was found within prescribed limits. The tablets of all formulations were found uniform with respect to thickness (2.46 - 2.56mm), hardness (3.3 – 3.6kg/cm²). Friability was also within the prescribed limits for all formulations. Wetting time of all the ten formulations were between29.8 – 65.8sec. Wetting time of cross povidone was rapid followed by croscarmellose sodium, Low hydroxypropyl cellulose, pre starch and Sodium starch glycollate ranging from 26.8 – 59.6sec. Drug content of all formulation was between 98.9 – 101.5%.

The results of in vitro drug release studies of all ten formulations in 0.1M Hcl are presented in Table 5 and graphs Figure 1 and 2.The data's reveled that as the concentration of disintegrant increase, cumulative drug release rate was also increased at the end of 6min formulations containing 10% croscarmellose sodium and crospovidone in F6 and F7 shows almost 100% drug release at the end of 6 min while conventional marketed tablet showed 100% release only at end 45min results are given in Table 6 and 7.

Stability studies were conducted at 30°C/65%RH and 40°C / 75%RH for F6 and F7 shows good results in In-Vitro Disintegration, Wetting time, and In-Vitro drug release studies, they were selected for stability studies. The tablets were analyzed for Hardness, Uniformity of drug content, In-Vitro disintegration time and In-Vitro dissolution studies at a

time interval of 10 days till a period of 30 days. The results are tabulated in Table 8 .Both the formulation showed no significant variations in all the parameters and were stable for a period of 30 days. The study shows that the dissolution rate of Pheniramine maleate can be enhanced to great extent by direct compression technique with the addition of super disintegrants which gives quick relief to motion sickness and emesis.

Table 1: Preformulation studies of Pheniramine Maleate

S.No.	Parameters	*Observations*
1	Solubility	*Freely soluble in water, in chloroform and in ethanol, very slightly soluble in ether.*
2	Determination of pH	*pH of 5*
3	Bulk Density(gm/ml)	*0.55 gm/ml*
4	Tapped Density (gm/ml)	*0.62 gm/ml*
5	% Compressibility	*1.12 %*
6	Loss On drying	*0.4 %*
7	*Melting Point*	*107℃ to 109℃*

Table 2: Composition of Orodispersible tablet of Pheniramine Maleate

Ingredients* (mg per tablet)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	***F10***
Pheniramine Maleate	25	25	25	25	25	25	25	25	25	*25*
M.C.C.(102)	38.91	38.91	38.91	38.91	38.91	30.41	30.41	30.41	30.41	*30.41*
Mannitol	90.62	90.62	90.62	90.62	90.62	90.62	90.62	90.62	90.62	*90.62*
Croscarmellose sodium	8.5	–	–	–	–	17	–	–	–	–
Crospovidone	–	8.5	–	–	–	–	17	–	–	–
S.S.G.	–	–	8.5	–	–	–	–	17	–	–
L – H.P.C.	–	–	–	8.5	–	–	–	–	17	–
Pre-Starch	–	–	–	–	8.5	–	–	–	–	*17*
Aspartame (1%)	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	*1.7*
Magnesium Stearate (1%)	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	*1.7*
Talc (2%)	3.4	3.4	3.4	3.4	3.4	3.4	3.4	3.4	3.4	*3.4*
Strawberry flavor	0.175	0.175	0.175	0.175	0.175	0.175	0.175	0.175	0.175	0.175
Total Weight	170	170	170	170	170	170	170	170	170	170

*All the quantities are in mg

Table 3: Results of precompression parameters (n=3)

Formulation Code	Bulk Density (g/cc)	Tapped Density (g/cc)	Angle of Repose (°)	Porosity (%)	Carr's Index (%)	Hausner Raito
F1	0.52±0.38	0.61±0.28	25.18±0.22	16.58±.88	14.75	1.173
F2	0.52±0.28	0.60±0.31	26.34±0.98	14.07±0.16	13.33	1.153
F3	0.51±0.34	0.60±0.32	27.14±1.09	13.1±0.29	15.01	1.176
F4	0.51±0.16	0.61±0.57	26.22±0.73	17.16±0.46	16.39	1.196
F5	0.52±1.26	0.62±1.20	25.16±0.65	15.86±0.38	16.12	1.192
F6	0.50±0.14	0.59±0.96	24.36±0.16	16.03±1.81	15.25	1.180
F7	0.49±0.23	0.58±1.12	25.18±1.23	16.81±0.37	15.51	1.183
F8	0.53±0.42	0.61±1.08	26.34±0.14	13.53±1.16	13.12	1.150
F9	0.49±0.52	0.61±0.29	33.43±1.18	16.67±0.98	19.67	1.244
F10	0.54±0.76	0.63±0.82	27.38±0.84	15.61±0.30	14.28	1.166

Table 4: Evaluation of Physical Parameters of Orodispersible Tablets of Pheniramine Maleate (n=3)

Formulation Code	Weight Variation	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Uniformity of drug content (%)	Disintegration Time (sec.)	Dispersion Time (sec.)	*Wetting Time (sec.)*
F1	Passes	3.5±0.47	2.46±0.05	0.80±0.01	100.4±1.66	31.2±037	35.0±0.71	37.8±0.84
F2	Passes	3.4±0.83	2.52±0.08	0.79±0.14	98.9±0.50	27.4±0.53	31.4±0.89	35.6±0.70
F3	Passes	3.5±0.84	2.54±0.05	0.68±0.11	99.8±0.30	51.2±0.70	59.6±0.55	65.8±0.85
F4	Passes	3.5±0.50	2.54±0.04	0.78±0.02	100.3±0.61	32.2±1.78	46.6±1.14	50.2±1.30
F5	Passes	3.5±0.65	2.5±0.01	0.48±0.07	99.3±0.57	41.3±0.83	53.3±1.01	7.1±0.83
F6	Passes	3.4±0.43	2.5±0.02	0.65±0.10	100.2±0.84	25.6±1.14	30.2±0.83	33.2±1.48
F7	Passes	3.4±0.41	2.5±0.01	0.88±0.09	99.7±0.33	20.0±1.58	26.8±1.92	29.8±1.01
F8	Passes	3.6±0.87	2.46±0.06	0.45±0.09	100.11±0.4	47.4±0.54	56.4±1.09	61.5±0.70
F9	Passes	3.5±0.86	2.48±0.07	0.65±0.04	99.6±0.28	26.5±0.84	35.2±0.45	38.4±1.14
F10	Passes	3.6±0.80	2.56±0.04	0.56±0.08	101.5±0.57	28.6±1.14	39.2±0.70	42.6±1.67

Table 5: Dissolution studies of the formulated ODTs.

S.No	Time (Min)	Cumulative percentage 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	2	88.99	89.42	61.48	81.07	71.42	97.52	98.28	78.33	94.32	93.24
3	1	92.40	94.25	85.96	91.87	89.28	98.35	98.90	89.71	96.54	95.52
1	6	97.05	97.49	96.04	95.42	97.34	100.2	99.98	97.63	98.10	98.49
5	8	99.85	99.97	98.78	98.35	98.64			98.06	99.93	99.49
6	10			99.2	99.76	100.3			99.58		
7	12			100.1							

Table 6: **Comparison of physical parameters of optimized formula with marketed tablet (n=3)**

Formulation Code	Hardness (Kg/cm^2)	Friability (%)	Uniformity of drug Content (%)	*In vitro* Disintegration Time (sec)	Wetting Time (sec)	In-Vitro Dispersion Time (sec)
F6	3.4±0.43	0.65±0.10	100.25±0.84	25.6±1.14	33.2±1.48	30.2±0.83
F7	3.4±0.41	0.88±0.09	99.94±0.33	20±1.58	29.8±1.01	26.8±1.92
Marketed Tablet (M1) (n=3)	6.3±0.1	0.31±0.01	99.98±0.65	281±0.012	819.3±1.52	650.6±2.81

Table 7: Dissolution Profile of Marketed Tablet (M1)

S.No.	Time (min)	Cumulative % Drug Release
1	0	0
2	5	66.81
3	10	73.37
4	15	81.04
5	20	90.28
6	30	96.69
7	45	99.37

Table 8: Result of stability studies of selected formulation at 30°C/65 % RH

Parameter	Formulation Code	Initial	10 days	20 days	30 days
Hardness (kg/cm^2)	F6	3.4	3.4	3.5	3.6
	F7	3.5	3.5	3.5	3.5
Disintegration Time (sec)	F6	25.5	26	27.1	28.2
	F7	20	21.2	22.4	20.5
Uniformity of Drug Content	F6	100.1	99.7	99.67	99.66
	F7	99.98	99.85	99.74	99.78
Cumulative % Drug Release (at 6 min)	F6	99.97	99.53	99.83	99.48
	F7	100.1	99.55	99.52	99.64

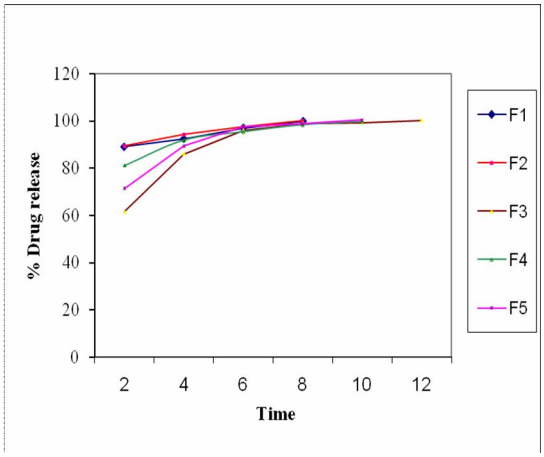

Figure 1: Comparision of invitro dissolution profiles of Pheniramine maleate ODT (F1 to F5)

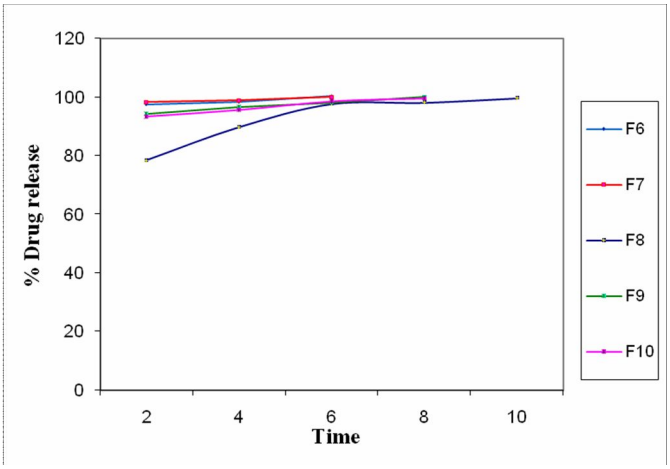

Figure 2: Comparision of invitro dissolution profile of Pheniramine maleate ODT (F6 to F10)

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