Taste Masked Oro Dispersible Compacts of an Antiemetic Drug

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Abstract

Objective: The aim of the study was to develop a taste masked oro dispersible tablet of Promethazine Hydrochloride.**Methodology:**Taste masking was achieved by complexation with β-cyclodextrin. The tablets were formulated using cross carmellose sodium as superdisintegrant and camphor, menthol, ammonium bicarbonate as sublimating agent. **Results:**The vaporization of the sublimating agents from the tablets resulted in creation in a porous surface morphology as seen in the SEM.Satisfactory results were obtained when the formulations subjected to different pre-compression tests like Angle of Repose, Hausner's Ratio, Carr's Index, Bulkiness and post compression tests like Hardness, Thickness, Uniformity of Weight, Friability, Drug Content, Wetting Time, Water Absorption Ratio, Disintegration Time and Dispersion study and In vitro dissolution study showed a drug release of 90.15% to 95.82% within 30 minutes.Studies for taste analysis was carried out using E-tongue and the results showed satisfactory taste masking for all the tablet formulations. **Conclusion:**Taste masked oro dispersible tablets of promethazine HCl were successfully prepared with good preformulation and post compression results.

Key Words: *Promethazine HCl, Oro Dispersible Tablets, SuperDisintegrant, Sublimation, antiemetic*

1. INTRODUCTION

Oral drug administration is the most accepted route for drug delivery. Among different oral drug delivery systems available, tablets are the most popular. Over the years, we have seen considerable modifications in this highly accepted dosage form. One of them is the development of oro dispersible tablet that rapidly dissolve and disintegrate. Average disintegration time in the oral cavity is 15 to 60 seconds. Since the drug dissolves rapidly, the absorption and onset of action can also be expected to be immediate[1].

US FDA defines fast dissolving tablet as a solid dosage form which disintegrates and dissolves rapidly usually within a matter of seconds[2].Promethazine hydrochloride is an antiallergic, antihistaminic agent. It is available in tablet, syrup, oral suspension and injectable form. It is extremely bitter intaste. Masking of unpleasant taste of this active ingredient of oro-dispersible tablets is highly needed. There is no commercially available mouth dissolving tablets of promethazine Hydrochloride. Hence forth, present research work is based on taste masking and formulation of oro-dispersible tablet of promethazine.

2. MATERIALS AND METHODS

2.1 Chemicals and Reagents

Promethazine hydrochloride and β-cyclodextrin and cross carmellose sodium was procured from Yarrow Chem Products, Mumbai. All other chemicals and reagents used were of analytical grade unless otherwise indicated.

2.2 Preparation of Promethazine HCl - β Cyclodextrin Inclusion Complex

Promethazine HCl and β-cyclodextrin were weighed accurately and mixed in equimolar ratio. The mixture was triturated in a mortar and pestle. A little amount of ethanol was added to the mixture and trituration continued for 30 min. Then mixture left for drying at room temperature[3].

2.3 X-Ray Diffraction

Radiation. Samples were scanned within the 2θ range of 3^0C to 80^0C.[4] The X-Ray diffraction study was carried out for the pure drug promethazine

2.4 Differential Scanning Calorimetry

Differential scanning calorimetric study is carried out to check the complexation between the drug and β cyclodextrin by observing melting temperature, crystallinity, softening of the samples. Thermogram of samples (Promethazine HCl, inclusion complex of Promethazine HCl and β cyclodextrin) were recorded using the instrument DSC 60 (Shimadzu, Japan)[5].

2.5 Solubility Study

A saturated aqueous solution of the drug was prepared in a 10 ml volumetric flask. Equivalent amount of drug-cyclodextrin complex was dissolved in another 10 ml volumetric flask. Both the flasks were sonicated for 10 min in an ultrasonic bath. The solutions were filtered to remove undissolved solids by using Whattman filter paper. The absorbance of the filtrate was measured using a UV Spectrophotometer. The solubility was calculated using the dissolution factor and regression equation from the standard graph[6].

2.6 Formulation of Promethazine HCl Oro Dispersible Tablets

The Promethazine HCl orodispersible tablets were prepared by using superdisintegrant cross carmellose sodium and different subliming agents like ammonium bicarbonate, menthol and camphor. Mannitol was used here as a diluent, aspartame as sweetening agent, aerosil as hardness imparting agent as well as lubricant. hydrochloride and the inclusion complex using AXS D8 Advance Diffractometer using nickel filter and CuKα

The drug cyclodextrin complex equivalent to 20 mg of promethazine HCl was incorporated into each formulation. The different excipients and their amounts used in Formulation of ODT of promethazine HCl is represented in Table 1.

Table 1. Formulation of Promethazine HCl Oro dispersible tablets

Ing.(mg)	F1	F2	F3	F4	F5	F6
PM-βCD*	100	100	100	100	100	100
Mannitol	80	67.5	80	67.5	80	67.5
Cross carmelose sodium	25	37.5	25	37.5	25	37.5
Camphor	37.5	37.5	-	-	-	-
Menthol	-	-	37.5	37.5	-	-
Ammonium bicarbonate	-	-	-	-	37.5	37.5
Aspartame	2.5	2.5	2.5	2.5	2.5	2.5
Aerosol	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5

*PM-βCD: Promethazine HCl – beta cyclodextrin inclusion complex

2.7 Pre compression evaluation tests

The tablet compression mix was evaluated for various pre compression parameters like bulk density, tapped density [7], Carr's index[8] and Hausners ratio[9].

2.8 Post compression evaluation tests

Post compression, the tablets were evaluated for hardness[10], thickness[11], weight variation[12] *in vitro* disintegration, dispersion [13], drug content, water absorption ratio and wetting time[14].

2.9 *In vitro* drug dissolution studies

All the formulations were subjected for drug release study. The test was performed in pH 6.8 phosphate buffer by using USP dissolution test apparatus- Type II, rotating paddle method. The dissolution study was carried out for 30 minutes for all the formulations.

2.10 Taste Analysis

Taste analysis of all the formulations and the pure drug was carried out using E-Tongue (at Kangshabati tea co-operative Pvt. Ltd, Siliguri, West Bengal). The samples, 10 mg were dissolved in 10 ml of distilled water and placed in the beaker attached with electrodes

of the instrument. The bitter taste was assessed on a scale of 1-10[5].

2.11 Scanning Electron Microscopy

SEM studies were carried out to comparethe surface morphology of the tablet before and after sublimation process. Samples prepared by attaching tablet onto a slab with a double sided tape and then coated with gold prior to examination. The accelerated voltage was adjusted to 15 KV. The scanning electron photomicrographs were taken at different magnifications for better interpretation[5].

3. RESULTS AND DISCUSSIONS

3.1 X- Ray Diffraction

The X Ray diffractogram of promethazine hydrochloride is represented in Fig. 1

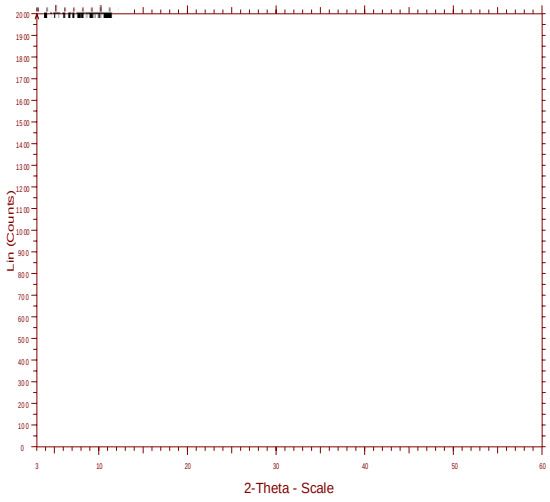


Fig. 1 X-Ray diffractogram of Promethazine Hydrochloride

At 2θ angle the XRD spectra pure drug showed sharp peaks at 19.290^0, 20.759^0, 21.773^0, 24.612^0, 26.402^0 and 27.657^0, indicating the crystalline nature of the drug.

The X Ray Diffractogram of the inclusion complex is represented in Fig. 2. The diffractogram indicates fewer drug peaks compared to the diffractogram of the pure drug. The XRD pattern of Promethazine-β-cyclodextrin shows a broad diffraction profile indicating a more amorphous distribution of the dug as inclusion complex in β- cyclodextrin.

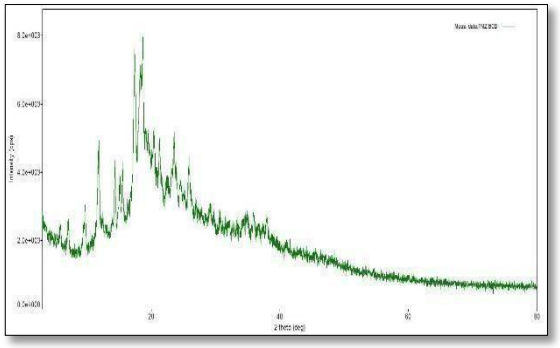


Fig. 2 X-Ray Diffractogram of the inclusion complex

3.2 Differential Scanning Calorimetry

Differential scanning calorimetric study was carried out to check the complexation study between the drug and β-cyclodextrin by observing melting temperature, crystallinity, softening of the samples. Fig. 3 and Fig. 4 shows the differential thermogram of promethazine hydrochloride and the inclusion complex respectively.

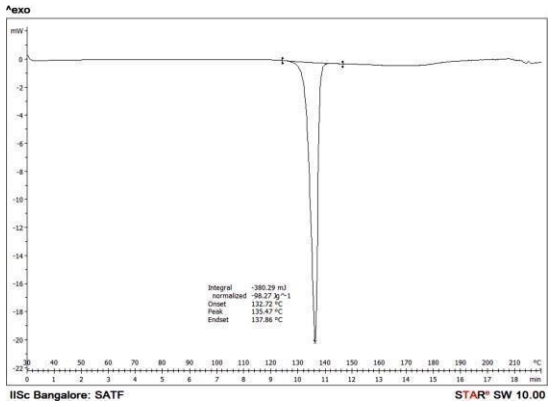


Fig. 3 Differential theromogram of promethazine hydrochloride

The differential thermogram of promethazine shows a sharp endothermic peak at 138^{0}C which corresponds to the drug's melting point this also indicates the crystalline state of the drug. The thermogram of the inclusion complex is found to be considerably reduced in size, broadened and shifted to a lower temperature of the drug melting point. Which may be attributed to formation of drug- cyclodextrin complex and loss of drug crystallinity.

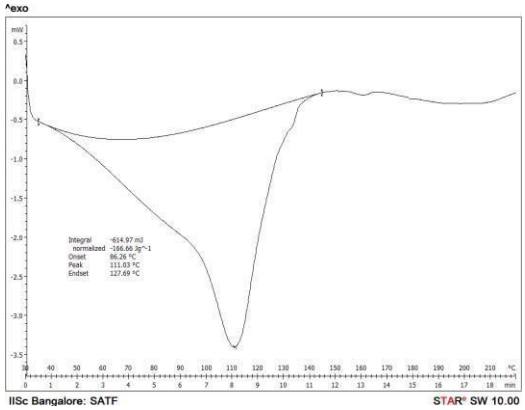


Fig. 4 Differential thermogram of the inclusion complex

3.3 Solubility Study

The use of cyclodextrins as complexing agents have shown to increase the aqueous solubility of poorly water-soluble drugs. The results of solubility study carried out for the pure drug indicated a solubility of 0.027mg/ml while the complex had a solubility of 0.062 mg/ml. The higher solubility of drug-β cyclodextrin complex may be due a change in the form of drug from crystalline to amorphous which was further observed in the DSC and XRD studies.

3.4 Pre-compression Evaluation Parameters

The results of the pre-compression tests carried out on the powder blends are indicated in Table 2. Theulkdensityvaluesfor the formulations was found between 0.543 g/ml to 0.581 g/ml. The tapped density values ranged between 0.634 g/ml to 0.702 g/ml. Hausner's ratio for all the 6 formulations showed values less than 1.25, highest being 1.209 for F4. This confirms the free flowing property of the powder blends. Carr's index value raged between 13.01% to 17.23%, indicating that all the powder blends would have good flow property and good compressibility. The angle of repose for the powder blends ranged from 25.7^0 to 27.29^0. The angle of repose valuesconfirms the good flow property of the powder blends.

3.5 Post Compression Valuation Tests

The various post compression studies conducted on the tablets after the sublimation process the results of which are indicated in Table 3. All the tablets were found to have satisfactory hardness in the range of 3 kg/cm^2 to 3.5 kg/cm^2. This is specifically of importance for tablets subjected to sublimation. The porous nature of the tablets tends to make the tablets more friable. Hence formulating tablets with satisfactory hardness is of importance. The thickess of the oro dispersible tablets ranged from 3.3mm to 3.6mm. Also the tablets showed good uniformity of thickness among the formulations. All 6 formulations were checked for uniformity of weight. The weight of all tablets formulations ranged between 240 mg to 262 mg.

The acceptable range of weight variation for tablet weight of 250 mg is between

Table 2. Pre compression evaluation parameters

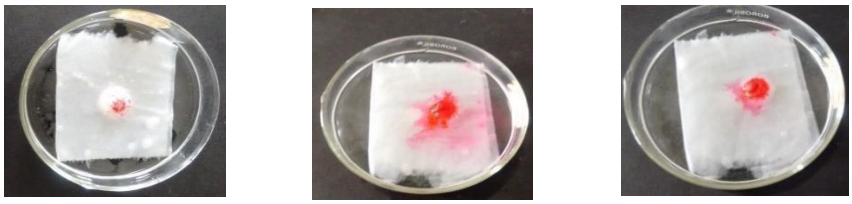
Sl. No.	Formulation Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner's Ratio	Carr's Index (%)	Angle of Repose (°)
1	F1	0.555 ± 0.003	0.638 ± 0.001	1.150 ± 0.001	13.10 ± 0.001	25.76 ± 0.02
2	F2	0.555 ± 0.006	0.648 ± 0.002	1.168 ± 0.002	14.35 ± 0.001	27.09 ± 0.04
3	F3	0.568 ± 0.002	0.657 ± 0.004	1.157 ± 0.002	13.54 ± 0.001	26.07 ± 0.02
4	F4	0.581 ± 0.005	0.702 ± 0.006	1.209 ± 0.004	17.23 ± 0.001	27.29 ± 0.04
5	F5	0.543 ± 0.060	0.634 ± 0.003	1.169 ± 0.001	14.35 ± 0.001	26.26 ± 0.01
6	F6	0.555 ± 0.011	0.648 ± 0.002	1.168 ± 0.002	14.35 ± 0.001	26.82 ± 0.02

Table 3. Pre compression evaluation parameters

FC	Hardness (kg/cm^2)	Thickness (mm)	Weight Variation	Friability (%)	Disintegration Time (sec)	Dispersion Time (sec)	Wetting Time (sec)	Water Absorption Ratio (%)	Drug Content (%)
F1	3.5 ± 0.057	3.4 ± 0.057	250 ± 4%	0.806± 0.05	24.66 ± 0.577	25 ± 1	28 ± 0.57	89.2 ± 0.49	96.25± 0.1
F2	3.4 ± 0.057	3.5 ± 0.217	251 ± 3.5%	0.808± 0.07	14.66 ± 0.018	21 ± 0.57	16.1 ± 0.12	88.1 ± 0.38	97.75 ± 0.3
F3	3.1 ± 0.251	3.3 ± 0.132	252 ± 3.6%	0.816± 0.04	28.121 ± 0.52	30 ± 0.577	32.3 ± 0.09	85.3 ± 0.47	95 ± 0.25
F4	3.0 ± 0.056	3.4 ± 0.002	248 ± 4%	0.819± 0.07	16.66 ± 0.65	22 ± 1.527	22 ± 0.057	83.3 ± 0.65	96.25 ± 0.4
F5	3.5 ± 0.017	3.5 ± 0.011	248 ± 3.8%	0.614± 0.10	26.24 ± 1.0	027.66 ± 0.5	28.3 ± 0.42	85.1 ± 0.27	95.75 ± 0.3
F6	3.4 ± 0.153	3.6 ± 0.024	250 ± 4%	0.617± 0.08	16.02 ± 2.0	20.3 ± 1.5	22.3 ± 0.18	83.9 ± 0.14	97.5 ± 0.1

At zero second After5 seconds After10 seconds After 15 seconds

Fig. 5 *In vitro* dispersion time



After 5 seconds After 10 seconds After 15 seconds

Fig. 6 In *vitro* wetting time

229.4 mg to 268.82 mg. (±7.5%). Theresults indicate that all the weight variation of the formulated tablets was within the acceptable pharmacopoeia limits. The results of friability determination showed <1% indicating that all the tablets were mechanically stable and would be resistant to chipping and abrasion during handling, packaging or transportation. The disintegration time of all the formulations was within the range of 14.66 sec to 28 sec. The in vitro dispersion time of all the tablets was found within 21 sec and 30 sec. The Dispersion of the tablets with respect to time is shown in Fig. 5. Formulation F2 showed the fastest in vitro dispersion of 21 sec. The content of Promethazine in the tablets was found in the range of 95 mg to 97.75 mg.

The wetting time (Fig. 6) of all the formulations was found in the range of 16.1 seconds to 32.3 seconds. Formulation F2 showed best result among all other formulations.

3.6 *In vitro* Dissolution Studies

The comparative in vitro dissolution of the tablet formulations is show in Fig.7. The drug release from all the tablets was in the range of 90.15% to 95.82%. According to Indian pharmacopoeia oro dispersible tablets should exhibit 85% of drug release within 30 min. All the formulations showed more than 90% drug release in 30 min, indicating a fast drug release as expected from oro dispersible tablets. The formulation F2 (15% Croscarmellose sodium & 15% Camphor) showed best drug release with 95.82% drug release at the end of 30 min.

3.7 Taste Analysis

All the formulations were evaluated for bitter taste using E-tongue and the bitterness values were compared with the pure drug. The results are represented in Table 4. The pure drug has a value of 10 on bitterness scale, indicating that the drug is extremely bitter in taste. The powdered formulations had values between 5.7 and 6.3 on the bitterness scale which represent acceptable taste. These values indicate successful taste masking of promethazine HCl by complexation with β cyclodextrin.

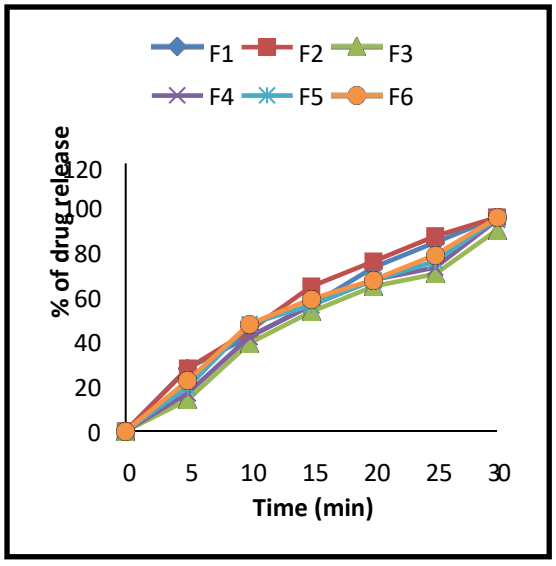


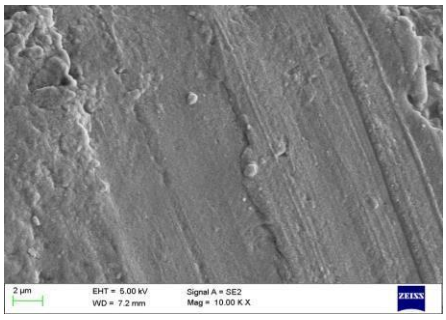
Fig. 7 Comparative *in vitro* dissolution profile

Table 4. Taste analysis of the formulations using E-tongue

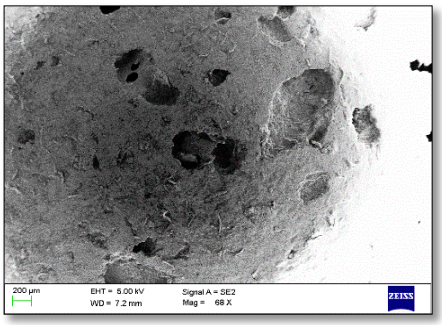
Standard reference value	Taste	Formulation Code	Obtained Values
1-2	Very Sweet	Pure Drug	9.8
3-4	Sweet	F1	5.9
5-7	Acceptable	F2	5.9
8-9	Bitter	F3	5.7
10	Very Bitter	F4	5.8
		F5	6.1
		F6	6.3

3.8 Scanning Electron Microscopy

The surface morphology of the tablets(Fig. 8) was observed before and sublimation using Scanning Electron Microscopy. The morphology of tablet before sublimation shows a relatively smooth non-porous surface.



A



B

Fig. 8 Surface morphology of the tablets before (A) and after (B) sublimation

The sublimation process resulted in formation of porous morphology in thetablet surface due to the vapourisation of the subliming agents, namely camphor, menthol and ammonium bicarbonate.

The pores on the tablet surface may be responsible for imbibition of water into the tablets and rapid disintegration of the tablets. This is further aided by the presence of superdisintegrant, cross carmellose sodium in the formulations.

4. CONCLUSION

An Oro dispersible tablet of promethazine HCl with effective taste masking was successfully developed. Promethazine being a highly bitter drug, it required effectivetaste masking in order to develop oro dispersible tablets. The taste masking was achieved by complexing the drug with β cyclodextrin. The combination of subliming agents with superdisintegrant resulted in faster disintegration and dissolution of the tablets. The oro dispersible tablets may also help in enhancing the bioavailability of promethazine due to the possibility of pre-gastric absorption. Also the complexation with β-cyclodextrin resulted in better solubility and faster dissolution of the drug which may further have positive results with respect to bioavailability. Hence the dosage form developed may be very useful for the treatment of motion sickness, where availability ofpotable water may be difficult. Due to oral disintegration, geriatric population having difficulty in swallowing conventional tablets may also be benefitted.

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