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Taste masking of Promethazine Hydrochloride using Eudragit E100 via solid dispersion technique to develop fast disintegrating tablets

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Abstract

The purpose of present study was to mask the intensely bitter taste of promethazine HCl and to formulate fast disintegrating tablets (FDTs) of the taste masked drug. The taste masking was done via solid dispersion (SD) technique using Eudragit E100 (amino-alkyl methacrylate copolymer) in different ratios. The drug-polymer compatibility and their compatibility with process condition were evaluated on the basis of FTIR spectroscopy and there was no sign of any interaction between drug and polymer and within the prepared system. The SD prepared with different ratio of drug and polymer was evaluated for drug release in phosphate buffer (pH 6.2), and for in vivo taste. The SD with drug polymer ratio of 1:4 did not give any taste and shows minimum release in phosphate buffer (pH 6.2); therefore that ratio was selected as best candidate for development of FDTs. The nine batches were prepared using crospovidone and croscarmellose to find out effect of both the polymers on in vitro and in vivo disintegration time. The prepared batches were also evaluated for different parameters such as hardness, friability, wetting time, in vitro dispersion time, and for in vivo taste. Crospovidone 20% w/w gave the minimum disintegration time. The tablets of the final formulation containing 38.16 % mannitol and 9.14 % of microcrystalline cellulose showed the minimum disintegration time of 23 sec. The taste evaluation of the tablets in comparison to quinine sulfate in human volunteers revealed a considerable taste masking. Thus results conclusively demonstrated successful masking of taste and fast disintegration of the developed formulation in the oral cavity.

Keywords: fast disintegrating tablets, taste masking, solid dispersion, promethazine HCl, Eudragit E100.

INTRODUCTION

During emesis rapid peak plasma concentration is required to achieve desired pharmacological response [1]. In addition to this, in clinical conditions like nausea and vomiting, administration of conventional dosage form with water is quite difficult [2]. In these circumstances, fast disintegrating drug delivery system began to gaining popularity and acceptance since they can disintegrate or dissolve quickly in oral cavity upon contact with saliva, resulting in solutions or suspensions of the administered medicine [3-5]. Advantages of fast disintegrating drug delivery system over conventional dosage forms include rapid drug absorption, quick drug therapy intervention, convenience of administration and patient acceptance, especially for pediatric, geriatric, dysphagic, psychiatric patients and travelers [6-8].

Promethazine HCl is a potent phenothiazine derivative which is widely used to prevent motion sickness. The Promethazine HCl is bitter in taste and which was selected as model drug to formulate fast disintegrating drug delivery system. So first aim of the study was masking the bitter taste of Promethazine HCl. Various methods are available to physically mask the undesirable taste of drugs, such as the addition of sweeteners and flavors, coating with water insoluble materials, creating a wax matrix by spray congealing, adsorption to ion-exchange resin, solid dispersions, formation of salts or derivatives, use of amino acids and protein hydrolysates, viscosity modifications, precipitation method and complexing with cyclodextrins [9-14]. Initially the taste of Promethazine HCl was tried to mask by using precipitation method but due to low percentage yield, that method was neglected. Solid dispersion technique [15, 16] was then selected as alternate for mask the bitter taste of solid active particles.

The main features of the study were to completely mask the bitter taste of Promethazine HCl using solid dispersion technique and to develop an optimum formula and process conditions to manufacture a fast disintegrating drug delivery system. Developed system than serve us as a patient-favorable dosage form.

MATERIALS AND METHODS

Materials

Promethzine HCl was a gift from Windlas Biotech Ltd. (Dehradun, India). Aminoalkyl methacrylate copolymer (Eudragit E100) was a gift from Torrent Pharmaceutical Ltd. (Himachal Pradesh, India). The superdisintegrants were crospovidone (Polyplasdone XL-10, ISP Technologies, Inc, Calvert City, KY), croscarmellose sodium (Ac-Di-Sol, FMC Biopolymer, Wallingstown, Ireland). The diluents were microcrystalline cellulose (Ceolus KG 802, Asahi Kasei Chemicals Corporation, Tokyo, Japan) and spray-dried mannitol (Parteck M 200, Merck, Darmstadt, Germany). All other chemicals used in the study were of analytical grade.

Preparation of SD

Promethazine HCl was mixed with powdered Eudragit E-100 using a mortar and pestle in different ratios (1:1, 1:2, 1:3 and 1:4). The mixture was transferred in a stainless steel vessel. Then 10% ethanol (15ml) was added to the mixture of each ratio of drug with Eudragit E-100 in stainless steel vessel. The mixture was stirred constantly on a magnetic stirrer till a thick gel was formed. The temperature was kept at 40 $^{\circ}$C with stirring speed of 350 rpm. The ethanol was

removed by evaporation overnight and subsequently the solidified gel was crushed into particles using mortar and pestle.

Selection of Best Taste Masked Candidate

The best taste masked candidate for FDTs was selected on the basis of percentage yield, drug content, drug release in phosphate buffer of pH 6.2 within 60 sec and *in vivo* taste evaluation.

The prepared taste masked particles were collected and weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the taste masked particles.

$$\text{Percentage yield} = [W_p/W_t] \times 100 \quad (1)$$

Where, W_p is actual weight of taste masked particles obtained and W_t is the total weight of drug and polymer (promethazine HCl and Eudragit E-100).

Drug content was determined by dissolving 10 mg of taste masked particles in 50 ml of simulated gastric fluid (SGF). The solution was shaken for 24 h, filtered and the filtrate was analyzed for the drug content by UV-spectrophotometer at 249.4 nm after suitable dilution.

Drug release in phosphate buffer solution of pH 6.2 was determined to predict the release of drug in the human saliva. Taste masked particles, equivalent to 10 mg of promethazine HCl was placed in 10 ml of phosphate buffer solution of pH 6.2 and shaken for 60 seconds. The amount of drug released was analyzed at 249.4 nm.

Taste evaluation was done by the panel of 10 members using time intensity method. The mouth was rinsed with safe drinking water; 10 ml of the most diluted quinine sulfate was swirled in the mouth for 30 seconds. The solution was spit after 30 seconds and waited for 1 min, then rinsed with safe drinking water. Then the prepared taste masked particles were evaluated for its taste. Bitterness level was recorded after 60 seconds. Volunteer`s opinion for bitterness value were rated by giving different score values.

Molecular Properties

Molecular properties on complexation were studied by X-ray powder diffraction (XRPD) and Fourier transform infrared spectroscopy (FTIR). The X-ray powder diffractograms (Figure 1a & 1b) were recorded using a Philips PW 1729 X-ray diffractometer (Legroupe Interconnection, Saint Jurie, Clubac, Canada) with monocrotized Cu Kα radiation (1.314 A0), at a speed of 2θ min–1 from 10- to 60- (2θ) under the voltage and current of 40 Kv and 30 Kv respectively. Infrared (IR) spectra (Figure 2a & 2b) were obtained by KBr disc method (8400 S, Shimadzu Japan).

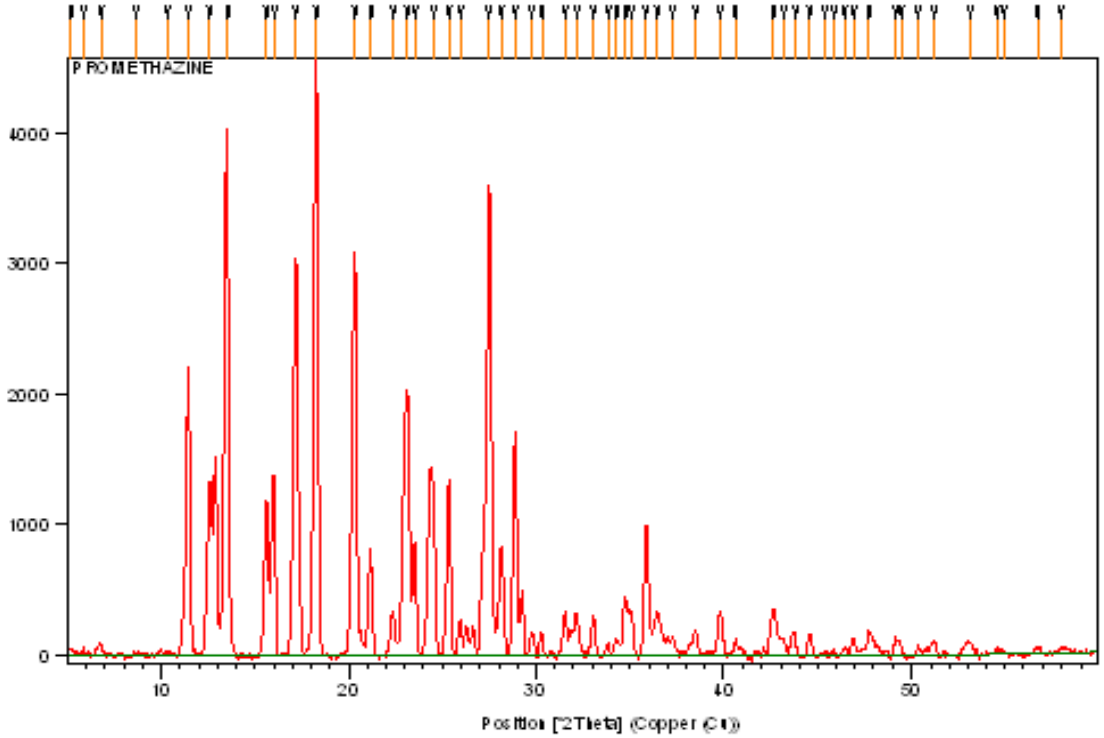

Figure 1a X-ray diffraction pattern of pure promethazine HCl

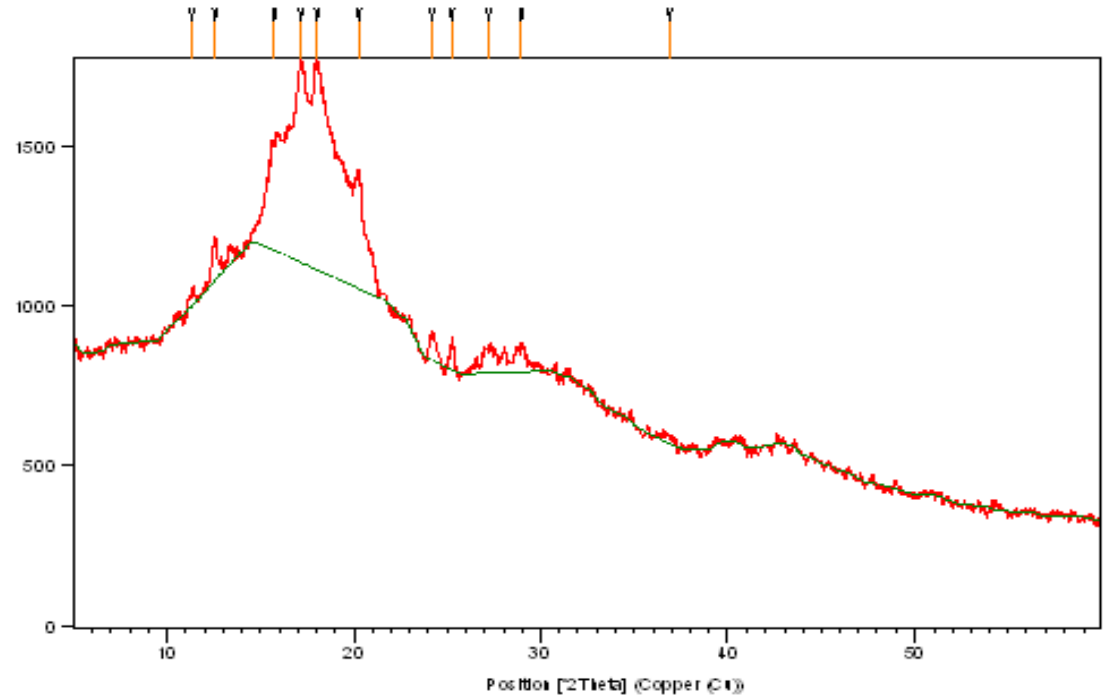

Figure 1b X-ray diffraction pattern of 1:4 drug-polymer ratio

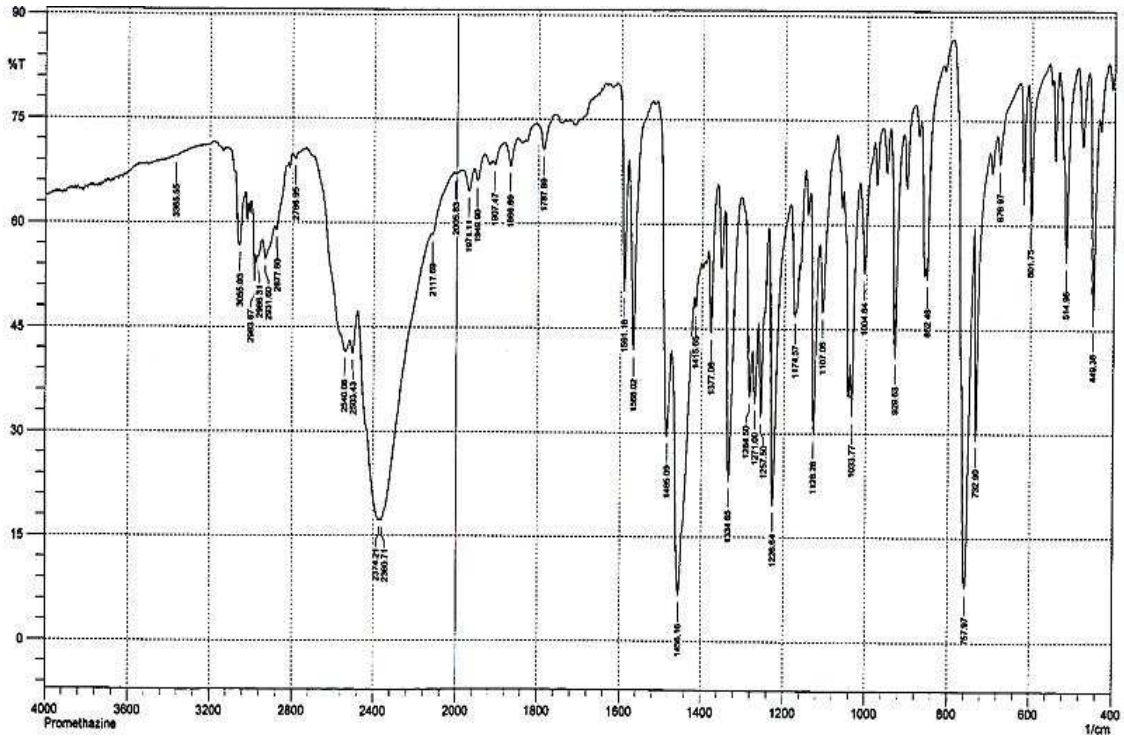

Figure 2a Infrared spectrum of promethazine HCl

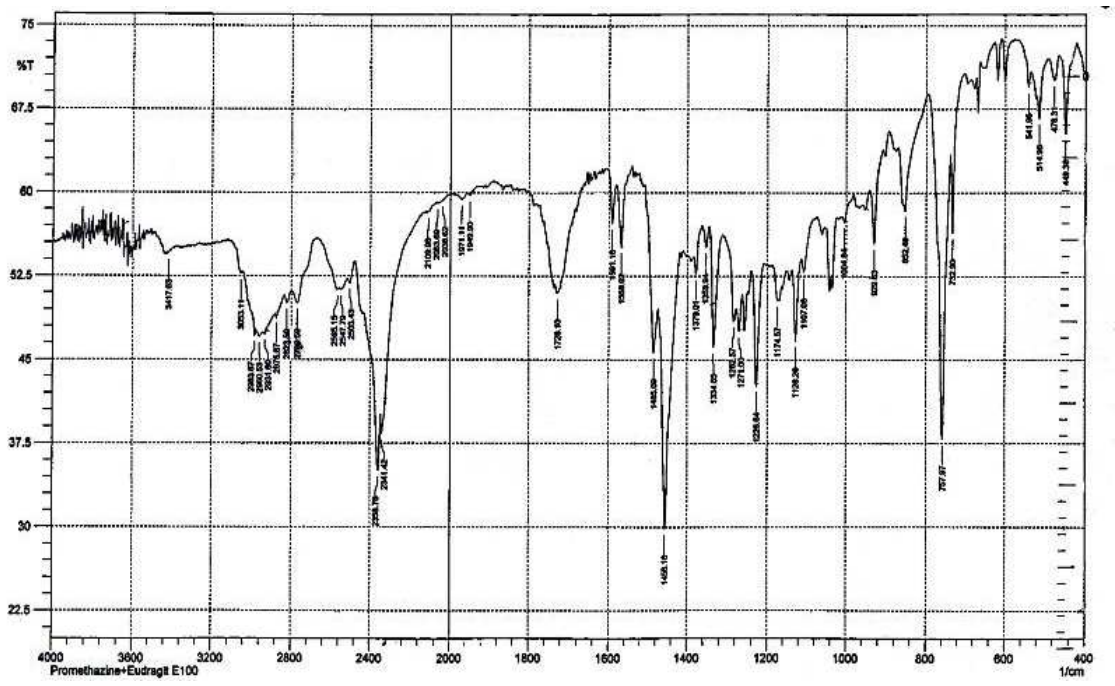

Figure 2b Infrared spectrum of physical mixture

Preparation of FDTs

The FDTs were prepared using crospovidone, croscarmellose (superdisintegrants), mannitol and micro-crystalline cellulose (MCC) via wet granulation method. Total nine formulations were

prepared by varying the concentration of superdisintegrants and mannitol (Table 1). Aspartame was used as sweetening agent and mint was used as flavoring agent to give the tablets a more palatable feel. Magnesium stearate was used as a lubricant in the formulation. Mannitol, microcrystalline cellulose, crospovidone/croscarmellose, and aspartame were granulated by adding purified water into mortar and pestle and a wet mass was prepared. The wet mass was then passed through sieve of aperture size 1.7 mm (sieve no.10). After drying the sizing was done through sieve of aperture size 710 µm (sieve no. 22). The mixed granules were compressed with a rotary tablet press (Type No: CMD-16//MT, Serial No: A/2836/08-09, Cadpress, Ahmadabad, India). Tablets (350 mg) were prepared by using 12 mm round, flat faced punches with compression force of 24 kN.

Table 1 Various formulations with varying concentrations excipients

Code	Taste masked granule (mg/tablet)	Execipients (mg/tablet)						Mint	Purified water
		CP	CC	Manniol	MCC	Mg Stearate	Asp		
CPX_1	104.43	9	-	194.57	32	8	2	q.s.	q.s.
CPX_2	104.43	17.5	-	186.07	32	8	2	q.s.	q.s.
CPX_3	104.43	35	-	168.57	32	8	2	q.s.	q.s.
CPX_4	104.43	52.5	-	151.07	32	8	2	q.s.	q.s.
CPX_5	104.43	70	-	133.57	32	8	2	q.s.	q.s.
CCX_6	104.43	-	17.5	136.07	32	8	2	q.s.	q.s.
CCX_7	104.43	-	35	118.57	32	8	2	q.s.	q.s.
CCX_8	104.43	-	52.5	101.07	32	8	2	q.s.	q.s.
CCX_9	104.43	-	70	83.57	32	8	2	q.s.	q.s.

CP: crospovidone, CC: Croscarmellose, MCC: Micro-crystelline cellulose, Mg stearate: megnisium stearate, Asp: Aspartame

Characterization of Prepared Granules

The prepared granules were evaluated for different parameters such as Percentage yield, Drug content, Loose Bulk Density, Tapped Bulk Density, Hausner's Ratio, Void volume, Percent Porosity, and Percent Compressibility.

Percentage yield was calculated as similar as procedure given above. Drug content was determined by dissolving the granules equivalent to 2 mg of promethazine HCl in 50 ml of SGF. The solution was shaken and filtered. The filtrate was analyzed for the drug content by UV-spectrophotometer at 249.4 nm after suitable dilution.

Loose bulk density was determined by the USP method I; tapped density was determined by USP method II using a tapped density tester (Electrolab, ETD 1020, Mumbai, India). Hausner's Ratio, Percent Compressibility, Void volume and Percent Porosity were calculated using Equations given below.

Hausner's ratio = D_t / D_b (2)

Percent Compressibility = $D_t - D_b / D_t \times 100$ (3)

Where D_t and D_b are Tapped bulk density and Loose bulk density

Void volume (v) = $V_b - V_p$ (4)
% porosity (€) = $(1 - V_p / V_b)$ X 100 (5)

Where V_b and V_p are Bulk volume (volume before tapping) and Tapped volume (volume after tapping)

Evaluation of FDTs

Wetting Time and *In vitro* Dispersion Time

A piece of tissue paper (12 cm × 10.75 cm) folded twice was placed in a small petridish containing 6 ml of phosphate buffer solution of pH 6.2. A tablet was placed on the tissue paper, and the time for complete wetting was measured. *In vitro* dispersion time was measured by dropping a tablet in a beaker containing 50 ml of phosphate buffer of pH 6.2. Tablets from each batch were randomly selected and *in vitro* dispersion time was performed.

***In vitro* Disintegration Time**

In vitro disintegration time for FDTs was determined using USP and modified disintegration apparatus with phosphate buffer (pH 6.2) as the disintegrating medium. During this study we made an attempt to develop a more suitable apparatus for FDTs (Figure 3) because many reports [17-20] indicated the unsuitability of the conventional disintegration test apparatus for FDTs. Briefly, the apparatus consisted of a 100 ml glass beaker placed on a magnetic stirrer. A glass tube of 20 mm in diameter, opened at one end and on the other end a mesh of aperture size 10 was fixed. The glass tube positioned in the beaker with the help of stand so that when the beaker contained 50 ml of disintegration medium, the glass tube had only 3 ml of this medium. The disintegration medium was stirred with small magnetic bead at 50 rpm and results obtained were compared with results from the USP disintegration test apparatus and the *in vivo* disintegration test.

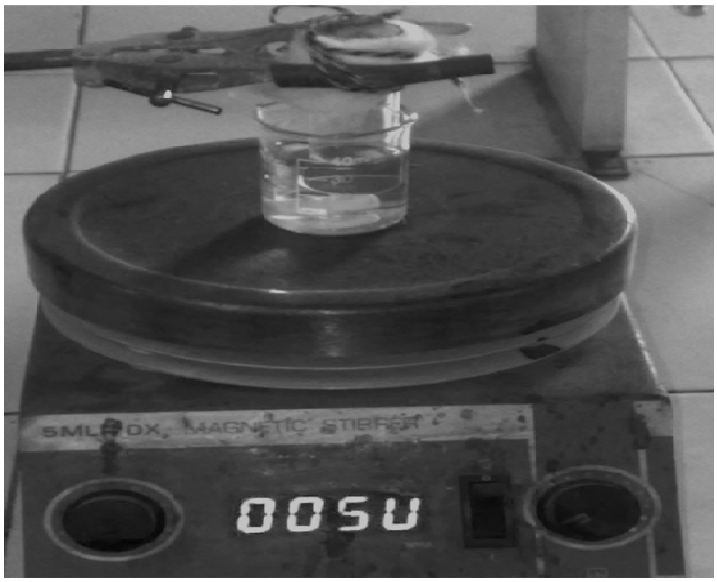

Figure 3 Modified disintegration test apparatus

In vivo Disintegration Time and Taste Evaluation

In vivo disintegration time of the prepared FDTs was determined in healthy human volunteers. A tablet was placed on tongue and time required for complete disintegration of the tablet was determined. The *in vivo* taste evaluation procedure was almost the same as that of procedure described above for taste evaluation of SD.

In vitro Dissolution Studies

In vitro dissolution study for fabricated FDTs was carried out by using USP Dissolution Apparatus II paddle type at 50 rpm in 500 ml of SGF as dissolution media, maintained at 37±0.5 ^{0}C. The study was carried for 1 h and at predetermined time intervals (0, 5, 10, 15, 30, 45, 60, minutes) 5 ml aliquots were withdrawn, filtered and assayed spectrophotometrically at λ_{max} 249.4 nm. An equal volume of fresh medium, which was pre-warmed at 37°C, was replaced into the dissolution medium after each sampling to maintain the sink condition throughout the study. Dissolution study was performed in triplicate for each batch.

RESULTS AND DISCUSSION

The dispersion of promethazine HCl in Eudragit E100 as an inert carrier or matrix in solid state was used to mask the taste of bitter drugs. On the basis of the results (Table 2), ratio 1:4 was selected as best taste masked candidate for development of FDTs. The drug release from ratio 1:4 in phosphate buffer pH 6.2 was found 7.84 and also found to have most satisfactory taste masking during the *in vivo* taste evaluation (Table 3), and thus selected for the development of the FDTs.

Table 2 Various drug polymer ratios with their evaluation results

S.No.	Drug-polymer Ratio	Yield (%)	Drug Contents in Simulated gastric fluid (%)	Release in phosphate buffer of pH 6.2 (%)
1	1:1	82.38	78.41033	41.3327
2	1:2	96.88	106.0633	39.0958
3	1:3	96.162	86.50667	24.0728
4	1:4	96.61	99.129	7.84

Table 3 *In vivo* taste evaluation of taste masked particles

S. No.	Volunteer score the ratio as	No. of volunteer score the ratio as				
		Quinine sulfate	Drug-polymer ratio			
			1:1	1:2	1:3	1:4
1	3+	3	-	-	-	-
2	3	2	-	-	-	-
3	2.5	2	-	-	-	-
4	2	-	5	3	-	-
5	1.5	-	2	2	-	-
6	1	-	-	2	5	-
7	0.5	-	-	-	2	1
8	0	-	-	-	-	6

The X-ray diffraction pattern of promethazine HCl confirms its crystalline nature, as there are a number of sharp and intense peaks. However, these peaks have disappeared in drug-polymer dispersion. X-RD peaks depends upon the crystal size; but in the present study, the drug-polymer dispersion particles were in amorphous state, which was very difficult to measure at the detection limit of the crystal size, which indicated that drug was dispersed at a molecular level in the polymer matrix and hence, no crystals were found in drug- loaded matrices. The intensity of characteristic peaks of pure drug was reduced and peaks were also found to be broadened. These findings suggested that there was the formation of a new solid phase with a lower degree of crystallinity due to solid dispersion.

The various Infrared spectral bands of pure promemethazine HCL are shown in Table 4. No significant shift or reduction in intensity of peaks of promemethazine HCl was found on comparison with FTIR spectrum of the solid dispersion and promemethazine HCL.

Table 4 Infrared spectral bands for promethazine HCl

S.No.	Wave Number (cm^{-1})	Vibration Mode
1	2800-3000	CH stretching
2	2200-2480	NH^+ stretching
3	1591	Aromatic C=C stretching
4	1430-1470	CH_3 and CH_2 bending
5	1378	CH_3 bending
6	1334	C-N stretching of tertiary amine
7	850-860, 757 and 731	Out plane CH bending of distributed aromatic

Usually the micro particulates are formulated as single unit dosage forms in the form of tablets. Thus the particles of the blend should possess the required microimeritic properties. For each of the designed formulation, the granules of drug and excipients were prepared and evaluated for different micromeritic properties (Table 5).

Table 5 Micromeritic properties of granules

Micromeritc Property	CPX_1	CPX_2	CPX_3	CPX_4	CPX_5	CCX_6	CCX_7	CCX_8	CCX_9
Yield (%)	87.33	96.48	98.64	89.18	97.63	97.80	93.44	96.43	97.69
Angle of repose	30.24	28.81	30.34	26.05	30.95	33.11	35.31	33.10	32.45
Loose bulk density	0.609	0.60	0.5614	0.59	0.543	0.617	0.561	0.609	0.617
Bulk density	0.617	0.62	0.5813	0.617	0.561	0.62	0.581	0.625	0.632
Tapped density	0.704	0.724	0.6410	0.684	0.641	0.746	0.704	0.694	0.694
Void volume	1.0	1.1	0.8	0.8	1.1	1.3	1.5	0.8	0.7
Hausner's Ratio	1.14	1.16	1.10	1.10	1.14	1.20	1.21	1.11	1.09
Porosity (%)	14.08	15.94	10.25	10.95	14.10	19.40	21.12	11.11	9.7
Compressibility (%)	14.10	14.36	10.27	9.7	12.48	16.89	17.47	9.94	8.93
Drug content (%)	92.86	94.07	98.21	97.55	105.7	111.33	111.72	109.7	105.02

The taste masked particles represented as a suitable material for formulating fast disintegrating tablets by means of traditional technology. No special equipment was adopted to compress the granules into tablets. Since the FDTs are less hard than conventional tablets due to lower compression force employed, but the present tablets had sufficient mechanical strength. The results of the different evaluation parameters for developed FDTs are shown in Table 6.

Table 6 Results of different parameters used for Evaluation of FDTs

S. No.	Formulation Code	Uniformity of weight	Hardness	Wetting Time (sec)	*In vitro* dispersion time (Sec)	Percent Friability
1	CPX_1	Passes	3.2	154	143	0.33
2	CPX_2	Passes	3.1	125	93	0.796
3	CPX_3	Passes	2.9	90.33	90	0.857
4	CPX_4	Passes	2.7	89	78	0.456
5	CPX_5	Passes	2.6	43.33	43	0.962
6	CCX_6	Passes	3.5	84.33	86	0.341
7	CCX_7	Passes	3.16	56.67	78	0.622
8	CCX_8	Passes	2.3	47.66	46	0.805
9	CCX_9	Passes	2.06	37.33	40	0.917

The disintegration time, which is affected by the hardness of the tablet, is related to the nature and concentration of the disintegrants that allow the tablet to break up into smaller fragments upon contact with physiological fluids. The disintegration time readings obtained by both modified and USP method were found to be significantly different. It was found that the disintegration obtained from modified method was slower than the obtained from USP method (Table 7). Both disintegration times in relation to the concentration of the superdisintegrants, reflecting higher the concentration, rapid the disintegration. The formulation CPX_5 containing 20% of crospovidone showed the minimum disintegration time. Crospovidone is completely insoluble in all commonly used solvents, as it swells in contact with water in very predictable manner. On the basis of the disintegration time of the tablets, all the formulations developed can be defined as the fast dispersible. The limit for disintegration is suggested as within 3 minutes. The compression force is the main factor which influence the disintegration time of a tablet, which was kept constant.

Table 7 Disintegration time of tablets

S.No.	Formulation Code	Disintegration Time (sec)	
		D.T. via USP method	Modified D.T.
1	CPX_1	124.33	151
2	CPX_2	86.67	111
3	CPX_3	78.333	107
4	CPX_4	69.67	84
5	CPX_5	23.33	45
6	CCX_6	92.33	113
7	CCX_7	79.33	102
8	CCX_8	55	70
9	CCX_9	42.33	61

Almost from the entire batches 80% drug was released within 1 h in SGF. The dissolution process might have involved both ion exchange and solubilization of Eudragit E100. Figure 4 shows the percentage cumulative release of drug from the all formulations.

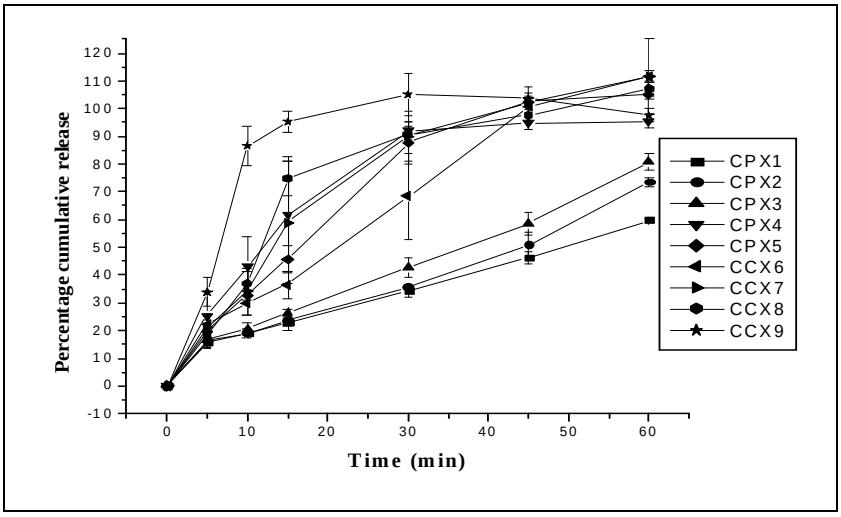

Figure 4 Release profiles of formulated formulations

The time intensity study for taste in human volunteers of the formulated FDTs in comparison to quinine sulfate revealed considerable masking of the bitter taste of promethazine HCl. Table 8 shows the data obtained after *in vivo* taste evaluation of formulated tablets. The *in vivo* taste evaluation study was carried out for 5 min. Seven volunteers out of ten told that the given fast disintegrating tablet had no taste i.e. tasteless but three volunteers told very slight taste after 4 min. The sensory evaluation of the final optimized formulation proved its good palatability and tasteless characteristics.

Table 8 *In vivo* taste evaluation data of FDTs

S.No.	Score values	No. of volunteer score the FDTs as	
		Quinine sulfate	Formulated FDT
1	3+	6	-
2	3	4	-
3	2.5	_	-
4	2	-	-
5	1.5	-	-
6	1	-	-
7	0.5	-	3
8	0	-	7

CONCLUSION

The study conclusively demonstrated the taste masking of promethazine HCl and fast disintegration of the FDTs. The taste masking and fast disintegration of the tablets formulated in this investigation may possibly help in the administration of promethazine HCl in more palatable form without water during emesis. Thus the patient friendly dosage form of bitter drugs, especially for pediatric, geriatric, bedridden and non-cooperative patients, can be successfully formulated using this technology.

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