



FORMULATION AND EVALUATION OF FAST DISPERSIBLE TABLETS OF A MODEL ANTIEMETIC DRUG USING NATURAL DISINTEGRANTS

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ABSTRACT

The present research work is an attempt to formulate and evaluate fast dispersible tablets of a model antiemetic drug, prochlorperazine maleate using natural disintegrants prepared by direct compression method. The drug excipients compatibility studies were carried out using FT-IR. The tablets were compressed by direct compression method, using directly compressible lactose as diluent. *Cassia tora* (10%, 15%, 20%), *Cassia nodosa* (10%, 15%, 20%), ispaghula husk powder (10%, 15%, 20%) were used as disintegrants at different concentration. Talc was used as glidant and magnesium stearate was used as lubricating agent. Sunset yellow (supra) FD&C yellow 6 was used as coloring agent on dry basis. The precompression parameters like bulk density, tapped density, Carr's index and angle of repose were determined. The post compression parameters like hardness, thickness, friability, weight variation, disintegration time, wetting time for all the formulations were carried out. Formulations containing *cassia nodosa* exhibited quicker disintegration of tablets than compared to those containing *cassia tora* and ispaghula husk powder. The most satisfactory formulation showed minimum disintegration time of 33 sec and released maximum amount of drug in shortest duration of time. It was found to be stable during stability studies conducted for 2 months as per ICH guidelines.

Key words: Dispersible tablets, direct compression, prochlorperazine maleate, natural disintegrants.

1. INTRODUCTION

Fast Dispersible Tablets (FDT), can be defined as an oral solid dosage form which when placed on tongue, disintegrates rapidly, releasing the drug, which dissolves or disperse in the saliva and then swallowed. Some drugs are absorbed from the mouth, pharynx, and oesophagus as the saliva passes down in to the stomach^{1,2}.

Disintegrants are substances or agents added to the tablet formulation facilitate the break-up or disintegration of tablet or capsule into smaller fragments in an aqueous environment, thereby increasing the larger surface area and promoting a more rapid release of the drug substance that dissolve more rapidly than in the absence of disintegrants. In recent years, several newer disintegrants have been developed, often called as “superdisintegrants”. Superdisintegrants are generally used at a low level in the solid dosage form, typically in concentration of 1-10 % by weight relative to the total weight of the dosage unit.

Prochlorperazine maleate: [2-chloro-10-[3-(4-methylpiperazine-1-yl)propyl]-10H-phenothiazine bis[hydrogen(Z)-butenedioate] comes under the class of drugs called Neuroleptics. These are potent antiemetics; act by blocking D2 receptors in the CTZ; antagonize apomorphine induced vomiting³.

2. Materials and methods:

Prochlorperazine maleate was obtained as a gift sample from Mehta Pharmaceutical Industries, Mumbai and Cassia tora, Cassia nodosa, Ispaghula husk powder, were obtained from FRLHT, Bangalore. Purified talc, magnesium stearate, lactose sunset yellow were used in the formulation

Method :

PREFORMULATION STUDIES - The major goal of the preformulation process is to permit the rational development of stable, safe and efficacious dosage forms and it is mainly concerned with the characterization of the physicochemical properties of the drug substance

Method development for drug estimation

UV Spectrum Analysis: 50 mg of prochlorperazine maleate was transfer to 50 ml volumetric flask with 0.1N hydrochloric acid. From this, standard concentrations of 2, 4, 6, 8, 10 and 12 µg/ml.were prepared and scanned in the range of 400 to 200 nm.

Drug-excipient compatibility studies^{10,12}:

. This study was carried out to establish that the therapeutically active drug has not undergone any changes, after it has been subjected to processing steps during formulation of tablets. This can be confirmed by carrying out Infrared light absorption scanning spectroscopy (IR) studies.

FORMULATION STUDIES

Active ingredient, selected superdisintegrants, lactose, sunset yellow supra were taken in required quantities and passed through 60 # sieve separately. In dry state, the drug with other ingredients was mixed to get uniform mixture powder. These powders were lubricated with magnesium stearate and talc. The lubricated powders were compressed into tablets using the rotary tablet punching machine.

EVALUATION OF PHYSICOCHEMICAL PARAMETERS

MICROMERITIC PROPERTIES^{4,5,6}

ANGLE OF REPOSE: The angle of repose of powder was determined by the funnel method. The accurately 1.2 gm weighed powder were taken in a funnel. The powder was allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated

BULK DENSITY: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 1.2 g of powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-sec intervals. The tapping was continued until no further change in volume was noted.

TAPPED DENSITY: The measuring cylinder containing known mass of blend was tapped till there was no reduction in volume of blend. The minimum volume (V_t) occupied in the cylinder and weight (M) of the blend as measured. The tapped density (ρ_t) was calculated.

PERCENTAGE COMPRESSIBILITY:

Percentage compressibility of powder mix was determined by Carr's compressibility index .

THICKNESS OF TABLETS⁵⁷: The thickness of six tablets was measured using Vernier calipers. The extent to which the thickness of each tablet deviated from $\pm 5\%$ of the standard value was determined.

HARDNESS OF TABLETS⁵⁷: The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. Hardness of the tablets was determined by Pfizer Hardness Tester. Six tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded.

FRIABILITY OF TABLETS²: Roche friabilator was used for testing the friability using the following procedure. Ten tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined..

WETTING TIME: A piece of tissue paper folded twice was placed in a small Petridish (Internal Diameter = 6.5 cm) containing 6 ml of simulated saliva (Phosphate buffer pH 6.8). A tablet was put on the paper, and the time required for complete wetting was measured. Six trials for each batch were performed; average time for wetting with standard deviation was recorded.

WEIGHT VARIATION TEST⁵⁸: Ten tablets were weighed individually and the average weight was determined. The % deviation was calculated and checked for weight variation as per IP. Since, the tablets made have the average weight in the range of 150 mg, the limit of % deviation to be taken as ± 7.5 .

UNIFORMITY OF DRUG CONTENT: Estimation of drug content test as described in the IP was followed. Ten tablets were weighed and crushed and powder equivalent to 5 mg drug was dissolved in 100 ml of 0.01 N HCl and shaken for 1 h Then 1 ml was diluted up to 10 ml, filtered and absorbance was measured

IN VITRO DISINTEGRATION TIME: *In vitro* disintegration time was performed by disintegration apparatus specified in USP using 0.1N hydrochloric acid, 900 ml as disintegration medium,

EVALUATION OF *IN VITRO* DISSOLUTION STUDIES

In-vitro dissolution study was performed by using USP Type II Apparatus (Paddle type) at 50 rpm. 0.1N hydrochloric acid 900 ml was used as dissolution medium, and the temperature of which maintained at $37 \pm 0.5^{\circ}\text{C}$. Aliquotes of dissolution medium (1 ml) was withdrawn at specific time intervals (5 minutes) and was filtered. The amount of drug dissolved was determined by UV spectrophotometer by measuring the absorbance of the sample at 254.0 nm. Three trials for each batch were performed and average percentage drug release with standard deviation was calculated and recorded.

Similar test was carried out for a commercial product for comparison^{35,36}.

KINETICS OF DRUG RELEASE:

In order to examine the release mechanism of drug from the tablets, the *In vitro* drug release data of the fast dispersible tablet were subjected to following release models zero order, first order, Higuchi, Peppas models.

STABILITY STUDIES OF FDTs OF PROCHLORPERAZINE MALEATE

The International Conference of Harmonization (ICH) Guidelines titled, “stability testing of New Drug substance and products” (QIA) describes the stability test requirements for drug registration application in the European Union, Japan and the United States of America. Stability studies were carried out at $30^{\circ}\text{C} \pm 2^{\circ}\text{C} / 65\% \pm 5\% \text{ RH}$ and $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \pm 5\% \text{ RH}$ (as per QIC) for the selected formulation F₆ for 60 days.

Method:

The selected formulation F₆ were packed in bottles, which are tightly plugged with cotton and capped. They were then stored at 30°C ± 2° C/ 65% ± 5% RH and 40°C ± 2°C / 75% ± 5% RH and evaluated for their hardness, friability, weight variation, active drug content, disintegration time and *in vitro* drug release at the interval of 30 days and at 60 days.

3. RESULTS

Table 1: Compositions of FDT of Prochlorperazine maleate

Quantity mg/tab	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Prochlorperazine maleate	5	5	5	5	5	5	5	5	5
Lactose	108	100.5	93	108	100.5	93	108	100.5	93
<i>Cassia tora</i>	15	22.5	93	-	-	-	-	-	-
<i>Cassia nodosa</i>	-	-	-	15	22.5	93	-	-	-
Ispaghula husk powder	-	-	-	-	-	-	15	22.5	93
Talc	10	10	10	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10	10	10	10
Sunset yellow	2	2	2	2	2	2	2	2	2

All the formulations contain 5 mg of Prochlorperazine maleate and the total weight of tablet is 150 mg.

Drug-excipient compatibility studies: Drug excipient compatibility study was carried out by infrared spectroscopy studies. IR studies were carried out on pure Prochlorperazine maleate and physical mixture of drug and individual superdisintegrants.

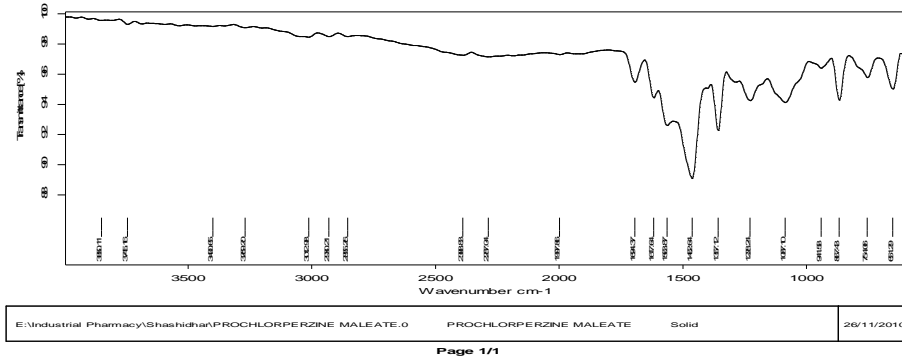


Figure 1: I R Spectra of Prochlorperazine maleate.

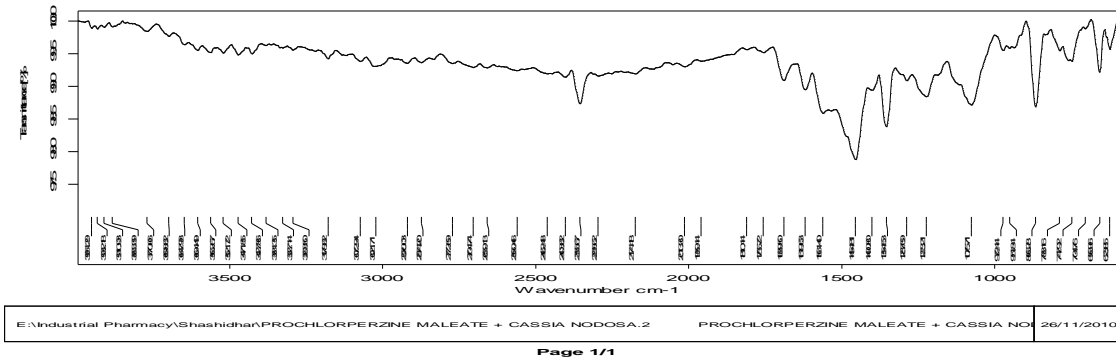


Figure 2: I R Spectra of Prochlorperazine maleate with *Cassia nodosa*

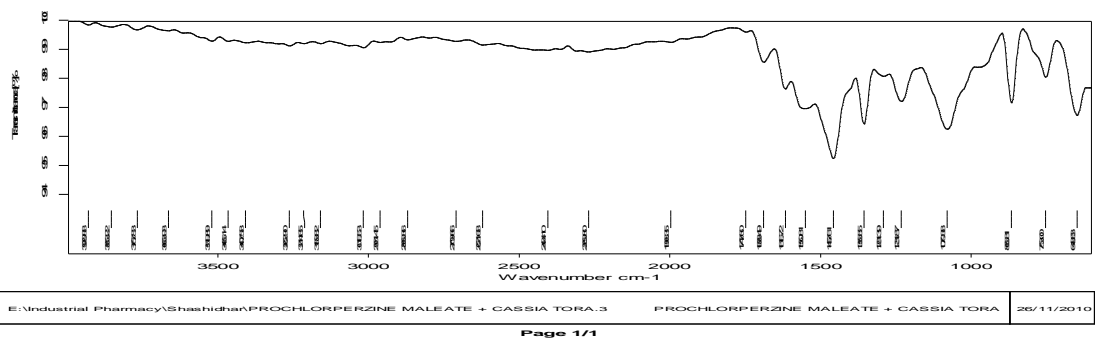
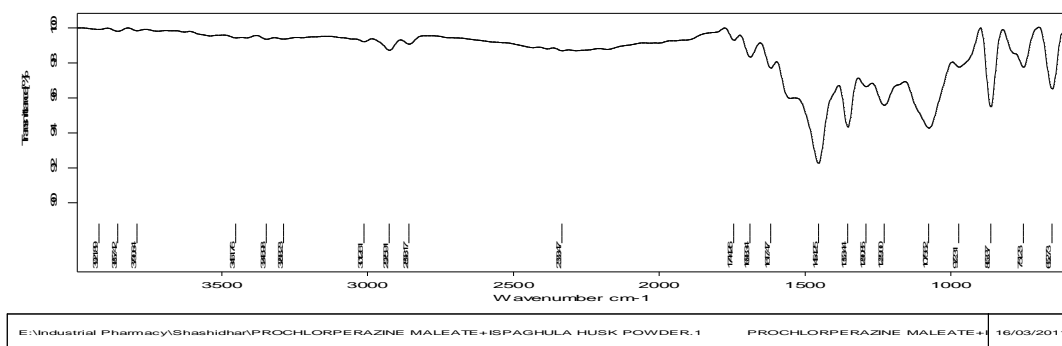


Figure 3: I R Spectra of Prochlorperazine maleate with *Cassia tora*



Page 1/1

Figure 4: I R Spectra of Prochlorperazine maleate with ispaghula husk powd

KINETIC MODELLING OF DRUG DISSOLUTION PROPERTIES

Table 2: Correlation coefficients of drug release curves for fast dispersible tablets of batch F6 based on three kinetic models.

Model	R ² (Correlation coefficient)
	F6
Zero order	0.916
First order	0.946
Higuchi	0.963
Mechanism	Erosion

The *in-vitro* release data obtained were fitted into various kinetic models. Correlation coefficients of formulation F6 batch showed higher correlation with Higuchi model plot. So, predominant drug release mechanism is by erosion.

STABILITY STUDIES**Table 3: Physico-chemical characterization of optimized formulation F6 during stability studies**

Parameters	At zero day	Stored at 30 ± 2°C temperature and 65 ± 5 % RH		Stored at 40 ± 2°C temperature and 75 ± 5 % RH	
		After 30 days	After 60 days	After 30 days	After 60 days
Weight variation (mg)	150.10 ± 2.99	150.05 ± 1.21	149.83 ± 1.40	149.48 ± 1.89	149.88 ± 1.72
Hardness(kg/cm ²)	2.4 ± 0.29	2.3 ± 0.14	2.6 ± 0.14	2.05 ± 0.07	2.7 ± 0.14
Disintegration time (s)	54.48 ± 0.16	55.14	55.21	57.37	49.16
Friability (%)	0.41 ± 0.002	0.60	0.53	0.76	0.59
Estimation of drug content (%)	98.08 ± 0.95	97.42%	97.42%	97.94%	97.08%

Table 4: *In-vitro* dissolution studies of formulation F6 stored at difference temperature during stability studies.

Time(min)	% Cumulative drug release			
	Stored at 30 ± 2°C temperature and 65 ± 5 % RH		Stored at 40 ± 2°C temperature and 75 ± 5 % RH	
	After 30 days	After 60 days	After 30 days	After 60 days
5	61.72	61.08	60.76	62.08
10	79.97	80.60	77.72	79.65
15	82.01	81.69	81.67	81.69
20	88.21	87.57	87.87	87.25
25	91.25	91.56	90.27	90.92
30	95.26	95.58	95.56	95.89
35	98.65	98.33	97.67	98.65

4.CONCLUSION

Prochlorperazine maleate is an antiemetic drug belongs to the category of Neuroleptics. The present investigation is concerned with the development of the FDTs which are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into stomach, thus enhance the bioavailability by avoiding first pass metabolism. By the results obtained from IR spectra, it is possible to conclude that the selected excipients are likely to be suitable for the preparation of tablets formulation, since no significant incompatibilities were detected.

Based on preliminary studies various formulations were developed by using a different concentration of three super disintegrants *Cassia tora*, *Cassia nodosa*, ispaghula husk powder and addition of lubricants followed by direct compression using 7 mm standard concave punch. The total tablet weight was 150mg.

Developed FDTs gave satisfactory results for various physicochemical evaluations like hardness, friability, weight variation, drug content, in-vitro disintegration time and in- vitro dissolution profiles.

Disintegration time of FDTs depends on concentration of superdisintegrants. The disintegration time of all the formulations varied from 32.32 ± 0.03 to 64.12 ± 0.35 sec.

In vitro drug release for various formulations ranged from 83.79 ± 0.66 % to 98.226 ± 0.66 % at the end of 35 min. And it was observed that formulation F₆ took shortest time to release the maximum amount of drug whereas the other formulations took more than 35 min to release the drug. This was due to the presence of 20% of *Cassia nodosa* as disintegrant in formulation F₆.

The analysis of the release profile of the most satisfactory formulation led to conclusion that highest water uptake due to capillary action of *Cassia nodosa* led to shortest disintegration time and maximum drug release at the end of 35th min. The concentrations used are 10, 15 and 20 %, in that 20% acts as the best and can be employed in the formulation of the FDTs.

The most satisfactory formulation F₆ showed no significant change in physicochemical properties, drug content, in vitro disintegration time, in vitro dissolution pattern after storage at $30^{\circ}\text{C} \pm 2^{\circ}\text{C} / 65\% \pm 5\%$ RH and $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \pm 5\%$ RH in stability chamber for 60 days and in concerned with dissolution profile was found superior than conventional formulation.

Therefore, it was concluded that the formulation F₆ satisfied the micromeritic parameters, post compression properties, disintegration time requirements, in vitro drug release profile requirements and stability requirements.

Thus, the objective of the proposed work of formulation of FDT of Prochlorperazine maleate by using different proportions of superdisintegrants can be successfully prepared and

undoubtedly the availability of various technologies and the manifold advantages of FDTs will surely enhance the patient compliance and its popularity in the near future.

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