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Formulation and Evaluation of Fast Dissolving Tablets of Prochlorperazine Dimaleate

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ABSTRACT

Prochlorperazine dimaleate (also known as Prochlorperazin, Compazine, Capazine, Stemetil, PCZ), the dimaleate salt of Prochlorperazine, is a dopamine (D_2) receptor antagonist that belongs to the phenothiazine class of antipsychotic agents that are used for the antiemetic treatment of nausea and vertigo. It is also a highly potent typical antipsychotic, 10-20 times more potent than chlorpromazine. Prochlorperazine dimaleate is also used to treat migraine headaches. The concept of formulating fast dissolving tablets containing PCZ offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increased bioavailability. Fast dissolving tablets of PCZ were prepared by direct compression methods and blend was evaluated for the pre-compression parameters such as bulk density, compressibility, angle of repose etc. The tablets were prepared by using crosscarmellose sodium, crospovidone and sodium starch glycolate, as super disintegrants in different concentration along with microcrystalline cellulose. Total six formulations were prepared and evaluated for hardness, friability, weight variation, content uniformity, wetting time, water absorption ratio, disintegration time and *invitro* drug release. *In-vitro* dissolution studies are performed by using 6.8PH buffer at 50 rpm by paddle method. Overall, the formulation F5containing of CP was found to be promising and has shown a disintegration time 65 sec. The stability studies were performed for two months (accelerated studies) as per ICH guidelines. The optimized formulation (F5) showed no significant variations for the tablets parameters and it was stable for the specified time period. Thus results conclusively demonstrated successful masking of taste and fastest disintegration of the formulated tablets in oral cavity.

Keywords: Fast dissolving tablets, Prochlorperazine dimaleate, Superdisintegrants, Pre-compression

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INTRODUCTION

Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. It is estimated that 70% of the population is affected by this problem [1]. Recent advances in novel drug delivery systems (NDDS) aimed to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is fast dissolving tablets (FDT) [1-4]. PCZ is a phenothiazine antipsychotic and widely used in prevention and treatment of nausea, vomiting including that associated with migraine or drug-induced emesis [5]. The concept of formulating fast dissolving tablets containing PCZ offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increased bioavailability by simple and cost effective direct compression technique. Upon ingestion, the saliva serves to rapidly disperse/dissolve the dosage form. The saliva containing the dissolved/dispersed medicament is then swallowed and the drug is absorbed in the normal way. Some drugs are absorbed from mouth, pharynx and esophagus as the saliva passes down into the stomach [6]. In such cases, bioavailability is significantly greater than those observed from conventional dosage form. In present study an attempt has been made to formulate the orally disintegrating tablets by direct compression method using sodium starch glycolate, crosscarmellose sodium and crospovidone as the superdisintegrants for rapid dissolution of drug and absorption, which may produce the rapid onset of action.

MATERIALS AND METHODS

Materials

Prochlorperazine dimaleate was purchased from Sigma Aldrich-Merck, Bengaluru, Karnataka, India. Crospovidone, sodium starch glycolate and sodium starch glycolate was obtained from Hi-Media Laboratories Pvt. Ltd., Mumbai,

India. Micro crystalline cellulose, mannitol, talc and magnesium stearate was procured from Central Drug House (P) Ltd. New Delhi. All other solvents and chemicals used were of analytical grade.

Methods

Preformulation studies

Standardization of PCZ by UV-Visible spectrophotometry

Accurately weighed 10 mg of drug was dissolved in 10 ml of phosphate buffer pH 6.8 solutions in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and volume make up with phosphate buffer pH 6.8 solution prepare suitable dilution to make it to a concentration range of 2-10µg/ml. The spectrum of this solution was run in 200-400 nm range in U.V. spectrophotometer (Labindia-3000+).

Drug-excipient compatibility study

FTIR spectra of pure drugs, polymers used and blends were recorded on KBr disk method using Brukers Alpha Spectrophotometer with IR solution software to confirm the compatibility between drug and excipients. Sample powder was thoroughly mixed by triturating with potassium bromide in a glass mortar with pestle and compressed into disks in a hydraulic press (Techno search Instruments, India). FTIR spectra of all the samples were recorded over a spectral region from 4700 to 400 cm-1 using 20 scans with 4 cm-1 resolution.

Preparation of tablets of PCZ

Fast dissolving tablets of PCZ were prepared by direct compression [7] according to the formulae given in Table 1. All the ingredients were passed through # 60 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 150 mg using 8 mm round flat punches on 10-station rotary tablet machine.

Table 1 Composition of PCZ fast dissolving tablets

Ingredients (mg)	Formulation code					
	F1	F2	F3	F4	F5	F6
Prochlorperazine dimaleate	25	25	25	25	25	25
Sodium Starch glycolate	10	20	-	-	-	-
Croscarmellose sodium	_	_	10	20	-	-
Crospovidone	-	-	-	-	10	20
Mannitol	10	10	10	10	10	10
Microcrystalline cellulose	94	84	94	84	94	84
Talc	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6
Total weight	150	150	150	150	150	150

Evaluation of fast dissolving tablets of PCZ

Precompression parameters

Angle of repose (θ)

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

$$\tan \theta = h/r$$

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

Where, θ is the angle of repose, h is the height, r is the radius.

The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

LBD (Loose Bulk Density) = Mass of Powder/Volume of Packing

TBD (Tapped Bulk Density) = Mass of Powder/Tapped Volume of Packing

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index (%) = [(TBD – LBD)/TBD] × 100.

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula [8].

Hausner's ratio = Tapped density/Bulk density.

Evaluation of Tablets

Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliper [9].

Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

Friability Test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator).

Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, de dusted and reweighed. The friability was calculated as the percentage weight loss.

% friability was calculated as follows

$$\% \text{ Friability} = (W1 - W2) \times 100/W1$$

Where W1 = Initial weight of the 10 tablets, W2 = Final weight of the 10 tablets after testing.

Friability values below 0.5-1% are generally acceptable.

Weight Variation Test

To study weight variation individual weights (WI) of 20 tablets from each formulation were noted using electronic balance. Their average weight (WA) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

Drug content

The test is mandatory for tablets with 10 mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F6) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml phosphate buffer pH 6.8 sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this solution take 1 ml and diluted up to 100 ml with phosphate buffer pH 6.8 and the drug content was determined spectrophotometrically at 256 nm.

In vitro disintegration time

The disintegration test was performed using an USP disintegration apparatus, with distilled water at 24±0.50C. The time reported to obtain complete disintegration of six tablets were recorded and average was reported.

Dissolution rate studies

The prepared tablets were evaluated for *in vitro* drug release. The drug release studies were carried out using USP XXII paddle type Dissolution test apparatus. A tablet placed in dissolution media (900 ml) which was stirred at 75 rpm maintained at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml Phosphate buffer pH 6.8. The samples withdrawn were assayed spectrophotometrically at 256.0 nm using UV visible spectrophotometer. The release of drug was calculated with the help of standard curve of PCZ [10, 11].

RESULTS AND DISCUSSION

Solubility of PCZ was freely soluble in methanol, sparingly soluble in chloroform, soluble in water, 0.1N HCL, 0.1N NaOH and 6.8 pH phosphate buffers. The λ_{max} of PCZ was found to be 256 nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 2-10 µg/ml Fig.1& 2. Tablet powder blend was subjected to various pre-compression parameters Table 2. The angle of repose values indicates that the powder blend has good flow properties. The bulk density, tapped density, compressibility index and Hauser's ratio of all the formulations was found to be within the range and showing that the powder has well flow properties. The results of post-compression parameters such as the uniformity of weight, hardness, thickness, friability and drug content of the tablets are given in Table 3. All the tablets of different batches complied with the official requirements of uniformity of weight. The hardness of the tablets ranged from 3.4±0.2 to3.6±0.2kg/cm^2 and the friability values were less than 0.9% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 2.2 to 2.5 mm. All the formulations satisfied the content of the drug as they contained 99.12 to 99.85 % of PCZ and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control. The result in vitro disintegration were within the prescribe limit and comply with the criteria for orally disintegrating tablets. The tablets were evaluated for in vitro dissolution studies in phosphate buffer pH 6.8 for 10 min. The results of the optimized formulation F5 showed maximum drug release i.e. 98.89 % at the end of 10 min. The results of release studies of formulations F5 was shown in Table 4. The *in vitro* drug release data of the optimized formulation F5 was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of first order was maximum i.e. 1.000 hence indicating drug release from formulations was found to follow first order kinetics Table 5 & Fig. 3-6.

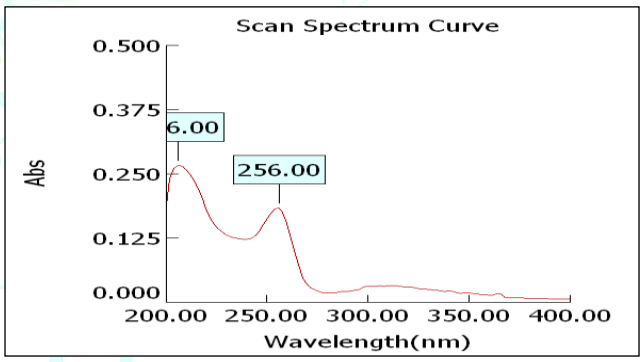

Figure 1 Determination of λ_{max} of PCZ

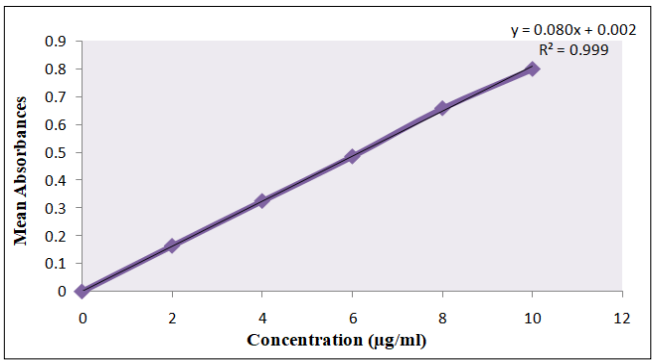

Figure 2 Calibration curve of PCZ at 256 nm

Table 2 Results of pre-compression parameters of PCZ

Formulation code	Parameters			
	Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	0.415	0.521	20.345	1.255
F2	0.426	0.529	19.471	1.242
F3	0.432	0.542	20.295	1.255
F4	0.436	0.541	19.409	1.241
F5	0.439	0.548	19.891	1.248
F6	0.438	0.542	19.188	1.237

Table 3 Results of Post-Compression parameters of all formulations

F. Code	Hardness (kg/cm²)*	Friability (%)*	Weight variation (%)*	Thickness (mm)*	Drug content (%)*	Disintegration Time (sec.)* Mean ± SD
F1	3.4±0.2	0.856±0.045	155±3	2.2±0.2	99.85±0.45	120±5
F2	3.5±0.3	0.845±0.012	154±4	2.3±0.1	99.65±0.25	85±4
F3	3.6±0.2	0.658±0.25	150±2	2.4±0.3	99.78±0.45	110±2
F4	3.5±0.1	0.896±0.032	148±5	2.2±0.1	99.45±0.65	75±6
F5	3.4±0.3	0.754±0.054	146±6	2.5±0.4	99.15±0.23	65±5
F6	3.5±0.4	0.754±0.045	153±4	2.4±0.2	99.12±0.41	112±3

*Average of three determinations (n=3)

Table 4 *In-vitro* drug release data for optimized formulation F5

Time (min)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
2	1.414	0.301	48.85	1.689	51.15	1.7088
5	2.236	0.699	75.65	1.879	24.35	1.3865
10	3.162	1.000	98.89	1.995	1.11	0.0453

Table 5 Regression analysis data

Batch	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
	R^2	R^2	R^2	R^2
F5	0.966	1.000	0.949	0.963

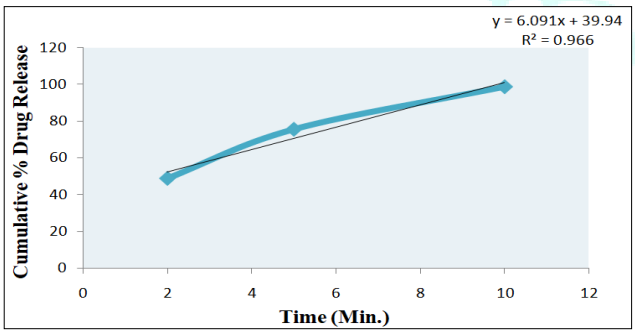

Figure 3 Zero order release Kinetics

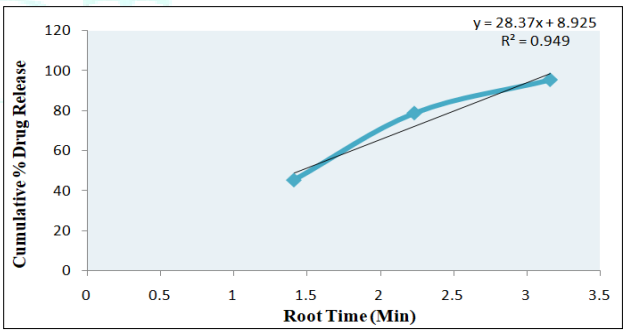

Figure 5 Higuchi release kinetics

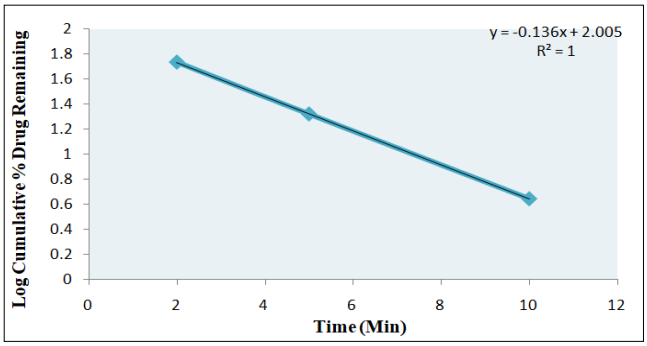

Figure 4 First order release kinetics

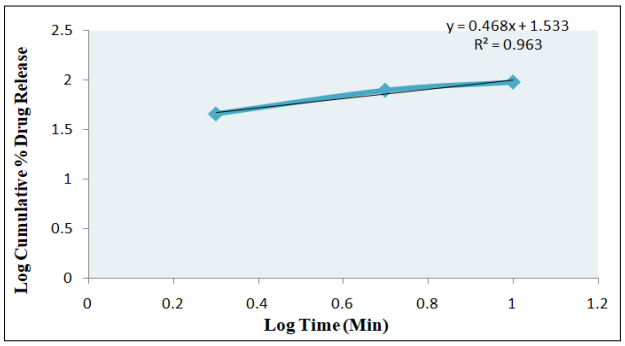

Figure 6 Korsmeyer-Peppas release kinetics

CONCLUSION

The oral fast dissolving tablet of PCZ were formulated and evaluated for various parameters from the compatibility studies by IR of drug it was found to be compatible with other formulation excipients. All evaluation parameter were within specification. The crospovidone shown faster drug release than sodium starch glycolate and crosscarmellose sodium. Formulation F5 release maximum drug within the 10mins.ie. 98.89 % and shown minimum disintegration time i.e. 65 sec than other formulation and hence considered best formulation.

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