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Formulation Design of Novel Fast Disintegrating Tablets of Prochlorperazine Maleate

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Abstract: In the present work, fast disintegrating tablets of prochlorperazine maleate were prepared with a view to enhance patient compliance by direct compression method. Three superdisintegrants i.e., crospovidone, croscarmellose sodium and sodium starch glycolate in different ratios with MCC (Avicel, PH-102) along with directly compressible mannitol (Pearlitol SD 200) to enhance mouth feel. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity, wetting time, water absorption ratio and *in vitro* dispersion time. Based on *in vitro* dispersion time (approximately 11 s), three formulations were tested for the *in vitro* drug release pattern (in pH 6.8 phosphate buffer), short-term stability (at 40º/75% RH for 3 m) and drug-excipient interaction (IR spectroscopy). Among the three promising formulations, the formulation prepared by using 8% w/w of crospovidone and 60% w/w of microcrystalline cellulose emerged as the overall best formulation ($t_{50\%}$ 4.4 min), based on the *in vitro* drug release characteristics compared to conventional commercial tablet formulation ($t_{50\%}$ 16.4 min). Short-term stability studies on the formulations indicated that there are no significant changes in drug content and *in vitro* dispersion time ($p<0.5$).
Keywords: Fast disintegrating tablets, prochlorperazine maleate, crospovidone, croscarmellose sodium, sodium starch glycolate.

Introduction

Many patients find it difficult to swallow tablets and hard gelatin capsules and thus does 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. Recent advances in novel drug delivery systems (NDDS) aim 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 disintegrating tablets (FDT)[1-4].

Prochlorperazine maleate 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 disintegrating tablets containing prochlorperazine maleate offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increased bioavailability.

Materials and Methods

Prochlorperazine maleate and super-disintegrants were the gift samples from Mehta Pharmaceuticals, Mumbai and Wockhardt Research Centre, Aurangabad respectively. Directly compressible mannitol (Pearlitol SD 200), microcrystalline cellulose (MCC) and sodium stearyl fumarate (SSF) were generous gifts from Strides Acrolabs, Bangalore. All other chemicals used were of Analytical Reagent grade.

Preparation of fast disintegrating tablets of prochlorperazine maleate:

Fast disintegrating tablets of prochlorperazine maleate (PCZM) were prepared by direct compression[6] 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 (Clit). A batch of 60 tablets was prepared for all the designed formulations.

Evaluation of tablets:

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation[7]. Hardness and friability of the tablets were determined by using Monsanto Hardness Tester and Roche friabilator respectively. For content uniformity test, ten tablets were weighed and powdered. The powder equivalent to 5 mg of PCZM was extracted into methanol and liquid was filtered (Whatmann No. 1 filter paper). The PCZM content in the filtrate was determined by measuring the absorbance at 254.5 nm after appropriate dilution with methanol. The drug content was determined using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations[8]. For determination of wetting time and water absorption ratio[9], a piece of tissue paper folded twice was placed in a small petridish (internal diameter of 5 cm) containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio 'R' was calculated using the equation: $R=100\ (W_b-W_a)/W_a$; where W_a is weight of tablet before water absorption and W_b is weight of tablet after water absorption. For determination of *in vitro* dispersion time, one tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37±0.5º and the time required for complete dispersion was determined[10]. IR spectra of PCZM and its formulations were obtained by KBr pellet method using Perkin-Elmer FTIR series (Model 1615) spectrophotometer in order to rule out drug-carrier interactions.

Dissolution study[11]

In vitro dissolution of PCZM fast disintegrating tablets was studied in USP XXIII type-II dissolution apparatus (Electrolab, Model-TDT 06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37±0.5º as dissolution medium. One tablet was used in each test. Aliquots of dissolution medium (5 ml) were withdrawn at specified intervals of time and analyzed for drug content by measuring the absorbance at 255.5 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent of PCZM released was calculated and plotted against time.

Stability Testing:

Short-term stability studies on the promising formulations (DCP_4, $DCCS_4$ and $DSSG_4$) were carried out by storing the tablets at 40º/ 75% RH over a 3 m period. At an intervals of one week, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time.

Results and Discussion

Fast disintegrating tablets of prochlorperazine maleate were prepared by direct compression method employing crospovidone, croscarmellose sodium and sodium starch glycolate as super-disintegrants in different ratios with microcrystalline cellulose. Directly compressible mannitol (Pearlitol SD 200) was used as a diluent to enhance mouth feel. A total of twelve formulations and a control formulation DC_0 (without super-disintegrant) were designed. As the blends were free flowing (angle of repose <30º, and Carr's index <15%) tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specification i.e., below 7.5%. Drug content was found to be in the range of 96 to 102%, which is within acceptable limits. Hardness of the tablets was found to be 2.4 to 3.0 Kg/cm². Friability below 1% was an indication of good mechanical resistance of the tablets. Water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 50-85% and 12-56 s respectively. Among all the designed formulations, three formulations, viz., DCP_4, $DCCS_4$ and $DSSG_4$ were found to be promising and displayed an *in vitro* dispersion time ranging from 10 to 25 s, which facilitates their faster dispersion in the mouth.

Overall, the formulation DCP_4 containing 8% w/w of crospovidone and 60% w/w of microcrystalline cellulose was found to be promising and has shown an *in vitro* dispersion time of 10 s, wetting time of 12 s and water absorption ratio of 85% when compared to control formulation (DC_0) which shows 244 s, 255 s and 50% values respectively for the above parameters (Table 2).

In vitro dissolution studies on the promising formulations (DCP_4, $DCCS_4$ and $DSSG_4$), the control (DC_0) and commercial conventional formulations (CCF) were carried out in pH 6.8 phosphate buffer, and the various dissolution parameter values viz., percent drug dissolved in 5 min, 10 min and 15 min (D_5, D_{10} and D_{15}), dissolution efficiency at 10 min ($DE_{10\ min}$)[12], $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ are shown in Table 3 and the dissolution profiles depicted in Fig. 1. This data reveals that overall, the formulation DCP_4 has shown four-fold faster drug release ($t_{50\%}$ 4.4 min) when compared to the commercial conventional tablet formulations of prochlorperazine maleate ($t_{50\%}$ 16.4 min) and released 5-times more drug than the control formulation in 10 min.

IR spectroscopic studies indicated that the drug is compatible with all the excipients. The IR spectrum of DCP_4 showed all the characteristic peaks of prochlorperazine maleate pure drug, thus confirming that no interaction of drug occurred with the components of the formulation. Short-term

stability studies of the above formulations indicated that there are no significant changes in drug content and *in vitro* dispersion time at the end of 6 m period ($p<0.05$).

Conclusion

The present study conclusively indicates that the formulation DCP_4 is very much promising as fast dissolving tablets of prochlorperazine maleate with an *in-vitro* dispersion time of less than 11sec.

TABLE 1. COMPOSITION OF DIFFERENT BATCHES OF FAST DISINTEGRATING TABLETS OF PROCHLORPERAZINE MALEATE

Ingredients (mg)	Formulation Code												
	DC_0	DCP_1	DCP_2	DCP_3	DCP_4	DCC S_1	DCC S_2	DCC S_3	DCC S_4	DSS G_1	DSS G_2	DSS G_3	DSS G_4
Prochlorperazine maleate	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Cross-povidone	--	3.0	3.0	6.0	12.0	--	--	--	--	--	--	--	--
Cros-carmellose sodium	--	--	--	--	--	3.0	3.0	6.0	12.0	--	--	--	--
Sodium starch glycolate	--	--	--	--	--	--	--	--	--	3.0	3.0	6.0	12.0
Microcrystalline cellulose	--	--	30.0	60.0	90.0	--	30.0	60.0	90.0	--	30.0	60.0	90.0
Aspartame	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Sod stearyl fumarate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Pine apple flavour	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol (Pearlitol SD 200)	136.0	133.0	103.0	70.0	34.0	133.0	103.0	70.0	34.0	133.0	103.0	70.0	34.0
Total Weight	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0

TABLE 2. POST-COMPRESSION PARAMETERS

Parameters	Formulation code												
	DC_0	DCP_1	DCP_2	DCP_3	DCP_4	DCCS 1	DCCS 2	DCCS 3	DCCS 4	DSSG 1	DSSG 2	DSSG 3	DSSG 4
Hardness (Kg/cm²)*	2.60 ±0.10	2.63 ±0.15	2.63 ±0.15	2.56 ±0.15 2	2.53 ±0.15 2	2.63 ±0.05	2.63 ±0.05	2.60 ±0.20	2.63 ±0.05	2.51 ±0.14 7	2.53 ±0.23 4	2.5 ±0.10	2.76 ±0.25
Thickness (mm)	2.52	2.80	2.92	2.62	2.82	2.78	2.73	2.55	2.74	2.72	2.95	2.93	2.72
Friability (%)	0.45	0.40	0.42	0.50	0.48	0.46	0.50	0.52	0.48	0.40	0.45	0.50	0.60
In vitro dispersion time (sec)*	244.50 ±2.0	46.76 ±2.50	42.50 ±0.58	23.82 ±1.22	10.50 ±0.82	51.88 ±3.00	45.46 ±0.69	27.67 ±1.19	15.64 ±1.10	55.51 ±2.90	47.66 ±1.52	35.33 ±3.04	25.66 ±2.08
Wetting time (sec)*	247.9 ±1.62	47.20 ±2.87	45.50 ±1.89	25.99 ±1.59	12.39 ±1.06	52.16 ±1.84	47.18 ±1.53	29.82 ±1.59	17.36 ±0.98	56.06 ±1.19	50.14 ±1.82	36.67 ±1.65	27.05 ±1.40
Water-absorption ratio (%)*	50.00 ±2.78	56.89 ±0.60	63.41 ±1.13	70.37 ±1.00	85.00 ±0.51	53.26 ±1.86	59.15 ±1.29	66.44 ±0.80	81.56 ±0.04	51.21 ±0.63	57.87 ±1.31	63.75 ±0.57	80.38 ±0.65
Percent drug content (%)*	95.68 ±0.59	97.96 ±1.38	99.03 ±0.78	97.76 ±0.73	97.74 ±0.62	99.46 ±0.71	99.42 ±1.02	101.27 ±0.74	101.14 ±1.30	100.45 ±0.70	100.50 ±0.84	101.50 ±0.56	100.53 ±0.36
Weight variation (%)	(148 – 156 mg)within the IP limits of ±7.5%												

*Average of three determinants

TABLE 3. *IN VITRO* DISSOLUTION PARAMETERS IN pH 6.8 PHOSPHATE BUFFER

Formulation code	D_5 (%)	D_{10} (%)	D_{15} (%)	$DE_{10\ min}$ (%)	$t_{50\%}$ (min)	$t_{70\%}$ (min)
DC_0	10.0	18.0	20.0	9.94	>30	>30m
DCP_4	53.00	66.00	70.00	47.02	4.2	15.1
$DCCS_4$	44.00	60.00	65.00	38.36	6.2	22.0
$DSSG_4$	39.00	55.00	60.00	30.48	8.2	25.3
CCF	14.00	32.00	44.00	15.42	17.4	>30

DC_0=control formulation, CCF=conventional commercial formulation, D5=percent drug released in 5 min, D10=percent drug released in 10 min, D15=percent drug released in 15 min, DE10min=dissolution efficiency in 10 min, t50%=time for 50% drug dissolution, $t_{70\%}$=time 70% drug dissolution.

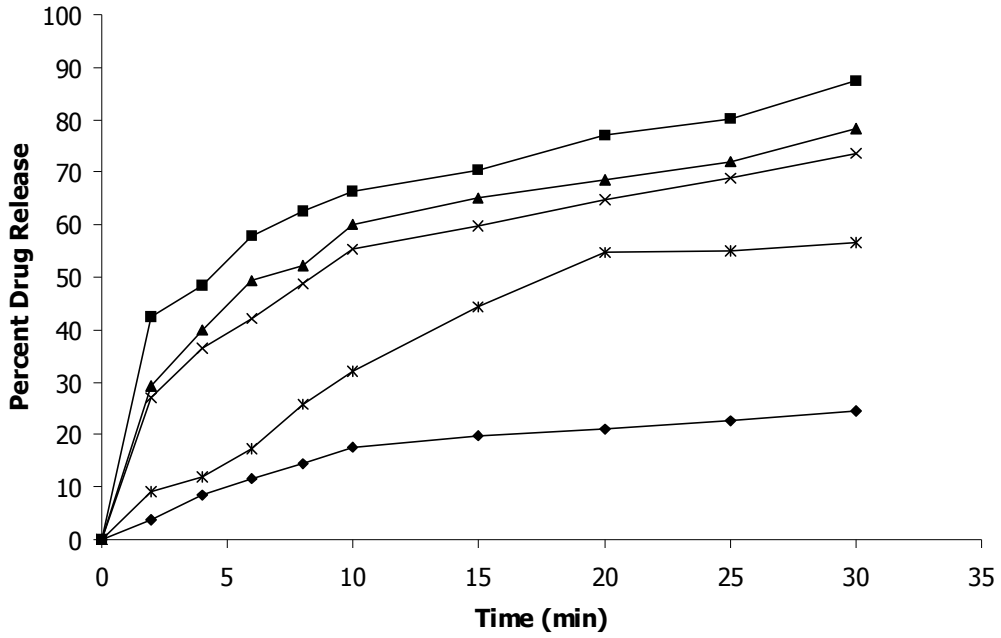

Fig. 1: Percent cumulative release of PCZM from FDTs in pH 6.8 phosphate buffer.
Plot showing percent cumulative release of prochlorperazine maleate from FDTs of pure drug (PCZM) and super-disintegrant used formulations at pH 6.8 (–υ–) Control drug tablet, (–ν–) Crospovidone used tablet, (–σ–) Croscarmellose sodium used tablets, (–x–) Sodium starch glycolate used tablet, (–T–) Commercial conventional tablet

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