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DESIGN AND EVALUATION OF LOW COST DIRECTLY COMPRESSIBLE EXCIPIENTS - II

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ABSTRACT

The aim of the present study was to develop dispersible / mouth dissolving tablets (orodispersible tablets) using piroxicam as a model drug for improving patient compliance, employing low cost directly compressible co-processed granular excipients developed in our laboratory, based on various sugars/polyols such as mannitol, maltodextrin and dicalcium phosphate dihydrate along with a native food grade corn starch. The designed tablet formulations were evaluated for hardness, friability, weight variation, *in vitro* dispersion time, wetting time, water absorption ratio, drug content, *in-vitro* dissolution rate (in pH 6.8 phosphate buffer), short-term stability and drug-excipient interaction (IR spectroscopy). Among the designed piroxicam tablets, one formulation prepared with the granular excipient containing 25% w/w corn starch and 75% w/w dicalcium phosphate dihydrate using starch paste for granulation, without super disintegrant addition was found to be promising dispersible tablet formulation (*in vitro* dispersion time of 17.66 s and wetting time 8.4 s). Another tablet formulation prepared with the granular excipient containing mannitol and food grade corn starch (50:50 ratio) and granulated with starch paste, along with 2% w/w crospovidone as superdisintegrant emerged as promising orodispersible tablet formulation (*in vitro* dispersion time 17.66 s and wetting time 14.3 s. Short-term stability studies of promising formulations (over a period of 3 months) indicated that there are no significant changes in drug content and *in vitro* dispersion time ($p<0.05$). IR-spectroscopic studies indicated that there are no drug–excipient interactions.

KEYWORDS: Piroxicam; co-processed granular excipients; corn starch; mannitol; maltodextrin and dicalcium phosphate dihydrate.

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INTRODUCTION

The choice of excipients in a tablet formulation depends on the active ingredient (drug), the type of tablet, the desired characteristics and the manufacturing process used. Over the past four decades, improvements in the availability of excipients with consistent physical properties (including particle size and shape, and improved functionality such as compaction and flow), have revolutionized tablet production on a commercial scale[1].

Direct compression technology is receiving increasing interest over conventional granulation technique due to the savings in equipments, materials, labour, time and energy coupled with other advantages such as improved drug stability due to elimination of heat and moisture. However most of the directly compressible excipients currently available in the market are imported and hence have prohibitive cost[2].

Hence, aim of the present study was to develop dispersible / mouth dissolving tablets (orodispersible tablets) using piroxicam (analgesic, anti-inflammatory and anti-pyretic) as a model drug for improving patient compliance, especially, those of pediatric and geriatric categories with difficulties in swallowing[3,4], employing promising low cost directly compressible granular excipients developed in our laboratory (as shown in Table 1), based on various sugars / polyols such as mannitol (M), maltodextrin (MD) and dicalcium phosphate dehydrate (DCP) along with a local variety of food-grade corn starch (FCS) as reported earlier[5]. The designed tablet formulations are evaluated for hardness, friability, weight variation, *in vitro* dispersion time, wetting time, water absorption ratio, drug content, *in-vitro* dissolution rate (in pH 6.8 phosphate buffer), short-term stability and drug-excipient interaction (IR spectroscopy).

MATERIALS AND METHODS

Piroxicam (PX) and maltodextrin were gift samples from M/s Microlabs Pvt. Ltd., Bangalore and S.A.Pharmachem Pvt. Ltd,.Mumbai,.respectively. Food grade corn starch (Manibhadra food products, Hubli) was purchased from the local market. Corn starch (laboratory grade) and mannitol were procured from Sd Fine Chem, Mumbai. Dicalcium Phosphate dihydrate was obtained from E. Merck (India) Pvt. Ltd., .Mumbai. All other chemicals used were of analytical reagent grade.

Development of Directly Compressible Granular Excipients

Directly compressible granular excipients were developed by co-processing technique, employing the wet granulation method. Corn starch, mannitol, dicalcium phosphate dihydrate and maltodextrin were used in different ratios. The designed granular excipients were evaluated for bulk density, tapped density, Carr's index and Hausner's ratio[6], and the promising granular excipients are enlisted in **Table 1**. Method: All the ingredients were powdered separately in a dry, clean porcelain mortar and passed through #60 mesh sieve and mixed well in geometrical ratio. Granulating fluid was added to the powder mixture, small quantity at a time, while mixing thoroughly after each addition, until a coherent mass was formed. Then it was passed through # 44 mesh sieve and the wet granules were spread on a paper and dried in hot air oven at 55-60^{o} C (after 30 minutes air drying to remove the residual alcohol). The dried granules were then passed through # 36 mesh sieve.

Preparation of Orodispersible Tablets of Piroxicam

Orodispersible tablets of piroxicam were prepared by direct compression[7] according to the formulae given in **Tables 2a and 2b**. All the ingredients were passed through #60 mesh sieve separately. Then the ingredients were weighed and mixed in geometrical order and tablets were compressed using 8 mm flat round punches to get tablets of 150 mg weight on a 10-station rotary tablet machine (Clit, Ahmedabad, India). 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[8]. 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 10 mg of piroxicam was extracted into methanol and the liquid was filtered. The piroxicam content was determined by measuring the absorbance at 366 nm after appropriate dilution with methanol. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations[9]. For determination of wetting time and water absorption ratio[10], a piece of tissue paper folded twice was placed in a small Petri dish (internal diameter of 5 cm) containing 6 ml 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 determined using the equation, $R=100 (W_b-W_a)/Wa$; 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 C and the time required for complete dispersion was determined[11]. IR spectra of piroxicam and its formulations were obtained by potassium bromide pellet method using Perkin-Elmer FTIR series (model-1615) spectrophotometer in order to rule out drug-carrier interactions.

Dissolution Study

In vitro dissolution of piroxicam orodispersible 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±0.5° C as dissolution medium[12]. One tablet was used in each test. Aliquots of dissolution medium were withdrawn at specified intervals of time and analyzed for drug content by measuring the absorbance at 366 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent of piroxicam released was calculated and plotted against time.

Stability Testing

Short-term stability studies on the promising piroxicam tablet formulations [$CPDC_{1b}$, MDC_{3b} (CP2) and MDC_0 (CP2)] were carried out by storing the tablets at 40±2° C / 75±5% RH over a 3 month period. At intervals of one month, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time.

RESULTS AND DISCUSSION

Co-processed directly compressible excipients by wet granulation method were prepared using a local variety of food-grade corn-starch (Manibhadra Food products, Hubli, Karnataka, India) along with mannitol, maltodextrin and dicalcium phosphate dihydrate in different ratios. The developed excipients were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and hygroscopicity, in comparison with commercial variety of corn-starch (SD fine chem., Mumbai, India), as the control. Among all the prepared granular excipients, eight (four of MD-FCS, two of DCP-FCS, one of DCP-FCS-MD and one of M-FCS combination) were found to be promising based on the above parameters (Carr's index <15% and Hausner's ratio <1.18%), as shown in **Table 1**.

Dispersible tablets of piroxicam were prepared using the above excipients and evaluated for pre-compression parameters such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose (Table 3) and for post compression parameters such as hardness, weight variation, drug content uniformity, wetting-time, water-absorption ratio and *in vitro* dispersion time (**Table 4**).

The hardness of the tablet formulations made by the direct compression method was found to be in the range of 2.56 to 3.4 kg/cm^2. The friability values were found to be in the range of 0.58 to 1.04%. The weights of all the tablets were found to be uniform with low values of standard deviation and within the prescribed IP limits. The percent drug content of all the tablets was found to be in the range of 97.6 to 99.7 of the expected PX content, which was within the acceptable limits. *In vitro* dispersion time, wetting time and water absorption ratio for all the PX tablet formulations were also determined and results are shown in **Table 4**.

Among the tablets prepared, formulation $CPDC_{1b}$ containing no super disintegrant was found to be promising, and has shown an *in vitro* dispersion time of 17.66 s, wetting time 8.4 s and water

absorption ratio 75%. The formulation MDC_{3b} (CP2) and MDC_o (CP2) containing 2% w/w crospovidone as superdisintegrant showed *in vitro* dispersion time of 17.66 and 24.33 s, wetting time of 14.3 and 31.0 s respectively and water absorption ratio of 40% for both.

In vitro dissolution studies were performed in pH 6.8 phosphate buffer , on the above promising formulations, namely, MDC_{3b} (CP2), MDC_0 (CP2) and $CPDC_{1b}$ along with commercial dispersible tablet formulation (CDT) of piroxicam. The tablet formulations MDC_{3b} (CP2), MDC_0 (CP2) and $CPDC_{1b}$ released 89.6%, 90.4% and 27.5% drug in 30 min compared to commercial dispersible tablet formulation (73.55%). The dissolution profiles of the above are depicted in **Fig. 1**.

When the drug release from MDC_{3b} (CP2) and MDC_0 (CP2) tablet formulations was compared with CDT, it can be seen that drug release from MDC_{3b} (CP2) and MDC_0 (CP2) is greater than CDT. But $CPDC_{1b}$ formulation showed lesser drug release when compared to CDT, which can be attributed to the insoluble nature of dicalcium phosphate dihydrate. Since the insoluble excipient gives gritty mouth-feel as an orodispersible tablet, this formulation may be considered as a promising dispersible tablet formulation for the drug piroxicam.

The various *in vitro* dissolution parameter values, viz., percent drug dissolved in 5 min (D_5), 10 min (D_{10}), dissolution efficiency[13] at 10 min ($DE_{10\ min}$), $t_{25\%}$, $t_{50\%}$ and $t_{70\%}$ of promising piroxicam tablet formulations in comparison with CDT in pH 6.8 phosphate buffer are shown in **Table 5**. From this data it is evident that the tablet formulations MDC_{3b} (CP2) and MDC_0 (CP2) display 2 to 3 times faster drug release compared to CDT when $t_{50\%}$ and $t_{70\%}$ values are considered. Hence, these formulations may be considered as promising cost effective orodispersible tablet formulations for the drug piroxicam. And overall, the formulation MDC_{3b} (CP_2) emerges as the best orodispersible tablet formulation with an *in vitro* dispersion time of 18 s compared to MDC_0 (CP2) which displays 24 s for the above parameter.

Drug Release Kinetics

The *in vitro* drug release data from the control, promising, commercial formulations were fitted into two popular models of data treatment: a) cumulative percent drug release versus time plots (zero-order), b) log cumulative percent drug remaining versus time plots (first-order). When the data was plotted as log cumulative percent drug remaining versus time, the plots obtained were linear indicating first order release kinetics. Statistical analysis of the data by the method of least squares gives correlation coefficient values in the range of -0.926 to -0.972.

Short-term Stability Studies

Short-term stability studies on the above promising formulations (at 40 ± 2^o C / 75 ± 5% RH for 3 mo) have shown no significant changes in physical appearance, drug content and *in vitro* dispersion time.

Statistical analysis ('t'-test) of drug content data gives 't' values of 3.75, 2.74 and 0.62 for MDC_{3b} (CP2), $CPDC_{1b}$ and MDC_0 (CP2) formulations respectively, which are much less compared to the table value of 4.3 ($p<0.05$). There are no appreciable changes in *in vitro* dispersion time up on storage at 40 ± 2^o C / 75 ± 5% RH for 3 months period.

The IR spectrum of PX exhibits characteristic peaks at 3336.85 cm^{-1}, 1679.29cm^{-1}, 1699.29 cm^{-1}, 1527.62 cm^{-1}, and 1039.63cm^{-1} due to N-H stretching, C=O ester, amide-I, amide-II and SO_2N groups respectively. All the above characteristic peaks were found in the IR spectra of stability formulations MDC_{3b} (CP2), MDC_0 (CP2) and $CPDC_{1b}$. The presence of above peaks confirms undisturbed structure of drug in the above formulations. Hence, there are no drug-excipient interactions.

CONCLUSION

The present study conclusively proves that the developed low cost directly compressible granular excipients can be successfully used in the design and development of dispersible and orodispersible tablet formulations of various medicaments, and thus help in improving patient compliance, especially, among the pediatric and geriatric categories with difficulties in swallowing solid oral dosage forms.

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Table 1: Promising Directly Compressible Granular Excipients based On the Carr's Index And Hausner's Ratio

Sl. No.	Formulation Code	Corn starch %w/w	Mannitol w/w%	DCP %w/w	Maltodextrin %w/w	Granulation fluid used	Carr's Index (%)	Hausner's ratio
1	$MDDC_1$	50	-	-	50	90% alcohol	12.24	1.16
2	$MDDC_2$	75	-	-	25	90% alcohol	14.28	1.22
3	$CPDC_{1a}$	25	-	70	5	70% alcohol	5.17	1.05
4	$MDDC_{1a}$	50	-	-	50	70% alcohol	13.16	1.14
5	$MDDC_{2a}$	75	-	-	25	70% alcohol	13.79	1.16
6	MDC_{3b}	50	50	-	-	Starch paste	14.28	1.22
7	$CPDC_{1b}$	25	-	75	-	Starch paste	8.0	1.13
8	$CPDC_{2b}$	50	-	50	-	Starch paste	11.62	1.21
9	$^{*}CPDC_o$	50	-	50	-	Starch paste	12.24	1.16
10	$^{*}MDC_0$	50	50	-	-	Starch paste	15.5	1.21

* Control formulations prepared using commercial corn starch (Sd Fine Chem, Mumbai)
DCP- Dicalcium phosphate dehydrate

Table 2a: General Formula For Piroxicam Dispersible Tablets without Super disintegrant

Sl. No.	Ingredients	Quantity for one tablet (mg)
1.	Piroxicam USP	10.0
2.	Sodium saccharin	1.5
3.	Sodium lauryl sulphate	3.0
4.	Flavor	1.5
5.	Purified Talc	3.0
6.	Directly compressible granular excipient	131
	Total weight	150

Table 2b: General Formulae For Piroxicam Dispersible Tablets With Superdisintegrant

Ingredients (mg/tablet)	Formulation code			
	MDC_0 (CP1)	MDC_0 (CP2)	MDC_{3b} (CP1)	MDC_{3b} (CP2)
Piroxicam USP	10	10	10	BI
Crospovidone	1.5	3	1.5	3
Sodium saccharin	1.5	1.5	1.5	1.5
Sodium lauryl sulphate	3	3	3	3
Flavor	1.5	1.5	1.5	1.5
Purified Talc	3	3	3	3
MDC_0	129.5	128	-	-
MDC_{3b}	-	-	129.5	128
Total weight	150	150	150	150

Table 3: Precompression Parameters of Piroxicam Tablet Formulations

Formulations	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (degree)	Carr's index (%)	Hausner's ratio
$MDDC_1$	0.53	0.60	34.10	11.66	1.13
$MDDC_2$	0.46	0.54	12.77	14.81	1.17
$CPDC_1a$	0.65	0.68	24.84	4.61	1.04
$MDDC_1a$	0.72	0.81	26.86	11.11	1.12
$MDDc_2a$	0.60	0.68	34.38	13.33	1.13
MDC_{3b}	0.46	0.54	18.97	14.81	1.17
$CPDC_{1b}$	0.56	0.62	19.03	9.67	1.10
$CPDC_{2b}$	0.48	0.56	20.22	14.28	1.16
$CPDC_0$	0.53	0.60	17.71	11.66	1.13
MDC_0	0.48	0.56	20.22	14.28	1.16
MDC_0 (CP1)	0.48	0.56	17.70	11.66	1.16
MDC_0 (CP2)	0.48	0.56	17.71	11.66	1.16
MDC_{3b} (CP1)	0.46	0.54	18.98	14.81	1.17
MDC_{3b} (CP2)	0.46	0.54	18.97	14.81	1.17

Table 4: Post Compression Parameters of Piroxicam Tablet Formulations

Formulations	Hardness (kg/cm^2)* ± SD	Friability (%)	*In vitro* dispersion time (s)* ± SD	Wetting time (s)* ± SD	Water absorption ratio (%)* ± SD	Percent drug content* ± SD
$MDDC_1$	2.9 ± 0.1	0.62	484 ± 3.60	41.0 ± 3.20	6.25 ± 3.12	98.35 ± 0.82
$MDDC_2$	2.9 ± 0.1	0.58	321.3 ± 2.88	33.1 ± 2.86	6.25 ± 2.16	97.60 ± 0.61
$CPDC_{1a}$	2.56 ± 3.05	1.04	102.3 ± 2.52	12.1 ± 2.51	40.0 ± 2.56	99.05 ± 0.33
$MDDC_{1a}$	3.3 ± 0.17	0.70	722.3 ± 2.51	41.1 ± 0.76	6.25 ± 1.81	98.35 ± 0.52
$MDDC_{2a}$	3.03 ± 0.05	0.79	421.6 ± 1.52	29.66 ± 1.15	6.66 ± 1.52	97.60 ± 0.71
MDC_{3b}	2.6 ± 0.1	0.72	82.33 ± 2.51	23.7 ± 2.88	20.0 ± 1.71	99.70 ± 0.62
$CPDC_{1b}$	2.66 ± 0.11	0.82	17.66 ± 2.51	08.4 ± 2.51	75.0 ± 2.56	98.56 ± 0.11
$CPDC_{2b}$	2.3 ± 0.1	0.75	33.33 ± 2.88	05.33 ± 2.56	75.0 ± 1.52	99.25 ± 0.61
$CPDC_0$	3.4 ± 0.1	0.76	34.0 ± 1.73	10.14 ± 1.17	25.0 ± 1.62	99.70 ± 0.19
MDC_0	3.13 ± 0.12	0.80	68.66 ± 1.15	13.7 ± 1.83	93.8 ± 1.62	99.25 ± 0.73
MDC_0(CP1)	3.03 ± 0.15	0.81	47.33 ± 1.52	25.33 ± 2.51	31.25 ± 1.81	98.80 ± 0.66
MDC_0(CP2)	0.06 ± 0.11	0.80	24.33 ± 0.57	31.0 ± 1.15	40.0 ± 0.66	98.81 ± 0.58
MDC_{3b}(CP1)	2.83 ± 0.15	0.74	27.0 ± 1.0	24.66 ± 2.51	40.0 ± 1.33	98.25 ± 0.33
MDC_{3b}(CP2)	2.80 ± 0.15	0.73	17.66 ± 1.53	14.3 ± 1.73	40.0 ± 1.81	98.90 ± 0.26

* Average of three determinations, SD- standard deviation. $CPDC_{1b}$ and MDC_{3b} (CP2) were selected as promising dispersible and orodispersible tablet formulations and used in further studies.

Table 5: Comparative *In Vitro* Dissolution Parameters Of Promising Px Dispersible Formulations, Control And Commercial Formulations In Ph 6.8 Phosphate Buffer

Formulation	D_5 (%)	D_{10} (%)	$DE_{10\ min}$ (%)	$t_{25\%}$ (min)	$t_{50\%}$ (min)	$t_{70\%}$ (min)
MDC_{3b} (CP2)	35.0	76.0	23.53	4.4	5.8	8.4
$CPDC_{1b}$	4.5	18.6	13.98	20.0	>30	>30
MDC_0 (CP2)	50.5	80.0	27.08	3.0	5.0	8.1
CDT	37.5	50.55	28.62	3.1	10.0	23.2

MDC_0 (CP2) is control formulation prepared using commercial corn starch (Sd Fine Chem, Mumbai, India) $CPDC_{1b}$ is promising dispersible tablet formulation, MDC_{3b} (CP2) is promising orodispersible tablet formulation, CDT is commercial dispersible tablet formulation, D_5 is percent drug released in 5 m, D_{10} is percent drug release in 10 m, DE_{10} is dissolution efficiency at 10 m, $t_{25\%}$, $t_{50\%}$ and $t_{70\%}$ are time for 25%, 50% and 70% drug dissolution.

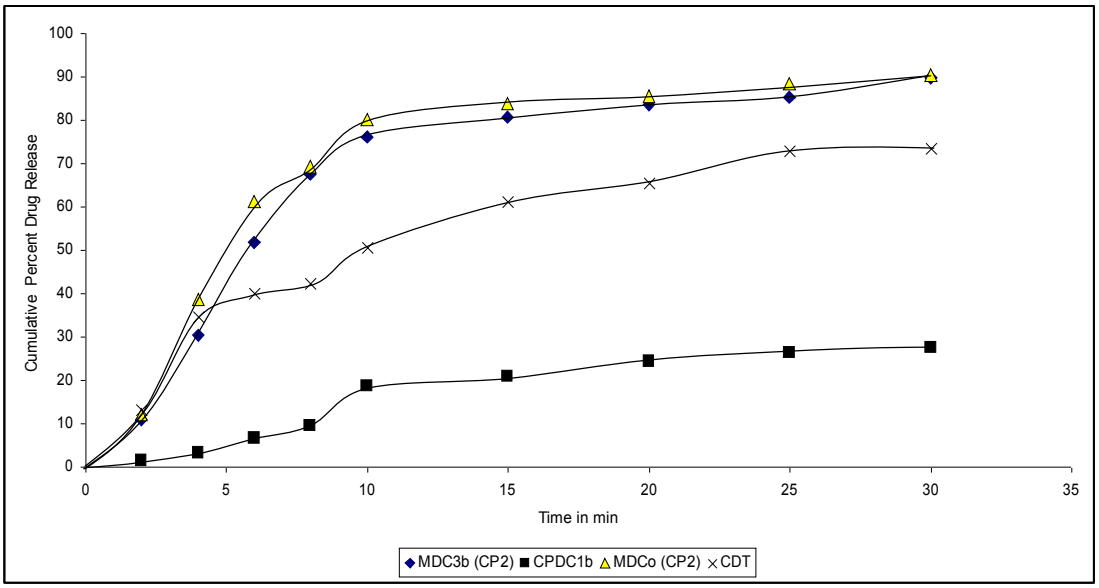

Figure 1: Comparative cumulative percent drug release versus time plots of promising piroxicam formulations, control and commercial dispersible tablet formulation in pH 6.8 phosphate buffer.

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