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Formulation development and evaluation of Piroxicam orodispersible tablets using different superdisintegrants

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ABSTRACT

The demand for mouth dissolving tablets has been growing during the last decade, especially for geriatric and pediatric patients who have swallowing difficulties. Piroxicam is a potent anti-inflammatory drug used in treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and acute gout disease. In the present work, 9 formulations of Orodispersible tablets of Piroxicam (F1 to F9) were prepared using three different superdisintegrants namely Crospovidone, Croscarmellose sodium and sodium starch glycolate with three concentrations (3% ,4% and 5%) and a control F10 (without superdisintegrant) by direct compression method. The final blend of the drug and excipients were evaluated for powder flow properties, bulk density, tapped density, compressibility index and hausner's ratio. All the formulations were evaluated for thickness, weight variation, disintegration time, hardness, friability, drug content, wetting time and water absorption ratio. Formulation F3 showed the lowest disintegration time and more water absorption ratio. In-vitro dissolution studies revealed that formulation F3 showed 99.53 % percent drug release at the end of 50 minutes. The short term stability studies for the formulations showed no significant changes in disintegration time, drug content and percentage drug release when stored at $4^0C\pm2^0C$, 27°C ±2°C and $45^0C\pm2^0C$ for 45 days.

Keywords: Anti-inflammatory, Direct compression, Orodispersible, Piroxicam, Superdisintegrant.

INTRODUCTION

Piroxicam is a potent anti-inflammatory drug. It is used in treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and acute gout disease[1].It has prolonged half life of about 45hrs[2].It is poorly water soluble drug and when administered orally it may cause bioavailability problems due to its poor solubility and dissolution rates in biological fluids[3]. Hence the present work was aimed at increasing the rate of dissolution of Piroxicam thus providing faster rate of absorption by adding potential superdisintegrants like Crospovidone, Croscarmellose sodium and Sodium starch glycolate in different concentrations. To mask the

bitter taste of Piroxicam, aspartame was used as sweetening agent. Nine formulations of orodispersible tablets of Piroxicam using three superdisintegrants namely Crospovidone (3%, 4% and 5%), Croscarmellose sodium (3%, 4% and 5%) and Sodium starch glycolate (3%, 4% and 5%) and a control formulation (without superdisintegrant) were prepared by direct compression method.

MATERIALS AND METHODS

Materials

Piroxicam was procured from Sun Pharmaceuticals Ltd, Mumbai, India. Microcrystalline cellulose, Sodium starch glycolate, Croscarmellose sodium and Aspartame were procured from Rajesh Chemicals, Mumbai; India. Mannitol was procured from Strides Arcolabs, Bangalore, India. Menthol was procured from Reachem Lab Chemicals Pvt.Ltd.Chennai, Magnesium stearate and Crospovidone were procured from Loba Chemie., Pvt. Ltd, Mumbai, India.

2.1 preparations of piroxicam orodispersible tablets [3, 4]

Piroxicam Orodispersible tablets were prepared by direct compression method according to the formula given in Table-I. A total of nine formulations (F1toF9) of Piroxicam orodispersible tablets were prepared using three superdisintegrants namely Croscarmellose sodium, Crospovidone and Sodium Starch Glycolate with three different concentrations (3%, 4% and 5%). A control tablet was also prepared without any superdisintegrant (F10).

Table-I: formulation of piroxicam orodispersible tablets

S.No	Composition(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Piroxicam	20	20	20	20	20	20	20	20	20	20
2	Croscarmellose sodium	6	8	10	-	-	-	-	-	-	-
3	Sodium starch glycolate	-	-	-	6	8	10	-	-	-	-
4	Crospovidone	-	-	-	-	-	-	6	8	10	-
5	Microcrystalline cellulose	110	108	106	110	108	106	110	108	106	116
6	Mannitol	54	54	54	54	54	54	54	54	54	54
7	Aspartame	8	8	8	8	8	8	8	8	8	8
8	Magnesium stearate	2	2	2	2	2	2	2	2	2	2
9	Menthol	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
	TOTAL WEIGHT (mg)	200	200	200	200	200	200	200	200	200	200

F1, F2, F3- Croscarmellose sodium (3%, 4% and 5%).
F4, F5, F6- Sodium starch glycolate (3%, 4% and 5%).
F7, F8, F9- Crospovidone (3%, 4% and 5%).
F10-Control (without superdisintegrant).

All the ingredients were passed through mesh no. 60 separately and collected. The drug, mannitol and microcrystalline cellulose were mixed uniformly with gentle trituration using mortar and pestle to get a uniform mixture. Required quantity of superdisintegrant and aspartame were taken for each specified formulation and mixed with the above mixture. Finally magnesium stearate and menthol were added and mixed well. The mixed blend of drug and excipients were compressed using 7 mm punch on 10 stations “B” Tooling Rotatory Tablet Punching Machine to produce convex faced tablets, weighing 200 mg each (Table-I). Before tablet preparation, the mixture blend of all the formulations were subjected to compatibility studies (IR) and Precompression parameters like Angle of repose, bulk density, tapped density, compressibility index and hausner’s ratio.

2.2 Evaluation of powder blend

2.2.1 Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weighed powder blend were taken in funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the powder blend. The powder blend were allowed to flow through the funnel freely onto the surface [5]. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

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

Where 'h' and 'r' are the height and radius of the cone.

2.2.2 Bulk Density

Bulk density P_b is defined as the mass of the powder divided by the bulk volume and is expressed as g/cm^3. Weighed quantity of powder blend from each formulation was taken in a measuring cylinder and the initial volume of the powder blend (V_b) in the measuring cylinder was noted [6]. This was calculated by using the formula

$$P_b = M / V_b$$

Where, P_b - Bulk density, M - Weight of the sample in g, V_b- volume of the blend in cm$^{3.}$

2.2.3 Tapped Density

It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder blend for 500 times. Then the tapping was done for 750 times and the tapped volume was noted. Tapped density was calculated by using the following formula

$$P_t = M / V_t$$

Where, P_t-Tapped density, M - Weight of the sample in g, V_t - Tapped volume of blend in cm$^{3.}$

2.2.4 Compressibility index and hausners ratio

The compressibility index of the powder blend was determined by Carr's compressibility index and the Hausners ratio is calculated by using the formula [7].

Hausner's ratio = Tapped density / Bulk density

Carr's index (%) = [(TBD-LBD) x 100] / TBD

TBD = Total bulk density, LBD = Loose bulk density

2.2.5 IR Spectral Analysis

It was used to study the interactions between the drug and the excipients.The KBR disk method was used for preparation of sample and spectra were recorded over the wave number 4000 to 400 cm^{-1} in a SHIMADZU FTIR (model-8400) spectrophotometer. IR spectral studies of Pure Piroxicam, Superdisintegrants and Piroxicam containing highest proportion of individual superdisintegrant were carried out [8].

2.3 evaluations of tablets

2.3.1 Weight Variation

Twenty tablets were randomly selected and individually weighed [9]. The average weight of tablets was calculated. Then the individual weight was compared with that of average weight.

2.3.2 Hardness

The tablets to be tested are held between a fixed and a moving jaw of hardness test apparatus (Monsanto) and reading of the indicator is adjusted to zero [10]. The screw knob was moved forward until the tablet breaks and the force required to break the tablet was noted.

2.3.3 Friability

Friability test was performed using Roche friabilator. Ten tablets were weighed and placed in the friabilator, which was then operated for 25 revolutions per minute [11]. After 100 revolutions the tablets were dusted and reweighed. The percentage friability was determined using the formula,

$$\text{Percentage friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

2.3.4 *In-Vitro* disintegration time

The test was carried out in a disintegration apparatus using distilled water as disintegration medium (at 37^0 C ± 0.5^0 C). A tablet was placed in each of six tubes of the apparatus and one disc was added to each tube [12]. The time taken for complete disintegration of the tablet with no mass remaining in the apparatus was measured in seconds.

2.3.5 Wetting time and water absorption ratio

A piece of tissue paper, folded double, was placed in a Petri plate containing 6 ml of distilled water. A preweighed tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The wetted tablet was then weighed [13]. Water absorption ratio was determined using the formula,

$$R = (Wa-Wb)/Wa \text{ X } 100$$

Where R = Water absorption ratio, Wa= Weight of tablet after wetting.
Wb= Weight of tablet before wetting.

2.3.6 Estimation of drug content

Five tablets from each formulation were weighed individually and powdered. The Powder equivalent to 20mg of Piroxicam was weighed and dissolved in 10ml of methanol and volume was adjusted to 100ml with pH 6.8 buffer [14]. From this solution 1 ml was taken and made up to 100 ml using pH6.8 buffer and the solution was analyzed at 333nm by UV–visible spectrophotometer using pH6.8 buffer as the blank.

2.3.7 *In Vitro* drug release

In-vitro dissolution studies for all the formulated tablets of Piroxicam was carried out using USP II paddle method at 50 rpm in 900 ml of pH 6.8 buffer solution as a dissolution medium. The dissolution medium was maintained at 37±0.5^0C.10ml of sample was withdrawn at 10 minutes intervals of time up to 60 minutes. 10 ml of buffer solution (pH 6.8) was replaced to maintain the constant volume throughout the experiment [15]. The samples were suitably diluted and the percentage of drug released from each formulation was measured at 333 nm using UV–visible spectrophotometer.

2.3.8 Kinetic Analysis

To analyze the mechanism of drug release rate kinetics of all the formulations, the results of *in-vitro* release profiles were plotted in models of data treatment as follows [16, 17, 18, and 19]:

1. Log cumulative percent drug remaining versus time (first order kinetic model)
2. Cumulative percent drug release versus time (zero order kinetic model)

2.4 Stability Studies

The stability test was carried out to evaluate the stability of Piroxicam in formulated tablets after storing at different temperatures for 45 days. The prepared tablets were kept at three different temperatures such as 4ºC±º2C, 27°±2°C and 45°C±2°C for 45 days [20, 21]. Every 15 days interval, the tablets were evaluated for the drug content, disintegration time and *in-vitro* drug release studies.

RESULTS AND DISCUSSION

Orodispersible tablets of Piroxicam were prepared by direct compression method using Croscarmellose sodium (CCS), Crospovidone (CP) and Sodium Starch Glycolate (SSG) as superdisintegrants. A total of 9 formulations (F1 – F9) and a control formulation F10(Without Superdisintegrant) were designed. Infra-red (IR) spectroscopy was used as means of studying drug – excipients compatibility which indicated no drug- excipient interaction. The values of precompression parameters evaluated were found to be within the prescribed limits and indicated good free flowing property (Table-II).

Table – II: evaluation of powder blend

Formulation code	Angle of repose*	Bulk density (gm/cm^3)*	Tapped density (gm/cm^3)*	Compressibility Index (%)*	Hausner's ratio*
F_1	29º.54 ±0.041	0.321±0.012	0.409± 0.015	14.42±0.054	1.17±0.058
F_2	30º.96±0.020	0.334±0.011	0.408±0.017	14.35±0.033	1.13±0.0624
F_3	31º.23±0.033	0.331±0.013	0.392±0.059	14.80±0.064	1.16±0.036
F_4	30º.92±0.021	0.372±0.015	0.431±0.075	14.79±0.064	1.16±0.038
F_5	31º.27±0.043	0.313±0.017	0.401±0.013	12.80±0.098	1.18±0.041
F_6	31º.31±0.026	0.310±0.031	0.392±0.028	13.70±0.064	1.15±0.065
F_7	28º.25±0.048	0.341±0.011	0.402±0.025	14.86±.0.061	1.17±0.037
F_8	26º.96±0.032	0.315±0.015	0.401±0.029	13.83±.0.069	1.17±0.095
F_9	29º.51±0.022	0.332±0.018	0.403±0.035	13.24±0.036	1.12±0.069
F_{10}	32º.02±0.035	0.345±0.012	0.432±0.038	14.40±.0.095	1.16±0.099

**All values are expressed as mean ± standard deviation, (n= 5)*

The data obtained of post-compression parameters such as hardness, thickness, friability, weight variation, drug content, disintegration time and water absorption ratio are shown in (Table-III).Tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specifications i.e. below 7.5%. Hardness of the tablets was found to be 2.5-2.9 kg/cm^2. The thickness of tablets was found to be 4.10±0.756 to 4.21±0.648 mm which shows uniform thickness due to uniform die fill. In all the formulations, the friability values were less than 1% and meet the Indian pharmacopoeia (I.P) limits. The percentage drug content of all the tablets were found in the range of 97.40± 0.710 to 99.37± 0.24% of Piroxicam, which was within the acceptable limits. The results of disintegration time of all the formulations were found to be within the prescribed limits and satisfied the criteria of orodispersible tablets. The values were found to be in the range of 29 ± 0.28 to 43 ± 1.10 Seconds. It was observed that when

Croscarmellose sodium is used as superdisintegrant, the tablet disintegrates rapidly within less time when comparing other superdisintegrants.This may be due to easy swelling ability of CCS when compared to other superdisintegrants namely CP and SSG. The water absorption ratio for all formulations was found to be in the range of 69.80 ± 0.205 to 97.06 ± 1.93 %. Among all formulations, formulation F3 showed more water absorption ratio due to its more swelling and water penetration capacity (Table-III).

Table-III: evaluation of orodispersible piroxicam tablets

Batch code	Weight Variation (mg)*	Thickness* (mm)	Hardness* (kg/cm^2)	Friability (%)*	Drug Content (%)*	Disintegration time (sec)*	Water absorption ratio% *
F1	200±1.2	4.18±0.09	2.5±0.756	0.83±0.054	98.66±0.23	32±0.31	88.91±0.96
F2	201±1.4	4.13±0.023	2.7±0.263	0.75±0.112	99.03±0.77	30±0.65	92.48±0.195
F3	200±0.9	4.16±0.518	2.5±0.682	0.69±0.198	99.37±0.24	29±0.28	97.06±1.93
F4	201±1.8	4.20±0.603	2.8±0.151	0.73±1.163	97.96±0.124	33±0.37	82.09±2.30.
F5	201±1.2	4.19±0.263	2.5±0.170	0.84±0.682	98.32±0.840	34±0.60	83.80±4.26
F6	199±1.3	4.21±0.648	2.6±0.131	0.61±0.263	98.36±0.671	36±0.63	85.25±1.05
F7	198±1.1	4.13±0.733	2.8±0.251	0.63±0.376	98.42±0.682	38±0.68	69.80±0.205
F8	202±2.6	4.10±0.756	2.9±0.110	0.56±0.358	97.40±0.710	41±0.15	71.20±1.09
F9	200±1.6	4.12±0.758	2.7±0.108	0.59±0.421	98.60±0.612	43±1.10	73.02±1.37
F10	200±1.8	4.19±0.985	3.2±0.648	0.54±0.594	98.90±0.630	125±1.32	65.08±3.85

**All values are expressed as mean ± standard deviation, (n= 5)*

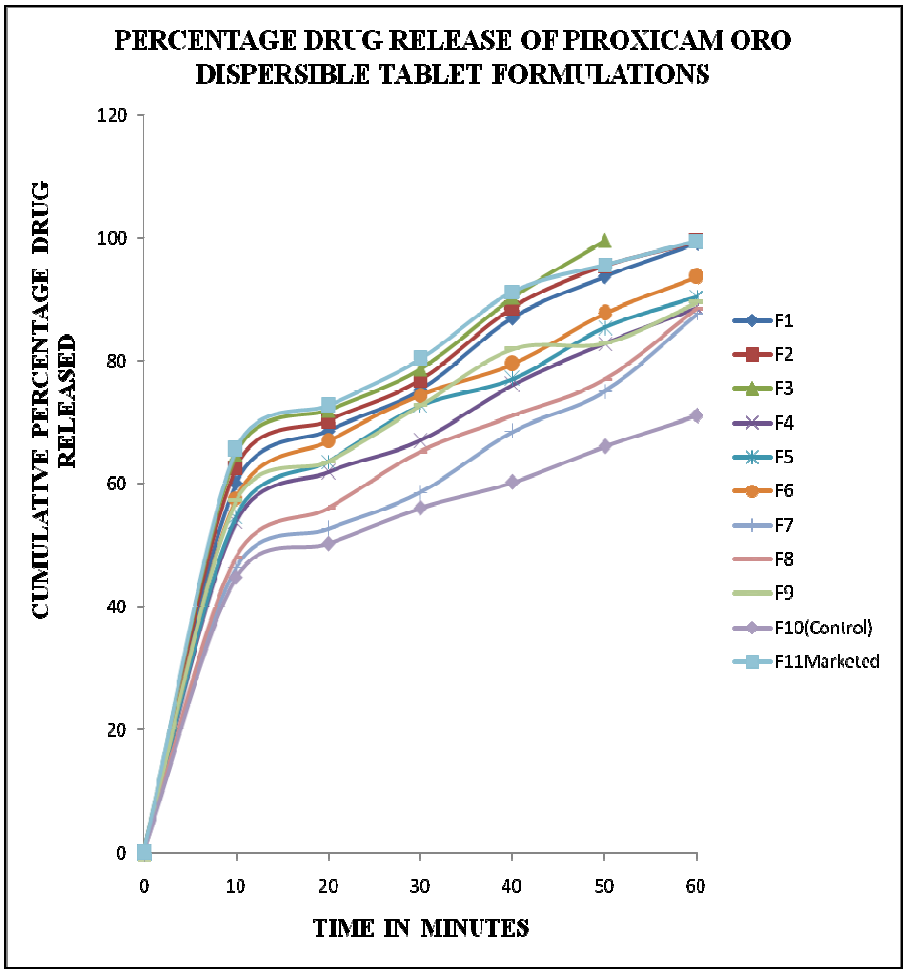

Fig-1-Comparative release profiles of Piroxicam formulations

Tablets from all the formulations were subjected for *in-vitro* release studies. The results are presented in (Fig-I). The percentage drug release from F1, F2 and F3 formulations prepared with CCS (3%, 4% and 5%w/w) was 99.22%, 99.36%, and 99.53% respectively in 60minutes.The percentage drug release from F4, F5 and F6 formulations prepared with SSG (3%, 4% and 5%w/w) was 88.70%, 90.37%, and 93.70% respectively and the percentage drug release from F7, F8 and F9 formulations prepared with CP (3%, 4% and 5%w/w) was 87.75%, 88.60%, and 89.50% respectively in 60 minutes. Among all nine formulations, tablet prepared with all three concentrations of CCS as superdisintegrant showed a rapid drug release. This may be due to easy swelling ability and more water penetration capacity of CCS when compared to other superdisintegrants. The percentage drug release of marketed sample of Piroxicam dispersible tablet was 99.42% in 60minutes and control formulation (F10) without superdisintegrant was 71.11% in 60minutes.(Fig-I).The delayed drug release of formulation F10 is due to longer disintegration time and lesser solubility in the dissolution medium. The kinetic studies revealed that the drug release from all the formulations followed first order release.

Further all formulations were subjected to stability studies for the period of 45 days at $4^0C\pm2^0C$, 27°C ±2°C and $45^0C\pm2^0C$ and were analyzed after specific time period of 15 days interval. No significant changes were observed in drug content, disintegration time and *invitro* drug release after 45 days.

CONCLUSION

The results of experimental studies of Piroxicam Orodispersible tablets proved that the Powder blend of Piroxicam showed good flow properties, tablet evaluation tests are within the acceptable limits, IR spectral analysis proved that there was no drug- excipients interaction, the kinetic studies revealed that all the formulations followed first order drug release and stability studies revealed that all the formulations were found to be stable after storing at $4^0C\pm2^0C$, 27°C ±2°C and $45^0C\pm2^0C$ for 45 days. The drawbacks of the conventional dosage forms of Piroxicam can be minimized by Piroxicam Orodispersible tablets formulated using three superdisintegrants Crospovidone, Croscarmellose sodium and sodium starch glycolate by direct compression method. The formulation F3 containing 5% Croscarmellose sodium was found to be better in terms of rapid disintegration and maximum percentage drug release when compared with all other formulations, marketed sample and control formulation (without superdisintegrant). Overall results indicated that Croscarmellose Sodium at a concentration of 5 %(F3) is better one which satisfied all the criteria for Orodispersible tablets of Piroxicam.

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ABBREVIATIONS

ODTs =Oro Dispersible Tablets.
SD = Standard Deviation
IP = Indian Pharmacopoeia
USP = United States Pharmacopoeia
RPM = Revolutions per Minute