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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF PIROXICAM FAST DISSOLVING TABLETS

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ABSTRACT
Piroxicam is an analgesic, antipyretic and anti-inflammatory effects drugs, used to reduce pain, swelling joint stiffness from osteoarthritis, rheumatoid arthritis and by inhibiting prostaglandin synthetase. In the research work, seven formulations (F1 to F7) were prepared direct compression method by using 3 superdisintegrants namely Crospovidone, Crosscarmellose sodium and Sodium starch glycolate in two ratio (1:0.5 and 1:1) and F7 (without superdisintegrant). All the formulations evaluated various post compression parameters thickness, weight variation, disintegration time, hardness, friability, wetting time, drug content water absorption ratio and in- vitro dissolution studies. The best formulation was studied anti-inflammatory activity in rats by using paw-edema method. Among all formulations (F1) which contains 1:0.5ratio of Crosscarmellose sodium, showed to be the optimized formulation as it give good wetting time (51.66 sec), fast disintegration time (29.16 sec), maximum drug release of 99% within 30 minutes and superior anti-inflammatory activity.

KEYWORDS: Anti-inflammatory, direct compression, fast-dissolving, Piroxicam, Superdisintegrants.

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INTRODUCTION
Piroxicam has prolonged half-life about 45 hrs, poorly soluble drug in water and it will appear in BCS class 2 and when dispense due to its low solubility and dissolution in biological fluids.[1] It is new drug delivery systems. These dosage forms in oral cavity dissolve or disintegrate within a few seconds with or without the need of water or chewing. The advantages of these tablets are easy manufacturing, accurate dose and easy hold by patients, no need of chewing and water for swallowing.[2] These dosage was explore for their potential in enhance the dissolution profile. These formulations, the small volume of saliva need to tablets disintegration and the medication then absorbed in sublingual mucosa to be swallowed in solution form. The aim of present work increasing the rate of Piroxicam dissolution and faster the absorption rate by adding capability superdisintegrants likes Crosscarmellose sodium, Crospovidone and Sodium starch glycolate in different ratio. Superdisintegrants provide faster disintegration due to shared effect of bulge and water absorption in the formulation. The wetted increases in surface of the carrier due to the swelling of superdisintegrants, which aid the dispersibility and wettability of the system, so improve the disintegration and dissolution.[3] To mask the Piroxicam taste by adding saccharin sodium as a sweetening agent.

MATERIALS AND METHODS
Materials: Piroxicam was procured from Pharmafabrikon Madurai, India. Microcrystalline cellulose and Magnesium stearate from S.D fine Chem Pvt.Ltd Biosar. Sodium starch glycolate, Crospovidone and Cross Carmellose Sodium and Crospovidone were from Yarrow Chem products Mumbai. Saccharin sodium di hydrate was from Loba chemie Pvt.ltd Mumbai. Mannitol was procured from Reachem Laboratory chemicals private limited Chennai and Talc was procured from Bharat pharmaceuticals Chennai.

Methods
Pre-formulation studies: Preformulation can be specify as the study of chemical and physical properties of drug substance only and (or) when combined with excipients, it is the first stage of the research and formation of dosage form.[4]
Organoleptic properties: The color, odor and taste of the Piroxicam were evaluated.
Solubility test: Piroxicam was dissolved in water, methanol and ethanol to determine by using Sonicator at room temperature.[5]
Drug–excipients compatibility studies: Compatibility studies were performed by blend of excipients with drug and stored at 40ºC/ 75% RH for one month. The samples were evaluated every 15 days for any changes.

Pre-compression parameters of powder blend
Angle of repose [6] It was determined by fixed funnel method by using the equation:
θ = tan-1 (h/r)
Where; h = Height of the pile, r = Radius of the pile, θ = Angle of repose.

Bulk density: It was determined as the ratio of total mass of powder and its bulk volume without any tapping and is expressed as g/cm^3[7], by using the following formula:
ρb = M/ Vb

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Where; ρb = Bulk density, M = Weight of the sample in g, Vb = volume of the powder blend in cm^3

Tapped density: Tapped density was determined by using the following formula:

ρt = M/ Vt

Where, ρt = Tapped density, M = Weight of the sample in g, Vt = Tapped volume of the powder blend in cm^3

Compressibility index: The compressibility index was calculated from the bulk and tapped density using the following formula:

Compressibility index (%) = [TD – BD/TD] x 100

Where, TD = Tapped density, BD = Bulk density

Hausner's ratio: Hausner's ratio was determined from the bulk and tapped density by using the equation:

Hausner's ratio = Tapped density / Bulk density

FORMULATION OF FAST DISSOLVING TABLETS

The composition Piroxicam fast dissolving tablets shown in Table 1.

Table 1: Composition of Piroxicam Fast Dissolving Tablets

INGREDIENTS	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)
Piroxicam	20	20	20	20	20	20	20
Cross carmellose sodium	10	20	-	-	-	-	-
Sodium starch glycolate	-	-	10	20	-	-	-
Crospovidone	-	-	-	-	10	20	-
Microcrystalline cellulose	130	120	130	120	130	120	140
Mannitol	75	75	75	75	75	75	75
Saccharin sodium	10	10	10	10	10	10	10
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Weight of each tablet	**250**	**250**	**250**	**250**	**250**	**250**	**250**

F1 = Croscarmellose sodium (1:0.5 ratio), F2 = Croscarmellose sodium (1:1 ratio), F3 = Sodium starch glycolate (1:0.5 ratio), F4 = Sodium starch glycolate (1:1 ratio), F5 = Crospovidone (1:0.5 ratio), F6 = Crospovidone (1:1 ratio) and F7 = without superdisintegrant.

Weighed quantities of Piroxicam along with appropriate ratio of Superdisintegrant, mannitol, microcrystalline cellulose and saccharin sodium were weighed and sieved no 40 and mixed well. Then magnesium stearate and talc was added to the above blend and mixed well for 2 minutes. Finally, the powder blend was compressed weighing 250 mg tablets using 7.93 mm round concave faced punches in 10 station rotary tablet punching machine.

Post compression parameters

General appearance: The tablets have no cracks, depressions, pinholes etc. The tablets should have the smooth surface.[8] The dimensions of the tablets are thickness and diameter. Thickness and diameter of tablets was measured using Vernier caliper measured in mm.

Hardness test: The hardness of tablets was determined by Monsanto hardness tester. The pressure is slowly increased to break the tablet. The value was expressed in Kg/cm^2.[9]

Weight variation test[10]: Each formulation selected twenty tablets in randomized and weighed individually. The percentage deviation was calculated by this formula:

$$\text{Percentage deviation} = \frac{\text{Individual weight - Average weight}}{\text{Average weight}} \times 100$$

Friability[11]: The weight of 10 tablets and placed in Roche friabilator. The percentage friability was calculated by the formula:

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

Where, W1 - Weight of ten tablets before test, W2 - Weight of ten tablets after test

Estimation of drug content[12]: Each formulation ten tablets were powdered and weighed 100mg and dissolved pH 6.8 buffer in 100 ml standard flasks, suitable dilution was prepared and analysed at 333nm using UV spectrophotometer using pH 6.8 as blank.

Drug content = Absorbance of sample/Absorbance of standard x 100

Wetting time and water absorption ratio[13,14]: 10 cm diameter five tissue paper placed in petri dish with 10 ml buffer pH 6.8 was poured to the tissue paper, eosin solution few drops was added into petri dish. A tablet was placed on the tissue paper the time noted the solution reach into upper surface of the tablet. The weight of the tablet before in the petri dish was noted (Wb). Fully wetted tablet from the petri dish was taken and reweighed (Wa). The water absorption ratio (R) can be determined by following formula:

$$\text{Water absorption ratio (R)} = \frac{Wa - Wb}{Wa} \times 100$$

Where, Wb - Weight of tablet before wetting, Wa - Weight of tablet after wetting.

Disintegration test[15]: It was carried out at 37ºC ± 2ºC in 900 ml of distilled water as disintegration medium. The test using six tablets in each of the six tubes contain one tablet and one disk . The time in seconds for complete disintegration of the tablets was noted.

***In vitro* dispersion time[16]:** It was measured by release of tablet in a 50 ml beaker in 10 ml of water and noted the time for the complete dispersion of tablet was determined.

Fineness of dispersion[17]: The fineness of dispersion test was done by using two tablets in a 200 ml beaker with 100ml of water, stirred gently to get a smooth dispersion and passes through a 710 mm (sieve no 22). No of particles should remain on mesh.

***In vitro* dissolution study [18,19]:** In this study by using Disso-2000 dissolution apparatus (paddle type). 900ml buffer pH 6.8 is dissolution medium and the temperature at 37ºC ± 0.5ºC at 50 rpm. Samples measuring 1ml was withdrawn at every 5 minutes intervals, replaced dissolution medium in same quantity to each jar. Collected samples was diluted to 10 ml

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pH 6.8 and analysed at 333nm using pH 6.8 as blank in UV spectrophotometer.

FT-IR studies[20]: FT-IR study in optimized formulation (F1) to determine the interactions between the drug and excipients. A drug and excipients (1:1) was prepared with potassium bromide and compressed to form transparent pellet. It was scanned between 4000-400cm-1 in a shimadzu FT-IR spectrophotometer.

Stability studies[21]: Stability study in optimized formulation (F1) stored at 25±2°C/60C±5%RH and 40±2°C/75%±5%RH for 45 days. The formulations were stored 45 days and their physical appearance, average weight, thickness, hardness, friability, disintegration test, assay and in vitro dissolution were evaluated at specified intervals of time (every 15 days).

Anti-inflammatory activity study: The anti-inflammatory activity was studied in optimized formulation (F1). Adult male albino rats, weighing (200 ± 20 gm), the study was approval by the Institutional Animal Ethical Committee (IAEC). The rats were housed in groups and kept fastened for 24 hours allowed free access to water. The rats divided into 3 groups each group contain 6 animals. First group (controlled group) animals were given saline (0.9% NaCl). The second group (standard group) was administered marketed Piroxicam dispersible tablets according to the dose of 1- 5 mg/kg Third group (test group) animals were given optimized formulation (F1). After 30 minutes of oral administration of optimized formulation and marketed sample, injected 0.1 ml carrageenan (1% w/v) in right hand paw of rats.[22] The thickness of the injected paw was measured instantly carrageenan injection and after 0, 1, 2, 3 and 4 hours using a micrometer.

The % inhibition of edema was calculated for each group using the following equation:

% inhibition in edema thickness = {1- (Tt/Tc)} x 100

Where, Tt = mean increase in thickness of carrageenan paw edema of treated groups, Tc = mean increase in thickness of carrageenan paw edema of control groups.

RESULTS AND DISCUSSION

Preformulation studies

Tests	Specifications	Observation	API	Solubility
Color	white to light tan	Off white to light tan	Piroxicam	Insoluble in water
				Sparingly soluble in ethanol
				Soluble in methanol
Odor	Odorless	Odorless		
Taste	bitter	bitter		

Pre-compression parameters

Table 2: Precompression Parameters

Formulation code	Angle of Repose (θ)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility Index (%)	Hausner's Ratio
F1	290.13'±0.02	0.591±0.002	0.692±0.001	14.492±0.005	1.16±0.021
F2	300.26'±0.34	0.553±0.002	0.644±0.001	14.062±0.002	1.26±0.023
F3	270.75'±0.02	0.310±0.001	0.360±0.001	13.891±0.002	1.16±0.021
F4	280.15'±0.01	0.552±0.003	0.648±0.002	14.062±0.002	1.18±0.021
F5	290.05'±0.02	0.573±0.001	0.660±0.002	13.639±0.140	1.15±0.011
F6	270.94'±0.03	0.594±0.002	0.685±0.001	13.23±0.140	1.15±0.011
F7	280.97'±0.01	0.640±0.001	0.745±0.003	14.09±0.002	1.16±0.021

Mean ±SD, n=3

The power blend of all formulations showed good flow properties.

Post compression parameters

The post compression parameters results are in table 3.

Table 3: Post Compression parameters

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)
F1	4.599 ± 0.009	3.95 ± 0.497	249.75 ± 5.495	0.409±0.001
F2	4.601 ± 0.008	3.45 ± 0.368	249.75 ± 5.495	0.596±0.002
F3	4.562 ± 0.042	3.75 ± 0.540	247.00 ± 5.231	0414±0.001
F4	4.611 ± 0.008	4.05 ± 0.368	248.75 ± 5.590	0.229±0.003
F5	4.435 ± 0.017	4.05 ± 0.550	249.25 ± 4.375	0.512±0.002
F6	4.195 ± 0.005	3.85 ± 0.579	248.25 ± 5.068	0.415±0.002
F7	4.38 ± 0.027	3.35 ± 0.320	249.25 ± 5.539	0.231±0.003

Mean ±SD, n=3

Table 4: Evaluation Parameter of Fast Dissolving Tablets

Formulation code	Disintegration time (sec)	Drug content (%)	Wetting time (sec)	Water absorption ratio	*In-Vitro* dispersion time (sec)	Fineness of dispersion
F1	29.16 ± 0.89	101.16±0.12	51.66 ± 2.35	67.6 ±0.33	49.10 ± 0.14	Passed
F2	30.00 ± 0.57	95.61±0.13	61.66 ± 4.71	71.3 ±0.65	60 .10 ± 0.12	Passed
F3	39.50 ± 0.50	95.02±0.15	61.66 ± 2.35	104.6±0.94	69. 50 ± 0.13	Passed
F4	54.16 ± 3.40	90.64±0.33	53.33 ± 2.35	113.0±1.15	104.16± 0.15	Passed
F5	30.33 ± 0.74	97.36±0.37	68.33 ± 2.35	98.10±0.81	60.33 ± 0.74	Passed
F6	57.16 ± 2.26	92.98±0.17	63.66 ± 5.18	83.16±0.57	107.16± 0.33	Passed
F7	184.16 ± 1.86	97.95±0.18	96.66 ± 2.35	118± 0.047	204.16± 1.86	Passed

Mean± SD, n=3

From the above results, it was concluded that formulation F1 showed better tableting properties of all other formulations and was selected as an optimized formulation.

In vitro dissolution study

The drug release profile data of all the formulations data were showed in table 5 and figure 1.

Table 5: *In Vitro* Drug Release profile of Piroxicam Fast Dissolving Tablets

S.No	Time in (minutes)	Percentage drug release (%) Formulation code F1	F2	F3	F4	F5	F6	F7
1	5	13.50±0.01	45.00±0.11	36.00±0.01	36.00±0.77	27.00±0.22	31.95±0.01	9.00±0.88
2	10	36.00±0.21	67.50±0.81	45.00±0.41	40.50±0.30	31.95±0.01	36.00±0.33	36.00±0.98
3	15	67.50±0.41	72.00±0.71	54.00±0.71	45.00±0.56	36.00±0.78	76.50±0.45	40.50±0.55
4	20	81.00±0.21	76.50±0.91	63.00±0.81	72.00±0.78	45.00±0.45	81.45±0.56	49.50±0.54
5	25	85.50±0.88	85.50±0.51	67.50±0.22	76.50±0.97	49.50±0.44	86.40±0.67	58.50±0.02
6	30	99.00±0.91	94.50±0.71	76.50±0.44	81.00±0.18	58.50±0.91	90.00±0.99	63.00±0.07

Mean± SD, n=3

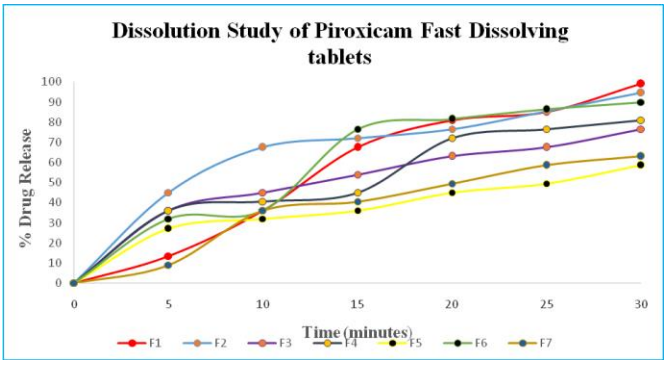

Figure 1: *In Vitro* Drug Release Profiles of Piroxicam Fast Dissolving Tablets

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In all the seven formulations, trial F1 containing 1:0.5 ratio of Croscarmellose sodium as superdisintegrant showed rapid drug release (99%) at the end of 30 min.

The comparative *in vitro* drug release data of optimized formulation and marketed tablet were shown in table 6 and figure 2.

Table 6: Drug Release Data of Optimized Formulation (F1) and Marketed tablet

S.No	Time in (minutes)	Percentage drug release (%)	
		Optimized formulation F1	Marketed tablet
1	5	13.50	20.29
2	10	36.00	32.16
3	15	67.50	54.57
4	20	81.00	70.59
5	25	85.50	82.52
6	30	99.00	85.22

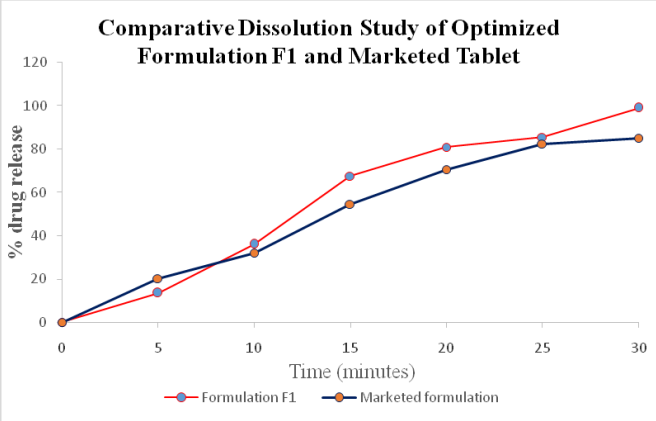


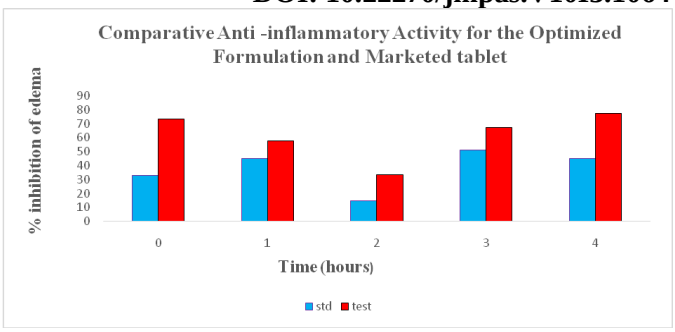
Figure 2: Drug Release profile of Optimized Formulation (F1) and Marketed Tablet

The percentage drug release of optimized formulation (F1) was nearby equal to marketed tablet at the end of 30 minutes study.

Stability study for optimized formulation: Stability studies there was no significant changes found in physical appearance, hardness, disintegration test, invitro dispersion test, dissolution and drug content during the period of 45 days after stored at 25 ±2°C/60%±5% RH. The study formulation F1 was revealed that stable even after stored at 40 ±2°C/60% ±5% for 45 days.

Anti-inflammatory activity: The results of the carrageenan-induced rat paw edema test are shown in Table 7 and Figure 4.

S.No	Time (Hours)	Percentage Inhibition of EDEMA		
		Control (%)	Standard (%)	Test (%)
1	0	0.0	33.07	73.23
2	1	0.0	45.01	57.51
3	2	0.0	14.67	33.23
4	3	0.0	51.22	67.49
5	4	0.0	45.08	77.49



Anti-inflammatory Profile of Optimized Formulation and Marketed Tablet

The percentage inhibition of marketed tablet and optimized formulation (F1) was found to be 51.22% at 3 hours and 77.49 % at 4 hours. The optimized formulation showed in acute anti-inflammatory activity.

FT-IR studies for optimized formulation: The FT-IR spectrum Piroxicam thus conforming that no interaction of drug occurred with the components of the formulation shown in figure 3.

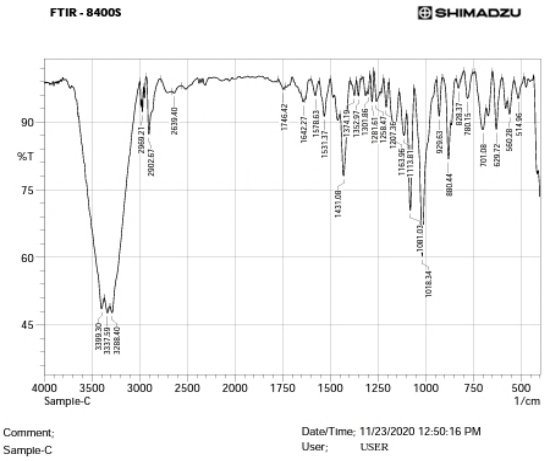


Figure 3: FT-IR Spectrum of F1 optimized formulation

CONCLUSION

From this study, the overall results disclose the formulation F1 containing crosscarmelose as superdisintegrant found to be better one which satisfied all the criteria for Piroxicam fast dissolving tablets and also showed better drug release. The work concludes that Piroxicam fast dissolving tablets could be successfully formulated by direct compression method using crosscarmelose as superdisintegrant. Also, there was a compelling observed in the anti-inflammatory activity between the optimized formulations (F1) and the standard marketed tablet.

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