ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 5, Issue, 02, pp. 3440-3446, February, 2015

International Journal of
DEVELOPMENT RESEARCH

Full Length Research Article

FORMULATION DEVELOPMENT AND CHARACTERIZATION OF PIROXICAM FAST DISSOLVING TABLETS APPROVED FOR THE TREATMENT OF ARTHRITIS

***[1]Sachan Anupam, K., [1]Tripathi, K., [1]Visnoi, G., [1]Rasheed, A., [2]Sharma, R. and [2]Gangwar, S. S.**

[1]Dayanand Dinanath College, Institute of Pharmacy, Ramaipur, Kanpur-209214, India
[2]Department of Pharmacy, G.S.V.M, Medical College, Kanpur-208012, India

ARTICLE INFO

Article History:
Received 06th November, 2014
Received in revised form
14th December, 2014
Accepted 14th January, 2015
Published online 27th February, 2015

Key words:
Anti inflammatory,
Direct compression,
Orodispersible,
Piroxicam,
Superdisintegrant.

ABSTRACT

Piroxicam has been the most widely used potent non steroidal anti inflammatory drug used in treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and acute gout disease for many decades. Since no systematic studies on design and development of Piroxicam FDT are available in literature, we propose to develop a suitable formulation to characterize fast dissolving tablet of Piroxicam. The aim of present study was to formulate various formulations of immediate release tablets of Piroxicam using different excipients by direct compression. The dispersible drug delivery system was developed using Croscarmellose Sodium, Sodium Starch Glycolate and Crospovidine as disintegrating agents. In the present work, formulations of Orodispersible tablets of Piroxicam were prepared using three superdisintegrants namely Crospovidone, Croscarmellose Sodium and Sodium Starch Glycolate in different concentrations (3%, 4%, 5% and 6%). The final blend and tablets of Piroxicam were evaluated for powder flow properties, bulk density, tapped density, compressibility index and hausner's ratio, weight variation, thickness, hardness, friability, wetting time, water absorption ratio, drug content, disintegration time and *in-vitro* release study. Formulation F8 showed the lowest disintegration time and more water absorption ratio. *In-vitro* dissolution studies revealed that formulation F8 showed 96.11% percent drug release at the end of 30 minutes. Accelerated stability studies conducted for three month at 40°C and 75% RH and were found within specification.

INTRODUCTION

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desired therapeutic concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment (Khanam *et al.,* 2013). This is possible through administration of conventional dosage form in a particular dose and at a particular frequency. Drugs are more frequently taken by oral administration (Akihiko *et al.,* 1996). Approximately one-third of the population, primarily the geriatric and pediatric populations, has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. A new tablet dosage form, the fast dissolving tablet has been developed which offers the combined advantages of ease of dosing and convenience of dosing in the absence of water or fluid (Shajaei 1998). These tablets are designed to dissolve or disintegrate rapidly in the saliva generally less than 60 seconds (Chiou *et al.,* 1969). Due to the constraints of the current FDDT technologies as highlighted above, there is an unmet need for improved manufacturing processes for fast dissolving tablets that are mechanically strong, allowing ease of handling and packaging with production costs similar to that of conventional tablets (Divate *et al*., 2011). Salient Features of Fast Dissolving Drug Delivery System are ease of administration to patients who refuse to swallow a tablet, such as pediatric, geriatric and psychiatric patients, No need of water to swallow the dosage from which is highly convenient feature for patients who are traveling and do not have immediate access to water, good mouth feel, rapid absorption and dissolution of drug which may produce rapid onset of action, an increased bioavailability particularly in cases of insoluble and hydrophobic drugs due to rapid disintegration and dissolution of these tablets (Chowdary and Hymavathy, 2000), stability for longer duration of time since the drug remains in solid dosage form till it is consumed (Bhowmik

Corresponding author: Sachan Anupam, K.,
Dayanand Dinanath College, Institute of Pharmacy, Ramaipur, Kanpur-209214, India

et al., 2009). In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. Tablet disintegration time can be optimized by concentrating the disintegrants. Below critical concentration tablet disintegration time is inversely proportional to disintegrants concentration. Above the critical concentration level, however, disintegration time remains approximately constant or even increases (Pouton, 2006).

Microcrystalline cellulose, cross linked carboxymethyl cellulose sodium, cross linked polyvinyl pyrrolidone and partially substituted hydroxypropyl cellulose, though water insoluble, absorbs water and swells due to capillary action and are considered as effective disintegrants in the preparation of fast dissolving tablets (Rai *et al*., 2012). Hence the aim of present was to formulate Piroxicam FDT for increasing the rate of dissolution, thus providing faster rate of absorption by adding potential superdisintegrants like Crospovidone, Croscarmellose sodium and Sodium starch glycolate in different concentrations. The overall objective of investigation has a three tier approach as below.

- Procurement, characterization and subsequent formulation of Piroxicam into FDT for fast bioavailability.
- Fabrication and optimization of compressed tablets.
- Pharmacotechnical characterization and *in vitro* evaluation of formulated tablet dosage form using conventional and advanced analytical tools.

MATERIALS AND METHODS

Piroxicam was obtained from Ranbaxy Pharma. Mannitol, Micro crystalline cellulose and Aspartame were procured from S.D Fine Chemicals Limited, Mumbai.

Analytical method development

Determination of λmax

The λmax of Piroxicam was determined before developing the standard curves. In this study 100 µg/mL solutions of Piroxicam were prepared in phosphate buffer pH 6.8. The resultant solution is scanned for maximum absorption from 200 to 400 nm wavelength range (Fathy *et al.,* 2011).

Calibration curve of Piroxicam

Calibration curve for Piroxicam was prepared in phosphate buffer of pH 6.8 at the obtained λ max. At first 1000 µg/ml solution is prepared by dissolving 100mg of pure drug in 100 ml of 6.8 pH phosphate buffer solutions and from this solution 5, 10, 15, 20, 25, 30 µg/ml solutions were prepared by suitable dilutions (Miranda *et al.,* 2012).

Preparation of Piroxicam by direct compression method

Piroxicam fast dissolving tablets were prepared by direct compression method according to the formula given in Table 1. In the present work, 13 formulations of Orodispersible tablets of Piroxicam (F1 to F12) were prepared using three different superdisintegrants namely Crospovidone, Croscarmellose Sodium and Sodium Starch Glycolate with four concentrations (3% ,4% ,5% and 6%) and a control F13 (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. All the ingredients were passed through mesh no. 60 separately and collected.

Table 1. Composition of formulation and their assigned codes

S.No.	Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
1	Piroxicam	20	20	20	20	20	20	20	20	20	20	20	20	20
2	Croscarmellose sodium	3	4	5	6	-	-	-	-					
3	crospovidone	-	-	-	-	3	4	5	6	-	-	-	-	-
4	Sodium starch glycolate	-	-	-	-	-	-	-	-	3	4	5	6	-
5	Micro crystalline cellulose	115	114	113	112	115	114	113	112	115	114	113	112	120
6	mannitol	53	53	53	53	53	53	53	53	53	53	53	53	53
7	Aspartame	7	7	7	7	7	7	7	7	7	7	7	7	7
8	Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	2

Table 2. The solubility of fast dissolving tablet

S.No.	Superdisintegrant	Superdisintegrant Concentration (%)	Amount of Drugs (mg)	Time for Solubility in water (Sec.)
1.	Crosscarmellose Sodium	3	20	36
		4	20	35
		5	20	32
		6	20	30
2.	Crospovidone	3	20	28
		4	20	27
		5	20	25
		6	20	23
3.	Sodium Starch Glycolate	3	20	32
		4	20	30
		5	20	28
		6	20	28

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 were added and mixed well. The mixed blend of drug and excipients were compressed using "B" Tooling Rotatory Tablet Punching Machine to produce convex faced tablets, weighing 200 mg each (Table 1). Before tablet preparation, the mixture blend of all the formulations was subjected to compatibility studies.

Optimization of direct compression method

The prepared fast dissolving tablets of direct compression, optimized on the basis of solubility of drug in water. After solubility analysis, the solubility of direct compression having drug to superdisintegrant 6% was found to be higher than other formulations as it get solubilised in water in minimum time of 23 sec. which is best when compared with time shown by any other formulation Since the formulation of direct compression having 6% showed best result in solubility analysis, it was selected for further preparation of fast dissolving tablets (Table 2).

Characterization of Powder blend

X-Ray powder diffractometry

Sample of direct compression was being taken on a slide and placed fixed with glycerin and then placed in the Diffractometer for obtaining the diffraction pattern. The diffraction spectrum of pure Piroxicam showed that the drug was of crystalline in nature as demonstrated by numerous, distinct peaks at 2θ of 5.6°, 10.5°, 12.9°, 18.8°, 20.6°.

FTIR Spectroscopy

IR spectra of pure drug, Superdisintegrants and physical mixtures were obtained using FT-IR-Perkin Elmer (UK). Sample was spread over cuvette and the IR spectrum was obtained. Scanning range was 400 to 4000 $cm^{-1}$with a resolution of per cm^{-1}. The IR spectra obtained were studied for possible drug excipients interaction.

Preparation of fast dissolving tablets

Optimized formulations of Piroxicam and final fast drug dissolving tablets were prepared according to the formula (Table 1). Powder was first introduced into the die cavity and final compression was done.

Evaluation of powder blend

Micromeritic Properties

Determination of Bulk density and Tapped density, **True density, Carr's index and Hausner's ratio**

Approximately 10g of Solid dispersion of Piroxicam were separately weighed and passed through a sieve. The powders were sieved in accordance with FDA guidelines that state that the powders must be sieved with apertures to break up agglomerates which may have formed during storage. This must be done gently to avoid changing the nature of the powder. Drug powder was then transferred into a separate 100ml graduated measuring cylinder where the bulk density was determined by measuring the volume that the powder occupied (V_b). The tapped density of each powder was determined with the aid of a Digital tapped density tester. Following the agitation, the volume of the tapped powder was read (V_{tp}). The Carr's index, porosity and Hausner's ratio were calculated using equations.

$$bulk\ density = \frac{mass}{Bulk\ volume} \quad \text{……Eq.1}$$

$$Tapped\ density = \frac{mass}{tapped\ volume} \quad \text{……..Eq.2}$$

$$Carrs\ Index\ (CI) = \frac{tapped\ density - bulk\ density}{bulk\ density} \times 100 \quad \text{…Eq.3}$$

$$Hausner's\ ratio\ (HR) = \frac{tapped\ density}{bulk\ density} \quad \text{……Eq.4}$$

Angle of Repose

The angle of repose was measured using a funnel method. Approximately 10g of powder was weighed and placed in a funnel. The height of the funnel was adjusted to a point where the tip of the funnel was just above the apex of the heap of powder. The powder was allowed to flow freely through the funnel onto a glass plate surface. The angle of repose was calculated using following equation.

$$tan\theta = \frac{h}{r} \quad \text{……..Eq.5}$$

Where,

h = height of the pile of powder
r = radius of the heap of powder
θ= angle of repose

Evaluation of tablets

Weight variation

To study weight variation individual weights (W_i) of 20 tablets from each formulation were noted using electronic balance (Leon Lachman et al., 1991). Their average weight (W_a) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

% weight variation = (Wa – Wi) x 100/ Wa …… Eq.6

Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using vernier calipers.

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

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, dedusted and reweighed. The friability was calculated as the percentage weight loss.

% Friability = (W1 – W2) x 100/W1 …… Eq.7

Where,

W1 = Initial weight of the 20 tablets.
W2 = Final weight of the 20 tablets after testing.

Drug content

Percentage drug content for the prepared formulations was estimated at 354 nm by UV-visible spectrophotometer using ph 6.8 buffer as the blank. For the spectrophotometric analysis performed in triplicate for all the samples, it was observed that percentage drug content of all the formulations ranged from 95.28% to 98.96%.

***In-vitro* studies**

The prepared fast dissolving tablets were placed in dissolution apparatus.

The assembly was maintained at a temperature of 37^0C in phosphate buffer pH 6.8. Samples were withdrawn at definite time intervals and replaced by equal volume of fresh medium. The absorbance of samples was measured from UV spectrophotometer and *in vitro* release profile was calculated.

Stability of fast dissolving tablets

The fast dissolving tablets are packed in suitable packaging and stored under the condition for a period as prescribed by ICH guidelines (at 40 ± 0.5 °C and RH 75% ± 5%) for 90 days and at every 30 days interval, tablets were evaluated for physical evaluation parameter.

RESULTS AND DISCUSSION

Analytical Method development

Determination of λmax: The λmax of Piroxicam was found to be 354 nm.

XRD for the nature of the direct compression

The spectrum of fast dissolving tablets, prepared with crospovidone showed that some peaks of pure Piroxicam were absent and intensity of peaks was reduced (Fig. 1, 2). The result indicates that the drug in direct compression is amorphous as compared to the pure drug. Hence, increased dissolution of the drug was observed.

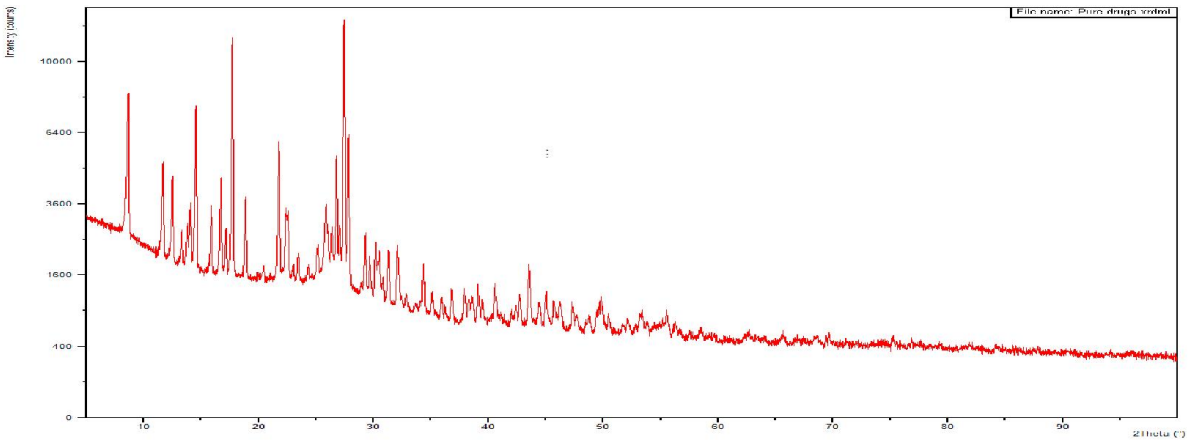

Figure 1. XRD of Drug Piroxicam

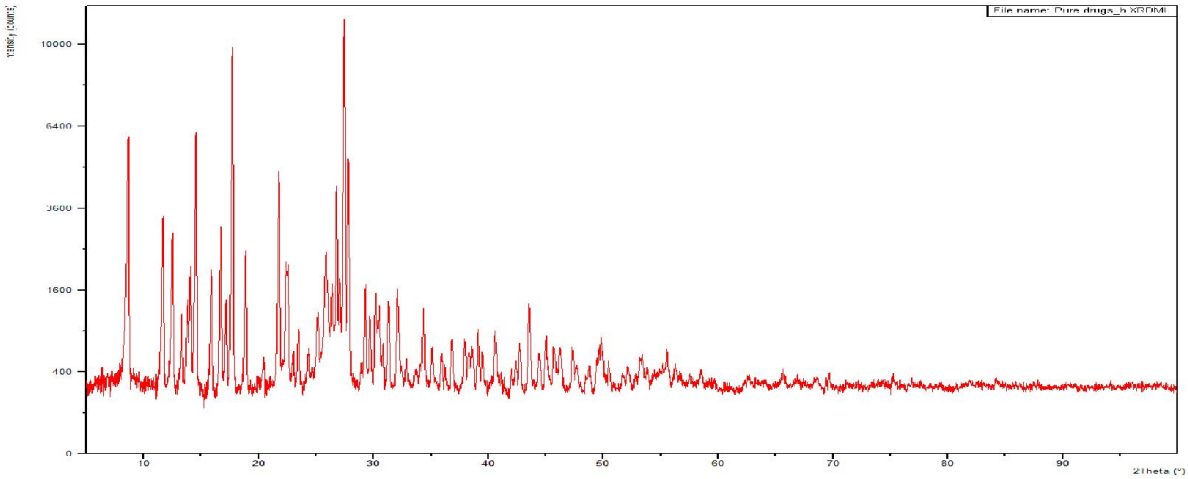

Figure 2. XRD of optimized formula

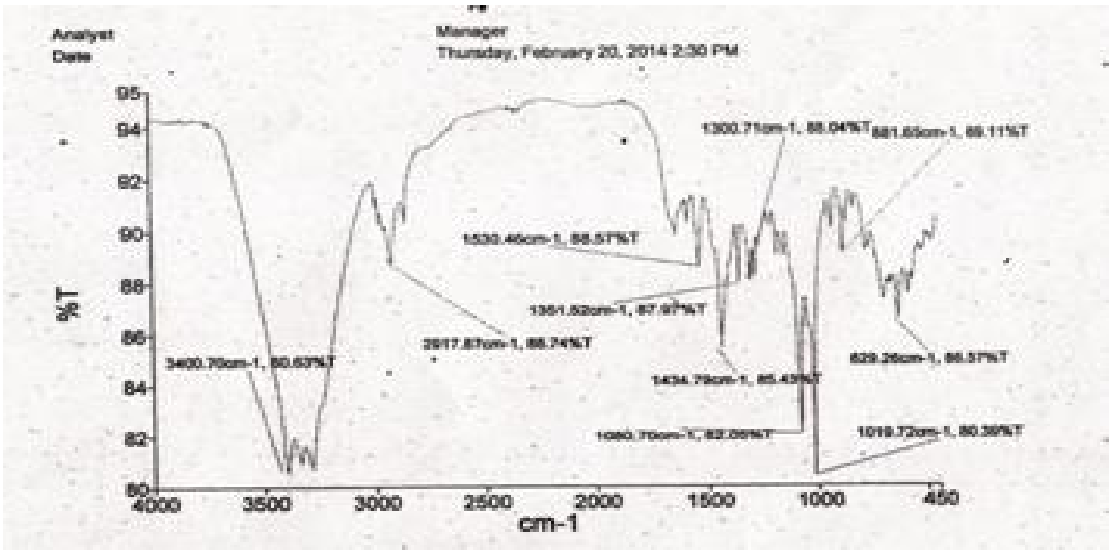

Figure 3. FT-IR spectra of Pircxicam fast release tablets (F8)

Table 3. Pre-compression characterization of fast dissolving tablets

S. no.	Formulation	Bulk Density	Tapped density	%Carr's index	Hausner's ratio	Angle of repose
1	F5	0.330±0.015	0.400±0.017	17.73±0.20	1.21±0.015	29.49 ±0.42
2	F6	0.329±0.012	0.408±0.015	19.32±0.03	1.22±0.015	29.90±0.71
3	F7	0.331±0.010	0.402±0.014	17.66±0.025	1.23±0.02	28.98±0.083
4	F8	0.330±0.011	0.401±0.017	17.72±0.025	1.21±0.020	29.09±0.11

Table 4. Post-compression characterization of fast dissolving tablets

S. No.	Formulation Code	Weight Variation	Thickness (mm)	Hardness (kg/cm^2)	Friability	Disintegration Time (Sec)	Drug content
1	F5	Pass	3.20±0.015	4.67±0.430	0.24±0.020	28 sec	96.28±1.01
2	F6	Pass	3.18±0.020	4.41±0.152	0.24±0.001	27 sec	98.16±2.22
3	F7	Pass	3.18±0.025	4.61±0.435	0.24±0.020	25 sec	98.96±2.44
4	F8	Pass	3.20±0.015	4.60±0.435	0.29±0.055	23 sec	98.15±3.25

Characterization of fast dissolving tablets by FTIR

Infrared (IR) spectroscopy was performed using FTIR Spectrophotometer (Shimadzu) the spectrum was recorded in the wavelength region of 4000 to 600 cm^{-1}. Pellets for the spectra were prepared using KBr hydraulic press, by dispersing a sample of drug in KBr and compressed into discs. The pellet was then placed in the FTIR and the spectrum was obtained (Fig. 3). The interpretation of spectra is shown in Table 6.

Micromeritic properties

The true density value of a powder provides useful information that can be applied to the characterization of the mechanical properties of powders on which properties of a tablet such as hardness and tensile strength are reliant. Due to the fact that powders flow under the influence of gravity, dense particles are generally less cohesive than low density particles of similar size and shape. Determination of the true density of the API and selected solid dispersions is a vital part of preformulation studies with regard to FDTs as these data are used to determine the porosity of a powder. The bulk and tapped densities calculated along with the true densities determined in these studies were used to calculate Carr's Index, Hausner's ratio and porosity of Piroxicam. It is generally thought that granules that exhibit a greater degree of porosity will dissolve faster than denser granules as water is known to pass rapidly through porous substances. F8 formulation showed excellent flow and flow of all other formulation was good this shows that particles were decreases their crystalline (Table 3).

Preparation and Evaluation of Fast dissolving tablets

Fast dissolving tablets of the optimized super disintegrant ratio were prepared according to the formula given in Table 1 by direct compression technique. Four different formulations were prepared with varying concentrations of super disintegrant. The compressed tablets were evaluated for different parameters like thickness, friability, hardness, wetting time, water absorption ratio and disintegration time. The details of findings are summarized in Table 4. From the results it has been found that formulation F5 and F8 has thickness 3.20±0.015mm. Maximum hardness is obtained in case of F5 and least in case of F6 i.e. 4.67±0.430 and 4.41±0.152kg/cm^2 respectively. Similarly disintegration time also varies from 23 to 28 sec. for formulations F8 and F5 respectively (Table 4).

In-vitro release studies

The prepared fast dissolving tablets were placed in dissolution apparatus. The assembly was maintained at a temperature of 37^{0}C in phosphate buffer, pH 6.8.

Table 5. Dissolution profile of fast dissolving tablets of optimized formulation

Time (min)	Cumulative % drug release data for FDT (Mean ± SD, n=3)			
	F5	F6	F7	F8
0	0±0.00	0±0.00	0±0.00	0±0.00
1	1.11±0.15	1.9±0.15	1.3±0.19	2.2±0.24
2	2.2±0.13	5.5±0.51	2.22±0.21	5.5±0.39
3	3.17±0.21	15.19±0.32	4.15±0.21	13.55±0.41
4	11.19±0.15	24.14±0.31	12.17±0.21	28.12±0.41
5	21.11±0.22	43.13±0.29	25.22±0.23	32.9±0.49
7	41.37±0.21	65.21±0.37	45.1±0.25	51.3±0.49
10	60.29±.31	70.11±0.45	68.12±0.26	66.9±0.56
15	65.11±0.33	74.21±0.39	75.1±0.85	81.22±0.79
20	71.17±0.33	81.9±0.69	86.11±1.13	89.11±1.31
25	77.73±0.37	85.23±0.79	89.12±1.14	93.23±1.57
30	87.40±1.39	90.21±1.01	93.60±1.89	96.11±1.75

Table 6. Interpretation of IR spectra of drug

S.no.	Functional Group	Range	Peak value	Vibration	Intensity
1	-OH	3600-3200	3338.64	-OH stretch	High
	-C=O	1750-1625	1630.04	-C=O stretch	High
2	$-C_6H_5$	3000-3100	2914.56	-CH stretch aromatic	Weak
3	$-C_6H_5$ substituted	700-800	773.18	Meta Substitution	Weak
4	-NH	3300-3500	3518.12	-NH stretch	Medium
5	Sec. amine	1550-1450	1435.36	-NH bend	Medium
7	Asymmetric –S=(O)2	1350-1430	1299.99	-S=(O)2 stretch	Medium
8	-C=C	1620-1680	1577.27	-C=C Stretch	Weak
9	-CH	1350-1480	1351.17	-CH Stretch	Weak

Table 7. Stability analysis during accelerated conditions

Month	40 ± 2 ^{0}C, 75 ± 5% RH (formulation F8)				
	Appearance	Drug content (n=5)	Friability	Weight variation (n=20)	Hardness (kg/cm^2) (n=10)
1	No change	99.6±0.05	0.24±0.020	201±1.0	4.6±0.430
2	No change	98.7±0.05	0.25±0.001	200±1.0	4.7±0.152
3	No change	96.9±0.0	0.28±0.055	200±1.0	4.6±0.152

Samples were withdrawn at definite time intervals and replaced by equal volume of fresh medium. The absorbance of samples was measured from UV spectrophotometer. Concentration and % cumulative release of drug from the formulation was then calculated. The *in vitro* release profile of all the formulations are shown in Table 5 and comparative release profile is shown in Figure 4.

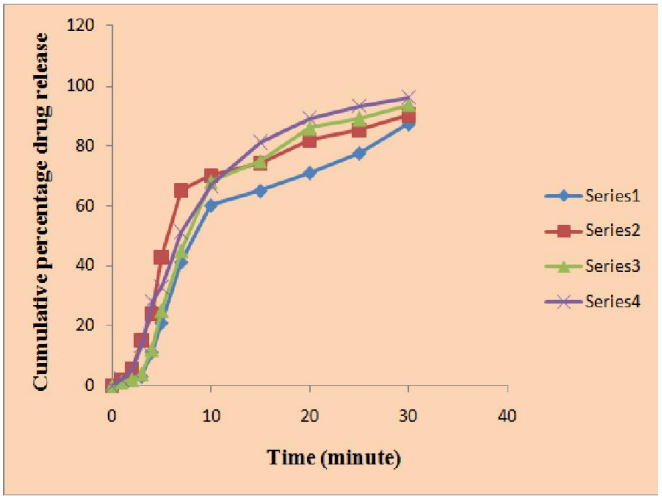

Figure 4. *In-vitro* release profile of Piroxicam fast dissolving tablets

Stability studies of drug

The fast dissolving tablets are packed in suitable packaging and stored at 40 ± 0.5 °C and RH 75% ± 5% for 90 days. At every 30 days interval, the tablets were evaluated for physical parameter such as appearance, wt. variation, hardness, friability, drug content and *in-vitro* drug release studies (Table 7) (Alkhatib *et al.,* 2014).

Conclusion

FDT concept evolved to overcome some of the problems that existed in conventional solid dosage form i.e. difficulty in swallowing of tablet in pediatric and geriatric patients who constitute a large proportion of world's population. FDT may lead to improve efficacy, bioavailability, rapid onset of action, better patient compliance due to its quick absorption from mouth to GIT as the saliva passes. Fast Dissolving tablets of Piroxicam were prepared by direct compression method using crospovidone, croscarmellose and sodium starch glycolate in different ratio. From the observed parameters it was concluded that the formulation (F8) satisfied all the official requirements. The tablets had acceptable hardness of average 4.0-5.5 kg/ cm^2, friability value less than 1%. The formulation F8 (containing 6% Crospovidone) was found to be better in term of rapid disintegration and maximum percentage drugs release. Hence it can be concluded that using a combination of synthetic superdisintegrants would be quite effective in

providing faster onset of action without the need of water for swallowing of orodispersible tablets containing Piroxicam.

REFERENCES

Akihiko, I. and Masayasu, S., 1996. Development of oral dosage form for elderly patient: use of agar as base of rapidly disintegrating oral tablets. *Chem. Pharm. Bull*., 44 (11), 2132-2136.

Alkhatib, M.H. and Almerabi, S.S., 2014. The apoptotic effect of microemulsion formulation of simvastatin/cremophor EL / transcutol / captex 355/ water in A549 non small cell lung cancer cells. *International journal of development research*, 4(3), 753-756.

Bhowmik. D., Chiranjib, B., Pankaj, K. and Chandira, M.R., 2000. Fast dissolving tablet: an overview. *Journal of Chemical and Pharmaceutical Research*, 1(1), 163–177.

Chiou, W.L. and Riegelman, S., 1969. Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. *Journal of Pharmaceutical Sciences,* 58, 1505–1509.

Chowdary, K.P.R. and Hymavathy, R., 2000. Formulation and dissolution rates studies on dispersible tablets of Ibuprofen. *Indian. J. Pharm.Sci*. , 62, 213-216.

Divate, S., Kavitha, K. and Sockan, G.N., 2011. Fast disintegrating tablets—an emerging trend. *International Journal of Pharmaceutical Sciences Review and Research*, 6(2), 18–22.

Fathy, I. A., Hamdy, M. D., Ahmed, M., and Ahmed, M. S., 2011. Evaluation of the antiinflammatory and analgesic effects of piroxicam loaded microemulsion in topical formulations. *International Journal of Pharmacy and Pharmaceutical Sciences*, 3(2), 66-70.

Khanam, N., Sachan, A.K., Alam, M.I., Gangwar, S.S. and Sharma, R., 2013. Recent trends in drug delivery by niosomes: a review. *Asian Journal of Pharmaceutical Research and Development*, 1(3), 115-122.

Lachman, L., *et al*., 1991. The Theory and Practice of Industrial Pharmacy – Tablets. Varghese publishing house, 3,370-300.

Miranda, A.S.D., *et al*., 2012. Design, Synthesis, Antinociceptive and Anti-inflammatory Activities of Novel Piroxicam Analogues. *Molecules*, 17, 14126-14145.

Pouton, C.W., 2006. Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. *European Journal of Pharmaceutical Sciences*, 29(3-4), 278–287.

Rai, R.R., Chirra, P., Thanda, V., 2012. Fast dissolving tablet: A novel approach to drug delivery- A review. *International journal of preclinical and pharmaceutical research*, 3(1), 23-32.

Shajaei, A.H., 1998. Buccal mucosa as a route for systemic drug delivery, *Journal of* Pharmacy *and* Pharmaceutical *Sciences*, 1(1), 15–30.

****