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Piroxicam double-compression coated pulsatile tablets: Formulation development and characterization

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Abstract: Pulsatile drug delivery systems are gaining importance in delivering the drug at a specific time as per the pathophysiological need of the disease, which results in improved patient therapeutic efficacy. The present study intended to develop pulsatile tablets of piroxicam using the double-compression coating method. In this study, pulsatile compression-coated tablets were prepared by the direct compression method. The inner compression coat is made of either sodium starch glycolate or hydroxypropyl methylcellulose E100 as a swelling layer. The outer compression coat (release controlling layer) was prepared using different polymers like ethyl cellulose, hydroxypropyl cellulose, sodium alginate, and hydroxypropyl methylcellulose K 15M and characterized for various parameters. From the *in vitro* drug release studies, F14 pulsatile tablets were considered the best formulation, and the percent drug release in 12 h was found to be 98.68±0.76%. The release process followed super case-II transport with zero order release kinetics. FTIR studies proved that there were no drug-excipient interactions. The best formulation showed good stability from the stability studies, and it was established by calculating the similarity factor, i.e., 82.39. In conclusion, developing piroxicam double-compression coated pulsatile tablets is a promising way to control drug release as per the therapeutic requirement.

Keywords: Compression coating; Pulsatile delivery; Release controlling layer; Rupturable layer.

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1.0 INTRODUCTION

A pulsatile drug delivery system is one of the promising time- and site-specific systems required for those diseases where a pulse of therapeutic concentration in a periodic manner is desired instead of constant drug levels. These pulsatile systems give a rapid and transient drug release within a short time immediately after a predetermined lag time[1]. Incorporation of this lag time into the dosage form depends on the nature of the therapeutic application. It is defined as the time between when a dosage form is placed into an aqueous environment and when the active ingredient begins to get released from the dosage form[2]. The pulsatile release of an active pharmaceutical ingredient is desirable when treating diseases sensitive to circadian rhythms[3]. Pulsatile drug delivery is required, especially for treating some common diseases, such as bronchial asthma, hypertension, angina pectoris, allergic rhinitis, and rheumatoid arthritis with mainly night or early morning symptoms[4]. Much literature can be found on oral pulsatile drug delivery systems, which have been accepted as potentially useful for chronotherapy[5]. Some of the recent research examples on pulsatile drug delivery systems are the colon-targeted pulsatile system of flurbiprofen for colonic inflammation[6], Time and pH-dependent colon-specific, pulsatile delivery of theophylline for nocturnal asthma[7], Pulsatile systems for targeted drug delivery of celecoxib for prophylaxis of colorectal cancer[8], Pulsatile intravenous insulin therapy[9], Glipizide loaded pellets for pulsatile delivery[10].

The current pharmaceutical tableting research focuses more on solventless compression coating rather than a solvent coating. Compression-coated tablets offer a coating methodology free of solvents that is safe and inexpensive and doesn't require special coating equipment. The coating formed through compression offers higher stability compared to film coating[11]. Recent research examples on compression-coated tablets include ketorolac tromethamine-sodium alginate compression-coated tablets[12], flurbiprofen-sodium alginate compression-coated tablets[13], flurbiprofen-guar gum compression-coated tablets[14], 5-fluorouracil-hydroxypropyl methylcellulose

compression coated tablets[15], 5-fluorouracil compression coated tablets[16], ketorolac tromethamine-hydroxypropyl methylcellulose compression coated tablets[11].

In the present study, piroxicam was selected as the model drug. Piroxicam is a non-steroidal anti-inflammatory drug, which is chemically, a phenyl alkanoic acid derivative[17]. Piroxicam is a widely used drug for the long-term treatment of rheumatoid arthritis and osteoarthritis. Rheumatoid arthritis is a circadian rhythms-sensitive disease requiring time-dependent drug release for maximum therapeutic benefit. Considering these factors, piroxicam double-compression coated pulsatile tablets were prepared using different polymers to facilitate timed drug release.

2.0 MATERIALS

Piroxicam and HPMC K15M are obtained as gift samples from MSN Laboratories, Hyderabad, India. Sodium Starch Glycolate, Ethyl cellulose, Hydroxypropyl cellulose, and Sodium alginate were obtained from Qualikems Pvt Ltd. All other chemicals used were of analytical grade.

3.0 EXPERIMENTAL METHODS

3.1. Powder characterization

The flow properties of powder mixtures of different formulations were evaluated by measuring the angle of repose, bulk density, tapped density, and compressibility index. The angle of repose (θ) was determined by utilizing the fixed funnel method and calculated using the following formula:

$$Tan\ \theta = h/r \qquad (1)$$

In which θ is the angle of repose, h is the height of the cone, and r is the radius of the cone base. In this method, a funnel was fixed to a stand so that the lower tip of the funnel was 2.5 cm above the surface, and graph paper was placed on a flat surface. Then the powder blend was allowed to fall freely on the graph paper through the funnel till the tip of the heap formed just touched the funnel. The radius of the heap was measured, and from this angle of repose was calculated.

The bulk density of a powder is calculated by measuring the volume of a known mass of powder sample that may have been passed through a screen into a 50 ml graduated cylinder. Tapped densities of powder samples were estimated by a tap density apparatus (Intelli, Kshitij Innovations, India). The apparatus was set for 500 tappings for 5 min at a stroke height of 20 mm[11]. The compressibility index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is calculated from the bulk and tapped densities and is calculated using the following formulas:

$$Carr's\ Index = ((\rho_{tap} - \rho_b) / \rho_{tap}) / \times 100 \qquad (2)$$

3.2. Preparation of piroxicam core tablets

Piroxicam core tablets were prepared by direct compression method. Piroxicam and excipients other than glidant and lubricant were accurately weighed, passed through a 60 # sieve, then blended for 5-10 min in a poly bag, lubrication, and finally, the resultant mixture was converted to tablets with 6 mm round flat punches on punching machine. The amount of piroxicam is 20 mg which is present in 100 mg tablet cores (Table 1).

Table 1 Composition and characterization of piroxicam core tablets

Ingredients	Quantity (mg)	Core tablet evaluation parameters	n	Observed values
Piroxicam	20	Weight variation(mg)	20	100.4±1.26
Avicel PH 102	72	Core thickness (mm)	20	1.94±0.03
Crospovidone	5	Core diameter (mm)	20	6.08±0.02
Talc	2	Hardness (kg/cm^2)	6	3.1±0.45
Magnesium stearate	1	Friability (%)	10	0.34
Core weight	100	Disintegration time (sec)	3	38.24 ± 1.74
		Content uniformity (%)	3	100.81±1.56
		% Drug release in 15 min (Q_{15})	3	99.72±0.78

3.3. Preparation of piroxicam compression-coated tablets

Then the tablet cores were subjected to compression coating using various compositions in Table 2. The core tablets were coated with two consecutive layers: sodium starch glycolate/HPMC low viscosity grade (E100) as an inner swelling layer (100 mg weight) and HPMC K15M/Ethyl cellulose/Hydroxypropyl cellulose/Sodium alginate as an outer release controlling coating (100 mg weight). Here compression coating of cores is done using 8 mm (inner compression coat) and 10 mm (outer compression coat) circular flat punches by placing half of the coating material in the die cavity, then cautious placing of cores in the middle, and finally placing the remaining half of the coating material.

Table 2 Composition of piroxicam compression coated tablets

Formulation Code*	Core Tablet (mg)	Inner Compression coat (100 mg)		Outer Compression coat (100 mg)				Total tablet weight (mg)
		Sodium starch glycolate (mg)	HPMC E100 (mg)	Ethyl cellulose (mg)	Sodium Alginate (mg)	Hydroxy propyl Cellulose (mg)	HPMC K4M (mg)	
F1	100	25	-	25	-	-	-	300
F2	100	50	-	50	-	-	-	300
F3	100	-	25	25	-	-	-	300
F4	100	-	50	50	-	-	-	300
F5	100	25	-	-	25	-	-	300
F6	100	50	-	-	50	-	-	300
F7	100	-	25	-	25	-	-	300
F8	100	-	50	-	50	-	-	300
F9	100	25	-	-	-	25	-	300
F10	100	50	-	-	-	50	-	300
F11	100	-	25	-	-	25	-	300
F12	100	-	50	-	-	50	-	300
F13	100	25	-	-	-	-	25	300
F14	100	50	-	-	-	-	50	300
F15	100	-	25	-	-	-	25	300
F16	100	-	50	-	-	-	50	300

*** Each compression coat formulation contains 1% Magnesium stearate, 2% Talc, and Avicel PH 102 to make up the compression coat weight.**

3.4. Evaluation of pulsatile tablets

The prepared tablets were studied for their physical properties like weight variation, hardness, and friability. For estimating weight variation, 20 tablets of each formulation were weighed using an electronic weighing balance (AW 120, Shimadzu Corporation, Japan). The strength of the tablet is expressed by measuring hardness and friability. The hardness of ten tablets was measured using a Monsanto

tablet hardness tester. Friability was determined on ten tablets in a Roche friability (Electro lab, Mumbai, India) for 4 min at 25 rpm. Ten tablets were crushed to estimate drug content, and the aliquot of powder equivalent to 50 mg of the drug was dissolved in a suitable quantity of pH 6.8 phosphate buffer solution. The solution was filtered and diluted, and drug content was determined by a UV-Visible spectrophotometer (Systronics 2202, India) at 332 nm. The drug concentration was calculated from the calibration curve.

3.5. *In vitro* drug release study

Drug release was assessed by dissolution test under the following conditions: n=3, USP type II dissolution apparatus (paddle method) at 50 rpm in 900 ml media (0.1N HCl for first 2 h and then in phosphate buffer pH 7.4 from 3 to 12 h) maintained at 37°C ± 0.5°C. An aliquot (5ml) was withdrawn at specific intervals and replaced with the same volume of pre-warmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through the Whatman filter paper, and the drug content in each sample was analyzed by UV-visible spectrophotometer at 332 nm.

3.6. *In vitro* drug release kinetics

To elucidate the drug release pattern and mechanism from the prepared compression-coated tablets, the data obtained from the *in vitro* dissolution studies were integrated into zero-order, first-order, and Higuchi models and Korsmeyer–Peppas model[18]. Then the dissolution data was also used to calculate the mean dissolution time[19] (MDT-the sum of different release fraction periods during dissolution studies divided by the initial loading dose), T10%, and T80%[11] (time in hours to take 10% and 80% drug release, respectively) to elucidate the drug release from compression-coated tablets.

3.7. Stability studies

With the help of ICH guidelines, stability studies were planned to assess the stability of piroxicam in compression-coated tablets. Three replicates of F14 tablets were sealed in aluminum coated inside with polyethylene pack and stored at 40±2 ºC and 75±5% RH in the humidity chamber for six months[20]. Specimens were gathered following six months of storage and estimated for the drug content and *in vitro* dissolution rate[21]. Then, the similarity index was calculated between dissolution rates of optimized tablets before and after storage to prove the stability of the dosage form. At this point, the data was statistically analyzed using paired *t*-test to test the significance of the difference at a level of significance 0.05.

3.8. FTIR spectroscopy

The infrared spectra of piroxicam, physical mixture of piroxicam and excipients, and placebo were recorded between 400 to 4000 cm^{-1} on FTIR to detect the drug-excipients interactions. The FTIR spectra for the test samples were obtained using the KBr disk method using an FTIR spectrometer (PERKIN ELMER BX-I SYSTEM). The resultant spectra were compared for any possible changes in the peaks of the spectra.

4.0 RESULTS

4.1. Powder characterization

Before going to compress the tablets, the powder mixtures of different formulations were evaluated for the angle of repose, bulk density, tapped density, and Carr's index, and their values are shown in Table 3. The bulk density and tapped density values ranged from 0.321 to 0.340 and 0.382 to 0.412, respectively. The results of the angle of repose and compressibility index ranged from 27.28±2.50 to 31.45±0.98 and 11.59 to 21.31, respectively. The core powder mixture's bulk density and tapped density values are 0.311 and 0.363, respectively. The angle of repose and Carr's index (%) values is 26.12±1.11 and 14.01, respectively. These results show that the core powder mixture has good flow properties.

Table 3 Characterization of powder mixture (*n=3)

Formulation	Angle of Repose*(⁰)	Bulk Density (g/cc)	Tapped Density (g/cc)	Carr's Index (%)
Core	26.12±1.11	0.311	0.363	14.01
F1	27.85±3.43	0.329	0.403	18.31
F2	27.86±3.13	0.330	0.412	19.71
F3	27.28±2.50	0.340	0.391	12.93
F4	28.90±1.24	0.324	0.387	16.22
F5	28.03±3.41	0.328	0.383	14.32
F6	31.45±0.98	0.336	0.392	14.24
F7	29.83±4.04	0.337	0.382	11.59
F8	31.13±0.93	0.324	0.382	15.14
F9	28.90±1.24	0.327	0.394	16.99
F10	30.14±3.50	0.335	0.390	14.08
F11	29.00±2.51	0.321	0.408	21.31
F12	29.74±2.63	0.324	0.401	19.03
F13	27.57±2.50	0.333	0.404	17.63
F14	30.42±3.76	0.335	0.392	14.53
F15	28.46±3.26	0.333	0.392	15.19
F16	29.71±1.43	0.324	0.401	19.03

4.2. Piroxicam core tablet characteristics

Piroxicam powder was compressed directly into a core tablet using a direct compression vehicle such as Avicel PH 102. The piroxicam core tablets' mean percent drug content was 100.4±1.26 of the labeled amount. The hardness of the core tablets of piroxicam was found to be 3.1±0.45 $kg/cm^{2,}$ and the friability was found to be 0.34% (Table 1). The core tablets disintegrated within 38 sec showing the required fast disintegration characteristics. The combined action of the super disintegrant (crospovidone) and microcrystalline cellulose (Avicel) might have contributed to such a fast disintegration property. Thus, the core tablets of piroxicam formulated in the study were found to have the required characteristics for compression coating. The dissolution results of piroxicam core tablets in 0.1N HCl and pH 7.4 buffer solutions were calculated, and the core tablets dissolved 7.4 and reached 100% in less than 1 h, and the dissolution rate was slower in 0.1N HCl, and 100% drug release was reached in 3 h.

Table 4 Physical properties of piroxicam tablets

Formulation	Weight variation* (mg)	Hardness† (Kg/cm²)	Friability (%)	Drug content‡ (%)
F1	300.20±3.83	6.07±0.29	0.50	98.69±1.12
F2	299.70±3.79	6.03±0.31	0.39	98.62±0.71
F3	301.05±4.03	6.40±0.10	0.44	100.20±1.01
F4	299.70±3.79	6.03±0.31	0.39	99.83±1.15
F5	300.75±4.84	6.23±0.31	0.16	98.33±1.82
F6	300.45±3.49	6.23±0.46	0.22	98.63±0.58
F7	300.00±4.21	6.33±0.29	0.45	98.47±1.39
F8	299.60±3.55	6.23±0.31	0.44	99.17±1.70
F9	299.75±3.99	6.20±0.36	0.39	98.73±1.45
F10	300.10±3.78	6.17±0.35	0.44	98.80±1.23
F11	299.70±3.79	6.03±0.31	0.39	97.87±1.29
F12	301.20±6.33	6.17±0.35	0.38	99.93±1.50
F13	301.42±6.24	6.12±0.15	0.38	99.12±1.45
F14	300.20±6.12	6.12±0.44	0.34	99.96±1.24
F15	299.80±3.91	6.23±0.38	0.22	98.48±0.56
F16	299.95±3.94	6.13±0.55	0.33	97.08±0.21

*** All values represent mean ± standard deviation, n=20; † All values represent mean ± standard deviation, n=10; ‡ All values represent mean ± standard deviation, n=3**

4.3. Evaluation of piroxicam compression-coated tablets

Table 4 shows all the physical parameters determined for compression-coated tablets. In the weight variation test, the pharmacopeial limits for the tablets were not more than 10% of the average weight and were 299.60±3.55 - 301.42±6.24mg. The tablet hardness and friability were around 6 kg/cm^2 and below 0.5 %, demonstrating the integrity and strength of the tablets. The prepared tablets assay was found to contain 97.08±0.21% - 100.20±1.01%. To sum up, all the tablets showed acceptable results in the sense of physical characteristics along with good mechanical integrity.

4.4. *In vitro* drug release studies

From the dissolution studies of ethyl cellulose formulations (F1-F4), the F2 formulation showed near to 90% drug release in 12 h when compared to other formulations (Fig. 1). In the case of sodium alginate formulations (F5-F8), these formulations showed some compressibility problem and sodium alginate was less effective as sustained release polymer when compared to other polymers (Fig. 2). Formulations with HPC (F9-F12) were less effective than ethyl cellulose and more effective than sodium alginate formulations (Fig. 3). In the case of HPMC K15M formulations (F13-F16), F14 is considered as the better formulation in the sense of drug release as it shows complete drug release in 12 h (Fig. 4). And finally, Fig. 5 explains the considerable difference in the drug release pattern from piroxicam core tablets and compression coated tablets.

4.5. *In vitro* drug release kinetics

The mechanism and kinetics of piroxicam drug release are determined by applying the Korsmeyer-Peppas model, Higuchi's model, zero-order, and first-order kinetics. Most tablet formulation follows the zero-order release as their r^2 values are between 0.9846 and 0.9915. The drug release mechanisms are non-fickian diffusion (super case-II) since they fit well with the Korsmeyer-Peppas models as their r2 values range from 0.9684-0.9913 with n value above 1. This indicates that drug release depends on swelling, relaxation, and erosion of polymer with zero order release kinetics. The MDT values were found to be 7.39-8.36. The T10% and T80% values of the best formulation F14, were 5.9 h and 10.4 h, respectively. All these results are given in Table 5.

Table 5 Drug release kinetics parameters of selected compression coated tablets

Formulation Code	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Korsmeyer & Peppas (R^2)	Peppas (n)	MDT (h)	T10% (h)	T80% (h)
F2	0.9897	0.9911	0.9718	0.9684	1.2322	8.36	5.8	10.3
F7	0.9846	0.9591	0.9303	0.9823	1.2383	7.62	4.9	7.7
F10	0.9915	0.7856	0.9334	0.9711	1.1610	7.39	5.0	9.4
F14	0.9898	0.8444	0.8972	0.9913	1.3729	8.34	5.9	10.4

R^{2-} Correlation coefficient, MDT- Mean dissolution time, T10%-Time to release 10% drug release and T80%-Time to release 80% drug release.

4.6. Stability studies

In consideration of the potential utility of the formulation, stability studies were carried out at 40±2°C and 75±5% RH for six months to assess their stability. After storage of six months, the formulation was subjected to a drug assay, and *in vitro* dissolution studies (Table 6), and from the statistical analysis, there was no significant difference between before and after storage (P<0.05). The similarity index value between dissolution profiles of optimized formulation before and after storage was 82.39.

Table 6 Stability studies of piroxicam compression coated tablets F14

Time (h)	Before storage	After 6 months	*t*-test at 0.05 LS	Similarity Factor (F2)
0	0.00±0.00	0.00±0.00	Not Significant	82.39
0.5	0.00±0.00	0.00±0.00		
1	0.00±0.00	0.00±0.00		
2	0.00±0.00	0.00±0.00		
3	0.86±0.23	0.82±0.67		
4	2.29±0.34	1.97±0.28		
5	6.96±1.67	5.12±1.31		
6	12.14±0.78	10.73±0.45		
8	40.24±0.94	38.46±0.71		
10	78.30±1.12	77.12±0.94		
12	98.68±0.76	96.19±0.38		
% Assay	99.96±1.24	99.08±1.42	Not Significant	–

4.7. FTIR Studies

The FTIR spectra of pure piroxicam drug showed the characteristic absorption bands as follows: tertiary amine at 3337.9cm^{-1}, aromatic C-H stretching at 3102, 3067 cm^{-1}, aliphatic CH_3 stretching at 2931, 2879cm^{-1}, C-H stretching of pyridine at 3067, 3031cm^{-1}, the amidic keto group showed absorption band at 1629 cm^{-1}, sulphoxide stretching

at 1065, 1039 cm^{-1}, and 2-substituted pyridine bending mode at 772-731cm^{-1} (Fig. 6).

5.0 DISCUSSION

In the pre-compression evaluation of powder mixtures, the angle of repose and % Carr's index was measured to determine the flow properties. The results of the angle of repose (<35) and compressibility index (<23) indicate fair to passable flow properties of the powder mixture. Significant flow properties make the flow of powder mixture easier during the tableting process.

One of the major challenges to formulation scientists is to formulate a tablet with acceptable physical properties and mechanical strength that could not adversely affect the drug release pattern. In the post-compression evaluation, measurements of physical properties like weight variation, thickness, hardness, and friability of all formulations were to check compliance with pharmacopeial standards. In the weight variation test, the average percentage deviation of all tablet formulations was within the pharmacopeial limits. From the physical characterization, all tablet formulations were uniform in hardness, friability, and drug content. The measurement of hardness and friability indicates the tablet's strength and integrity.

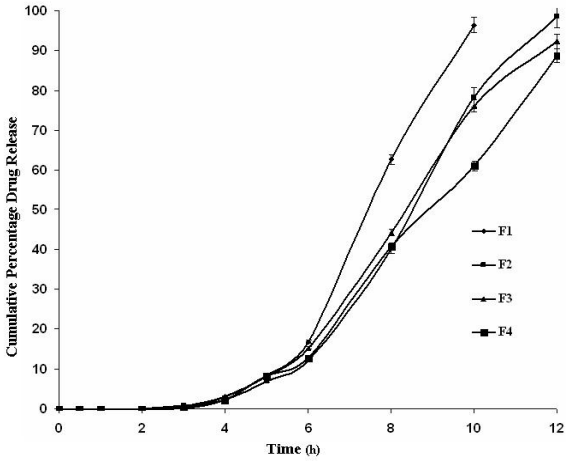

Figure 1 Drug Release profile from Ethyl cellulose compression coated tablets (F1-F4)

From the preliminary studies to optimize the compression coat weight, different formulations were prepared and evaluated for drug release, and from the dissolution studies, the formulation containing 200 mg coat weight showed well in controlled drug release with good integrity (data not presented). Dissolution study of F1-F4 formulations showed the effect of ethyl cellulose, F5-F8 showed the effect of sodium alginate, F9-F12 showed the effect of HPC, and finally, F13-F16 showed the effect of HPMC K15M on release profiles of piroxicam from the compression coated tablets (Given in Figure 1-4).

Formulations with HPMC E100 as an inner compression coat (swelling layer) showed better results when compared to sodium starch glycolate. From the dissolution studies of all formulations, tablets containing HPMC K15M as an outer compression coat (release controlling layer) showed good drug release patterns and acceptable compressibility and mechanical integrity. While the formulations with ethyl cellulose failed in compressibility, formulations with HPC failed in the released pattern, and formulations with sodium alginate failed in both. HPMC K15M was considered the successful compression coat 2 (release controlling layer) polymer by giving importance to both release pattern and compressibility and mechanical integrity[22].

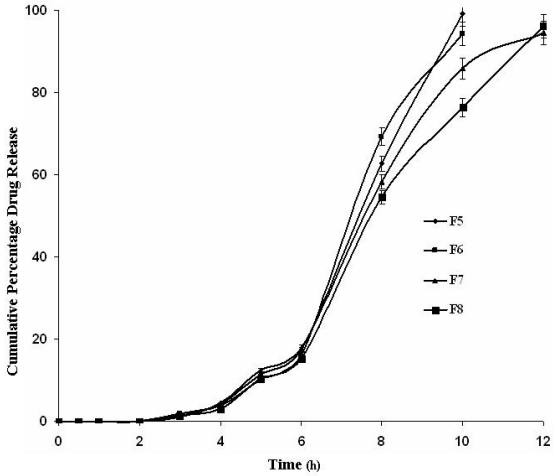

Figure 2 Drug Release profile from Sodium alginate compression coated tablets (F5-F8)

The drug release kinetics studies discovered high correlation coefficient values for zero order than first order indicating that the drug release from matrix tablets followed a zero-order profile. Zero-order release was also observed in a study with using HPMC in the compression coat[23]. The high regression value of the Higuchi model ensured that drug release from matrix tablets followed the diffusion mechanism. The n values calculated for different formulations indicate a super case-II transport. The MDT was higher for formulations with HPMC K 15M than other polymers, indicating better-controlled release. Time in hours to take 10% and 80% drug release (T10% and T80%) explained the ability of prolonged release[24].

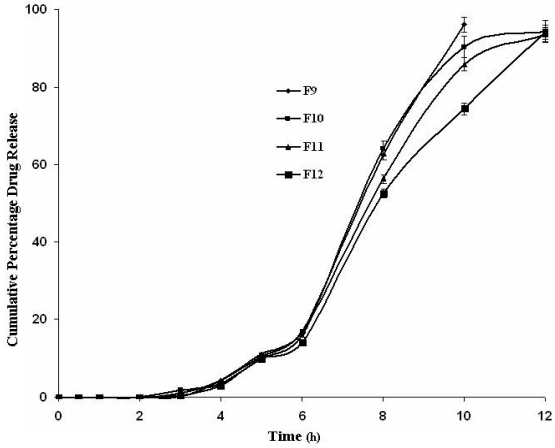

Figure 3 Drug Release profile from HPC compression coated tablets (F9-F12)

After six months of storage, the formulation was subjected to a drug assay and in vitro dissolution studies. The data showed no significant change in formulation in the sense of drug content and dissolution behavior. The similarity index value was 82.39, more than 50, indicating similarity between the dissolution profile before and after storage[2].

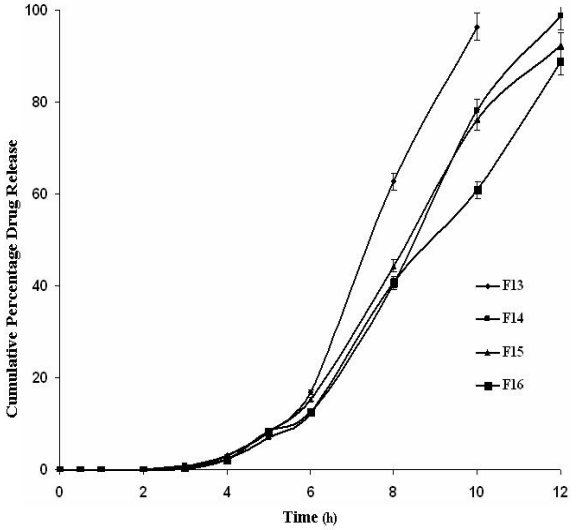

Figure 4 Drug Release profile from HPMC K15M compression coated tablets (F13-F16)

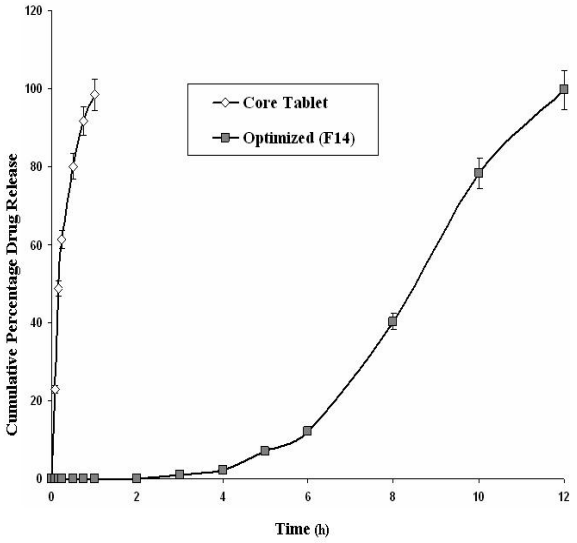

Figure 5 Comparison of drug release from core and F14 compression coated piroxicam tablets (n=3)

From the FTIR spectral analysis, all the principal peaks observed in the pure drug were present in the FTIR spectra of the best formulation (F14), and some additional peaks were observed with physical mixtures, which could be due to the presence of polymers. No drug-polymer interaction was observed in the FTIR spectra of the powder mixture of the best formulation since the absorption peaks of the drug could still be detected in the mixture.

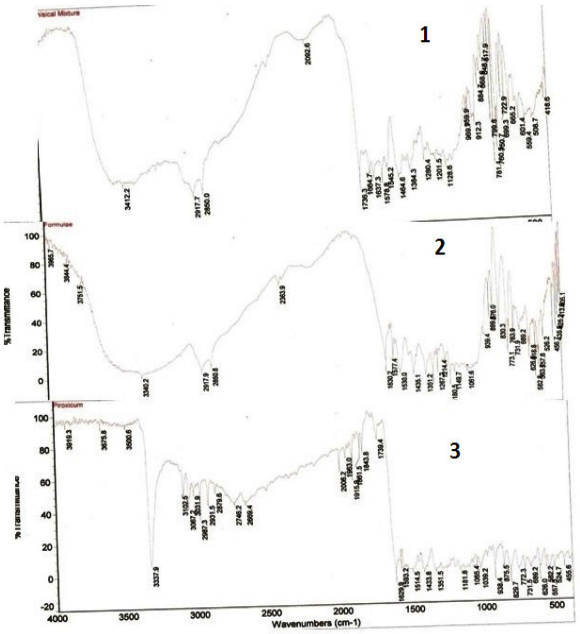

Figure 6 FTIR Spectra of F14 Formulation. 1) Optimized formulation, 2) Placebo, and 3) Piroxicam pure drug

6.0 CONCLUSION

Pulsatile double-compression coated piroxicam tablets can provide prolonged and site-specific drug release. The present study investigated formulating piroxicam pulsatile compression-coated tablets with the addition of release retarding polymers like HPMC, Ethyl cellulose, sodium alginate, and HPC. From the *in vitro* drug release studies, F14 containing HPMC K15M was the best formulation, sustaining the drug release for 12 h. The release process depends on swelling, relaxation, and erosion of polymer with zero order release kinetics. FTIR and stability studies proved no drug-excipient interactions and obtained the stable formulation.

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