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Research Article

FORMULATION AND EVALUATION OF PIROXICAM DELAYED RELEASE TABLETS

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Abstract
The present investigation of Piroxicam delayed release tablets, many research studies have completed the solution of above mentioned Non steroidal anti inflammatory drug one technology among of all to provide drug with enteric coated polymers so delay release and make release of drug in proximal small intestine. The sugar spheres will be taken into a FBP and drug will be coated onto the spheres and then they will be sub coated and enteric coated. The enteric coated pellets will be compressed into tablets by direct compression. The tablets will be prepared by using sugar spheres HPMC3cps, HPMC5cps, EL30D5, GMS, TEC etc. The prepared tablet will be coated by using pink and various parameters evaluated as per standard procedure. The FTIR studies will be conducted for optimized formula to prove that the formulas will no incompatibility between the drug and excipients. The drug release profile will be compared with the innovator, formulation has shown similar results, and it was said to be optimized of all formulations. Piroxicam is mainly used to reduce pain, swelling, and joint stiffness from arthritis. Reducing these symptoms helps you do more of your normal daily activities. They work by reducing the levels of prostaglandins, chemicals that are responsible for pain, fever, and inflammation. Piroxicam blocks the enzyme that makes prostaglandins, resulting in lower concentrations of prostaglandins in body.

Keywords: Piroxicam, Delay release, FTIR, Prostaglandins.

INTRODUCTION

The Extended release drug therapy: For many decades treatment of acute diseases or chronic illnesses have been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, suppositories, creams, ointments, liquids, aerosols and injectables. Even today, these conventional dosage forms are the primary pharmaceutical vehicles commonly seen in the prescription and over the counter drug market. The oral conventional types of drug delivery systems are known to provide a prompt release of the drug. Therefore, to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery system several times a day[1]. This results in a significant fluctuation in drug levels often with a sub-therapeutic and or toxic levels and wastage of drug. Recently several technical advancements have resulted in the development of new systems of drug delivery capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and targeting the delivery of drug to a tissue. The term controlled\extended release implies a system that provides continuous delivery of the drug for a predetermined period with predictable and reproducible kinetics and a known mechanism of release. This means that the release of drug ingredi-

ent(s) from a controlled release drug delivery system proceeds at a rate that is not only predictable kinetically but also reproducible from one unit to another. In other words, the system attempts to control drug concentration in the target tissue. The main aim of the present study was to develop robust formulation of Piroxicam multiple unit particulate system (pellets in tablets or MUPS) as a delayed release dosage form and study the *in vitro* release pattern of test product to compare with the marketed reference product[2]. Non steroidal drug delivery system (Piroxicam) is a acid labile drugs. These drugs will degrade in acidic environment of stomach and will lead to therapeutic inefficacy. It is necessary to bypass the acidic pH of the stomach which can be achieved by formulating Delayed release or enteric release dosage forms (multiple units) by using different enteric coating polymers.
The oral route of administration for extended release systems has received greater attention because of more flexibility in dosage form design. The design of oral extended release delivery systems is subjected to several interrelated variables of considerable importance such as type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug[3].

Limitations of Extended Release Tablets[4]:
Not all drugs lend themselves to the formulation of an extended duration product. There are a number of factors to be considered in the choice of drug candidates for controlled release preparations. The most important of which are as follows:

i. Biological half-life: Drugs having exceptionally long biological half-life would tend to accumulate in body tissues. A further extension of such an accumulation may result in chronic toxic manifestations.

ii. Therapeutic dose: Drugs that are effective only in relatively large doses simply cannot be processed into a multi dose, long acting preparation due to difficulties in technical manipulation and convenience of administration.

iii. Blood levels and pharmacological activity: Drugs that are metabolized to pharmacologically active products are not good candidates for an extended release preparation (e.g. Alprazolam, Clonazepam).

Piroxicam is a no steroidal anti-inflammatory drug it having a long plasma half-life. It is used in the treatment of various rheumatic disorders and dysmenorrhea, Arthritis like gout. Piroxicam is an NSAID and, as such, is a non-selective COX inhibitor possessing both analgesic and antipyretic properties [5]. Inhibits cyclooxygenase (an enzyme needed for prostaglandin synthesis), stimulating anti-inflammatory response and blocking pain impulses. It Inhibits prostaglandin synthesis by interfering with cyclooxygenase needed for biosynthesis.

Material & Methods: Piroxicam (Ranbaxy Laboratories Limited), Lactose BP (Bajaj Chemicals Pvt Ltd), Acrycoat 971 G (Corel Pharma Pvt Ltd), Xanthan gum (Rama chemical suppliers Pvt Ltd), Colloidal silica dioxide (Cobot sanmar), Purified talc (Bajaj Chemicals Pvt Ltd), Magneium stearate (Merck Pvt Ltd).

METHODOLOGY

Formualtion of Delayed Release Tablets: Weigh all ingredients accurately. Sifted Piroxicam, polymer, binder, diluent, lubricants through ≠ 40 sieve separately. Blended Piroxicam, polymer, binder, diluents in a poly-bag. Lubricant and glident are added to the above blend. Compressed the blend of Step 4 materials into round concave shaped tablets with the help of 7 mm concave shaped punches on double punch tablet machine [6].

Compatibility studies:
IR studies: In the preparation of drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug preformulation studies regarding the drug polymer interaction are therefore very critical in appropriate polymer [7]. FT – IR Spectroscopy was employed to ascertain the compatibility between Piroxicamand the chitosan polymer. (Perkin Elmer Jasco FTIR- 401, Japan).

Derived Properties of Powders [8]:
Density: Density of pellets can be affected by changes in formulation and or process variable.
Bulk density is important criteria as it can significantly affect fill volumes, can affect

batch size determination during coating operation. The bulk density of a powder is the weight of the powder divided by the volume it occupies, normally expressed as g/ml or kg/l.

Bulk density = $\frac{Wx}{100}$

Where, w_x = weight of powder in g

100=volume of cylinder in cm

Tapped density: It is defined as the maximum packing density of a powder (or blend of powder) achieved under the influence of well defined, externally applied forces. The minimum packed volume thus achieved depends on a number of factors including particle size distribution, true density, particle shape and cohesiveness due to surface forces including moisture.

Tapped density = $\frac{\text{weight of the blend}}{\text{Tapped volume of the blend}}$

Compressibility index: The bulk density and tapped density was measured and compressibility index was calculated using the formula.

Compressibility index= $\varrho_t - \varrho_o / \varrho_t * 100$

Where, ϱ_t= tapped density ϱ_o=bulk density

Haussner's Ratio: Haussner's ratio was determined as the ratio between the tapped density to that of the bulk density.

Haussner's ratio = ϱ_t / ϱ_o

Where ϱ_t = tapped density, ϱ_o = bulk density

Size and size distribution: Pellets are invariably coated, may it be for, enteric release, taste masking, stability or controlled release. Pellet size distribution is commonly determined by sieving and microscopy methods. Particle size analysis in most cases carried out by a simple sieve analysis.

Angle of Repose: When bulk granular materials are poured onto a horizontal surface, a conical pile will form. The internal angle between the surface of the pile and the horizontal surface is known as the angle of repose and is related to the density, surface area and shapes of the particles, and the coefficient of the material. Material with a low angle of repose forms flatter piles than material with a high angle of repose (Tan θ).

$$\text{Tan}\theta = \frac{h}{r}$$

Where, h = height of the heap

r= radius of the heap

Porosity: Porosity of pellets can affect the capillary action of the dissolved drug and consequently influence the rate of release of drug from pellets. It also affects film deposition and formation during coating. The pores can be analyzed qualitatively by scanning electron microscopy and quantitatively by mercury intrusion porosimetry.

Surface area: Surface area of pellets affect drug release rate, flow ability. Surface area of pellets can be controlled by particle size, shape, porosity, and surface roughness. Surface area of pellets drastically affects the film deposition and formation during coating. Surface area of pellets can be determined by particle size distribution, gas adsorption and air permeability methods [9].

Shape: Shape of pellets can be analyzed using an image analyzer. The other methods used for determining the shape of pellets are ring gap analyzer, scanning electron microscopy [10].

Evaluation of delay release formulations[11]: The prepared Piroxicam Delayed Release Tablets were evaluated for general appearance, thickness, hardness, weight variation, friability and drug content.

General appearance: The tablets prepared were white, round, spherical shape. They were smooth, uniform and free from cracking and chipping.

Hardness test: Hardness is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablets. The permissible limit for hardness is 4-12 kg/cm^2.

Uniformity of weight: This is an important In-process quality control test to be checked frequent-

ly (every half an hour). Corrections were made during the compression of tablets. Any variation in the weight of tablet (for any reason) leads to either under medication or overdose. So, every tablet in each batch should have a uniform weight[12]. The 20 tablets were weighed individually. Average weight was calculated from the total weight of all tablets.

Friability test: Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This In-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Roche friabilator was used to measure the friability of the tablets. It was rotated at a rate of 25 rpm. Five tablets were weighed collectively and placed in the chamber of the friabilator. Permitted friability limit is 1.0%. The percent friability was determined using the following [13].

Formula

$$(W_1 - W_2)/W_1 \times 100$$

Where,

W_1 = weight of the tablets before test

W_2 = weight of the tablets after test

***In-vitro* drug release studies:** *In-vitro* drug release studies were carried out using USP XXIV dissolution apparatus type II, with 500 ml of dissolution medium maintained at 37±0.5 °C for 20 hr, at 50 rpm, pH 6.8 ±0.2 phosphate buffer as dissolution medium. Sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid [14]. The samples withdrawn were filtered through 0.45µ membrane filter, and concentration of drug in each sample was analyzed by HPLC at 240 nm and cumulative percent drug release was calculated. The study was performed in triplicate. The commercial Toprol XL tablets were used as the reference formulation, and were also subjected to *In-vitro* drug release studies. The results of *In-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:

1. Log cumulative percent drug remaining versus time (first order kinetic model)
2. Cumulative percent drug release versus square root of time (Higuchi model)
3. Cumulative percent drug remaining versus time (zero order kinetic model)
4. Log cumulative Percent Drug released versus log time (korsmeyer's model)

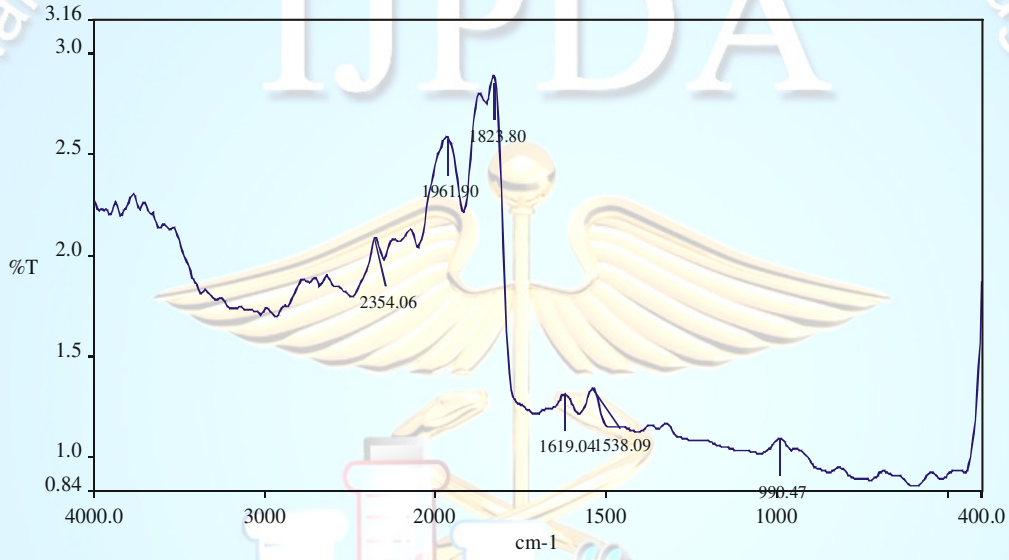
Table: 1 Formulations of Piroxicam Delayed Release Tablets

Sr no	Ingredients (mg/Tab)	P1	P2	P3	P4	P5	P6	P7
1	Piroxicam	23.75	23.75	23.75	23.75	23.75	23.75	23.75
2	Xanthan gum	45	52	-	-	-	-	-
3	Acrycoat 971 G	-	-	45	52	60	74	89
4	Lactose	63.75	56.75	63.75	56.75	48.75	34.10	19.10
5	Purified talc	5.0	5.0	5.0	5.0	5.0	5.0	5.0
6	Aerosil	10	10	10	10	10	10	10
7	Magnesium sterate	2.5	2.5	2.5	2.5	2.5	2.5	2.5
8	Total weight (mg)	150	150	150	150	150	150	150

Table: 2 Flow properties of Piroxicam all formulations

Sr no	Parameters	P1	P2	P3	P4	P5	P6	P7
1	Angle of repose	31.3	32.2	33.0	31.7	33.02	31.0	34.2
2	Bulk density(gm/ml)	0.296	0.307	0.313	0.301	0.320	0.301	0.301
3	Tapped density(gm/ml)	0.333	0.347	0.363	0.340	0.347	0.333	0.347
4	Hausner's ratio	1.13	1.13	1.15	1.12	1.08	1.10	1.15
5	Compressibility index (%)	11.1	11.5	13.7	11.3	12.0	10.4	13.2

Figure: 1 FTIR of Piroxicam



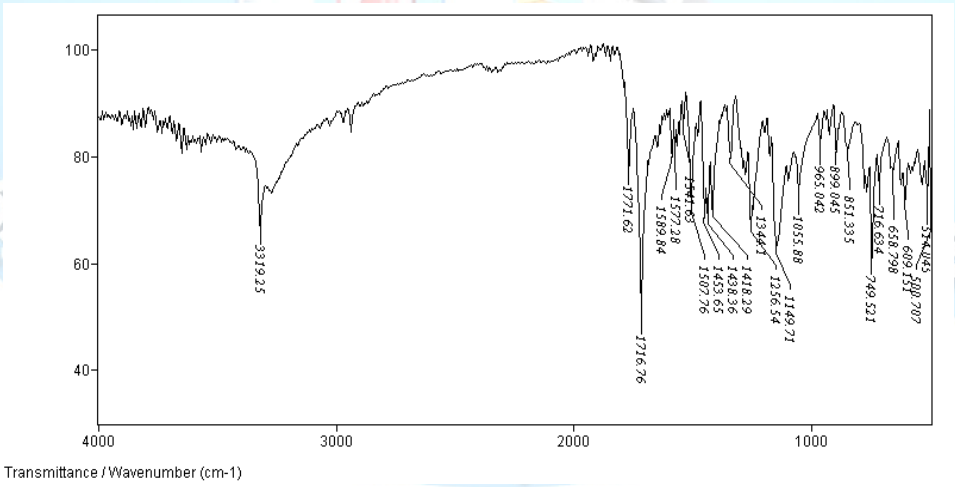


Figure: 2 FTIR of Piroxicam, Xantham gum, Acrycoat 971 G, Aerosil

Table: 3 Evaluation parameters of all formulations of Piroxicam tablets

S.no	Parame-ters	P1	P2	P3	P4	P5	P6	P7
1	Color	Cream white	Cream white	Cream white	Cream white	Cream white	Cream white	Cream white
2	Surface	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth
3	Thickness (mm)	3.3-3.4	3.3-3.4	3.3-3.4	3.3-3.4	3.3-3.4	3.3-3.4	3.3-3.4
4	Hardness (Kg/cm^2)	4.0±0.1	4.2±0.2	4.3±0.1	4.1±0.2	4.2±0.1	4.0±0.1	4.3±0.1
5	Weight (mg)	148.20±2.5	149.32±1.5	149.35±1.5	148.76±2.5	148.36±3.5	149.56±2.5	149.23±1.5
6	Friability	0.09±0.001 %	0.05±0.001 %	0.08±0.001 %	0.09±0.002 %	0.07±0.001 %	0.09±0.001 %	0.08±0.002 %
7	Assay (%w/w)	99.96	100.2	98.65	99.23	100.6	99.3	99.52

Table: 4 *In vitro* Dissolution drug profile for innovator and all formulations

Time	P 1	P 2	P 3	P 4	P 5	P 6	P 7	Innovator
0	0	0	0	0	0	0	0	0
5mints	26	24	31	26	20	11	8	12±1.2
10mints	48	43	51	46	35	31	26	30±0.1
15mints	77	70	86	75	63	54	48	52±0.9
20 mints	99	99	100	99	96	89	74	86±1.2

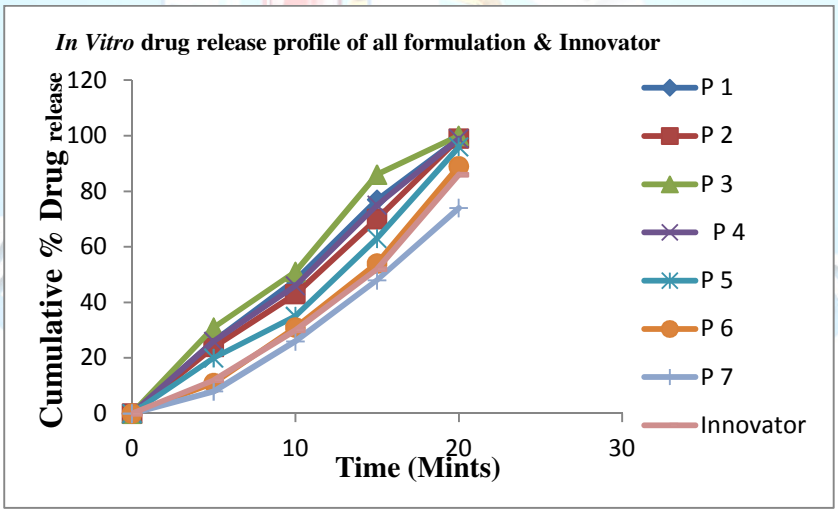


Figure: 3 Cumulative % of drug released versus time for innovator and all formulations.

Table: 5 Cumulative % of drug released versus time for innovator and different compositions of Acrycoat 971 G.

Time	P3 (Acry-coat 971 G)	P4 (Acry-coat 971 G)	P5 (Acry-coat 971 G)	P6 (Acry-coat 971 G)	P7 (Acry-coat 971 G)	Innovator
0	0	0	0	0	0	0
5mints	31	26	20	11	8	12±1.2
10mints	51	46	35	31	26	30±0.1
15mints	86	75	63	54	48	52±0.9
20 mints	100	99	96	89	74	86±1.2

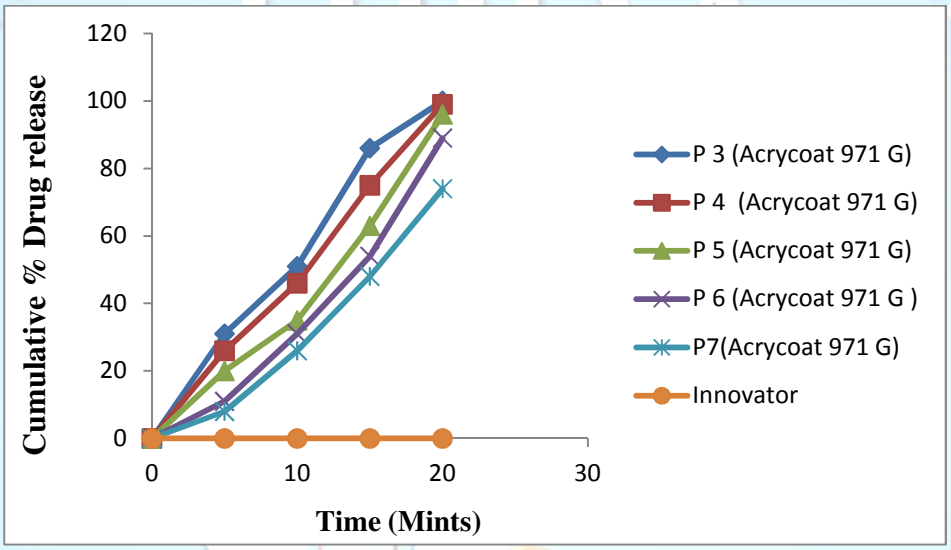


Figure: 4 Cumulative % of drug released versus time for innovator and different polymer concentrations of Acrycoat 971 G.

Table: 6 Similarity factor calculations for 7 formulations

Formula	P 1	P 2	P 3	P 4	P 5	P 6	P 7
Similarity factor F2	37%	42%	32%	38%	52%	81%	59%
Difference factor F1	39%	31%	49%	37%	19%	4.6%	12%

Table: 7 Similarity factor calculations for formulation 6

Time (hrs)	Reference ®	P 6(t)	/R_t-T_t/	/R_t-T_t/^{2}	P 2
0	0	0	0	0	**81%**
5mints	12	11	1	1	
15mints	30	31	-1	1	
30 mints	51	54	-3	9	
45 mints	86	89	-3	9	

DRUG RELEASE KINETICS

Table: 8 **Drug release kinetics for all 7 formulations with innovator**

Batch	Zero order R^2	First order R^2	First order rate constant K_1
Innovator	0.9697	0.997	0.096726
P 1	0.877	0.988	0.227997
P 2	0.9313	0.9749	0.227997
P 3	0.809	0.9922	0.227997
P 4	0.8969	0.9842	0.227997
P 5	0.9549	0.9858	0.158907
P 6	0.9596	0.9969	0.108241
P 7	0.9335	0.9914	0.066787

Table: **9 Drug release kinetics for all 7 formulations with innovator**

Batch	Higuchi R^2	Korsmeyer-peppas	
		R^2	N
INNOVATOR	**0.987**	**0.9983**	**0.6611**
P1	0.9641	0.9834	0.4611
P 2	0.6865	0.9892	0.4811
P 3	0.9149	0.9578	0.4144
P 4	0.9719	0.984	0.4611
P 5	0.991	0.9889	0.5333
P 6	**0.9849**	**0.9944**	**0.710**
P 7	0.9905	0.9825	0.6825

Drug release kinetics-model fitting of the dissolution Data

Whenever a new solid dosage form is developed or produces, it is necessary to ensure that drug dissolution occurs in an appropriate manner. Nowadays the pharmaceutical industry and the registration authorities focus on drug dissolution studies [15]. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q = f (t). Some analytical definitions of the Q (t) function are commonly used such as zero order, first order, Higuchi, korsmeyer's models. Other release parameters, such as dissolution time ($t_{x\%}$), dissolution efficacy , difference factor (f_1), similarity factor (f_2) can be used to characterize drug dissolution / release profile.

Stability Studies: Stability is defined as the ability of particular drug or dosage form in a specific container to remain within its physical, chemical, therapeutic, and toxicological specification. Drug decomposition or degradation occurs during stability, because of chemical alteration of the active ingredients or due to product instability or due to lowered concentration of the drug in the dosage form. The stability of pharmaceutical preparation should be evaluated by accelerated stability studies. The optimized formulation of piroxicam tablets were selected for the stability studies. The accelerated stability studies were carried out according to ICH guidelines by storing the samples at 40 $\pm$ 2 ^{o}C and 75 $\pm$ 5% RH for 1 month. These samples were analyzed and checked for changes in physical appearance, hardness, drug content, and drug release after 1 month and compared it with the data obtained from soon after prepared tablets.

Results and discussion: The Pre-formulation studies of drug were performed to characterize the Piroxicam. The powder flow properties of Piroxicam were studied to evaluate compressibility of the Piroxicam, since it has to be formulated as tablet. The results obtained are bulk density 0.334

mg/ml and tapped density was 0.356 mg/ml and Hausner's ratio 1.06. The results showed that the compressibility of Piroxicam is 6.56, which indicates that the Piroxicam has excellent flow properties. The drug solution was prepared in 6.8 buffer and scanned using UV-Spectrophotometer in the stage of 400 – 200 to determine the λ max. The λ max of Piroxicam was found to be at 240 nm. But Piroxicam has placebo interaction so, I shifted to HPLC method development. The drug excipients compatibility studies shows that there is no any physical incompatibility of Piroxicam with excipients studied at given conditions. Piroxicam was formulated by using direct compression method.

FTIR spectroscopy was used to ensure that no chemical interaction between the drugs and polymers had occurred. From the FTIR spectral interpretation the following result were obtained. The FTIR of Piroxicam show intense band at 1771.47 cm^{-1}, 1716.89 cm^{-1} , 1589.53 cm^{-1} and 1055.9 cm^{-1} corresponding to the functional groups C=O, COOH, NH and OH bending. The physical mixture of Piroxicam, 1876.47 cm^{-1}, 1712.89 cm^{-1}, Acrycoat 971 G 1689.3n2 cm^{-1}, 1259.13 cm^{-1}, Xanthum gum 1615.93 cm^{-1}, 1488.89 cm^{-1}, 1255.33 cm^{-1}, Aerosil 1486.84 cm^{-1}, 1151.88 cm-1. .

Selection of polymer concentration Piroxicam was formulated by using five different concentrations of Acrycoat 971 G (i.e) 30%, 35%, 40%, 50%, and 60%.

Selection of final formula

Based on F2 values comparison with reference product the final formulation was selected.

Release kinetics: The "n" value obtained from formulation 6 is 0.71 which is between >0.45 and < 0.89 hence it follows non fickian release, Showing anomalous transport. Also the drug release was best explained by the first order equation as the plot showed the highest linearity with (r^2 value = 0.9969) followed by Higuchi equation (r^2=0.9849). Formulation F-6 was seemed to be close to the innovator's release profile. Then similarity factor was calculated between formulation F-6 and innovator. Similarity factor was 81, so formulation F-6 has similar release profile to the marketed formulation.

Table: 10 Physical evaluation of tablet blend and tablets of optimization of stability formulations

	cumulative % drug release		
Time (Hr)	**Initial**	**One month**	**Two months**
1	11	13	12
4	31	33	35
8	54	57	52
20	89	91	87

parameters	**Initial**	**One month**	**Two months**
Color	Cream or White	Cream or White	Cream or White
Surface	Smooth	Smooth	Smooth
Thickness	3.3-3.4	3.3-3.4	3.3-3.4
Hardness	4	4	4
Assay	99.3	100.6	99.5

The samples analyzed at initial stage and after one month and after two months at accelerated stage.

Accelerated stability studies of the formulation 6 were done at 40° C, and at 75%RH for two months. It was seen that physically there was no change with respect to appearance hardness, thickness and drug content. The dissolution profiles of first month and second moth are similar. When compared to formulation 6.this indicates that the formulation was stable at 40°c and 75% RH for two months.

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Conclusion: The Precompressional and Postcompressional parameters were found to be within the satisfactory limits and hence suitable to formulate delayed release tablets. The delayed release formulation (F-6) was found similar and comparable to the innovator product based on the f2 value (81) obtained. The results of *in-vitro* drug release profile of delayed release tablets depicts that increase in polymer concentration, increases the retardation of drug release from the Piroxicam tablet. The flow properties of Piroxicam formulations Angle of repose of F6 was found to be 31.0 ^{0}, Bulk density F6 is 0.301 (gm/ml) , tapped density F6 is 0.333, Hausner's ratio was found to be 1.10, compressibility index was found to be 10.4%. The evaluation test of delayed release formulation perform the appearance is smooth surface & cream white in colour, thickness is 3.3-3.4 mm, weight variation was found to be 149.56±2.5, friability was found to be 0.009±0.001%, & Assay was found to be 99.3. drug content, invitro drug release studies by using basket method results was found to be 99 ± 7.77. The formulations F1 and F7 were suitable to sustain the drug release for a period of 12hrs, followed zero order, first order kinetics, & first order rate constant exhibited Higuchi's model and Krosmeyer-Peppas exponential The "n" value obtained from formulation 6 is 0.71 which is between >0.45 and < 0.89 hence it follows non fickian release. Hence can conclude that formulated delayed release tablets were developed successfully with DR tablets comprising of xantham gum, acrycoat 971 G, Lactose, talc, Aerosil, Magnesium sterate are excipients by Direct Compression technique and Wet Granulati on technique. Accelerated stability studies of the formulation 6 were done at 40^{o} C, and at 75%RH for two months. It was seen that physically there was no change with respect to appearance hardness, thickness and drug content.

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