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FORMULATION DEVELOPMENT AND EVALUATION OF PRESS COATED PULSATILE RELEASE TABLETS OF PIROXICAM CONTAINING HPMC AND ETHYL CELLULOSE

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Abstract
The main aim and objective of present investigation was to formulate and evaluate pulsatile drug delivery system for Anti-inflammatory drugs like piroxicam. Chrono modulated drug delivery systems release the drug at predetermined lag time in diseases like cardiovascular diseases, diabetes mellitus, asthma, arthritis, peptic ulcers. Piroxicam is an anti-inflammatory drug used in treatment of rheumatoid arthritis. Core tablets of piroxicam were prepared using various super disintegrants like Ac di sol and Explotab using direct compression method. The core tablets were then press coated with polymers to release the drug in early morning hours after predetermined lag period. Hydroxy propyl methyl cellulose and ethyl cellulose were used as release retarding polymers. FTIR studies were conducted to check interaction between drug and inactive ingredients. Evaluation tests like hardness, thickness, friability, weight variation, disintegration time and dissolution tests were carried out for prepared tablets. Dissolution tests were conducted in 0.1 N Hcl acidic buffer for 120 minutes and in phosphate buffer pH 6.8 for remaining 6 hours in USP dissolution apparatus. Core tablets initially released 95.85% drug in 60 minutes and press coated tablets released 98.82 % drug after 8 hours. Accelerated stability studies were carried out for 90 days. Formulation PC-9 of piroxicam containing Ac di sol and Explotab as super disintegrant and Hydroxy propyl methyl cellulose and ethyl cellulose as rate controlling polymers has shown better micromeritic properties, less weight variation, high drug content, better hardness, less friability, quick disintegration time and dissolution profile among all the formulations. Hence formulation PC-9 containing piroxicam is chosen as best optimized formulation after carrying out all evaluation tests

Keywords: Chrono-modulated drug delivery, Pulsatile system, HPMC, EC, Kinetics, Press coating.

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INTRODUCTION

Pulsatile drug delivery systems are time controlled systems which releases the active ingredient in fixed time after a predetermined lag time. Chrono modulated drug delivery systems are useful in certain diseases diabetes mellitus, asthma, arthritis, cardio vascular disorders which depends upon circadian rhythms. Hormonal levels changes depend upon biological cycle in case of arthritis, myocardial infraction, angina asthma, osteoarthritis, peptic ulcers, epilepsy and cardiovascular diseases. Broncho constriction is severe during night; rheumatic pain reaches to peaks during early morning hours, abdominal pain is more during night due to ulcers [1]. Pulsatile system releases the drug at pre programmed time in preplanned pattern at appropriate location without affecting gastro intestinal factors [2]. Chronobiology is combination of two words, chrono means time and biology means study of life. Chronotherapeutics is a discipline of science which deals with treatment of disease based on biological cycle and pathological state of disease. Chrono modulated drug delivery doesn't follow zero order release [3]. Pulsatile drug delivery systems are becoming popular because of their improved patient compliance. The aim of the present study was to prepare and evaluate of pulsatile tablets of piroxicam [4]. It involves preparation of immediate release core tablets and preparation of press coated tablets. Piroxicam is non-steroidal anti-inflammatory drug belonging to class of oxicam derivatives. Piroxicam inhibits cyclo-oxygenase (COX) enzyme which helps in production of prostaglandins that causes pain and inflammation in rheumatoid arthritis. Piroxicam is a used for musculoskeletal problems, surgical pains and in management of rheumatoid pain. It inhibits the prostaglandin synthesis process. It also blocks the migration of leukocytes to the site of inflammation [5-8]. During initial stages of development of new dosage form it is mandatory to check out physical and chemical properties of active drug alone and along with inactive ingredients. To design a stable formulation it is important to evaluate physical and chemical properties of active drug and excipients.

MATERIALS AND METHODS

Piroxicam (API) was obtained from Hetero labs, Hyderabad as gift sample. Identification of drug was carried out by various pharmacopoeial methods.

ORGANOLEPTIC PROPERTIES [9]

Organoleptic properties such as color and odour of the drug were evaluated and recorded.

SOLUBILITY

The solubility of the drug was tested using various solvents.

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MELTING POINT

Capillary method was used to determine the melting point of the active drug. A small amount of drug was taken in capillary tube with one of its end closed. The capillary tube was placed in the melting point apparatus and slowly the temperature of capillary tube was increased. The temperature at which the drug starts melting was recorded.

LOSS ON DRYING [10]

Piroxicam (3 grams) was transferred into a glass bottle and placed in hot air oven. The active drug was evenly distributed in the glass bottle by gentle shaking Distribute the sample evenly a gentle shaking. Place the LOD glass bottle in the hot air oven at a temperature of 105°c for 4 hours. After the completion of drying, allow the crucible to cool at room temperature in desiccator for half an hour. Weigh the crucible containing dried sample and calculate the percentage loss on drying.

FTIR STUDIES

Compatibility of the drug with excipients was evaluated using FTIR spectrum of drug alone and drug along with excipients. The presence of absorption bonds respective to the functional groups of piroxicam and the absence of any well-defined unknown peak is a confirmation of the purity of the drug sample.

POWDER CHARACTERIZATION [11]

Powder characterization of piroxicam was carried out to check parameters like bulk density, tap density, compressibility index, Hausner's ratio and angle of repose.

PRE COMPRESSIONAL PARAMETERS [12]

PHYSICAL PROPERTIES

Before compression the active drug and inactive ingredients, the mixture was evaluated for angle of repose, bulk density, tapped density, % compressibility, and Hausner's ratio. Flow properties of powder and density of the power blend are important to maintain the hardness and disintegration time of tablet. These properties of the drug and excipient mixture plays crucial role in flow of blend from hopper to die.

BULK DENSITY

Pour weighed quantity of powder blend (25gm) into a measuring cylinder using a funnel and check the volume occupied by the blend without tapping the measuring cylinder. It is expressed in gm/ml.

$$Db = M/Vo$$

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TAPPED DENSITY[13]

Tapped density is ratio of mass of the blend to its tapped volume and is expressed in gm/ml. tapped density is determined by pouring powder blend (10 gms) into a measuring cylinder with the help of funnel and note done the volume occupied by blend after tapping the measuring cylinder for 100 times on the table from a constant height. The tapped density of the powder blend [14] can be calculated using the following formula:

$$Dt = M/Vt$$

COMPRESSIBILITY INDEX

Carr's index [15] is a method to calculate consolidation index from tapped and bulk densities. Compressibility index is measure of the strength of a powder blend. Free flowing powders are easy to compress compared to poor flowing powders. Carr's index of powders are calculated by using following formula

$$\% \text{ compressibility} = (\text{tapped density} - \text{bulk density}) / \text{tapped density} \times 100$$

HAUSNER'S RATIO

The inter-particulate interactions between the particles of the powder blend has significant effect on the powder flow characteristics [16]. As the interactions are more the flow of powders will be less. Hausner's ratio is calculated using the following formula.

$$\text{Hausner's ratio} = Dt/Db$$

ANGLE OF REPOSE

Angle of repose is the defined as angle made by pile of powder with plane surface. Angle of repose was determined by pouring 25 grams of blend on plain white paper placed over the table through a funnel fixed to burette stand from a fixed height [17].

After pouring the powder through funnel, the height of the pile and diameter of the pile are determined**.** Angle of repose was calculated by substituting radius and height of pile in the equation given below

$$\theta = \text{Tan-1}H/R$$

DRUG EXCIPIENT COMPATIBILITY STUDIES

Stability of the final product is dependent on the type of the inactive ingredients used in the formulation of dosage form. So it is important to check drug excipient compatibility. The studies were conducted for 3 months and analyzed for physical and chemical changes before the compression of blend as tablets [18].

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FORMULATION DEVELOPMENT OF PIROXICAM PULSATILE RELEASE TABLETS

Piroxicam tablets were prepared by using compression coating technology. Initially internal core tablet containing drug and super disintegrant was formulated. For the prepared core tablet compression coating is done by using various compositions of polymers. Ethyl cellulose and HPMC are used as polymers for compression coating [19-22].

Tablets are developed in two stages

1) Preparation of core tablet containing drug and super disintegrants
2) Press coating of prepared core tablets.

PREPARATION OF CORE TABLET

In the preparation of core tablets 10mg of active drug, Explotab and Ac di sol are used as super disintegrants, Micro crystalline cellulose (Avicel) was used as diluent, talc and magnesium stearate were used as glidant and Lubricant respectively.

Piroxicam (10 mg) and all the ingredients were accurately weighed and passed through sieve #40 separately. Piroxicam was mixed with weighed quantity of super disintegrants in mortar for about 5-10 min. Micro crystalline cellulose was added and lubricated with the weighed quantity of magnesium stearate (lubricant) and talc to obtain the blend ready for compression. Then the lubricated blend was subjected to compression on a rotary tablet punching machine using circular standard flat faced punches[23-25]. The composition of core tablet is given in table 1.

PREPARATION OF PRESS COATED TABLET:

The upper and lower press coat consists of HPMC and ethyl cellulose in various concentrations with Avicel PH 102.

Table 1: Formulation of piroxicam pulsatile release tablets PC1-PC10

Ingredients for core tablet										
Ingredients	**PC1 (mg)**	**PC2 (mg)**	**PC3 (mg)**	**PC4 (mg)**	**PC5 (mg)**	**PC6 (mg)**	**PC7 (mg)**	**PC8 (mg)**	**PC9 (mg)**	**PC10 (mg)**
Piroxicam	10	10	10	10	10	10	10	10	10	10
Ac di sol	5	10	15	20	25	-	-	-	-	-
Explotab	-	-	-	-	-	5	10	15	20	25
Avicel PH 102	130	125	120	115	110	130	125	120	115	110
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Aerosil	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

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Ingredients for press coated tablet										
HPMC	60	70	80	90	100	100	100	100	100	100
Avicel PH 102	40	30	20	10	-	40	30	20	10	-
Ethyl Cellulose	200	200	200	200	200	160	170	180	190	200

ACCELERATED STABILITY STUDIES

Stability Studies of drug substance and final product is important for long term storage of final product. This data will be useful to prevent the degradation of material and to choose conditions for long term storage of products.

It also helps to maintain uniform drug content in final product from its initial preparation until its expiry.

The final product is placed in stability chamber maintained at 25^0C/ 60%RH; 30 $\pm$ 2^0 C and RH 65 % $\pm$5%; 40 $\pm$ 2^0 C and RH 75 % $\pm$5% for 90 days as per ICH guidelines.

At regular time intervals samples were withdrawn and evaluated for changes in color, appearance drug content and dissolution profile.

The data collected after the completion of stability studies was compared with the data collected immediately after preparation of tablets.

RESULTS AND DISCUSSION

Organoleptic properties of Piroxicam

Colour : White

Odour : Odour less

Meltingpoint : 198-200°C

WaterSolubility : 23 mg/L (at 22 °C)

Micromeritic properties

API characterization

Bulk densities and tapped density of drug were evaluated by using measuring cylinder. Angle of repose of was evaluated by funnel method.

Table 2: Powder characterization for piroxicam

Sample Weight (gm)	Bulk Density (Db)	Tapped Density (Dt)	Compressibility Index (%)	Angle of Repose (ɵ)	Hausner's ratio
25	0.475	0.564	15.78	25.56	1.18

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FTIR spectrum of Piroxicam: FTIR spectrum of Piroxicam confirms that the drug is pure without any adulterants.

Fig. 1: FTIR spectrum of Piroxicam

Drug excipient compatibility studies

FTIR spectrum confirms that there is no interaction between and drug Excipients

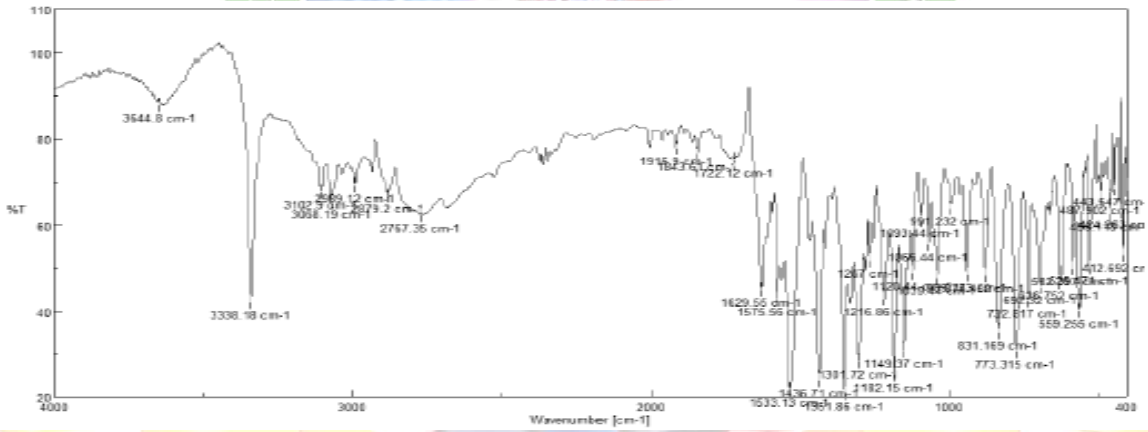

Fig 2: FTIR spectrum of Piroxicam and croscarmellose

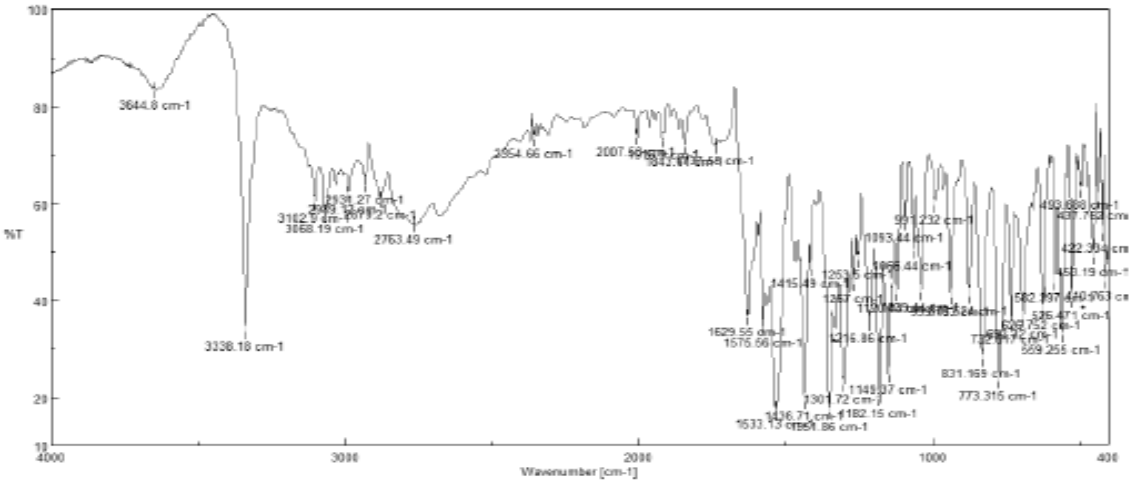

Fig 3: FTIR spectrum of Piroxicam and SSG

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Table 3: EVALUATION OF PIROXICAM CORE TABLETS (PC1-10)

Formulation	Weight Variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Drug Content
PC1	151 ±1.9	5.9±1.2	0.45±0.08	91.14
PC2	152±1.6	5.2±0.4	0.46±0.02	92.19
PC3	148±0.5	5.6±0.4	0.48±0.08	91.65
PC4	142±1.3	5.8±0.2	0.49±0.10	91.47
PC5	145±1.4	5.5±0.6	0.59±0.08	92.65
PC6	154±1.3	5.6±0.7	0.44±0.07	85.55
PC7	152±1.1	5.5±0.7	0.45±0.08	86.32
PC8	145±0.9	5.9±0.8	0.48±0.06	91.62
PC9	150±0.1	6.1±0.3	0.43±0.02	99.65
PC10	148±0.4	5.8±0.2	0.45±0.01	92.77

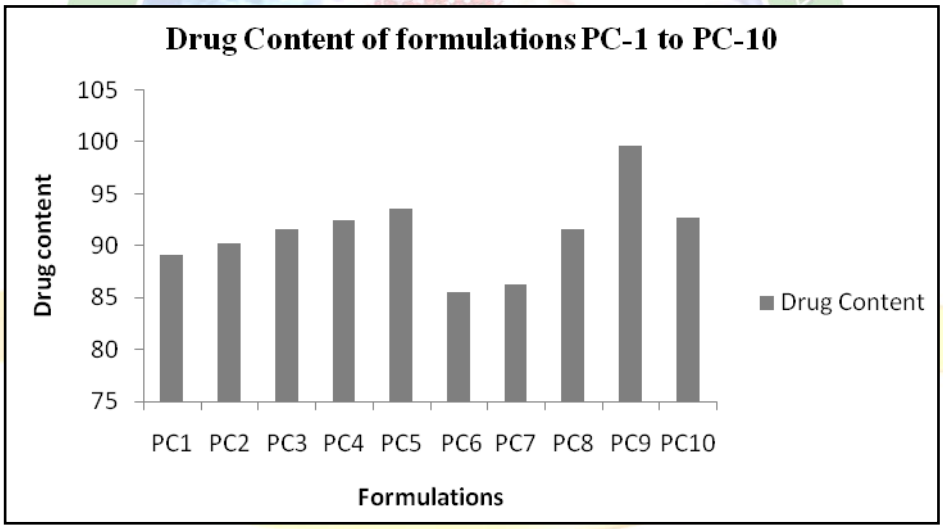

Fig. 4: Drug Content of formulations PC-1 to PC-10

Table 4: Dissolution profile of piroxicam core tablets (PC1-PC10)

Time (mins)	% cumulative drug release									
	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9	PC10
10	11.24	13.24	11.55	14.23	17.65	12.85	14.27	15.52	20.18	19.84
20	13.17	16.49	18.78	19.78	21.75	15.25	19.77	18.85	39.78	29.48
30	19.48	21.36	22.45	24.85	29.85	25.85	29.45	31.48	48.18	47.84
40	25.54	35.89	37.82	44.57	46.75	39.87	43.78	45.41	65.78	60.14
50	60.15	59.98	61.45	63.85	65.54	58.15	64.85	69.49	85.75	75.48
60	84.75	86.87	88.43	89.89	87.48	81.54	83.85	93.79	95.85	92.18

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Table 5: Dissolution profile of piroxicam press coated tablets (PC1-PC10)

Time (Hrs)	% cumulative drug release									
	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9	PC10
1	3.02	3.14	3.04	3.63	3.12	3.85	4.09	4.85	2.75	3.65
2	7.05	8.23	8.45	8.15	9.54	6.14	6.56	6.41	5.48	6.95
3	14.47	17.48	18.71	35.65	39.82	2.55	15.48	11.97	10.73	11.54
4	29.87	28.74	50.14	48.87	55.78	8.74	30.48	15.12	12.49	15.54
5	47.17	38.47	59.78	57.84	44.15	9.84	45.72	17.97	16.75	18.95
6	45.48	48.47	68.95	67.48	69.73	16.71	62.32	19.74	18.45	19.44
7	90.45	78.71	78.45	75.84	76.44	76.78	73.84	21.95	20.54	35.74
8	91.85	85.47	86.94	86.74	87.71	91.47	92.48	92.75	98.82	89.65

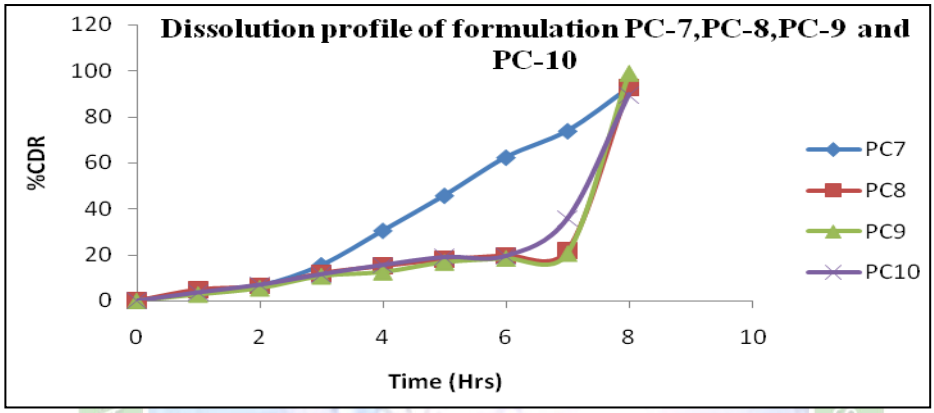

Fig. 5: % CDR of formulations PC-7,PC-8,PC-9 and PC-10

ACCELERATED STABILITY STUDIES:

Table 6: Protocol for Stability testing of optimized batch of press coated tablet - PC9

S.No	Conditions	1 month		3 months		6 months	
		% CDR	Drug content	% CDR	Drug content	% CDR	Drug content
1	25^0c/ 60%RH	98±0.82	97.50	99±0.13	96.58	94±0.41	97.88
2	30^0c/ 65% RH	98±0.65	96.51	96±0.45	95.40	97±0.75	95.96
3	40^0c/ 75% RH	98±0.22	97.95	98±0.41	95.44	94±0.91	97.54

Table 7: Protocol for Stability testing of optimized batch of press coated tablet - PC9

S.No	Conditions	1 Month			6Months		
		Colour Change	Hardness	Friability	Colour Change	Hardness	Friability
1	25^0c/ 60%RH	No	6.1±0.5	0.43±0.04	No	6.1±0.8	0.45±0.14
2	30^0c/ 65% RH	No	6.0±0.8	0.41±0.07	No	6.0±0.4	0.47±0.17
3	40^0c/ 75% RH	No	6.1±0.4	0.44±0.09	No	6.1±0.4	0.45±0.29

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Optimized batch of press coated tablet - PC9 had not shown any visible changes after 3 months. Changes in hardness, friability, drug content and %CDR are within the ranges.

DISCUSSION

Organoleptic properties, melting point, solubility of active pharmaceutical ingredient was determined using suitable analytical techniques. Powder characterization of API was determined using funnel method. Powder had shown good flowing properties.

Formulation PC-9 has less weight variation and friability. Assay values obtained had shown good drug content.Formulation PC-9 had released very less amount of drug during initial 2 Hrs and had shown pulsatile release at 8th hour. Hence it is selected as best formulation.

DRUG RELEASE KINETICS OF PIROXICAM PULSATILE RELEASE TABLETS

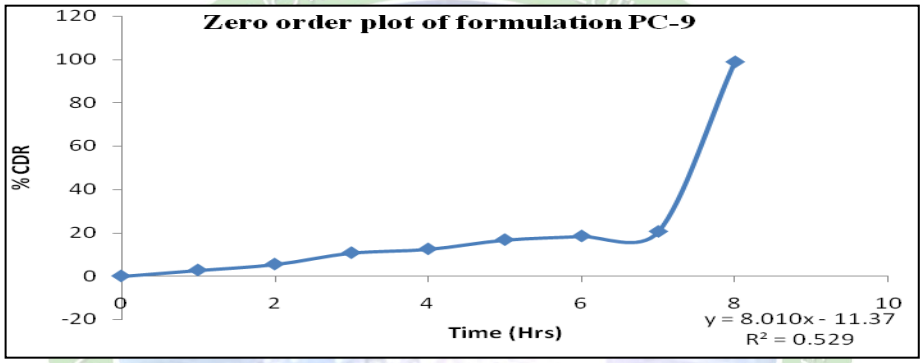

Fig 6: Zero order plot of formulation PC-9

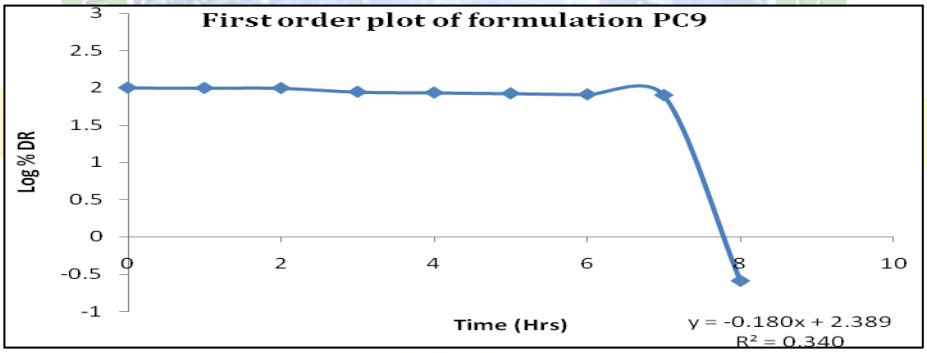

Fig 7: First order plot of formulation PC-9

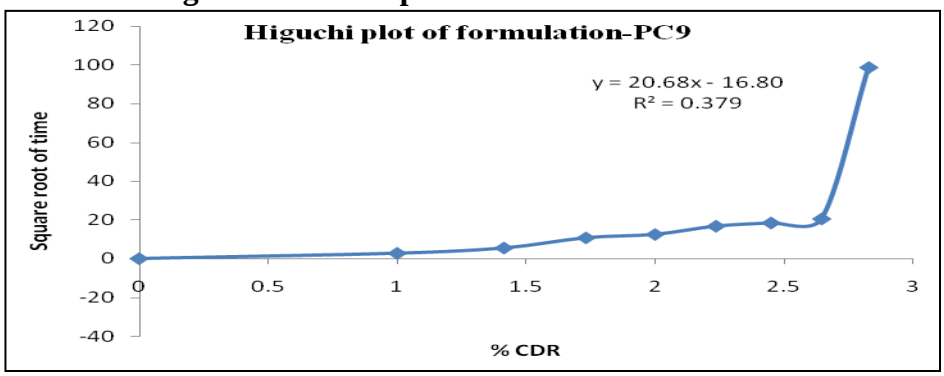

Fig 8: Higuchi plot of formulation PC-9

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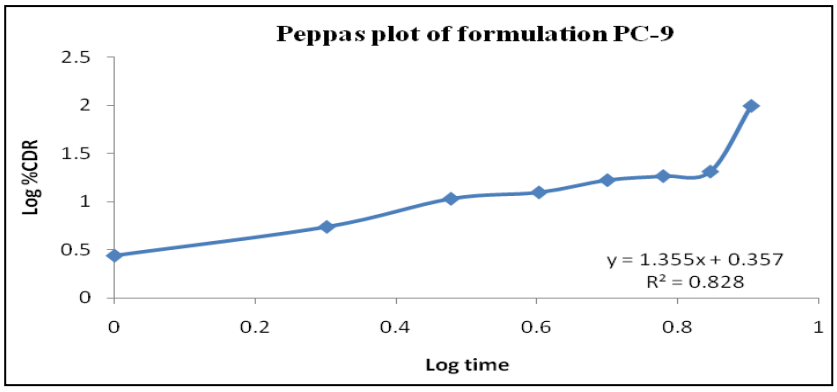

Fig. 9: Peppas plot of formulation PC-9

CONCLUSION

Piroxicam is an anti-inflammatory drug used in treatment of rheumatoid arthritis. Core tablets of piroxicam were prepared using various super disintegrants like Ac di sol and Explotab using direct compression method. The core tablets were then press coated with polymers to release the drug in early morning hours after predetermined lag period. Formulation PC-9 had shown good hardness, thickness, friability, weight variation values. Dissolution tests were conducted in 0.1 N Hcl acidic buffer for 120 minutes and in phosphate buffer pH 6.8 for remaining 6 hoursin USP dissolution apparatus. Core tablets initially released 95.85% drug in 60 minutes and press coated tablets released98.82 % drug after 8 hours. Accelerated stability studies were carried out for 90 days. Formulation PC-9 of piroxicam containing Ac di sol and Explotab as super disintegrant and hydroxy propyl methyl cellulose and ethyl cellulose as rate controlling polymers has shown no visible color changes and had not shown any deviation in dissolution profile after 3months. Drug release kinetics does not follow on zero order kinetics. Drug is released slowly by diffusion Hence formulation PC-9 containing piroxicam with 20mg Explotab, 100mg HPMC and 190mg EC was chosen as best optimized formulation after carrying out all evaluation tests

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