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Research article

PREPARATION AND EVALUATION OF PULSATILE RELEASE TABLETS OF KETOPROFEN CONTAINING AC DI SOL AND SODIUM STARCH GLYCOLATE

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ABSTRACT

The main aim and objective of present investigation was to formulate and evaluate pulsatile tablets delivery system for Anti-inflammatory drugs like ketoprofen. Chrono modulated drug delivery systems release the drug at predetermined lag time in diseases like cardiovascular disorders, diabetes mellitus, bronchial asthma, rheumatoid arthritis, peptic ulcers. Ketoprofen is an anti-inflammatory drug used in treatment of rheumatoid arthritis. Core tablets of ketoprofen were prepared using various super disintegrants like Ac di sol and sodium starch glycolate 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. Carrageeenan and xanthum gum were used as release rate 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 KP-14 of ketoprofen containing Ac di sol and Explotab as super disintegrant and Carrageeenan and xanthum gum 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 KP-14 containing ketoprofen is chosen as best optimized formulation after carrying out all evaluation tests.

Keywords: Pulsatile drug delivery system, Ac-di-sol, SSG, pharmacokinetics, LOD, Press coating.

INTRODUCTION

Chrono modulated drug delivery systems are time controlled systems which releases the drug in fixed time after a predetermined lag time. Pulsatile drug delivery systems are useful in certain diseases bronchial asthma, arthritis, cardio vascular disorders which depends upon circadian rhythms. In case of arthritis, myocardial infarction, angina asthma, osteoarthritis, peptic ulcers, epilepsy and cardiovascular diseases hormonal levels changes depending upon biological cycle. 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]. Chrono modulated drug delivery system releases the drug at preprogramed 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. Pulsatile drug delivery doesn't follow zero order release [3]. Chrono modulated drug delivery systems are becoming popular because of

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their improved patient compliance. The aim of the present study was to develop and evaluate of chrono modulated tablets of ketoprofen [4]. It involves preparation of immediate release core tablets and press coated tablets.

Ketoprofen,(RS)-2-(3-benzoylphenyl)-propionic acid is a non-steroidal anti-inflammatory drugs (NSAID) drug [5, 6]. Chemical Formula of ketoprofen is $C_{16}H_{14}O_3$. Ketoprofen is a white or off-white, odorless, non-hygroscopic, granular powder with molar mass of 254.28 g/mol. It is freely soluble in ethanol, chloroform, acetone, ether and soluble in benzene and strong alkali, but practically insoluble in water. Ketoprofen inhibits the prostaglandin synthesis in the body [7]. Ketoprofen undergoes hepatic metabolism by conjugating with glucuronic acid and CYP2C9. It undergoes hydroxylation reactions. Ketoprofen inhibits cyclooxygenase-1 and cyclooxygenase-2 (COX-1 and COX-2) enzymes and decreases production of prostaglandin synthesis [8-10].

Ketoprofen is used in arthritis, inflammation, pains or toothaches that result in the oral gum inflammation. Ketoprofen is also used for treatment of musculoskeletal pain and nerve pain such as sciatica, neuralgia as cream, ointment, spray, or gel.

Preparation and evaluation of ketoprofen pulsatile release tablets

Preformulation studies

Some physical and chemical properties of drug and excipients are determined before the development of dosage forms. Preformulation is defined as a major step in research and development process where the physicochemical properties of drug and excipients used are determined in order to formulate stable and effective dosage forms.

API characterization and identification

Ketoprofen was procured from aurobindo pharma, Hyderabad as gift sample. Identification of drug was carried out by various pharmacopoeial guidelines.

Organoleptic properties

Colour and odour of API were characterized and recorded.

Solubility

The solubility of ketoprofen was tested in various solvents.

Melting point

Test was carried out by taking a small amount of API in a capillary tube with one end closed and placed in melting point apparatus. The melting point was tested in triplicate.

Loss on drying

3gms of Ketoprofen was taken in glass plate and kept in hot air oven. Temperature was set at 105^0C and the powder was weighed to constant weight. Distribute the sample to a depth not crossing 10 mm. Place the loss on drying bottle in the oven at 105°c by for 4 hours. After drying is completed, open the oven allow it to cool at room temperature in desiccators for 30 minutes. Weigh the crucible and calculate the percentage LOD.

LOD (% w/w) = (W2 - W3)/(W2 - W1)**x** 100

FTIR study

Drug was mixed with KBr dried overnight at 110^0C .Drug and KBr was triturated in mortar with pestle to form uniform dispersion. Mixture was made as pellets in IR compression machine to develop a transparent pellet. The pellet was studied by using FTIR spectrometer. The FTIR spectra of pure Ketoprofen showed the peaks at particular wave numbers (cm^{-1}) which correspond to functional groups present in the API.

The presence of absorption bonds respective to the functional groups present in the structure of API and the absence of any well-defined unknown peak is a confirmation of the purity of the API sample. The Fourier Transform Infra-Red analysis was conducted for the analysis of drug polymer interaction. Fourier transform infra-red spectrum of pure API and physical mixture were recorded using Fourier Transform Infrared Spectrophotometer Shimadzu, Japan. The spectrum was scanned over a frequency range 400-4000 cm-1.

Powder characterization

Powder characterization of ketoprofen was performed for parameters like bulk density, tap density, compressibility index, Hausner's ratio and angle of repose [11].

Pre compressional parameters

Physical properties

The mixture of active pharmaceutical ingredient and excipients were evaluated for angle of repose, bulk density, tapped density, % compressibility, and Hausner's ratio. Properties like hardness, disintegration time are dependent on the flow characteristics of powder and density of the power blend. The flow properties of the drug and excipients play important role in flow of mixture from hopper to die.

Bulk density (Db)

It is defined as mass to bulk volume ratio. The bulk density depends on particle size and shape of drug and excipients.

Method: Pour weight amount of powder (25gm) blend into a measuring cylinder using a funnel and note done the volume occupied by the powder blend without tapping the measuring cylinder. It is expressed in gm/ml.

Db = M/Vo

M = weight of powder,

Vo = bulk volume

Tapped density (Dt)

Tapped density is ratio of mass of the blend to its tapped volume. It depends upon the void spaces between the particles and it is expressed in gm/ml.

Method: powder blend (10 gm) is poured into a measuring cylinder with the help of funnel and note done the volume occupied by the powder blend after tapping the measuring cylinder for 100 times on the table from a constant height. The tapped density of the powder blend can be calculated using the following formula:

Dt = M/Vt

M = mass of powder,

Vt = tapped volume of the powder.

Compressibility Index

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

% compressibility = (tapped density - bulk density) / tapped density x100

Hausner's ratio: The inter-particulate interactions between the particles of the powder blend has significant effect on the powder flow characteristics. Higher the interactions, poorer the flow of powders Hausner's ratio is calculated using the following formula.

Hausner's ratio = Dt/Db

Db = Bulk density

Dt = Tapped density

Angle of repose

Angle of repose is the angle made by pile of powder with plane surface. Determination of angle of repose was carried out using of 25grams of powder. Powder was poured over the plain white paper is placed over the table through a funnel fixed to burette stand from a fixed height. After passing the powder through the 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

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

θ = Angle of repose

H =Height of pile

R =Radius of pile

Standard curve of ketoprofen in 0.1 N HCl

An accurately weighed quantity of Ketoprofen was taken in 100 ml volumetric flask and sufficient quantity of pH 1.2 HCL & pH 6.8 Phosphate Buffer solutions were added and diluted to 100 ml with the same solvent so as to get the concentration of 100µg/ml. For various concentration of drug solution, appropriate aliquots were pipette out from standard stock solution into the series of 10 ml volumetric flask and the volume was made up to the mark with respective buffers to get concentration of 10-50 µg/ml of Ketoprofen and absorbance is measured at 260nm.

Drug excipient compatibility studies

Stability of the product is also dependent on the type of the inactive ingredients used in the preparation of product. So it is necessary to carry out suitable drug excipient compatibility studies for 3 months and analyze the blend for physical and chemical changes before the formulation [12].

Formulation development of ketoprofen pulsatile release tablets

Preparation of Core Tablets Using Direct Compression

Core tablets of ketoprofen were prepared using direct compression technique. Drug and super disintegrants were passed through sieve and mixed uniformly with help of mixer. Lubricants and glidants are mixed at the end and compressed using rotary tablet. Tablet hardness was adjusted to get maximum strength. Various concentrations of super disintegrants were used in preparation of core tablet.

Preparation of press-coated tablets

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

Evaluation of ketoprofen pulsatile tablets

Post compression parameters

Following quality control tests are conducted to check the properties of pulsatile release tablets [11-19].

Weight variation test

Randomly select 20 tablets and weigh them individually. Calculate the individual weight of each tablet and note it .Now compare individual weight of each single tablet with average weight of 20 tablets. Weight variation can be calculated using following formula

Percentage deviation= average weight – individual weight/average weight*100

Thickness: The thickness of 20 tablets was measured by using vernier calipers. Tablet is placed horizontally between two arms of vernier calipers and the thickness was measured. The average values should not deviate from ±5%.

Hardness: Monsanto tablet hardness tester is used to test the hardness of the tablet. The tablet is held between the two jaws of hardness tester. Initial reading of the Scale was adjusted to zero; slowly the force was applied the tablet is broken. The pressure at which the tablet breaks is

noted from the scale. Hardness of the tablet is expressed in kg/cm^2.

Friability: Tablets require some amount of strength to withstand mechanical shock of during packaging the product, manufacturing, and shipping of final product.20 tablets were weighed and placed in friabilator which is operated for 25 RPM for 4 minutes, again the tablets were weighed and % friability of tablets was calculated

F=1-(Wo/W)*100

Drug content: For this test 10 tablets were crushed using mortar pestle. The quantity equivalent to 100 mg of drug was dissolved in 100 ml of pH 6.8phosphate buffer, filtered and diluted to get 50µg/ml and analyzed UV spectrophotometrically at 260nm. The concentration of drug was determined on basis of standard curve.

In-vitro drug release studies

Drug release studies of ketoprofen core tablets: The core tablets containing 10mg ketoprofen of were tested in Phosphate buffer (pH 6.8) for their dissolution rates. Dissolution studies were performed using USP paddle type apparatus. 5ml sample was withdrawn and replaced with equal volume of fresh medium. The samples were analyzed spectrophotometrically at respective 333nm.

Application of Release Rate Kinetics to Dissolution Data

Kinetics of drug release are tested with various models. Mechanism of the drug release of the dosage form were analyzed. The data was fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model [20].

Zero order release rate kinetics

To study the zero–order release kinetics the release rate data are fitted to the zero order equation.

First order release rate kinetics

A plot of log cumulative percent of drug remaining to be released vs. time was plotted then it gives first order release.

Higuchi release model

To study the Higuchi release kinetics square root of time vs % CDR was plotted.

Korsmeyer and Peppas release model

The mechanism of drug release was evaluated by plotting the log % CDR versus log time according to Korsmeyer-Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

Results of ketoprofen pulsatile release tablets

Preformulation studies of ketoprofen

Organoleptic Properties

Colour : White crystalline powder
Solubility : Insoluble in water
Odour : Odour less

Powder characterization

Bulk densities and tapped density of drug were evaluated by using measuring cylinder. Angle of repose of was evaluated by funnel method. Hausner's ratio and Carr's index were calculated as follows.

FTIR Studies

Drug was mixed with KBr dried overnight at 110^0C .Drug and KBr was triturated in mortar with pestle to form uniform dispersion. Mixture was made as pellets in IR compression machine to develop a transparent pellet. The pellet was studied by using FTIR spectrometer.

The FTIR spectra of pure Ketoprofen showed the peaks at particular wave numbers (cm-1) which correspond to functional groups present in the API.

Drug and Excipient Compatibility Studies

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

Standard curve of ketoprofen in 0.1 N HCl

An accurately weighed quantity of Ketoprofen was taken in 100 ml volumetric flask and sufficient quantity of pH 1.2 HCL & pH 6.8 Phosphate Buffer solutions were added and diluted to 100 ml with the same solvent so as to get the concentration of 100µg/ml. For various concentration of drug solution, appropriate aliquots were pipette out from standard stock solution into the series of 10 ml volumetric flask and the volume was made up to the mark with respective buffers to get concentration of 10-50 µg/ml of Ketoprofen and analyzed at 260nm.

Invitro drug release studies

Dissolution of ketoprofen tablets were performed in a USP dissolution tester (Lab India), paddle method with 900 ml of 0.1 N HCL for 2hrs and then with pH 6.8 Phosphate buffer for 6 hrs, as a medium at 37±0.5ºC. The speed of the paddle was adjusted 50 RPM. A predetermined time intervals aliquot of the samples were collected, filtered and analyzed under UV spectrophotometer at 260nm. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Accelerated stability studies

Stability of drug substance and final product is essential for long term storage of drug product. Data regarding physical or chemical changes or degradation of drug substances and drug product is required to place the drug product in best suitable conditions. Fixing **s**uitable

conditions for storage of final drug product helps to maintain uniformity of dose during shelf life period.

To carry out stability studies of final product 'stability chamber' are used, which maintain suitable temperature and relative humidity during the test period. Tablets are packed in covers and placed as per ICH guidelines for studies 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 6 months. Stability studies for the optimized formulations were carried out by placing the formulations in stability chambers at 40ºC /75 RH for 6 months period. After fixed time intervals required number of tables were taken and evaluated for changes in color, appearance drug content and dissolution profile. The data obtained after the studies is compared with the data generated immediately after manufacturing of tablets. The data obtained is used to determine proper storage conditions and shelf life of final drug product.

Table 1. Angle of repose values with corresponding flow pattern

Angle of repose values	Flow pattern
25-30	Excellent
31-35	Good
36-40	Fair
41-45	Passable
46-55	Poor
56-65	Very poor

Table 2. Formulation of ketoprofen pulsatile release tablets KP 11-KP20

Ingredients for core tablet										
Ingredients	**K11 (mg)**	**KP12 (mg)**	**KP13 (mg)**	**KP14 (mg)**	**KP15 (mg)**	**KP16 (mg)**	**KP17 (mg)**	**KP18 (mg)**	**KP19 (mg)**	**KP20 (mg)**
Ketoprofen	200	200	200	200	200	200	200	200	200	200
Ac di sol	2	4	6	8	10	-	-	-	-	-
SSG	-	-	-	-	-	2	4	6	8	10
Lactose	53	51	49	47	45	53	51	49	47	45
MagnesiumStearate	5	5	5	5	5	5	5	5	5	5
Aerosil	5	5	5	5	5	5	5	5	5	5
Ingredients for press coated tablets										
Carrageeenan	25	50	75	100	125	-	-	-	-	-
lactose	110	85	60	35	10	110	85	60	35	10
Xanthum gum	-	-	-	-	-	25	50	75	100	125

Table 3. Specifications for Average weight and percentage deviation allowed

Average weight of tablets (mg) (I.P.)	% Deviation allowed
Less than 80	10
80–250	7.5
More than 250	5

Table 4. Powder characterization for ketoprofen

Sample weight(gm)	Bulk density(gm/cc)	Tapped Density(gm/cc)	Compressibility Index (%)	Angle of Repose(Ø)	Hausner's ratio
25	0.348	0.412	15.53	24.75	1.18

Table 5. Standard curve of ketoprofen in 0.1 N HCl

Sr. No	Concentration(µg/ml)	Absorbance
1	0	0
2	2	0.185
3	4	0.374
4	6	0.567

5	8	0.754
6	10	0.982

Table 6. Evaluation of ketoprofen core tablets (KP11-KP20)

Formulation	Weight Variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug Content
KP11	265±0.4	5.2±0.2	5.8±0.8	0.41±0.01	89.10
KP12	263±0.5	5.4±0.3	5.5±0.1	0.47±0.05	85.72
KP13	269±1.6	5.4±0.7	5.9±0.1	0.41±0.10	86.47
KP14	265±0.1	5.5±0.1	6.0±0.1	0.30±0.02	99.45
KP15	264±0.7	5.1±0.8	5.3±0.4	0.36±0.11	86.95
KP16	258±3.5	5.3±0.5	5.5±0.3	0.44±0.08	87.10
KP17	257±1.6	5.4±0.4	5.5±0.2	0.59±0.14	85.84
KP18	261±2.8	5.0±0.9	5.3±0.8	0.54±0.02	89.70
KP19	258±2.5	5.3±0.5	5.3±0.2	0.55±0.06	85.74
KP20	265±1.4	5.2±0.5	5.5±0.5	0.58±0.04	89.58

Table 7. Evaluation of press coated ketoprofen pulsatile tablets (KP11-KP20)

Formulation	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)
KP11	405±0.4	5.6±0.5	5.7±0.4	0.51±0.08	92.73
KP12	403±.5	5.8±0.5	5.4±0.3	0.47±0.07	94.59
KP13	399±0.6	5.6±0.9	5.9±0.6	0.41±0.01	93.73
KP14	400±0.1	6.0±0.1	6.0±0.1	0.37 ±0.12	99.43
KP15	404±2.4	5.1±0.9	5.8±0.5	0.36±0.11	95.19
KP16	398±1.4	5.8±0.4	5.8±0.3	0.44±0.07	89.16
KP17	397±2.4	5.8±0.4	5.9±0.8	0.49±0.07	84.97
KP18	402±2.8	5.6±0.3	5.7±0.6	0.54±0.04	91.74
KP19	403±1.5	5.5±0.4	5.9±0.2	0.55±0.03	92.45
KP20	405±1.4	5.7±0.1	5.7±0.5	0.58±0.03	85.15

Table 8. Dissolution profile of ketoprofen core tablets (KP11-KP20)

Time (mins)	% cumulative drug release									
	KP11	KP12	KP13	KP14	KP15	KP16	KP17	KP18	KP19	KP20
10	10.21	14.24	16.45	14.23	17.65	10.85	11.27	14.52	15.65	18.74
20	22.27	35.49	28.78	29.78	31.75	22.25	35.47	27.85	39.74	35.88
30	38.48	41.36	32.45	44.85	49.85	31.85	55.45	39.48	52.55	45.78
40	44.57	65.89	57.82	54.57	56.75	59.87	61.28	46.91	71.96	69.76
50	59.48	69.98	61.45	73.85	75.54	68.15	74.85	77.49	81.46	78.44
60	85.84	86.87	88.43	95.89	87.48	81.54	83.85	86.79	89.58	91.48

Table 9. Dissolution profile of ketoprofen press coated tablets (KP11-KP20)

Time (hrs)	% cumulative drug release									
	KP11	KP12	KP13	KP14	KP15	KP16	KP17	KP18	KP19	KP20
1	2.42	2.78	2.95	1.02	2.54	1.12	1.21	1.95	1.44	1.47
2	14.26	8.48	4.48	1.14	7.84	2.68	2.45	2.74	2.24	2.55
3	26.87	18.74	17.84	12.04	15.45	9.585	11.95	14.25	18.74	29.96
4	34.75	20.25	19.84	14.07	19.48	17.28	25.54	29.32	25.87	35.65
5	44.84	31.49	28.74	16.15	22.65	25.39	38.74	44.32	44.65	38.44
6	56.74	44.75	32.54	18.75	23.95	45.84	46.84	49.54	57.87	49.75
7	60.48	56.51	36.48	20.44	25.48	61.54	68.41	69.21	66.36	69.48
8	87.87	89.32	88.96	99.74	94.85	85.22	84.94	87.42	84.74	86.52

Table 10. Protocol for Stability testing of optimized batch of press coated tablet – KP14

S.No	Conditions	1 month		3 months		6 months	
		% CDR	Drug content	% CDR	Drug content	% CDR	Drug content
1	**25^{0}c/60%RH**	95±0.25	56.58	95±0.53	98.51	99±0.95	96.18
2	**30^{0}c/65% RH**	94±0.15	95.19	97±0.55	92.84	96±0.21	97.56
3	**40^{0}c/75% RH**	99±0.41	94.11	96±0.51	98.11	97±0.75	96.14

Table 11. Protocol for Stability testing of optimized batch of press coated tablet – KP14

S.No	Conditions	1 Month			6Months		
		Colour Change	Hardness	Friability	Colour Change	Hardness	Friability
1	**25^{0}c/60%RH**	No	5.8±0.4	0.35±0.01	No	5.8±0.8	0.35±0.16
2	**30^{0}c/65% RH**	No	6.0.±0.7	0.34±0.05	No	5.7±0.1	0.31±0.10
3	**40^{0}c/75% RH**	No	5.9±0.3	0.39±0.01	No	5.9±0.5	0.38±0.10

Fig 1. FTIR Spectrum of Ketoprofen

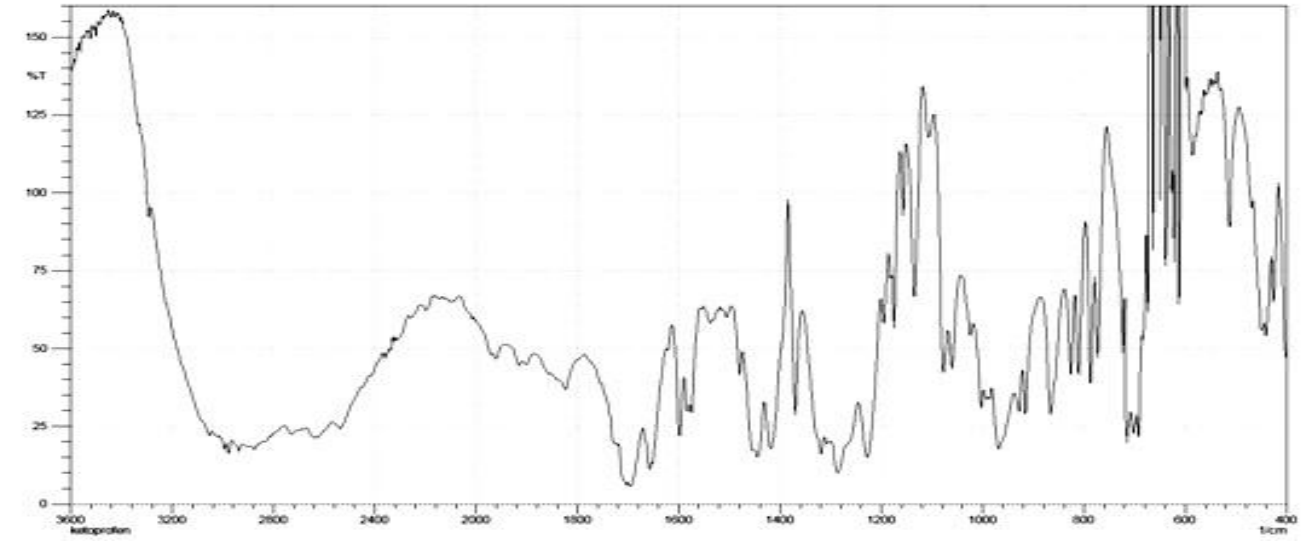


Fig 2. FTIR spectrum of Ketoprofen and crospovidone

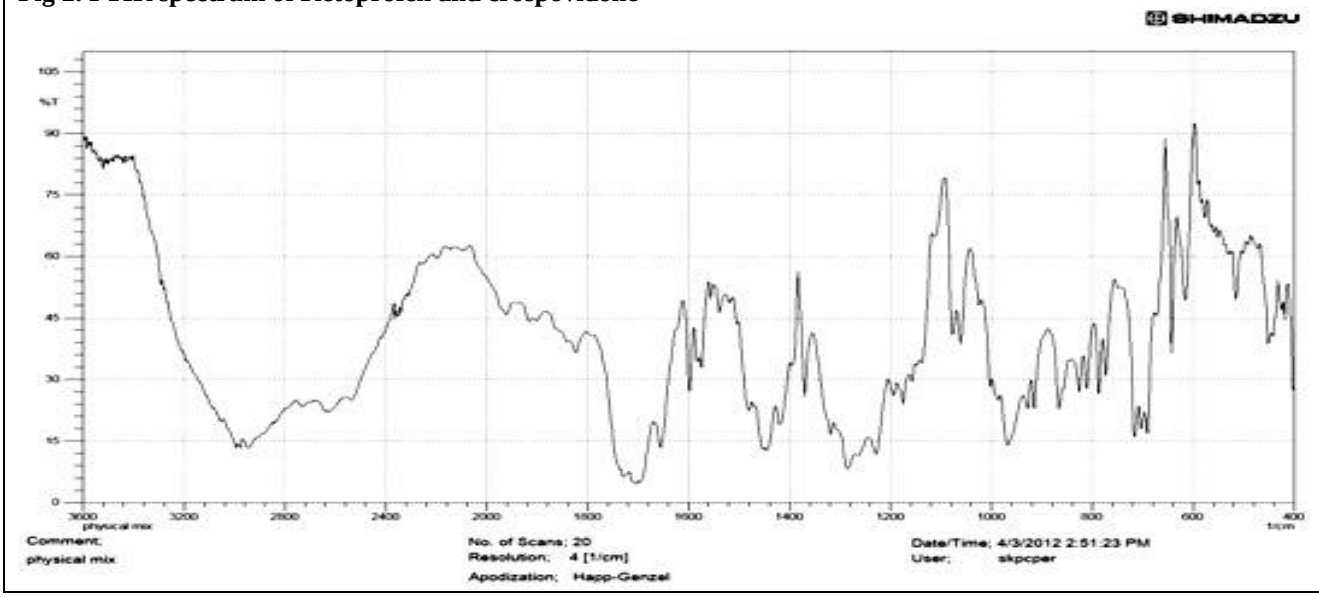


Fig 3. FTIR spectrum of Ketoprofen and carrageenan

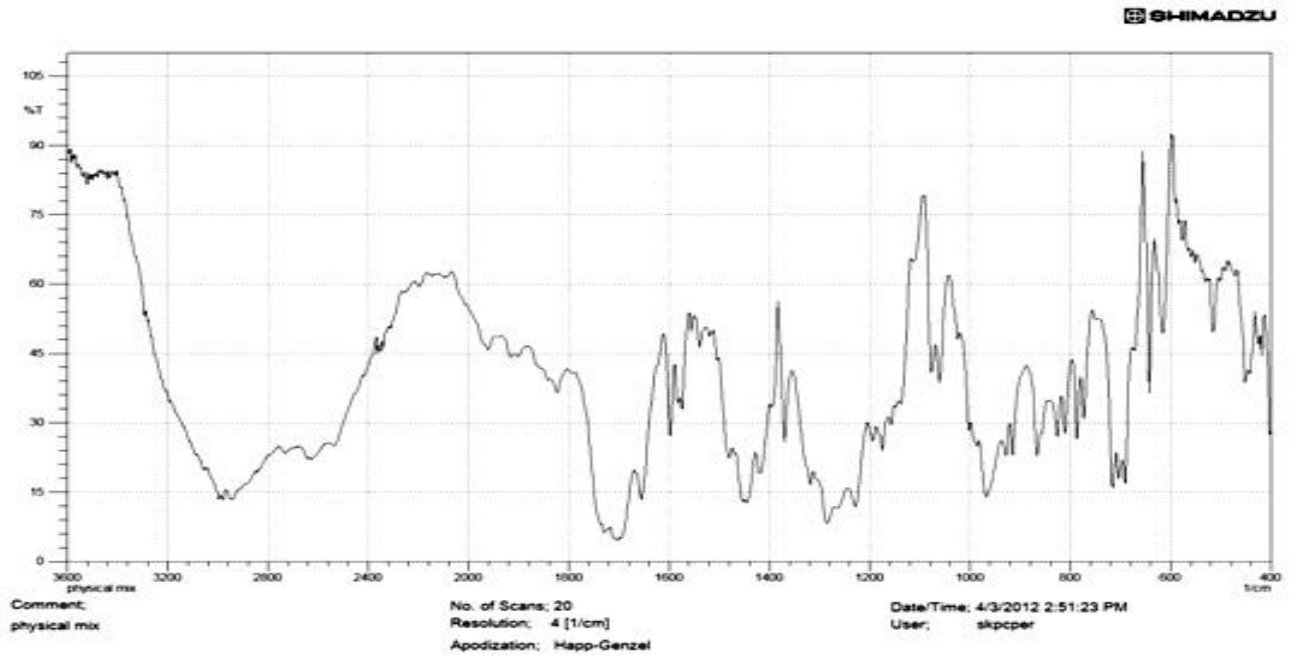


Fig 4. Standard curve of ketoprofen in 0.1 N HCl

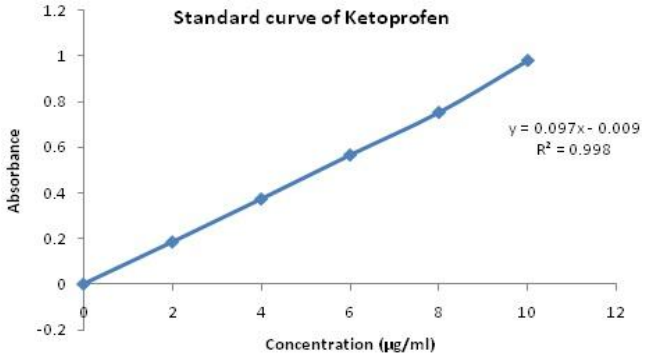


Fig 5. Drug Content of core tablet- formulations KP11 to KP20

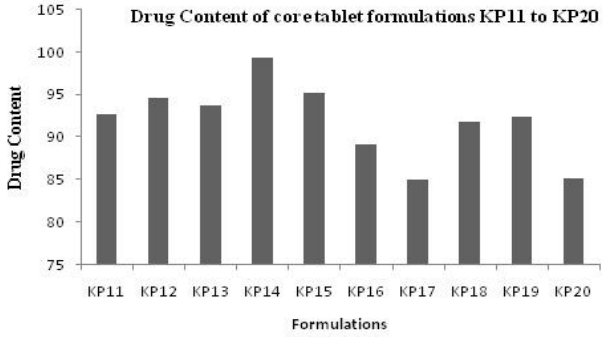


Fig 6. Drug Content of press coated tablet-formulations KP11 to KP20

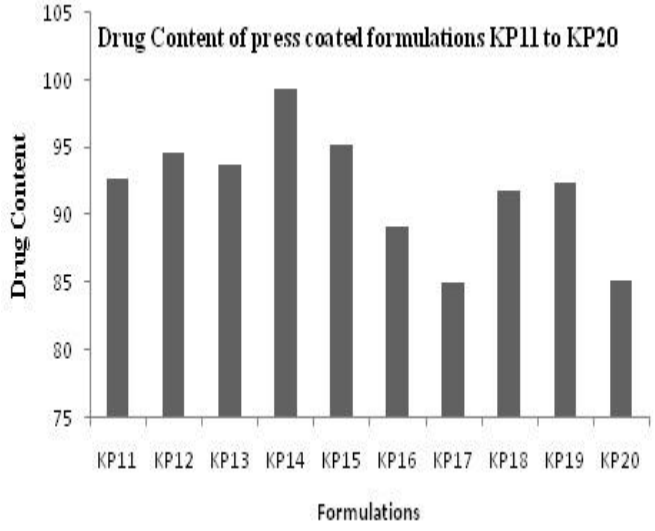


Fig 7. % CDR of optimized formulation KP14

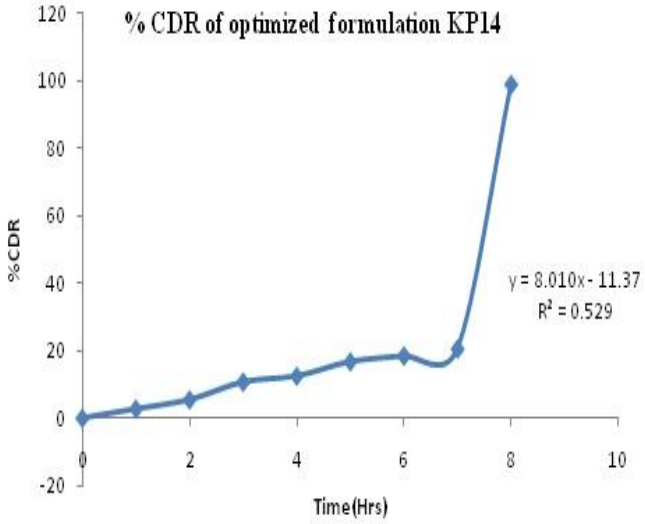


Fig 8. Zero order plot of optimized formulation KP14

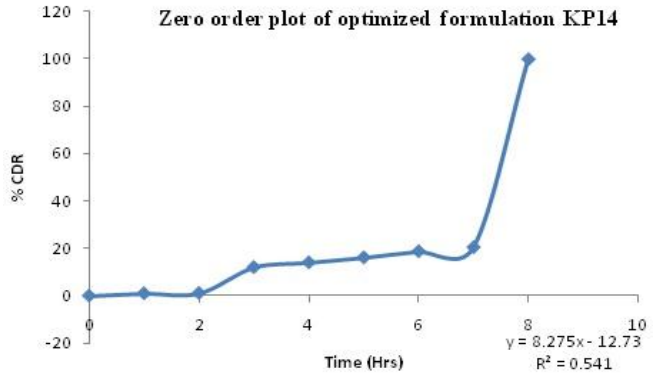


Fig 9. First order plot of optimized formulation KP14

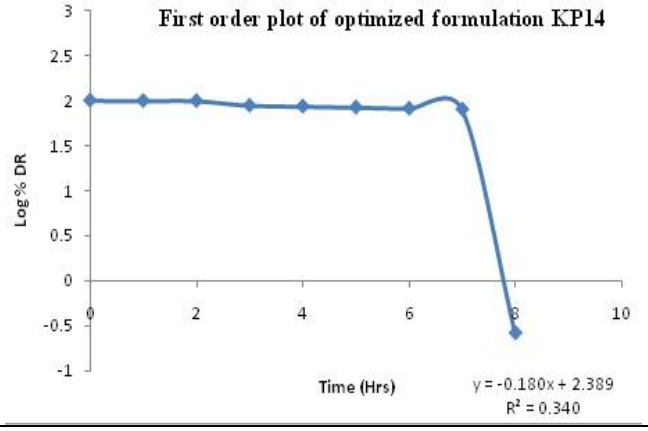


Fig 10. Higuchi plot of optimized formulation-KP14

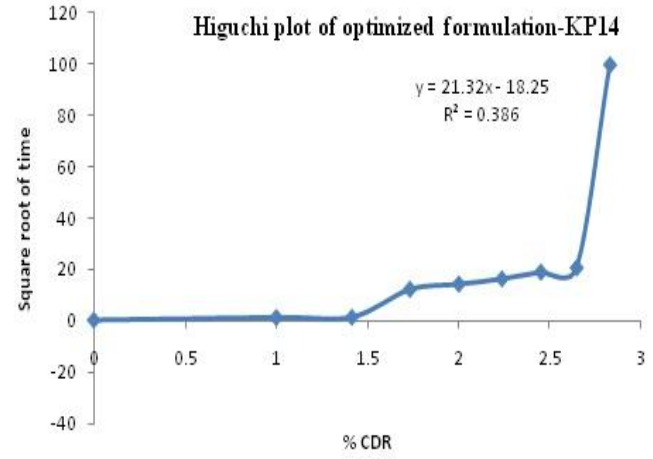
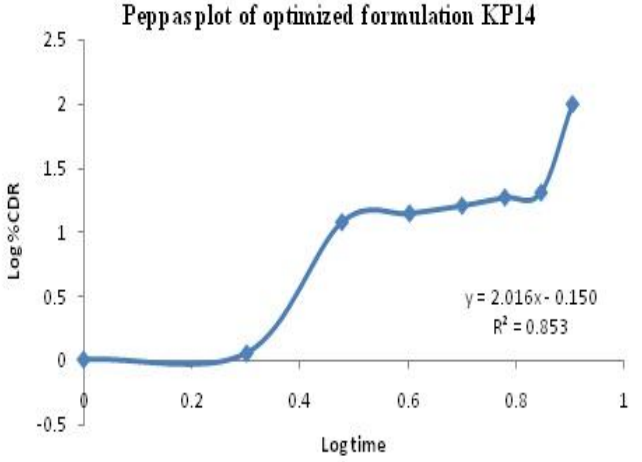


Fig 11. Peppas plot of optimized formulation KP14



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 is good flowing properties. Formulation KP-14 has less weight variation and friability. Assay values shown good drug content values. Formulation KP-14 has released very less amount of drug during initial 2 Hrs and has shown pulsatile release at 8th hour. Hence it is selected as best formulation.

CONCLUSION

Ketoprofen is an anti-inflammatory drug used in treatment of rheumatoid arthritis. Core tablets of ketoprofen 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 KP-14 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 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 ketoprofen containing Ac di sol and SSG as super disintegrant and xanthum gum and carrageenan 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 KP-14 containing ketoprofen with 20mg Explotab, 100mg HPMC and 190mg EC was chosen as best optimized formulation after carrying out all evaluation tests

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REFERENCES

1. Hu T. Discrete chemical release from a microfluidic chip. *J. Micro electro mech. Syst*., 16(4), 2007, 785–794.
2. Susan S. Biocompatibility of silicon-based electrode arrays implanted in feline cortical tissue. *J. of Biomedical materials research*, 27(11), 1993, 1393-1399.
3. Evans AC. Diamond-like carbon applied to bioengineering materials. *Surface and Coating technology*, 47(1-3), 1991, 662-667.
4. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J Pharm Sci*, 52, 1963, 1145-9.
5. Malhotra S, Shafiq N, Pandhi P: COX-2 inhibitors: a CLASS act or Just VIGORously promoted. *MedGenMed*, 6(1), 2004, 6.
6. Parsadaniantz SM, Lebeau A, Duval P, Grimaldi B, Terlain B, Kerdelhue B: Effects of the inhibition of cyclo-oxygenase 1 or 2 or 5-lipoxygenase on the activation of the hypothalamic-pituitary-adrenal axis induced by interleukin-1beta in the male Rat. *J Neuroendocrinol*, 12(8), 2000, 766-73.
7. Kurahashi K, Shirahase H, Nakamura S, Tarumi T, Koshino Y, Wang AM, Nishihashi T, Shimizu Y: Nicotine-induced contraction in the rat coronary artery: possible involvement of the endothelium, reactive oxygen species and COX-1 metabolites. *J CardiovascPharmacol*, 38(1), 2001, S21-5.
8. Zuniga J, Fuenzalida M, Guerrero A, Illanes J, Dabancens A, Diaz E, Lemus D: Effects of steroidal and non steroidal drugs on the neovascularization response induced by tumoral TA3 supernatant on CAM from chick embryo. *Biol Res*, 36(2), 2003, 233-40.
9. Martic M, Tatic I, Markovic S, Kujundzic N, Kostrun S: Synthesis, biological activity and molecular modeling studies of novel COX-1 inhibitors. *Eur J Med Chem*, 39(2), 2004, 141-51.
10. Levoin N, Blondeau C, Guillaume C, Grandcolas L, Chretien F, Jouzeau JY, Benoit E, Chapleur Y, Netter P, Lapicque F: Elucidation of the mechanism of inhibition of cyclooxygenases by acyl-coenzyme A and acylglucuronic conjugates of ketoprofen. *BiochemPharmacol*, 68(10), 2004, 1957-69.
11. Lachman.The theory and Practice of Industrial Pharmacy 3rd edition,114-115.
12. Ahmad M, Andrei D. pHindependent pulsatile drug delivery system based on hard gelatin capsules and coated with aqueous dispersion Aquacoat ECD. *European Journal of Pharmaceutics and Biopharmaceutics*, 64, 2006, 173-179.
13. Dasharath M Patel, Rushiraj H Jani, Chhagan N Patel. Design and evaluation of colon targeted modified pulsincap delivery of 5-fluorouracil according to circadian rhythm. *International Journal of Pharmaceutical Investigation*, 1(3), 2011, 172-181.
14. Santanu G and Barik B. A comparative study of the pharmacokinetics of conventional and sustained-release tablet formulations of aceclofenac in healthy male subjects. *Tropical Journal of Pharmaceutical Research*, 9(4), 2010, 395-399.
15. Maha A, et al. In-vitro release, Thermodynamics and Pharmacodynamic Studies of Aceclofenac Transdermal Eudragit Patches. *Drug Invention Today*, 1(1), 2009, 16-22.
16. Kale VV, Kasliwal RH, Avari JG. Attempt to design continuous dissolution-absorption system using everted intestine segment for in vitro absorption studies of slow drug release formulations. *Dissolution Technologies*, 14, 2007, 31–36.
17. Mariappan TT, Singh S. Evidence of effluxmediated and saturable absorption of rifampicin in rat intestine using the ligated loop and everted gut sac techniques. *Mol Pharm*, 1, 2004, 363–367.
18. Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J Pharm Sci*, 52, 1963, 1145-9.
19. Hixson AW and Crowell JH. Dependence of reaction velocity upon surface and agitation (I) theoretical consideration. *IndEngChem*, 23, 1931, 923-31.
20. Bhargava A, *et al*. Oral sustained release dosage form: an opportunity to prolong the release of drug. *IntJ ARPB*, 3, 2013, 7-14.

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