Research Article

Development and Optimization of Controlled Release Tablet of Ketorolac Using Natural Polymers

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ABSTRACT

The objective of the present work was to develop and optimize ketorolac loaded controlled release tablet using a natural polymer. In this study, we utilized a combination of two natural polymers like Almond gum and guar gum to prepare Ketorolac controlled release tablets. The natural polymers are used in controlled release tablets because has numerous advantages and it is occurs naturally, relatively safe, cheap and do not have any side effects. Ketorolac controlled release tablet were prepared by direct compression method. First Pre-formulation studies were carried out such as FTIR, solubility, bulk and tapped density, housners ratio, Carr's index, angle of repose etc. Then the tablets were prepared by direct compression using natural polymers. To obtain the desired optimum formulation several formulations had been performed with different excipients and their ratio. For each formulation, post formulation parameters are determined including hardness, weight variation, friability, disintegration and in vitro dissolution, etc. From the test performed it is found that the formulation F3 is best and satisfies all the criteria as controlled release tablet.

Keywords: Controlled release tablet, Ketorolac, Natural polymer, Development, Optimization

INTRODUCTION

Controlled-release drug delivery systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, to reduce the number of single dose per day improving patient compliance of treatment and to decrease the fluctuations of plasma levels, in order to obtain better therapeutic efficacy and lower toxicity. Controlled release tablets are used for prolonged duration of action with minimal therapeutic effect. They are formulated with natural high intense polymer to achieve sustained release of the API.[1] Hydrophilic matrix tablets are the most promising controlled release system among researchers in oral solid formulations due to the simplicity of their formulation, ease of manufacturing, their low cost, FDA acceptance and applicability to drugs with a wide range of solubility. The polymer of choice must exhibit good compression characteristics and suitable swelling properties in contact with the aqueous medium in order to ensure the rapid formation of an external layer as a "protective" coat for the matrix and is consider being the element controlling the drug release the kinetics.[2] In addition, the cost of formulation development, raw material, and manufacture technology are among the principal factors in CR delivery systems formulation for oral dosing. The controlled drug therapy is improved efficiency in treatment that is, achieving the desired effect and maintaining it for an extended period of time.[3]

The aim and objective of present work is to formulate and evaluate controlled release tablets by direct compression method using the drug Ketorolac as a model drug. It was aimed to designed the release of active content in a predictable pattern in vivo over an extended time period albeit for some, faster release is desirable. The general design objective of a controlled release system is to fabricate a device capable of constant zero-order drug release over a prolonged time period. Evaluation of formulated tablets was done using various quality parameters like hardness, friability, wetting time, disintegration time, in vitro dissolution study.

Clinical Advantages of Oral CRDDS[4]

- Reduction in frequency of drug administration and low plasma concentration and improvement of bioavailability of some drugs

- Reduction in health care costs through improved therapy and improved patient convenience and compliance

- Reduction in drug level fluctuation of steady state levels and therefore better control of disease condition and reduction intensity of local or systemic side effects

- Increased safety margin of high potency drugs due to better control of plasma levels and reduction in drug toxicity

- Maximum utilization of drug enabling reduction in total amount of dose administered and Stabilization of medical condition (because of more uniform drug levels)

Potential Limitations of Oral CRDDS[5]

- Delay in onset of drug action

- Possibility of dose dumping in the case of a poor formulation strategy

- Increased potential for first pass metabolism

- Greater dependence on GI residence time of dosage form

- Cost per unit dose is higher when compared with conventional doses

Materials and methods

Materials: Ketorolac, was a gift sample from Zim Laboratories, Kalmeshwar, India; Natural polymers: Almond gum and Guar gum purchased from the local market, Nagpur, India; Microcrystalline cellulose (MCC), Magnesium stearate, Talc, Mannitol were purchased from Loba chemie Pvt Ltd. Mumbai, India. All other chemicals and solvents were of analytical reagent grade.

Evaluation of controlled release tablet

Pre-compression parameters[6]

Organoleptic properties

A small amount of sample is examined by simple visualization and colour, texture etc. were determined.

Solubility studies

A small quantity of the drug sample was taken in a test tube and the solubility was determined by dissolving the drug in 1 ml of various solvents.

Bulk Density (ρB)

Bulk density is determined by a constant mass method using measuring cylinder. The bulk density of a powder is the ratio of the mass of an untapped powder sample to its volume, including the contribution of the inter-particulate void volume.

It is expressed in gm/ml and is given by

$$Bulk\ density\ (\rho B) = M/Vo$$

Where, M = mass of the powder (weight taken in g)

Vo = Void volume (Untapped Volume in ml)

Tapped density (ρT)

Tapped volume is measured by taping measuring cylinder till there is no change of reading. It is expressed in gm/ml and is given by

$$Tapped\ density\ (\rho T) = M/Vf$$

Where M = mass of the powder (weight taken in g)

Vf= Tapped Volume (Final bulk volume after tapped in ml)

Hausner ratio

Hausner ratio is an indirect index to predict of powder flow. It is calculated by the following formula.

$$Hausner\ ratio = Tapped\ density\ (\rho T)/Bulk\ density\ (\rho B)$$

Compressibility index (Carr's index): Compressibility index (Carr's index) is an indirect parameter to assume flow property of powder. Compressibility index determined by measuring the initial volume (Vo) and final volume (Vf) after complete tapings of powder sample in a measuring cylinder.

$$Compressibility\ index\ (CI) = (Vo–Vf)/Vo\ X\ 100$$

Alternatively, compressibility index may be calculated using measured values for bulk density (ρB) and tapped density (ρT) as follows.

$$Compressibility\ index = 100\ x\ \{(\rho T-\rho B)/\rho T\}$$

Angle of repose

The angle of repose is the three-dimensional angle assumed by a cone-like pile of material formed by different methods. The method is fixed height method. In the fixed funnel, the method employs a funnel that was secured with its tip at a given height (2 cm), above the graph paper that was placed on a flat horizontal surface. Granules or tablet blend were carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. Thus, with r being the radius of the base of the conical pile. The angle of repose is calculating using formula.

$$Angle\ of\ repose\ (\theta) = tan^{-1}(h/r)$$

Where, h = height of the powder pile

r = radius of pile circle

Absorption spectra of ketorolac

The absorption spectra were prepared using phosphate buffer 6.8, in the range of 200-400 nm.[7]

Calibration curve of Ketorolac

It was prepared by using UV spectrophotometer for this 100 mg of the drug was dissolved in phosphate buffer 6.8 and shaken for complete dissolve. Then it was filtered and dilution was done in such a way that the resultant sample was of 20, 40, 60, 80, 100 etc and was analysed under UV spectrophotometer at the λmax 323 nm.[7]

FTIR study

The infrared spectrum was taken for the pure Ketorolac. FT-IR studies were carried by KBr disk method using computer mediated Fourier transformed infrared spectroscopy.[8]

Preparation of Ketorolac controlled release tablets
Accurately weighed amounts of Ketorolac and diluents were blended. To this varying amount of sifted Almond

gum and other excipients were added together blended and pass through sieve no. 40 and thus the mixture is ready for compression which was then compressed by an 8 mm punch in tablet punching machine.[9] Controlled release tablets of ketorolac were prepared by direct compression according to the formula given in table no. 1.

Table 1: Formulation table of Controlled release tablet of ketorolac

Sr. No.	Composition (mg)	F1	F2 (1:0.5)	F3 (1:1)	F4 (1:1.5)	F5 (1:2)	F6 (2:0.5)	F7 (3:0.5)
1.	Ketorolac	10	10	10	10	10	10	10
2.	Almond gum	10	10	10	10	10	20	30
3.	Guar gum	-	5	10	15	20	5	5
4.	Microcrystalline Cellulose	266.94	261.94	256.94	251.94	246.94	251.94	241.94
5.	Magnesium Stearate	5	5	5	5	5	5	5
6.	Talc	8	8	8	8	8	8	8
7.	Mannitol	0.06	0.06	0.06	0.06	0.06	0.06	0.06
	Total	**300**	**300**	**300**	**300**	**300**	**300**	**300**

*All the quantities are in mg and for one tablet.

Post formulation studies

Appearance

Prepared tablets were observed and determined for any physical appearance including elegance, shape, colour, surface textures.[10]

Dimensional analysis

Dimensional analysis includes Thickness and diameter of tablets were determined using Vernier Calliper. Randomly three tablets select from each batch and average values are calculated.[10]

Hardness test

Hardness is measuring the force required to break the tablet using Monsanto hardness tester. The hardness of 3 tablets from a batch are determined. Hardness measured in kg/cm2.[10]

Weight variation test

Weight variation test is carried out by taking Individual weights of 20 tablets randomly from the whole batch. Individual weights then compared with the average weight for the weight variations.[10]

$$PD = [(Wavg–Winitial)/(Wavg)] \times 100$$

Where, PD = Percentage deviation,

Wavg = Average weight of tablet,

Winitial = Individual weight of tablet.

Friability test

10 tablets were accurately weighted and place in the drum. Rotate the drum 100 times that means 25±1 rpm for 4 min, and remove the tablets. Remove any loose dust from the tablets and accurately weighed. A maximum mean mass loss from the three samples of not more than 1.0% is considered acceptable for most products.[10]

% friability = (Initial weight-final weight)/Initial weight x 100

Drug content

5 tablets were powdered and 100 mg drug equivalent powder dissolved in buffer pH 7.5. The volume of the solution made up to 100 ml by that media. The solution was filtered and diluted 100times and analysed spectrophotometrically (Shimadzu, Model no: UV 1800240V) and further calculation carried out to determine drug content in one tablet.[11]

In vitro drug release study

Those tests were carried out using dissolution test apparatus containing specified volume of 900 ml phosphate buffer 6.8 and the temperature were maintained at 37 ± 0.5^{0}C. The tablets are directly placed in a medium and immediately the paddles were started at the specified rate. Within the time interval specified 10 ml of sample are withdrawn. The samples were filtered and from the filtrate 1 ml was dilute to 10 ml. These samples are analysed and further calculation is carried out to get drug release. The drug released data were plotted and tested with zero order.[12]

Drug release kinetic model studies[13,14]

Zero order kinetics

It describes the system in which the drug release rate is independent of its concentration. C represents the cumulative amount of drug released in time t and K_0 is zero order release constant.

$$C = K_0 t$$

First order kinetics

It describes the drug release from the systems in which the release rate is concentration dependent. Whereby, Ct is the amount of drug released in time t, C0 is the initial concentration of drug and K1 is the first order release constant.

$$\text{Log } Ct = \log C0 - K_1 t = 2{:}303$$

Higuchi kinetics

It describes the release from systems where the solid drug is dispersed in an insoluble matrix and the rate of drug release is related to the rate of drug diffusion. W represents the cumulative amount of drug released in time t and K2 is the Higuchi dissolution constant.

$$W = K_2 t^{1/2}$$

Hixson Crowell kinetics

It describes the release from the systems, where it depends on the change in surface area and diameter of the tablets with time and mainly applies in systems, which erode over time. W represents the cumulative amount of drug dissolved at time t and K3 is the release constant.

$$(100-W)^{1/3} = 100^{1/3} - K_3 t$$

Korsmeyer Peppas equation

It describes the drug release from the polymeric system in which release deviates from Fickian diffusion, as expressed in following equation. Where K4 is release constant, n is release exponent, indicative of the drug release mechanism and F represents the cumulative amount of drug dissolved in time t. For matrix tablets, if the release exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if 0.45 < n < 0.89, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero order release

$$Mt/M\infty = K_4 t^n$$

RESULTS AND DISCUSSION

Pre-compression evaluation parameter

Determination of melting point

The melting point of Ketorolac was determined by capillary tube method. The temperature at which the drug melted was found to be 165±2°C.

Tapped density

The values obtained for tapped density for all (F1-F7) formulations are tabulated in table no. 2. The values were found to be in the range from 0.477-0.714. This indicates good flow property of the powder.

Bulk density (g/ml)

The values obtained for Bulk density for all (F1-F7) formulations are tabulated in table no.2. The values were found to be in the range from 0.402-0.513.

Hausner's ratio

The values obtained for hausner's ratio for all (F1-F7) formulations are in fig.table no.2. Hausner's ratio value ranges between 1.101-1.140 indicating that the granules have the required flow property for compression.

Compressibility index (%)

The values obtained for compressibility index for all (F1-F7) formulations are tabulated in table no.2. Compressibility index value ranges between 11.19-16.01 indicating that the powder have the good flow property for compression.

Angle of repose (ϑ)

The values obtained for angle of repose for all (F1-F7) formulations are tabulated in table no.2.The values were found to be in the range from 23.53-27.23.

Table 2: Pre-compression parameters of Controlled release tablet

Sr. No.	Formulations	Angle of repose (θ)	Bulk Density(g/ml)	Tapped Density(g/ml)	Compressibility Index or Carr's Index (%)	Hausner's ratio
1.	F1	25.24±0.04	0.451±0.07	0.481±0.18	13.21±0.11	1.122±0.06
2.	F2	23.99±0.16	0.481±0.05	0.517±0.06	11.59±0.98	1.112±0.07
3.	F3	23.53±0.05	0.402±0.09	0.477±0.23	11.19±0.18	1.101±0.13
4.	F4	24.19±0.13	0.432±0.14	0.506±0.01	12.91±0.15	1.120±0.17
5.	F5	24.77±0.18	0.511±0.03	0.714±0.11	14.09±0.06	1.124±0.15
6.	F6	26.99±0.15	0.491±0.29	0.542±0.17	14.91±0.14	1.139±0.08
7.	F7	27.23±0.17	0.513±0.12	0.498±0.19	16.01±0.06	1.140±0.05

Determination of λ-max

The maximum absorption for the drug ketorolac in Phosphate buffer pH 6.8 is shown in fig.1 and was found to be 323nm.
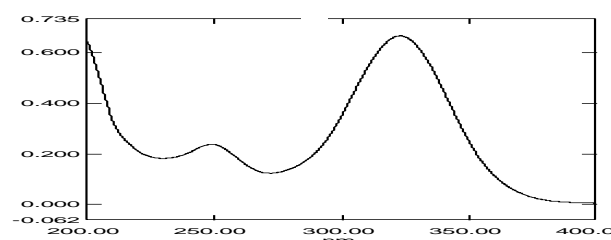
Figure 1: λ-max of Ketorolac

Calibration curve of a Ketorolac

The calibration curve of pure Ketorolac is shown in fig.2 and it was found to be linear and it was found to obey Beer's- Lambert law within the concentration of 2µg/ml - 10µg/ml and the regression co-efficient was found to be 0.9993.
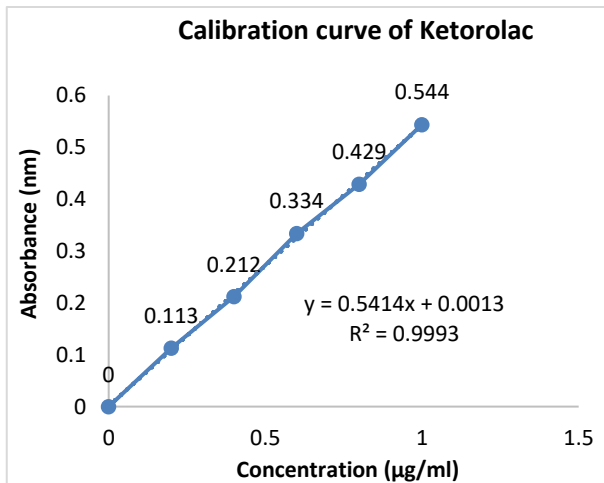

Figure 2: Calibration curve of ketorolac

Fourier Transformer-Infra red (FT-IR) studies

The IR spectra of the drug and polymer combinations were compared with the standard and the characteristic peaks associated with specific functional groups and bonds of the molecule and their presence/ absence were noted. The overlay of the IR spectra of ketorolac and physical mixture of drug and polymers is shown in the Fig.3. The prominent peaks associated with functional groups like =C-H at 725 cm-1, C-F at 149 cm-1, C-N at 1274cm-1, C-H at 1456 cm-1, C=C at 1471 cm-1 were analysed. The range of peak values were found to be the same indicates that there was no interaction of ketorolac with different polymers confirming the stability of the drug in the formulations.
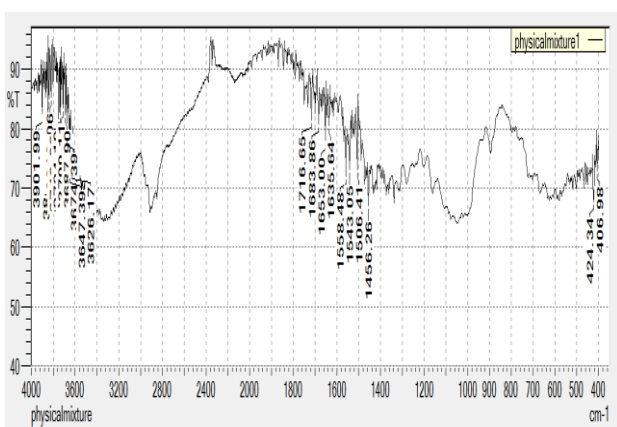

Figure 3: FTIR spectra of optimized formulation

Post-compression evaluation parameter

Dimensional analysis

The dimensions determined for formulated tablets were tabulated in fig.4. Tablet mean thicknesses were almost uniform in all the formulations and were found to be in the range of 3.14mm– 4.10mm.
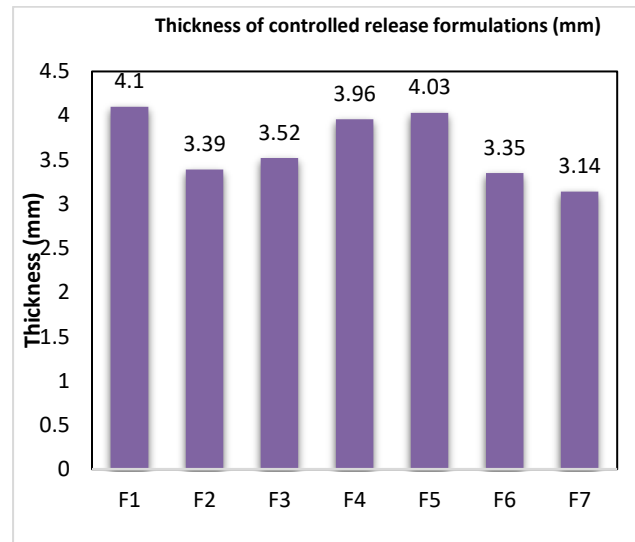

Figure 4: Thickness of controlled release formulations

Hardness test

The hardness test determined for formulated tablets were tabulated in fig.5.The measured hardness of tablets was range between 4.48kg/cm^2– 5.51kg/cm^2. Tablet hardness was increased as increasing the compression force. This ensure good handling characteristics of all batches.
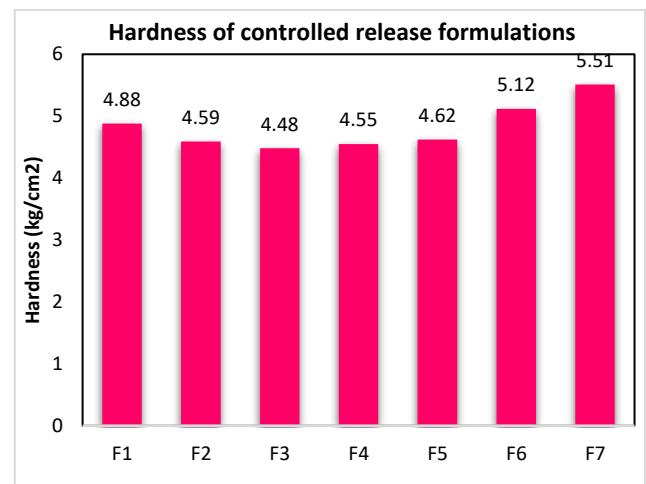

Figure 5: Hardness of controlled release formulations

Weight variation test

The percentage weight variation for all formulations was shown in fig.6. All the tablets passed weight variation test as the % weight variation was within the pharmacopeial limits. The weight of all the tablets was found to be uniform with low standard deviation values.
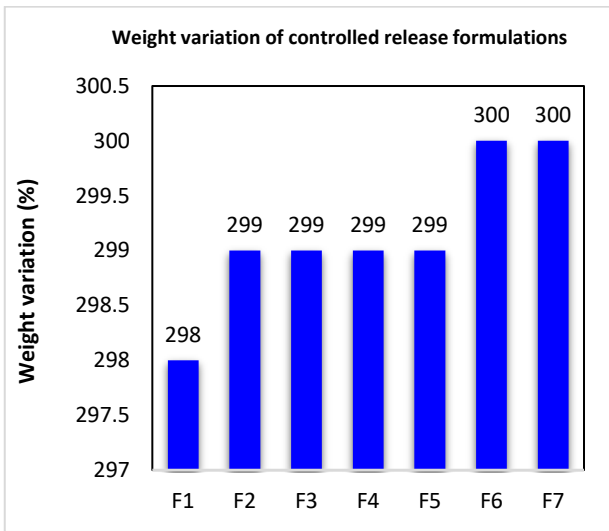
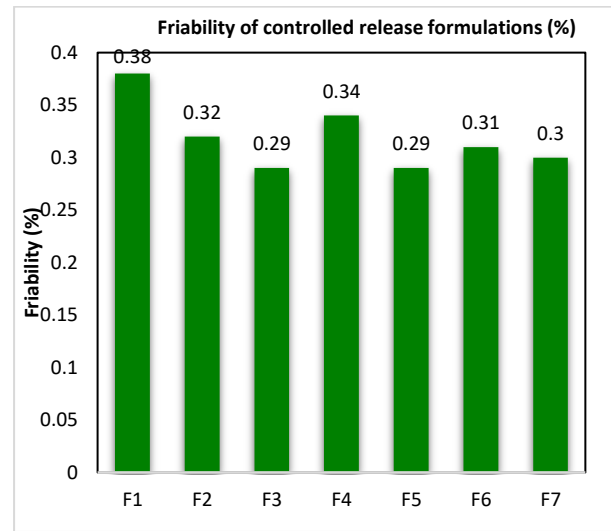**Figure 6:** Weight variation of controlled release formulations

Friability test

The values of friability test were tabulated in fig.7. The % friability was not more than 1% in all the formulations ensuring that the tablets were mechanically stable.

Figure 7: Friability of controlled release formulations

Content uniformity

The content uniformity of the tablet was shown in fig.8 and the percentage of drug content was found to be between 96.59%-98.68% of ketorolac, which was within acceptable limits.
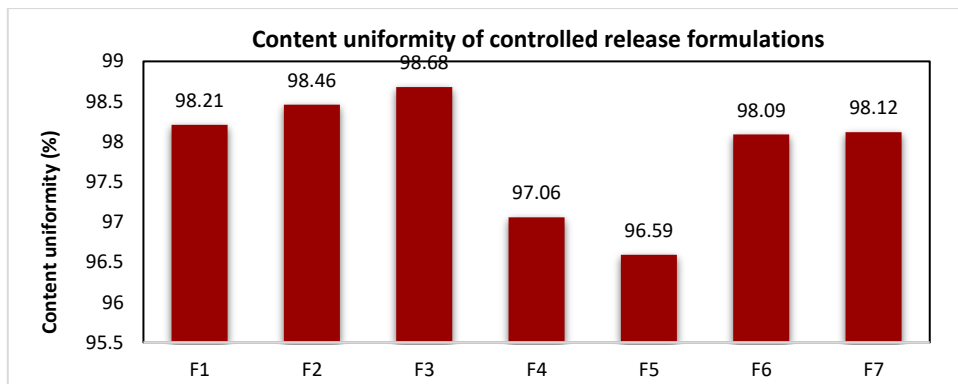

Figure 8: Content uniformity of controlled release formulations

In-vitro drug release study

The cumulative % drug release of Ketorolac tablet is shown in fig.9. Among all the 7 formulations F3 shows the maximum drug release as compared to other formulation.
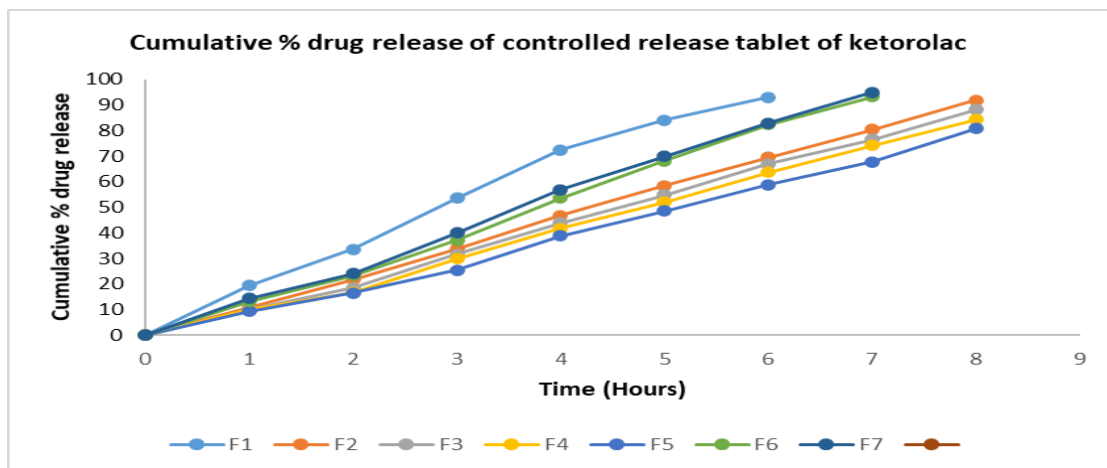

Figure 9: Cumulative % drug release of Ketorolac tablet

Drug Release Kinetics Models: The drug release kinetic study was shown in table.3

Table 3: Drug Release Kinetics Models

Formulations	Zero Order Kinetics		First Order Kinetics		Higuchi Kinetics		Korsmeyer-Peppas		Hixson- Crowell Kinetics	
	R^2	K	R^2	K	R^2	K	R^2	N	R^2	K
F1	0.677	3.806	0.918	-0.321	0.888	22.523	0.954	0.446	0.842	-0.191
F2	0.839	4.028	0.973	-0.245	0.972	22.387	0.985	0.513	0.982	-0.172
F3	0.958	3.716	0.990	-0.090	0.988	19.503	0.998	0.693	0.999	-0.100
F4	0.919	4.155	0.926	-0.216	0.991	21.761	0.997	0.532	0.988	-0.161
F5	0.959	4.122	0.918	-0.145	0.982	21.552	0.993	0.650	0.994	-0.135
F6	0.884	2.333	0.951	-0.036	0.990	12.680	0.990	0.599	0.934	-0.048
F7	0.947	4.281	0.946	-0.161	0.999	22.457	0.994	0.750	0.997	-0.144

CONCLUSION

In this study, we utilized a combination of two natural polymers like Almond gum and guar gum to prepare Ketorolac controlled release tablets. The natural polymers are used in controlled release tablets because has numerous advantages and it is occurring naturally, relatively safe, cheap and do not have any side effects. The FTIR Spectra indicated the absence of probable chemical interaction between the drug and polymers. The physicochemical evaluation data indicates that almost both the natural polymers were found to be good and demonstrated satisfactory physicochemical characteristics. Surface pH of drug and natural polymers was very close to the Gastric pH, indicated negligible irritation to the GIT. The drug content studies showed uniform and homogeneous distribution of drug into the tablets.

In this study, among 7 formulations, F3 is optimized based on the pre and post compression evaluation parameters. This indicates that the similar quantity of polymers required to prepare the controlled release tablet of ketorolac and the release data of the controlled release tablet best fit korsmeyer-peppas model with n=0.693 value.

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