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Research Article

Formulation And Evaluation Of Sustain Release Matrix Based Tablet Of Ketorolac Tromethamine Using Tamarind Gum And Tapioca Starch Natural Polymers As Release Modifiers

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ABSTRACT

The objective of the study was to formulate ketorolac tromethamine, a non-steroidal anti-inflammatory drug, into a sustained-release tablet. Using the wet granulation method, tamarind gum, tapioca starch, and chitosan, as well as their individual and combined polymers, were used to create sustain-release matrix tablets containing ketorolac tromethamine. UV spectroscopy was used for the identification of drugs, and FTIR and DSC were used for compatibility studies. Pre- and post-compression parameters were performed as part of the evaluation process. The dissolution aperture was used for the in-vitro drug release investigations. Kinetic analysis was performed on the optimized formulation's in-vitro drug release data. A stability analysis of the KT12 optimized formulation was conducted. The formulation KT12, which combines chitosan and tamarind gum, demonstrated the highest drug release (99.89%) after 24 hours. It was evident from the release statistics and swelling properties that the formulation KT12 had the best sustaining capabilities. According to stability studies, formulation KT12 exhibits physical stability. Thus, it was determined that a mixture of polymers (chitosan and tamarind gum) was effective in producing ketorolac tromethamine sustain-release matrix tablets, which delay drug release for up to 24 hours.

Keywords— ketorolac tromethamine, Sustain release, Natural polymers, tamarind gum, tapioca starch

1. INTRODUCTION

The oral route of drug administration is the most common, desired and preferred mode of delivering therapeutic agents for systemic effects since it is natural, convenient for the patient, and cost efficient to manufacturing process. Pharmaceutical products intended for oral administration are largely traditional drug delivery approach, which are designed for immediate release of drugs for fast absorption [1-2]. In recent years, different modified-release drug products have been created that modify the release rate of the drugs and/or the amount of time for drug release.

A sustained-release drug product is a sustained-release dosage form intended to provide a drug at a fixed rate by sustaining a steady drug level for a definite amount of time. Usually, the drugs may be delivered in an initial therapeutic dosage, followed by a slower and steady release [3]. They have various advantages, such as improving the bioavailability of medicines, ease of administration frequently, stability of the drug, maintaining uniform drug concentration in plasma, reducing gastrointestinal irritation and adverse effects, and reducing toxicity [4].

Matrix technologies are frequently employed because of the simplicity of the production processes needed, degree of repeatability, stability of the raw materials and dosage form as well as ease of scale up operation, validation and good in-vitro in-vivo correlation (IVIVC). These technologies increase patient compliance and lowered frequency of adverse medication responses. The launch of the matrix tablet as a continuous discharge (SR) has achieved another significant milestone for novel drug delivery methods in the field of pharmaceutical innovation [5].

The drug release rate from the measured form is mostly governed by the kind and amount of polymer used in the formulations, therefore reducing complex manufacturing procedures such as coating and pelletization during assembly. A hydrophilic polymer matrix is often used to provide a measurement frame for SR. Oral continuous release (or sustained release) medicines surpass conventional dosage forms by enhancing the bio pharmaceutics, pharmacokinetics, and pharmaco -dynamic characteristics of drugs. This minimizes the need for several administrations to the extent that a single dose per day is enough for entry, polymer expansion, drug dissolution, drug distribution, and lattice disintegration. The materials that are most frequently used to prepare network architectures include both hydrophilic and hydrophobic polymers [6-8].

The preparation of sustained release matrix tablets involves the direct compression of blend powder mixture of drug, retardant material and other additives to formulate a tablet in which the drug is dispersed in a matrix of the tablet. These systems continuously releases the drug by dissolution-controlled and diffusion-controlled mechanisms [9].

There are certain demerit of synthetic polymer used in preparation of sustain release tablet like, High cost, lead toxicity, may cause environmental pollution during synthesis, produces side effects, poor patient compliance, acute and chronic adverse effects (skin and eye irritation) observed in workers handling the related substances methyl methacrylate and poly- (methyl methacrylate), poor biocompatibility and release of acidic degradation products [10].
Above disadvantage can be solved by using natural polymer (gum) which have following merits

Advantages of natural gums in pharmaceutical sciences [11]

- **Biodegradable**: - Naturally accessible biodegradable polymers are created by all living organisms. They form truly renewable supply and they have no detrimental impact on individuals or environmental health (e.g., skin and eye irritation).
- **Biocompatible and non-toxic**: - chemically, virtually all of these plant components are carbohydrates made up of repeated sugar (monosaccharides) units. Hence, they are nontoxic.
- **Low cost**: - The manufacturing cost is also significantly inferior linked with that for synthetic material. India and many emerging nations are reliant on agronomy.
- **Environmental-friendly processing**: - Gums from various sources are readily obtained in varying seasons in vast volumes owing to the easy fabrication methods involved.
- **Local availability (particularly in developing nations)**:- In developing countries, governments promote the development of plant mimicking guar gum and tragacanth as of the extensive uses in a number of industries.
- **Better patient tolerance as well as public acceptance**: - There is lower probability of side and bad effects with natural resources linked with synthetic one. For example, PMMA, povidone.
- **Food sources**: - Most gums are acquired from food sources

Ketorolac tromethamine (KT) is a non-steroidal drug with potent analgesic and moderate anti-inflammatory activity and has been shown to be useful for mild to severe pain relief, such as postpartum and postoperative pain. KT is administered orally, intravenously, intramuscularly, and as a topical ophthalmic solution. The oral dosage of ketorolac is 20 mg as an initial dose, followed by 10 mg every 4–6 hours. Among patients over 65 years of age or whose weight is less than 50 kg, the oral dose is 10 mg initially, followed by 10 mg every 4–6 hours. Because of the short biological half-life of 4–6 hours, consistent dosing of KT is recommended to maintain a therapeutic effect. The purpose of our study was to produce a sustained-release tablet of KT utilizing natural gums like tamarind gum, tapioca starch, and chitosan that may be administered once a day and that would maintain the appropriate therapeutic concentration over 24 hours [12 -13].

2. MATERIALS AND METHODS

2.1 Material

Ketorolac Tromethamine was obtained as a gift sample from Lincoln Pharmaceuticals Ltd., Ahmedabad. HPMC K110M and microcrystalline cellulose pH 101 were supplied by Aurobindo Pharma Ltd., Hyderabad provided as a gift sample. Lactose, and Aerosil 200 were purchased from S.D. Fine chemicals. Analytical grade chemicals were employed for all other purposes.

2.2. Methods

2.2.1. Calibration curve of ketorolac tromethamine:

Standard calibration curve of ketorolac tromethamine in distilled water and pH 6.8 phosphate buffer

To achieve a concentration of 1 mg/ml (1000 mcg/ml), 100 mg of ketorolac tromethamine was precisely weighed and dissolved in 100 ml of distilled water and pH 6.8 phosphate buffer in a volumetric flask which is served as stock solution. Using distilled water, 1 millilitre of this solution was increased to 50 millilitres, yielding concentrations of 20 milligrams per millilitre (stock solution). Pipetting aliquots of 1, 2, 3, 4, and 5 millilitres of this stock solution into 10-milliliter volumetric flasks was done. Distilled water (pH 6.8 phosphate buffer) was added to the volume to make it appropriate. Concentrations of 2, 4, 6, 8, and 10 mcg/ml are obtained from this dilution. The diluted solution's absorbance was measured at 322.5 nm, and the results were used to create a standard plot. Linear regression analysis was used to get the correlation coefficient. The absorbance at the concentration mentioned above [14].

2.2.2. Compatibility Studies

The technique of comparing IR spectra was employed to identify any potential chemical interactions between the medication and the polymer. The appropriate amount of potassium bromide was added to a physical mixture of medication and polymer. Using a hydraulic press set to 6 tonnes of pressure, about 100 mg of the mixture was compacted into a clear pellet. In the FTIR spectrometer, it was scanned from 4000 to 400 cm-1. The physical mixture's infrared spectrum was compared to that of the pure drug and polymers, and peak appearance or disappearance was identified through matching. The infrared spectra of the sample and the working/reference standard for ketorolac tromethamine in the 4000 cm^{-1} to 400 cm^{-1} range were obtained by making a dispersion in dry potassium bromide under the previously described operating conditions.

Differential Scanning Calorimetry

The thermal behaviour of ketorolac tromethamine was examined by DSC, using instrument. Accurately weighed sample of ketorolac tromethamine (1 mg) was run at the scanning rate of 10°C/min over a temperature range of 150 to 300°C. The DSC thermo gram was recorded and reported [15].

2.2.3. Isolation of Polymer

a) Tamarind Gum

The endosperm of tamarind tree seeds is used to make tamarind gum. After being removed off the tree, the seeds are roasted in sand for a while. This is how the coat is taken off. After that, it is ground with the aid of a grinder and hammer milled. After then, sieve number 100 is used to filter it [16-17].

b) Tapioca Starch Extraction

To isolate cassava starch, the wet technique as outlined by Ihekoronye and Ngoddy was employed. The tubers of fresh cassava were peeled by hand, cleaned with tap water, and ground into slurries. The slurries were sieved to remove the fibrous debris and leave the starch in solution after being suspended in cold deionized water. After the starch layer settled and formed a solid, dense deposit at the bottom, it was suspended in deionized water and centrifuged six or seven times. To prevent the cell wall from getting into the starch slurry, the final sediment was screened through a 150 µm screen and suspended in cold deionized water. After that, the leftovers were gathered and left in a quiet spot for six hours.After obtaining the starch suspension, it was dried at 50 °C in a convection oven until it reached a consistent weight. To extract the starch, the dried material was ground and sieved using a 75 µm screen [18].

2.2.4. Preformulation Studies

It is crucial to ascertain a few basic physical and chemical characteristics of the drug candidate and excipients before developing a novel dosage form with a drug moiety. The IP process was followed in determining the preformulation methods parameters, such as bulk density, tapped density, compressibility index Hausner ratios, etc [19-22]. The following lists the steps for the various tests.

a) Angle of repose

This is done in order to ascertain the granules' flow characteristic. The funnel method determines it. A funnel with a closed bottom was maintained vertically at a predetermined height. Ten grams of sample powder were added to the funnel. The powder was then released from the funnel to create a smooth, conical mound that barely touched the funnel's tip. The measurements of the heap's height (h) and radius (r) were obtained from the powder cone.

The angle of repose, denoted as "θ," can be computed by applying the subsequent equation:

$$Tan\ \theta = \frac{h}{r} \qquad \text{.....Equation 1}$$

Where h = Height of the pile, r = Radius of the pile

b) Bulk density

A predetermined amount of the grains are weighed and then put into a graduated measuring cylinder with a capacity of 50 millilitres. Both the starting and ending volumes are mentioned.

$$\text{Bulk Density} = \frac{\text{Weight of Sample}}{\text{Bulk volume}} \text{.....Equation 2}$$

c) Tapped density

After weighing and pouring a certain amount of granules into a graduated 50 ml measuring cylinder, the tapped density equipment is used for a predetermined number of taps. It was indicated what the final volume was.

$$\text{Tapped Density} = \frac{\text{Weight of Sample}}{\text{Tapped volume}} \text{.....Equation 3}$$

d) Compressible index

The bulk volume and tapped volume are used to calculate the compressible index (%C.I.).

$$\%\ \text{C.I} = \frac{\text{Tapped Density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \text{.....Equation 4}$$

e) **Hausner's Ratio**:

The ratio of the powder mass's starting volume to its final volume after a certain number of tapings is known as Hausner's ratio.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \text{.....Equation 5}$$

2.2.5. Formulation of Ketorolac tromethamine SR Matrix Tablets

Sustained release tablets of ketorolac tromethamine were prepared by direct compression using different natural polymers like Chitosan, Tamarind Gum and Tapioca Starch by using individual and combination of above polymers [23].

Granules of ketorolac tromethamine SR tablets were formulated by classic wet granulation by various proportions of Chitosan, Tamarind Gum and Tapioca Starch polymers with drug. The ketorolac tromethamine was screened through sieve no. 40. The release retarding polymer namely Chitosan, Tamarind Gum and Tapioca Starch and additives namely MCC as diluent, magnesium stearate as glidant with lubricant respectively were screened through sieve no. 60. Both were well mixed well in mixer. Polyvinyl pyrolidone in isopropyl alcohol was added to the mixture as granulating agent to get coherent mass. The wet granules prepared were exposed for drying at the room temperature. The dried granules were screened through sieve no. 24, mixed with magnesium stearate. The dried lubricated solid aggregates were compressed into matrix tablets on 16 station cadmach machine.

Table 1: Compositions of Ketorolac tromethamine SR matrix tablets

Ingredients (mg)	KT1	KT2	KT3	KT4	KT5	KT6	KT7	KT8	KT9	KT10	KT11	KT12
Ketorolac tromethamine	30	30	30	30	30	30	30	30	30	30	30	30
Tamarind Gum	30	35	40							20		25
Tapioca Starch				30	35	40					20	
Chitosan							30	35	40	20	20	10
PVP -K30	10	10	10	10	10	10	10	10	10	10	10	10
Isopropyl alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Mg. stearate	2	2	2	2	2	2	2	2	2	2	2	2
MCC	128	123	118	128	123	118	128	123	118	118	118	123
Total weight (mg)	200	200	200	200	200	200	200	200	200	200	200	200

2.2.6. Post Compression Parameters

All developed matrix tablets were examined for their uniformity of hardness, weight variation test, friability, and thickness according to standard procedures [23-25].

Weight Variation

Weight variation test for the tablets was performed as per the IP procedure. 10 tablets were weighed individually, and the average weight was calculated. The individual weight of all the ten tablets was weighed down. The percentage deviation of the individual weights from the average weight was then calculated.

Tablet hardness

Tablet hardness has been characterized as the factor necessary for breaking a tablet in a diametric consciousness test. A tablet had been placed between two anvils of the hardness tester, force was applied to the anvils, and the crushing strength that caused the tablet to break was recorded. Tablet hardness was measured for 10 tablets using a Monsanto hardness tester.

Friability test

The friability of the tablets was measured in a friability assessment (Roche Friaberator Camp-bell Electronics, Mumbai). Ten tablets were initially weighed ($W_{initial}$) and placed into the friabilator. The friabilator had been operated at 25 rpm for 4 minutes, and afterwards the tablets were deducted and weighed (W_{final}). Percentage friability was calculated from the loss in weight, as indicated in the equation below. The weight loss should not be more than 1%. Determination has been made in triplicate.

$$\%\ \text{Friability} = \frac{\text{Winitial} - \text{W final}}{\text{Winitial}} \times 100 \text{.....Equation 6}$$

Assay of tablet

10 tablets were carefully weighed and crushed. Calculated the average weight and taken the powder equivalent to 10 mg of ketorolac tromethamine in a 100-ml volumetric flask. Incorporate a few ml of pH 6.8 phosphate buffer and simmer for 30 minutes. Then volume was made up to 100 ml with pH 6.8 phosphate buffer. The 1 mL of resultant solution was diluted to 100 mL with pH 6.8 phosphate buffer, and the absorbance was measured using a UV spectrophotometer at 322.5 nm.

Swelling Study

Three SR ketorolac tromethamine hydrochloride tablets were weighed individually (W_1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37 ± 1 °C. After 4 and 8 hours, the tablet had been removed from the Petri dish, and excess surface water was gently removed using blotting paper [26]. The swelled tablet was then reweighed (W_2), and the swelling index (SI) was determined using the procedure stated in the equation.

$$\text{Swelling index}(\%) = \frac{(W2-W1)}{W2} \times 100 \quad \text{.....Equation 7}$$

Where, W_1 = Initial weight of the tablet

W_2 = Final weight of the tablet

In-vitro dissolution study

The current study utilized the USP dissolution test equipment-II paddle method (Electrolab, test apparatus, USA) to examine in vitro drug dissolving for Ketorolac tromethamine SR matrix tablets. The following conditions were employed in the dissolution study: 900 ml of the dissolving media, a 50 rpm paddle speed, and a 37±0.5°C average temperature. The experiment was done employing two distinct dissolving media, namely simulated intestinal fluid (SIF), and distilled water. At stated time intervals of 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 hours. The test solution of 5 ml was calculated and refilled using the same quantity of the dissolving media. Following that, the mixtures were passed through a 0.45 µm Whatman filter paper (Whatman, NJ, USA). Before being spectro photometrically analysed at 322.5 nm using a UV-visible spectrophotometer, the obtained samples were suitably diluted. Every sample has been collected three times [27].

2.2.7. Release kinetic analysis

To investigate the release kinetics, data obtained from in-vitro drug release studies was converted to drug release data, and with the help of DD Solver dissolution kinetic modeling software, data were plotted in various kinetic methods: zero order as cumulative amount of drug released vs. time, first order as log cumulative percentage of drug remaining vs. time, and Higuchi's model as cumulative percentage of drug released vs. square root of time [28].

2.2.8. Stability Study

Stability studies has been carried out for the optimized formulations. Tablets of optimized formulation SR matrix tablets of Ketorolac tromethamine were striped packed and maintained in humidity chamber at accelerated condition (40 °C ± 2 °C & 75% ± 5 % RH) for thirty days [29].

2. RESULTS AND DISCUSSION

3.1 Calibration curve of ketorolac tromethamine in distilled water and pH 6.8 phosphate buffer

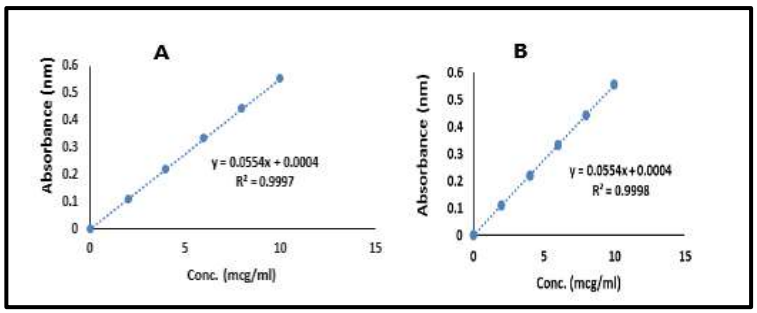

Figure 1: a) Standard graph of ketorolac tromethamine in a) distilled water (λmax 322.5nm), b) pH 6.8 phosphate buffer (λmax 322.5nm)

3.2. Compatibility Studies

DSC curves obtained for pure ketorolac tromethamine and physical combination of pure drug and polymers are presented in Figure 2 a and b accordingly. Pure powdered ketorolac tromethamine exhibited a melting endothermic at 169.11°C, whereas physical mixing of drug and excipients revealed the melting peak of the drug at 167.75 °C which suggests that all constituents are compatible with each other.

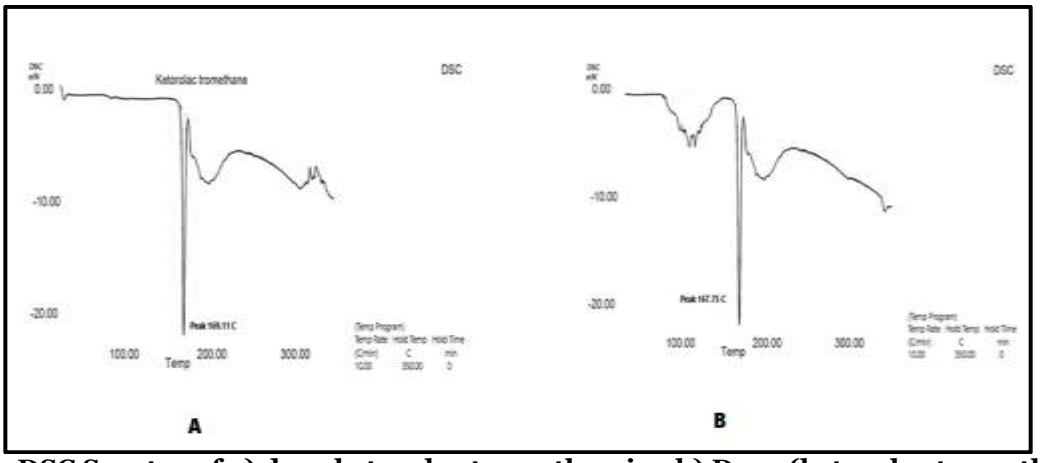

Figure 2: DSC Spectra of a) drug ketorolac tromethamine b) Drug (ketorolac tromethamine) + Mixture

The IR spectra of the pure drugs reveal typical peaks at 1308.52 cm1 and 1378.89 cm1 due to the -CH and -CN groups, respectively. Formulations KT12 also demonstrated similar peaks at 1315.07 and 1379.40 cm^{-1} and 1310.10 and 1384.94 cm^{-1}, respectively, for the aforesaid groups. This ensures the unchanged structure of the drugs in the formulations. Hence, there are no drug-excipient interactions.

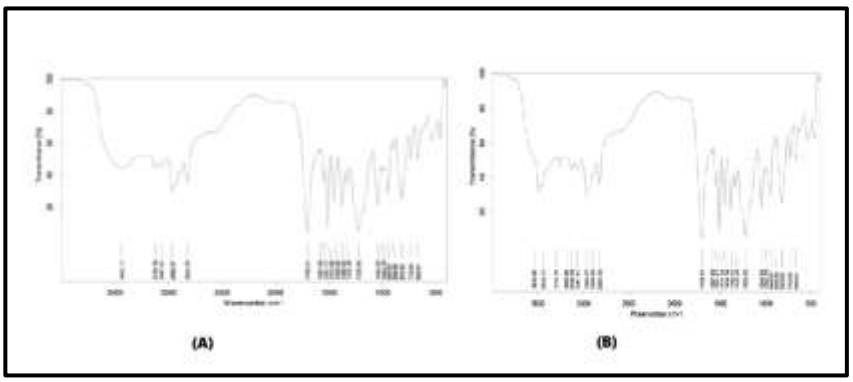

Figure 3: IR Spectrum of a) drug ketorolac tromethamine b) Drug (ketorolac tromethamine) + Mixture

3.3. Preformulation Studies

The preformulation parameters like angle of repose, bulk density, tapped density and compressibility index and Hausner's ratios were studied to evaluate the flowability and compressibility of the powder of Ketorolac tromethamine SR matrix tablets. The bulk density and tapped density was found to be in the range of 0.421 to 0.665 gm/cm^3 and 0.529 to 0.891 gm/cm^3 the compressibility and hausner's ratio were found to be 17.81% to 30.41% and 1.17 to 1.43. This indicates the granules have good flow character and have good compression property. All the results are shown in table 2 that are within the prescribed limits.

Table 2: Preformulation Studies of Ketorolac tromethamine SR Matrix Tablets

Formulation Code	Angle Of Repose	Bulk Density	Tapped Density	Carr's index	Hausner's Ratios
KT1	31° 33'	0.620	0.894	30.41	1.42
KT2	33° 17'	0.615	0.811	24.16	1.31
KT3	33° 23'	0.601	0.807	25.52	1.34
KT4	33° 13'	0.431	0.552	21.92	1.28
KT5	33° 61'	0.617	0.821	24.66	1.31
KT6	33° 07'	0.625	0.830	24.69	1.33
KT7	36° 12'	0.602	0.809	25.58	1.34
KT8	35° 73'	0.421	0.529	20.41	1.25
KT9	38° 05'	0.665	0.875	22.19	1.30
KT10	26° 18'	0.512	0.623	17.81	1.21
KT11	27° 07'	0.458	0.537	14.71	1.17
KT12	29° 16'	0.465	0.571	18.56	1.22

3.4. Post Compression Parameters

The tablets were evaluated for thickness, hardness, friability, average weight and drug content as mentioned in table 3. The thickness of the formulated tablets was found to be in the range of 3.33mm to 3.65 mm. Hardness and friability was found to be 5.5-8.30 kg/cm² and 0.1- 0.25% which indicates the tablet has adequate mechanical strength. Weight variation of the tablets was found to be within the specified limits. The drug content of all the formulations ranged from 95.38-101.11% indicating the presence of an acceptable amount of drug in the formulations.

Table 3: Evaluation of Ketorolac tromethamine SR Matrix Tablets

Batch	Weight Variation (%)	Friability (%)	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm²)	Drug Content
KT1	201.36±05.8	0.24	7.70±0.10	3.55±0.089	5.50±0.25	101.11±3.25
KT2	202.31±17.5	0.20	7.58±0.05	3.33±0.014	5.75±0.48	99.80±2.01
KT3	199.26±06.4	0.18	7.71±0.08	3.65±0.168	6.50±0.35	99.23±3.85
KT4	200.40±5.6	0.25	7.70±0.05	3.65±0.212	5.60±0.26	99.90±2.74
KT5	198.93±07.4	0.18	7.72±0.07	3.57±0.078	6.20±0.56	96.38±4.45
KT6	199.65±06.6	0.10	7.8±0.05	3.39±0.235	6.50±0.26	95.88±5.45
KT7	202.01±05.2	0.20	7.72±0.05	3.55±0.245	5.60±0.26	99.16±4.74
KT8	199.95±5.6	0.18	7.82±0.03	3.51±0.114	5.90±0.78	97.51±4.68
KT9	199.69±09.6	0.15	7.70±0.08	3.65±0.212	6.50±0.68	100.35±5.36
KT10	201.32±03.6	0.20	7.78±0.09	3.59±0.124	7.30±0.68	100.15±3.36
KT11	200.10±04.5	0.22	7.85±0.05	3.35±0.090	7.80±1.25	99.95±5.70
KT12	199.96±06.4	0.15	7.77±0.04	3.55±0.230	8.30±0.49	101.11±3.25

3.5. In vitro drug release of formulations

Effect of Tamarind gum on Ketorolac tromethamine release

The figure 4 displays the cumulative percentage drug release at various concentrations of Tamarind gum, namely 30%, 35%, and 40%. These formulations effectively managed and prolonged the release pattern for the necessary duration. It was shown that higher polymer content resulted in a decrease in the rate of drug release. This phenomenon may be attributed to the augmented expansion of the polymer as the concentration is increased, resulting in an increase in the viscosity of the medium [28]. Consequently, this extends the average distance that the drug molecule has to travel in order to be released into the diffusion medium.

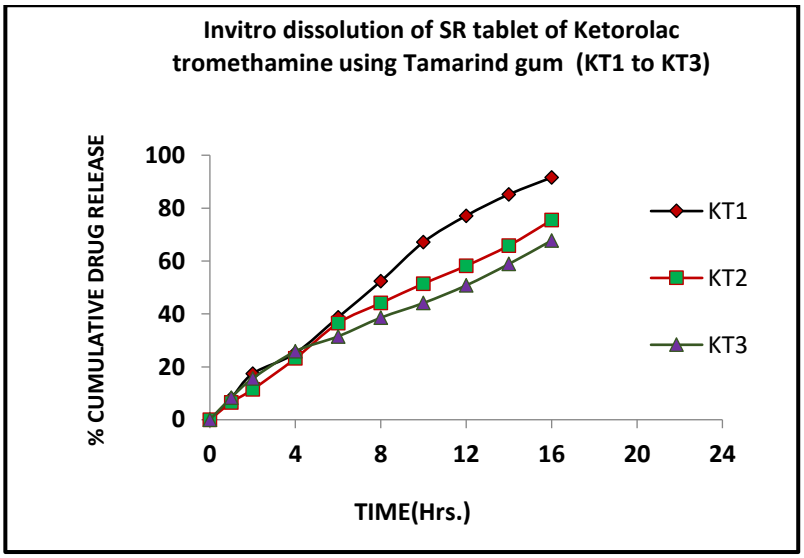

Figure 4: Invitro dissolution of SR tablet of Ketorolac tromethamine hydrochloride using Tamarind gum (KT1 to KT3)

Effect of Tapoica starch on Ketorolac tromethamine release

The figure 5 displays the cumulative percentage drug release for various concentrations of Tapoica starch, namely 30%, 35%, and 40%. These formulations successfully prolonged and regulated the release pattern for a certain duration. An inverse relationship was seen between a drug's release rate and the concentration of polymers. The effect may arise from the enhanced expansion of the polymer as its concentration increases, resulting in an increased viscosity of the surrounding substance. Consequently, the average distance that the drug molecule has to travel to be released into the diffusion medium is increased.

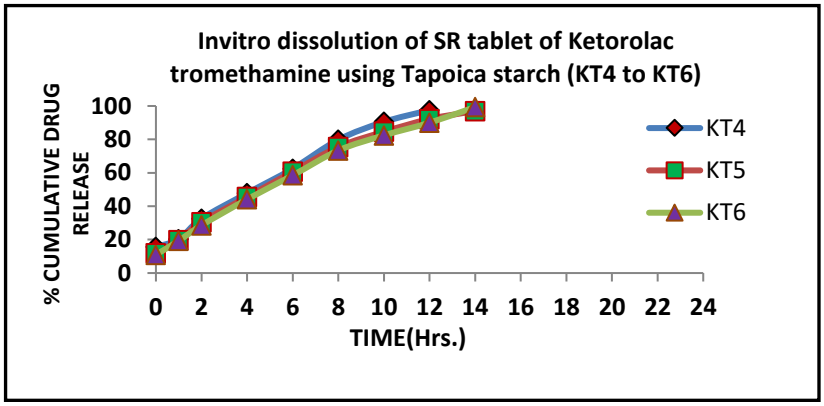

Figure 5: Invitro dissolution of SR tablet of Ketorolac tromethamine hydrochloride using Tapoica starch (KT4 to KT6)

Effect of Chitosan on Ketorolac tromethamine release

The figure 6 displays the cumulative percentage medication release for various concentrations of Chitosan (30%, 35%, and 40%). These formulations successfully prolonged and regulated the release pattern for a specified duration. The medication release rate was observed to be lowered when concentration of polymers was raised. This may be due to increased swelling of the polymer when concentration is raised which leads to increased viscosity of the medium and therefore increases the mean diffusion path length of the drug molecule to be released into the diffusion medium.

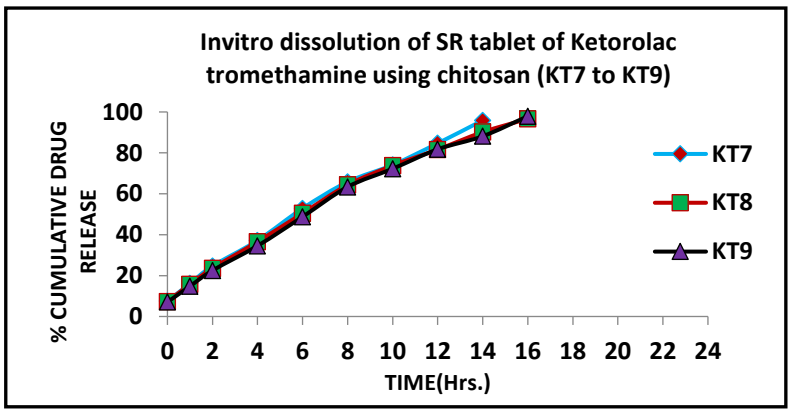

Figure 6: Invitro dissolution of SR tablet of Ketorolac tromethamine hydrochloride using Chitosan (KT7 to KT9)

Effect of combination of polymer on Ketorolac tromethamine release

Cumulative percentage drug release for the combination of varied concentration of Tamarind gum, Tapoica starch and Chitosan polymers is displayed in figure 7. These formulations were able to prolong and regulate more as compared to individual polymer and thus their release pattern to desired length of time. The medication release rate was observed to be lowered when concentration of mixture of polymer polymers was raised. This may be due to increased swelling of the polymer when concentration is raised which leads to increased viscosity of the medium and therefore increases the mean diffusion path length of the drug molecule to be released into the diffusion medium [27]. So, by employing mixture of polymer we may delay the medication release up to 24 hours.

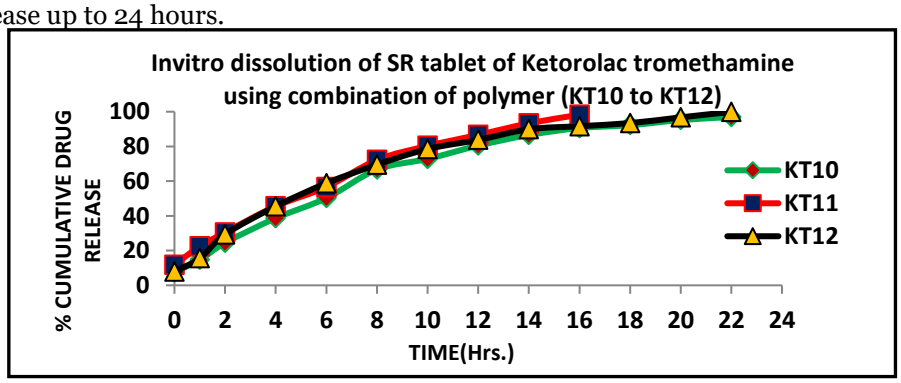

Figure 7: Invitro dissolution of SR tablet of Ketorolac tromethamine hydrochloride Using Combination of Polymer (KT10 to KT12)

3.6. Swelling study

The drug release profiles of tablets are controlled by their swelling behavior, with the swelling index rising proportionately to the tablets' weight growth and hydration rate [26]. Tamarind gum and Chitosan-based tablets demonstrated larger swelling indices compared to those employing Tapoica starch gum, attributable to the enhanced hydrophilicity of Tamarind gum and Chitosan. Furthermore, Tamarind gum polymer displayed excellent swelling characteristics owing to polyacrylic acid derivatives, exceeding Chitosan and Tapoica starch. Combining distinct polymers (Tamarind gum, Tapoica starch, and Chitosan) resulted in even more swellable tablets compared to separate polymers. Trial batches KT1 to KT12, particularly formulation KT10, KT11, and KT12, demonstrated substantial swelling after 8 hours, as shown in figure 8.

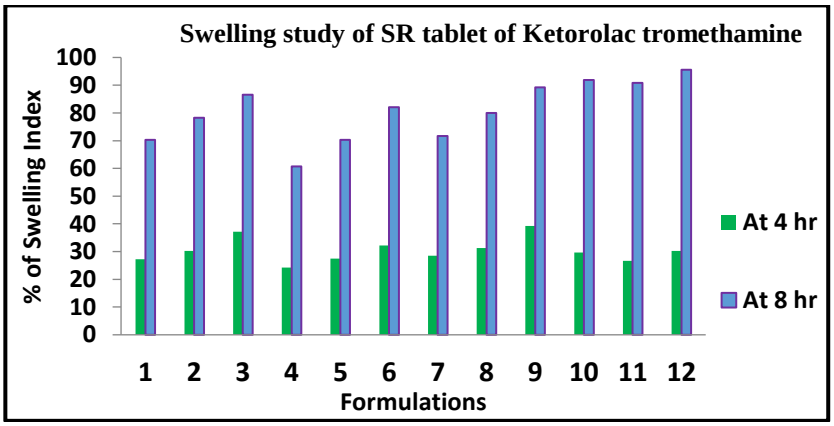

Figure 8: Swelling study of SR tablets of Ketorolac tromethamine

3.7. Drug Release Kinetics analysis:

The in-vitro drug release data of the optimized formulation was submitted to kinetic analysis by plotting several kinetic equations such zero order, the first order and Higuchi plot. The kinetic analysis data of the formulation was presented in the table. The kinetic model that best matches with the release data of formulation was assessed by the correlation coefficient (R^2) values. According to the results obtained higher linearity was identified with linear plot (zero order) with R^2 value of 0.938. Thus the formulation may follow zero order drug release.

Table 4: Drug Release Kinetics analysis

Formulation	Zero order (R^2)	First order (R^2)	Higuchi kinetics (R^2)	Korseyer Peppas (R^2)
KT12	0.938	0.5394	0.6975	0.8751

Mechanism of drug release data may be assissed by displaying the drug release data in linear, exponential and power equations. From the regression coefficiant value, it may follow zero order kinetics.

3.8. Stability Study

The storage conditions utilized for stability testing were accelerated condition (40 °C ± 2 °C & 75% ± 5 % RH).Stability investigation was carried out for the enhanced formulations KT12. Tablets of enhanced formulation KT12 were striped packed and stored in humidity chamber for 30 days on above required temperature. The improved formulation KT12 went through a one-month stability study being done. The stability study's results are given in Table 5. According to the stability study's findings table 5, there was no apparent modification in the variables of hardness, thickness friability, percentage of drug content, and swelling index. The stability analysis further indicated in figure 9 that the drug release profile of the KT12 formulation had not changed appreciably. This confirms the stability and reproducibility of the enhanced batch KT12.

Table 5: Stability Study of Batch KT12 SR tablet of Ketorolac tromethamine

Parameters	Initial	After 30 days
Average Weight(mg)	199.96±06.4	199.10±02.4
Hardness (kg/cm2)	7.77±0.04	7.58.±0.69
Thickness(mm)	3.55±0.230	3.55±0.210
% Friability	0.15±0.2	0.17±0.3
% Drug Content	99.95±5.70	99.74±03.4
Swelling Index after 8 hr	98.56± 0.05	98.22± 0.04

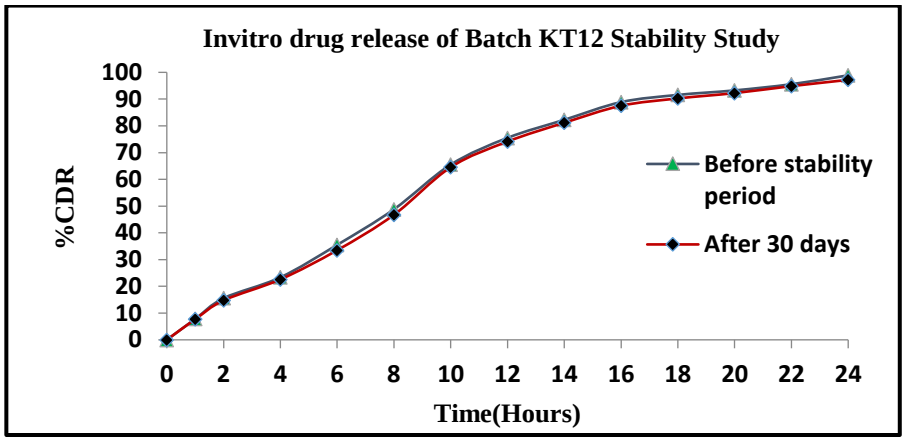

Figure 9: Invitro drug release of Batch KT12 Stability Study

4. CONCLUSION

In conclusion, this work effectively employed wet granulation to produce sustained-release (SR) tablets containing ketorolac tromethamine utilizing hydrophobic polymers such as chitosan, tapioca starch, and tamarind gum as retardants. The KT12 formulation displayed good matrix integrity, controlled drug release, and desirable tablet properties. The tablets' swelling behaviour influenced drug release patterns, with tamarind gum and chitosan-based tablets demonstrating higher flexibility than those produced with tapioca starch. Optimized formulation KT12 exhibited zero-order drug release, and stability tests over 30 days passed ICH standards, indicating possible advantages over conventional dose forms in terms of effectiveness and patient compliance. While the research fulfilled its aim, more preclinical and clinical studies are necessary to examine the efficacy of different ketorolac tromethamine formulations for treating moderately severe pain.

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CONFLICTS OF INTEREST

No conflict of interest was declared by the authors.

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