Original Article

Ketorolac Tromethamine Nanoparticles Based Trilayer Matrix Tablets For Sustained Drug Delivery System

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Abstract

The major drawback of oral drug delivery is inadequate concentration of active pharmaceutical ingredients in systemic circulations. The study set out to design and test matrix tablets containing Ketorolac tromethamine (KT) nanoparticles for sustained activity. The goal of this research was to create a sustained-release medication delivery system using a tablet matrix composed of KT nanoparticles and to analyse its performance. The nanoparticles loaded with KTwere further compressed into matrix tablets in this investigation. They were developed by using factorial design to optimize the specific concentrations of drug and polymers. The KT loaded nanoparticles were formulated by employing combined method i.e. Nano precipitation and probe sonication method. The matrix tablets of KT nanoparticles were developed by wet granulation method. KT nanoparticles were discovered to have a particle size range of 199-441 nm and 17.07 ± 0.09 to 22.43 ± 0.23 mv, respectively. Moreover, all the formulations were producedpoly dispersibility index (PDI) in optimum ranges. *In vitro* drug release through nanoparticles were provides sustained action up to 8 hrs. KT nanoparticles loaded matrix tablets showed characteristics of delayed drug release.

Keywords: Ketorolac tromethamine; nanoparticles: Nano precipitation; probe sonication; lyophilization

1. INTRODUCTION

Medications taken orally can have three distinct outcomes, depending on whether theyundergo I rapid delivery and absorption; (ii) slow delivery from an adherent drug delivery system (DDS), followed by absorption or local action; or (iii) transport to the gastrointestinal region, where they can either be absorbed or have their intended effect. The second option is the gold standard in the pharmaceutical business and the most common means of self-medication. Developments in buccal permeation (items I and ii) methods have increased rapidly in recent years [1–5]. Sensitive drugs benefit from this route since they are protected from the liver and intestines. In terms of medication delivery methods; the oral route continues to dominate, particularly when drugs are self-administered. The therapy benefits from improved dose accuracy and medication stability for solid-formulation. However, not all pharmacologically active compounds are suitable for use in traditional matrices due to insufficient dissolution, permeation, or solubilization [6-8].

A novel and underutilized option that could have various advantages is the combining of nanostructured medicines with these matrices [9-11]. The burst effect, which involves a quick early drug-release trailed with a slow or regulated release, is a notable drawback of nanoparticles. Burst behaviour is often unpredictable and unreplicable [12-15], but in some therapies, fast plasma peaks or local drug concentrations are sought. Medicines that are only weakly bound, molecules that migrate to the particle surface, and nanomatrix heterogeneity are all potential sources of this phenomenon. Coating or nanomatrix reformulation are two prevention methods, however these are not always simple because they alter the nanoparticles physicochemical properties [16-18].

Drug solubility can hinder effective release from drug delivery system and subsequent mucosal crossing regardless of the method. Because of this, a variety of solubilization techniquesare available, including salt versions of active compounds, pH modification, co-solvent, amorphous forms, solid dispersion, and Nano-technological products. The latter comprises a sizable section of the literature but has few commercial goods and no buccal-based alternatives. Because most oral DDSs are made from biodegradable materials, they eventually disappear. [19]. In fact, both of these features are used as a release mechanism in some systems. The carrier may be vulnerable to degradation by enzymes or pH changes during transport or at the site of action, even if it releases its payload as planned. The ideal drug liberation profile may be hampered by an early instability, as in the case of ordinary gelatin. Regular gelatin NPs, for example, must be coated, chemically altered, or embedded in an outer matrix to prevent

Intestinal release due to their stomach-degradation. This potential instability at an earlier time point [20] may prevent the drug release profile that was intended.

In the Biopharmaceutical Classification System (BCS), KT is included in the anti- inflammatory medication class I. This study set out to determine how polymer matrix might factor towards the development of stable KT nanoparticles that

exhibit prolonged activity and enhanced intestinal permeability. Second, tablets with KT nanoparticles added for prolonged medication delivery.

2. MATERIALS AND METHODS

2.1 Materials

KT provided courtesy of Zhejiang Medicines and Health Products Imports & Exports Co., Ltd. When researching drugs, China served as a stand-in for the ideal product. Evonik Industries, of Mumbai, generously provided us with a sample of their Eudragit RS-100. Sigma Aldrich was the supplier for the polyvinyl alcohol (PVA), poloxamer 188, and sodium dodecyl sulphate (SDS). Colorconpvt.ltd. provided us with HPMC and Xanthan Gum. In every step of theprocess, we employed only analytical-grade chemicals, reagents, and distilled water.

2.2 Selection and preliminary optimization of polymer and surfactant by determination of drug entrapment efficiency (%), particle size and zeta potential.

To begin, test batches were made with varying quantities of three different surfactants (Tween 80, Poloxamer 407, and PVA) (Table 1). Different amounts of the polymer Eudragit RS-100 were used. Full KT The probe sonication approach was used to prepare the nanoparticles after nanoprecipitation. The drug and polymer were dissolved in a 10 ml organic solution (1:1 methanol and acetone). We used a high speed homogenizer spinning at 2500 rpm to gradually infuse the above solution into 100 cc of distilled water with surfactant. All of the organic solvent was boiled out. The resultant nanoparticles were then subjected to 5 minutes of probe sonication at 20-25 kHz to ensure uniformity. The surfactant and polymer concentration were optimised by centrifuging trial batch samples (10 ml) in a cooled centrifuge and analyzing the resulting supernatant using a UV/Visible spectrophotometer.

2.3. Preparation of physical mixture

All physical mixture needed for future study has been made according to usual technique.For the purpose of contrasting the optimized nanoparticles, a mixture of KT, Eudragit RS-100, and Poloxamer 188 was created. Mildly triturating in mortar, followed by sieving (40# mesh), and storage in a desiccator resulted in a homogenous mixture.

2.4. Preparation of KT loaded nanoparticles

Table 2 displays the composition of the several batches of KT-loaded nanoparticles generated using the nanoprecipitation followed by probe sonication approach. Several different drug/polymer combinations were dissolved in a 1:1 methanol/acetone organic solution and then added to a 10-milliliter volume. Drop by drop, the aforementioned solution was added to 100 ml of surfactant-laced distilled water within a high-speed homogenizer operating at 2500 rpm. The entire organic solvent was evaporated. Probe sonication at 20–25 kHz for five minutes was applied to the resulting uniform nanoparticles. The optimized batch KT6 was further lyophilized (Christ, Alpha, 12LD PLUS) using mannitol as a cryoprotectant. The freeze-dried item was stored in a sealed container until it was ready to be used.

2.5. Characterization of KT loaded Nanoparticles

2.5.1. Particle size distribution and zeta potential

Nanoparticle PDI and particle size analyses were performed using a particle size analyzer equipped with a Zetasizer (Model SZ-10, Horiba Scientific, Japan). A Laser Doppler Anemometer combined with a Nanoparticles Analyzer was used to measure the Zeta potential, orparticle surface charge, of each formulation (SZ-100, Horiba Scientific, Japan). All of the samples that were analysed had the appropriate amount of de-ionized water diluted into them [3, 16]. At least three repetitions of each reading were made [3].

2.5.2. Percent entrapment efficiency determination

Polymer entrapment efficiency was calculated by measuring the percentage of trapped molecules. At 5 °C and 10,000 rpm for 30 minutes, a cooling centrifuge (Remi C30 PLUS) was used to spin down 10 mg of KT Nanoparticles. The concentration of free medicine in the supernatant was calculated using UV/visible spectrophotometer analysis (Shimadzu UV Spectrophotometer 1800) at 322 nm. The percentage of successful drug entrapment according onequation [17]:

$$\text{Entrapment efficiency (\%)} = \{(\text{Initial drug concentration} - \text{Final drug concentration})/\text{Initial drug concentration}\} \times 100$$

2.5.3. Fourier transforms infrared spectroscopy (FTIR)

All compositions' FTIR spectra were taken with an IR spectrophotometer (Alpha T Bruker). Dry potassium bromide (KBr) was used to combine all of the samples before they were scanned between 4000 and 400 cm^{1}.

2.5.4. Differential scanning calorimetry (DSC)

To predict the possible interaction and the thermal behavior of all the samples, the Differential Scanning Calorimetry was performed. In this experiments, pure KT, Eudragit RS- 100, Poloxamer 188, physical mixture (KT+Eudrgit RS-100+Poloxamer 188) and lyophilized nanoparticles were traced on DSC (Mettler Toledo) at a rate of 10°C/min over the

temperature range of 40°C to 300°C in an atmosphere of nitrogen having flow rate of 40 ml/min.

2.5.5. Powder X-ray diffraction (PXRD)

The understand the x-ray diffraction patterns of pure KT, Eudragit RS-100, poloxamer 188, physical mixture (KT+EudrgitRS-100+Poloxamer 188) and lyophilized nanoparticles were recorded on diffractometer (Miniflex 600 X-ray diffractometer, Japan). Samples were scanned from 10-80°C 2θ at a scan rate of 2°C/min.

2.5.6. Transmission electron microscopy (TEM)

Morphological characteristics of drug loaded nanoparticles were performed by using TEM techniques (Hitachi H7500 Japan). In this technique, distilled water was used to create a suspension of nanoparticles and all the images were observed at various magnifications ranges.

2.5.7. In vitro Drug Release study

The modified two-sided open glass cylinder USP dissolution device type I (EDT-08 Lx,Electrolab) was employed for the In Vitro drug release research on the optimised batch [18]. Several formulae, including zero order kinetics, first order kinetics, the Higuchi model, and the Korsemeyer-Peppas equation, were used to assess the release kinetics profile of KT from nanoparticles. The Korsmeyer-Peppas equation was used to ascertain the release mechanism by calculating the regression coefficient (denoted by "R") and the release exponent (denoted by "n").

2.6. Formulation of KT Nanoparticles based matrix tablets

Matrix tablets were made using an optimised batch of KT loaded nanoparticles chosen for their desirable particle size and in vitro drug release. Direct compression was used to make the matrix tablets, and 3^2 factorial designs were used (Table 3). To achieve this, we used drug content, swelling index, and in vitro drug release studies as independent variables and Xanthan gum and HPMC amounts as independent variables.

2.6.1. Preliminary Screening and optimization of concentrations of xanthan gum and HPMC by considering the Drug Content and Swelling index

Firstly, all the preliminary trial tablets formulations were prepared using three different xanthan gum and HPMC (Table 4). Techniques involving direct compression were used to create the matrix tablets. Three different concentrations of xanthan gum and HPMC were used like 30-60 mg in case of both polymers. API and other excipients were passed through sieve no.20 for before further treatment. After proper sieving, all ingredients were mixed in specified weight. Additionally, the powder blend was blended thoroughly with talc and magnesium stearate, and the needed quantity was compacted into a 400 mg tablet using a single rotatory punching machine (KI-150, Khera Instruments Ltd. New Delhi, India). Trial tablet batches were evaluated for swelling index and drug content.

2.6.2. Experimental Design

Initial screening of prepared batches was carried by considering optimum drug content and maximum swelling index. Concentration of xanthan gum and HPMC are the important key parameters for the formulations. Factorial design is used for understanding thoroughly knowledge about evaluation and optimization of formulation parameters. An in vitro drug releaseresearch, the medication's swelling index, and its content were all chosen for response or held constant.

2.7. Evaluation of KT nanoparticles loaded matrix tablets

A. Angle of repose:

Every batch of tablets was tested for their angle of repose by employing the funnel method with their powdered forms. The appropriate measure of powdered medicine was taken to the funnel, with the thumb covering the opening. Angle of repose was determined when all the quantity of powder was cleared from funnel by using following equation:-

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

B. Bulk density and tap density

Powder's bulk density is calculated by dividing its whole mass by its total volume. The formula is:

$$Bulk\ density = weight\ of\ powder\ bulk/Bulk\ volume$$

The ratio of the blend's mass to the smallest volume of powder in the measuring cylinder is known as the blend's tap density. The density of the tap water was measured with specialized density equipment.

$$Tapped\ density = weight\ of\ powder\ blend/Tapped\ volume\ of\ packing$$

C. Carr's index

On the basis of density results, the % compression capacity of granules was calculated.
The formula is:

$$Carr's\ index = \frac{Tapped\ density - Bulk\ density}{Tapped\ Density} \times 100$$

D. Hausner's ratio

In order to comprehend how granules or powders move, Hausner's ratio was established. The Formula is:

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

2.8. Post Compression Evaluations of tablets

In this type of evaluation, all tablets were subjected for thickness, hardness, friability, drug content assay and *in vitro* drug release study.

2.9. In vitro drug release study

To predict and understand the cumulative drug release of KT nanoparticles loaded matrix tablets,USP type II (paddle type) apparatus was used (D5 8000, Lab India dissolution apparatus). In dissolution bowel, phosphate buffer pH, 7.0 (900ml) was taken and rotate at 100 rpm and 37 ± 1°C temperature was maintained through out of the study. At specific time interval, 5 ml aliquotswere withdrawn and maintain sink condition by adding fresh quantity of buffer solution. After every sampling, all samples were analyzed for KT presence in the solution by using UV/Visible- spectrophotometer at 276 nm. *In vitro* drug release mechanism from matrix tables using natural gum and synthetic polymer can be predicated by treating different mathematical expressions. All the formulations were treated for release kinetics study by considering its release pattern. Zero order, first order, the Higuchi square root, and the Kosmeyer-Peppas equation were all used to assess the kinetic drug-release data. The goodness-of-fit test was used to choose the proper equation.

3. RESULT AND DISCUSSION

3.1. Optimization of polymer and surfactant

The absence of agglomeration and sediment in test formulations led to the selection of polyvinyl alcohol as the surfactant of choice. Because of Eudragit RS 100's inert polymeric resinous characteristic, it was employed as a polymer. Its insolubility at body pH values and swelling capacity make it an ideal medium for medication dispersion [12]. In order to find the optimal drug: polymer ratio, entrapment efficiency is utilised as a metric [17]. The results showed that a ratio of 1:4 between the drug polymer and the trial batch was best, with an entrapment efficiency of 84.430.08684.43±0.086 %.

3.2. Characterization of KT loaded Nanoparticles

3.2.1. Particle Size determination and Zeta potential determination

Mean particle size, polydispesity index and zeta potential were indicated in Table 3, of formulations. Investigational mean particle size of all batches was found in the range of 110.40±0.988-147.50±1.353nm, among the formulations, batch KTN4 showed minimum particlesize i.e. 110.40±0.988nm. Nanoparticles were observed to have a somewhat larger mean size in Eudragit RS100 [13], and its content of quaternary ammonium groups was found to be greater. Very good uniformity and mono-dispersity of nanoparticles were observed across all batches of nanosuspension, with PDI values ranging from 0.358±0.006 to 0.452±0.003. Depending on the surface charge of the particles, the zeta potential can be used as a stability indicator for nanoparticles [25, 26]. The positive surface charge of the Eudragit caused the zeta potential of all nanoparticles to range from 14.300.87414.30±0.874 mV to 19.43±0.953 mV, with the optimised nanosuspension (KTN4) having a zeta potential of 19.43±0.953 mV.

3.2.2. Percent Drug entrapment efficiency determination

The percentage of medicine that was able to be encapsulated in the polymeric matrix is known as the entrapment efficiency. Each formulation had an entrapment efficiency for the medication ranging from 78.300.147% to 84.430.086%, as shown in Table 3. The development of a polymeric matrix with an appropriate viscosity allowed the optimised formulation KTN4 to show a drug entrapment efficiency of 84.430.086%. The highest recorded entrapment efficiency in nanoparticles was achieved using Eudragit RS 100. Since the surfactant (Polyvinyl Alcohol) coats the Eudragit particles, it is more conducive to the encapsulation of the medication. Results showed that the drug entrapment efficiency was greatly improved with a higher drug: polymer ratio, likely as a result of the increased viscosity.

3.2.3. Fourier transforms infrared spectroscopy (FTIR) analysis

Figure 1 shows that the C-N and C=O stretch (diaryl ketone) peaks of KT are at 1373.50 and 1144.07 cm^1, while the aromatic (C-H bending) peaks of KT are at 703.36 cm^1. Because KT was found on the nanoparticles' exterior, these peaks were seen. There was little overlap betweenthe Eudragit and drug absorption peaks in lyophilized KT-loaded nanoparticles (KTN4). Similar absorbance patterns were seen in spectra of physical mixture and lyophilized nanosuspension, demonstrating that KT, polyvinyl alcohol, and Eudragit RS-100 are all compatible with one another. Neither the medication nor the polymers have been shown to cause any functional grouprelocation or to interact significantly with one another. DSC and XRD analyses corroborated the safety and compatibility of these results.

3.3.3. Differential scanning calorimetry (DSC) analysis

Data fusion of DSC thermograms (Figure 2) reveals that KT is crystalline, with two endothermic peaks at 162.66 and 170.88 degrees Celsius, characteristic of tromethamine salt's melting point. As a result of a partial loss of residual humidity, Eudragit RS 100 polymer exists as an amorphous state with a glass transition temperature of around 60 °C and a peak around 61

°C. Physical combination DSC spectra showed endothermic peaks at 160.82 °C and 168.20 °C, showing a minor shift in melting point relative to pure drug, presumably due to electrostatic interaction between the drug and polymer. There are two endothermic peaks visible in the DSC spectra of lyophilized KT nanoparticles (KTN4) at 160.80°C and 169.80°C, indicating the presence of free drug on the nanoparticles' surface. XRD analysis corroborated these DSC findings.

3.3.4. Powder X-ray diffraction (PXRD) analysis

Scanning X-rays of Powder The physical properties of the capsuled medicine were studied using a diffraction technique. Pure KT was characterised by prominent crystalline peaks at 2 values in XRD patterns (Figure 3). Broad and diffuse maxima peaks at 2 values were observed in Eudragit RL-100, suggesting an amorphous structure. X-ray powder diffraction (XRD) spectra of a physical combination revealed that medication crystallisation was unaffected.The drug's crystalline property is retained in the nanosuspension, as seen by the visible, crisp, intense peaks in the pattern of the lyophilized formulation (KTN4). The FTIR and PXRD data together show that the drug is uniformly disseminated in the Eudragit-polyvinyl alcohol polymeric matrix, retaining its crystalinity, polymorphism, and lack of amorphization. Neitherthe drug's potency nor its quality were affected by the polymer network, as seen by the diffraction pattern. Finally, the drug particles were found to have been present in the polymeric matrix as discrete moieties.

3.3.5. Surface morphology by TEM study

The TEM investigation proved the shape of KT nanoparticles in nanosuspension. Reduced clustering can be seen in Figure 4 TEM micrographs of the improved nanosuspension. Different levels of magnification were used to get TEM images of the same sample. The images with the smallest particles were chosen (5-50 nm). The morphology points to discrete, spherical, smooth, and uniformly dispersed particles.

3.3.6. Dissolution study

The drug release profile from KT-loaded nanoparticles was biphasic. The presence of free drug not entrapped in the polymer system allowed for rapid drug release during the first phase. The second phase involved a gradual release of the medication due to KT's slow diffusion into the polymer matrix. It's possible that the rapid drug release saw at the outset was caused by the drug being released unencapsulated. Since Eudragit encapsulated the medicine in a polymer, the drug was able to be released in a rapid burst initially and then at a more steady rate over time since it is water soluble.

Because the medication was able to penetrate the polymer matrix more deeply, the dissolving profile improved at lower drug concentrations. The uniformity of the drug's distribution and the homogeneity of the polymer matrix are the two most important factors determining the dissolution profile. The medicine is released slowly over time from a Eudragit RS-100 matrix that expands in aqueous conditions regardless of pH. The burst release effect was seen in batchesthat had smaller particles and less drug trapping. The drug release profile was maintained throughout time in all of the formulations. Drug release pattern was also modified by the amount of polymer used and the drug: polymer ratio. Because of its decreased leakage of the contained drug in matrix and its inhibition of drug desorption, KTN4 showed 77.210.68% drug release in 12 hours. As can be seen in Table 2, the release profile of the optimised KT nanoparticles (KTN4) was best suited by zero order kinetics, with a regression coefficient value (R2) of 0.994. Korsmeyer-Peppas model (R2=0.974) showed that KTN 4's release exponent (n) was less than 0.45, indicating that the medication was released by a Fickian diffusion mechanism. The high water permeability and swelling feature of Eudragit RS100, which is rich in quaternary ammonium groups, likely accounted for the material's quick initial drug release. The drug releaseis increased because the polymeric ammonium groups are gradually saturated.

3.4. Pre-compression Evaluation of KT nanoparticles loaded granules

The angle of repose for the resulted blend was performed and the study concludes, all theformulations blend were found to be in the range 28.00° to 34.00°. A range of 0.4389±0.09 to0.4889±0.10 g/ml was found for the bulk density, while the range for the tapped density was 0.4233±0.14 to 0.47810±0.11g/ml. Carr's index and Hausner's ratio, two measures ofcompressibility, had values in the range of 16.00±0.18 to 18.82±0.10 and 1.17±0.04 to1.21±0.07 respectively. The analysis of the powder blends produced by each batch prior tocompression found that the blends had superior flow property features relative to the normativevalues.

3.5. Evaluation of Post compression parameters of KT loaded matrix tablets

After loading matrix tablets with KT nanoparticles, the weight range obtained was from 0.3870.003 to 0.3990.007 g. The average thickness was determined to be 1.2 0.1 m, while the average friability ranged from 0.09 0.008 to 0.15 0.003 throughout the several batches tested. From 5.5 0.1 to 6.1 0.1 kg/cm2 was the range found for tablet hardness across all batches. Figure7 shows the results of an in vitro drug release study conducted with formulations comprising HPMC and xanthan gum. The % in vitro drug release from formulations KTNT1 to KTNT9 atthe end of 24 h was found to be in

the range of 95.40 - 98.56 %. A phosphate buffer with a pH of 7.0 was used for the in vitro drug release. The findings showed that water penetrating into the polymeric matrix was a prerequisite for the initial drug release. The enhanced formulation profiledelivered by KTN9 contained higher amounts of HPMC K4M, which has hydrophilic rate retardant qualities. According to this, synthetic polymers exhibited better release retardant qualities than natural polymers. Since there was enough time for swelling and gelling, the drug's release was postponed. Matrix tablets worked better with HPMC K4M because it had a higher viscosity than xanthan gum. Moreover, the kind of the substituents, such as the presence of hydroxypropyl groups, influences how rapidly HPMC hydrates. HPMC K4M afterwards produced a potent reaction with aqueous medium.

Linear regression analysis was used to determine whether or not the zero order, first order, Higuchi's, and Korsmeyer-equations Peppa's for release kinetics provided a sufficiently good fit to the data, which in turn allowed for an evaluation of release and the mechanism of drug action. The *in vitro* release kinetics profile for each formulation revealed a regression coefficient rangeof R^2 values between 0.980 and 0.988 for zero order. So, zero order kinetics was used to follow the drug release. It was determined that the drug release followed zero order kinetics. The Noyes Whitney equation is necessary for the first order equation to function. According to Higuchi, the square root t depends on how quickly the drug is released from the insoluble matrix, and the R^2 value ranged from 0.988 to 0.998. It was discovered that Korsmeyer-Peppas' explanation of the drug release mechanism (Table 7).

3.6. Physical stability study

All formulations were subjected to room temperature stability testing for 180 days, during which time the first-order degradation rate constant, time to 90% of starting drug concentration, and initial drug concentration for shelf life (t90) of 2 years were calculated (Table 8). The degradation rate constants in room temperature were found to be in between 1.12 -2.12 for all formulations. Based on the average degradation across all formulations, the ICH recommendations suggest a two-year shelf life as a ballpark figure. However, on the basis of degradation data under room temperature storage, some overages would be needed for the formulations to ensure 2 years shelf life.

4. CONCLUSIONS

The design, development, and effective characterization of KT nanoparticles loaded in matrix tablets for sustained action was successfully done. Moreover, exploration of Eudragit RS- 100 in the form of nanoparticles was well presented in the current study. The study comprises thenano form of KT was able to provide minimum range particles for better permeation in GI fluid. The polymer matrix was demonstrated to be a workable oral medication delivery system with theintended results. Polyvinyl alcohol was demonstrated to be effective in the creation of stable KT loaded nanoparticles as compare to other stabilizer presence. All KT nanoparticles put in matrix tablets produced a biphasic *in vitro* drug release. The study also suggested that a larger percentage of drug entrapment efficiency in KT loaded nanoparticles slows the release of the drug. The formulation has kept the drug's crystalline structure, especially at low temperatures.

The disclosed formulation holds promise as a patient-friendly oral medication deliverymechanism.

Conflicts of interest

This article's authors report no conflicts of interest.

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Table 1. Composition and observation of preliminary trail batches of Ketrolac Tromethamine(KT) Loaded Nano-particles

Optimization Parameters	Surfactant	Drug (mg)	Drug : polymer	Surfactant Conc. (%,w/v)	Observations				
					Physical Appearance	Entrap. efficiency(%)	Amount permeated * (mg)	Permeation (%)	Corneal Hydration (%)
Surfactant	Tween 80	1	1:1	0.5	Particles Sediment	-	-	-	-
		1	1:1	1.5	Particles Sediment	-	-	-	-
		1	1:1	2	Particles Sediment	-	-	-	-
	Cabopol	1	1:1	0.5	Particles Agglomerate	-	-	-	-
		1	1:1	1	Particles Agglomerate	-	-	-	-
	Polyvinyl Alcohol	1	1:1	1.5	Bluish opalescence	-	-	-	-
		1	1:1	2	Bluish opalescence	-	-	-	-
		1	1:1	2.5	Bluish opalescence	-	-	-	-
		1	1:1	1	Bluish opalescence	-	-	-	-
Concentration of polyvinyl alcohol	Polyvinyl alcohol	1	1:10	0.5	-	45.45	0.076±0.003	3.8±0.200	77.23±0.002
		1	1:10	1	-	34.36	0.064±0.002	3.2±0.100	76.45±0.001
		1	1:10	1.5	-	40.00	0.050±0.008	2.5±0.400	78.87±0.021
		1	1:10	2	-	31.72	0.054±0.002	2.7±0.100	77.83±0.003
		1	1:10	2.5	-	16.36	0.031±0.001	1.55±0.050	76.93±0.001

Table 2. Composition of Eudragit RS-100 based KT loaded nanoparticles.

Formulation code	Ketrolac Tromethamine (mg)	Eudragit RS-100 (mg)	Stabilizer (PVA) (% w/v)
KTN 1	100	100	0.5
KTN 2	100	200	0.5
KTN 3	100	300	0.5
KTN 4	100	400	0.5
KTN 5	100	500	0.5

Table 3. Physiochemical profile of Eudragit RS-100 based KT loaded nanoparticles.

Formulationcode	Entrapment efficiency(%)	Particle Size(nm)	PDI	Zeta potential
KTN 1	78.45±0.134	111.20±1.079	0.452±0.003	16.30±1.041
KTN 2	77.31±0.246	147.50±1.353	0.370±0.015	15.33±0.296
KTN 3	79.95±0.154	134.10±1.938	0.358±0.006	14.47±1.445
KTN 4	84.43±0.086	110.40±0.988	0.416±0.015	19.43±0.953
KTN 5	78.30±0.147	130.70±0.819	0.436±0.001	14.30±0.874

Table 4. KT nanoparticles loaded matrix tablets by using 3^2 factorial design and differentevaluation response.

Formulation Code	Formulation variables (X1)	(X2)	Formulation response (Y1)	(Y2)	(Y3)
	Amount ofXanthan Gum (Mg)	Amount of HPMC K100M	Drug Content %	SwellingIndex	*In vitro* DrugRelease
KTNT1	40	20	93.89	78.13	95.40
KTNT2	40	30	94.03	78.23	95.80
KTNT3	40	40	94.23	78.99	95.89
KTNT4	50	20	95.09	80.13	96.66
KTNT5	50	30	95.20	80.23	97.42
KTNT6	50	40	96.23	80.88	97.56
KTNT7	60	20	97.43	90.03	98.20
KTNT8	60	30	98.78	91.05	98.50
KTNT9	60	40	99.05	92.23	98.56

Table 5. Pre-compression micrometrics profile of powder blend

Formulation	Angle of repose(θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Hausner's ratio
KTNT1	0.34±0.14	0.4889±0.10	0.4880±0.09	17.82±0.09	1.18±0.07
KTNT2	0.31±0.24	0.4389±0.09	0.4708±0.12	18.82±0.10	1.20±0.09
KTNT3	0.29±0.17	0.4289±0.10	0.4389±0.10	18.19±0.11	1.21±0.07
KTNT4	0.34±0.15	0.4589±0.09	0.4645±0.17	16.00±0.18	1.17±0.04
KTNT5	0.28±0.11	0.4880±0.13	0.4770±0.14	17.02±0.07	1.19±0.05
KTNT6	0.33±0.18	0.4670±0.15	0.4470±0.15	18.22±0.19	1.20±0.04
KTNT7	0.30±0.19	0.4900±0.14	0.4233±0.14	17.09±0.01	1.18±0.09
KTNT8	0.31±0.10	0.4880±0.08	0.4870±0.08	17.82±0.09	1.24±0.03
KTNT9	0.28±0.12	0.48810±0.11	0.47810±0.11	17.77±0.05	1.22±0.04

Table 6. Post-compressional evaluation parameters of KT nanoparticles loaded matrix tablets.

Formulation	Weight variation	Hardness (kg/cm^2)	Thickness(mm)	% Friability	% Drugrelease
KTNT1	0.391±0.004	5.4±0.4	1.3±0.4	0.12±0.002	95.40
KTNT2	0.399±0.007	6.1±0.1	1.3±0.4	0.10±0.004	95.80
KTNT3	0.387±0.003	5.7±0.3	1.3±0.4	0.11±0.001	95.89
KTNT4	0.388±0.005	5.8±0.8	1.3±0.4	0.13±0.005	96.66
KTNT5	0.388±0.004	6.1±0.7	1.3±0.4	0.14±0.007	97.42
KTNT6	0.388±0.002	5.7±0.1	1.3±0.4	0.10±0.008	97.56
KTNT7	0.393±0.004	6.0±0.6	1.3±0.4	0.15±0.003	98.20
KTNT8	0.389±0.005	5.5±0.1	1.3±0.4	0.09±0.008	98.50
KTNT9	0.392±0.001	5.8±0.7	1.3±0.4	0.13±0.007	98.56

Table 7. *In vitro drug* Release kinetics profile of KT nanoparticles loaded matrix tablets

Formulationcode	Zero order (R2)	First order (R2)	Higuchi (R2)	Korsmeyer-Peppas (R2)	Value of n
KTNT1	0.988	0.970	0.997	0.990	0.493
KTNT2	0.985	0.978	0.994	0.991	0.452
KTNT3	0.987	0.980	0.990	0.994	0.421
KTNT4	0.981	0.988	0.994	0.990	0.433
KTNT5	0.989	0.980	0.989	0.988	0.409
KTNT6	0.983	0.974	0.997	0.990	0.411
KTNT7	0.990	0.967	0.991	0.983	0.409
KTNT8	0.980	0.980	0.994	0.991	0.410
KTNT 9	0.999	0.974	0.992	0.994	0.417

Table 8. Stability profile KT nanoparticles loaded matrix tablets under Room Temperature Storage.

Formulations Code	KT content					$K_{cal}(day^{-1} \times 10^4)$	T90 days	Int calc 2 years
	0 D	3 W	6W	3M	6M			
KTNT1	100±0.07	99.00±0.03	98.78±0.06	97.25±0.06	96.25±0.06	2.12	490	105.1
KTNT2	100±0.03	99.25±0.04	99.00±0.02	98.75±0.04	98.00±0.02	1.12	926	97.7
KTNT3	100±0.08	99.20±0.03	98.75±0.06	98.00±0.08	97.01±0.11	1.69	617	101.8
KTNT4	100±0.08	99.09±0.05	98.70±0.06	98.00±0.08	97.50±0.20	1.41	739	99.7
KTNT5	100±0.27	98.99±0.11	98.15±0.03	97.00±0.26	96.55±0.00	1.95	533	103.8
KTNT6	100±0.10	99.00±0.02	98.00±0.08	97.58±0.13	97.00±0.04	1.69	614	101.8
KTNT7	100±0.00	99.20±0.03	98.75±0.06	98.00±0.08	97.01±0.11	1.62	622	101.2
KTNT8	100±0.09	99.19±0.03	98.25±0.06	98.09±0.08	98.01±0.11	1.28	712	100.4
KTNT9	100±0.20	99.12±0.03	98.35±0.06	98.23±0.08	98.09±0.11	1.29	713	101.5

*Values are mean ± SE (*n*=3

* K_{calc}: calculated first-order degradation rate constant, t_{90}: time to reach 90% of initial drugconcentration, Int_{calc}: calculated initial drug concentration for shelf life (t_{90}) of 2 years

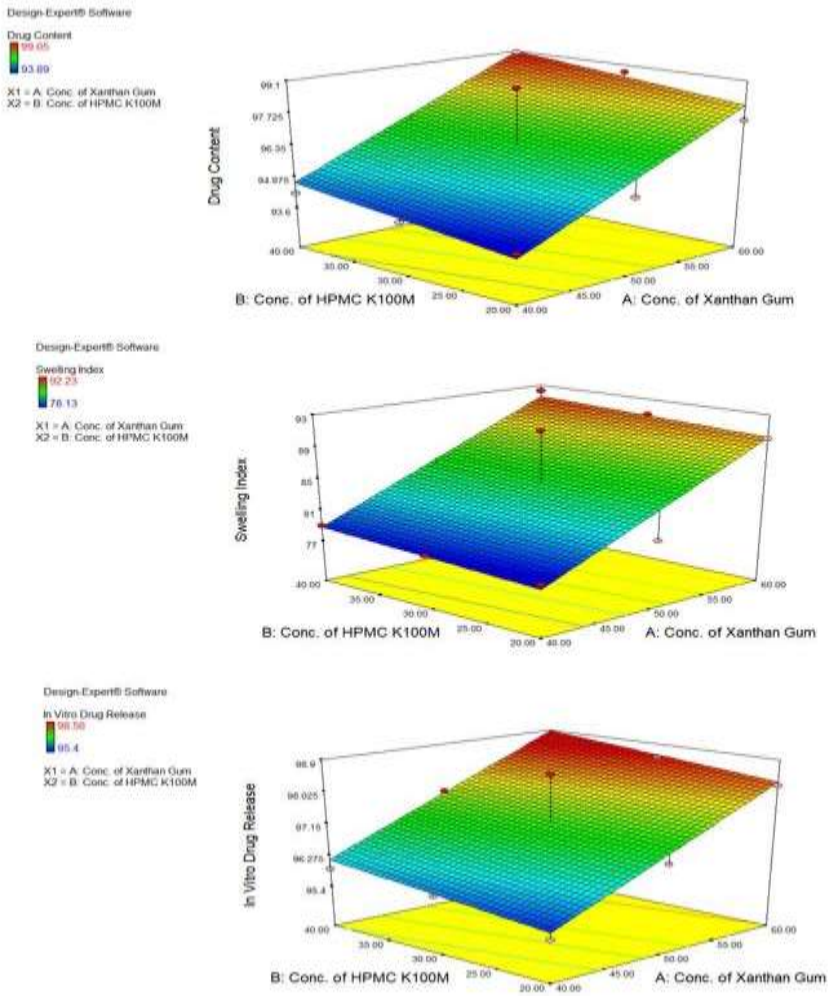

Figure 1. Response surface plots illuminating the KT effect Xanthan gum: Effects of HPMC K100M concentrations and stirring rates on drug content, swelling index and drug release (A),(B), and (C), respectively

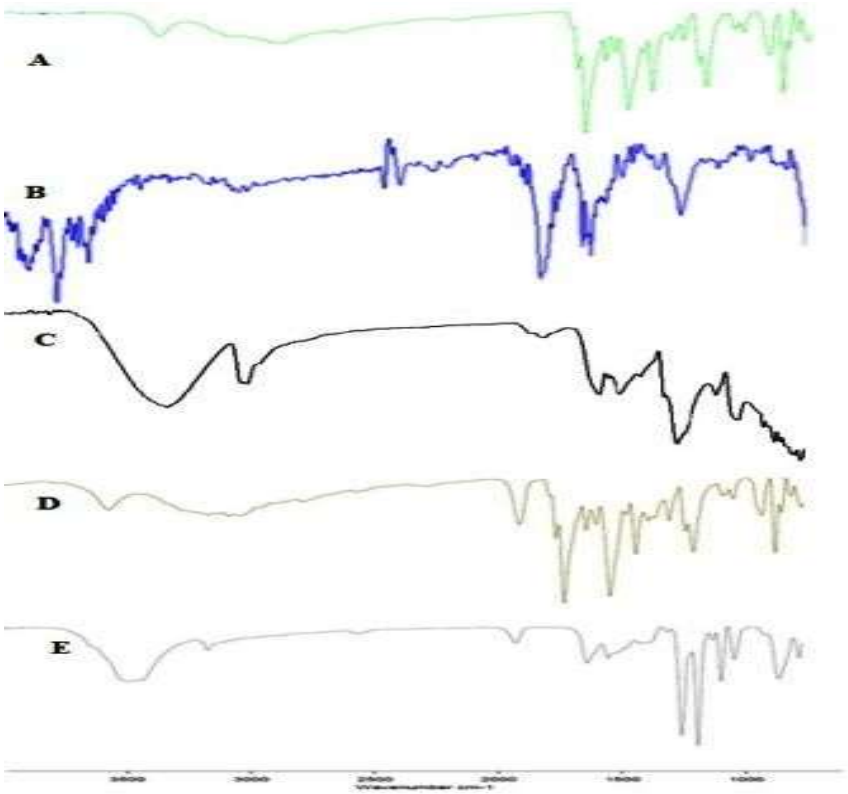

Figure 2. FTIR spectra of pure KT (A), Eudragit RS-100 (B), Polyvinyl alcohol (C), Physicalmixture of Pure drug and

Eudragit RS-100(D) and Lyophilized nanoparticles KTN 4 (E)

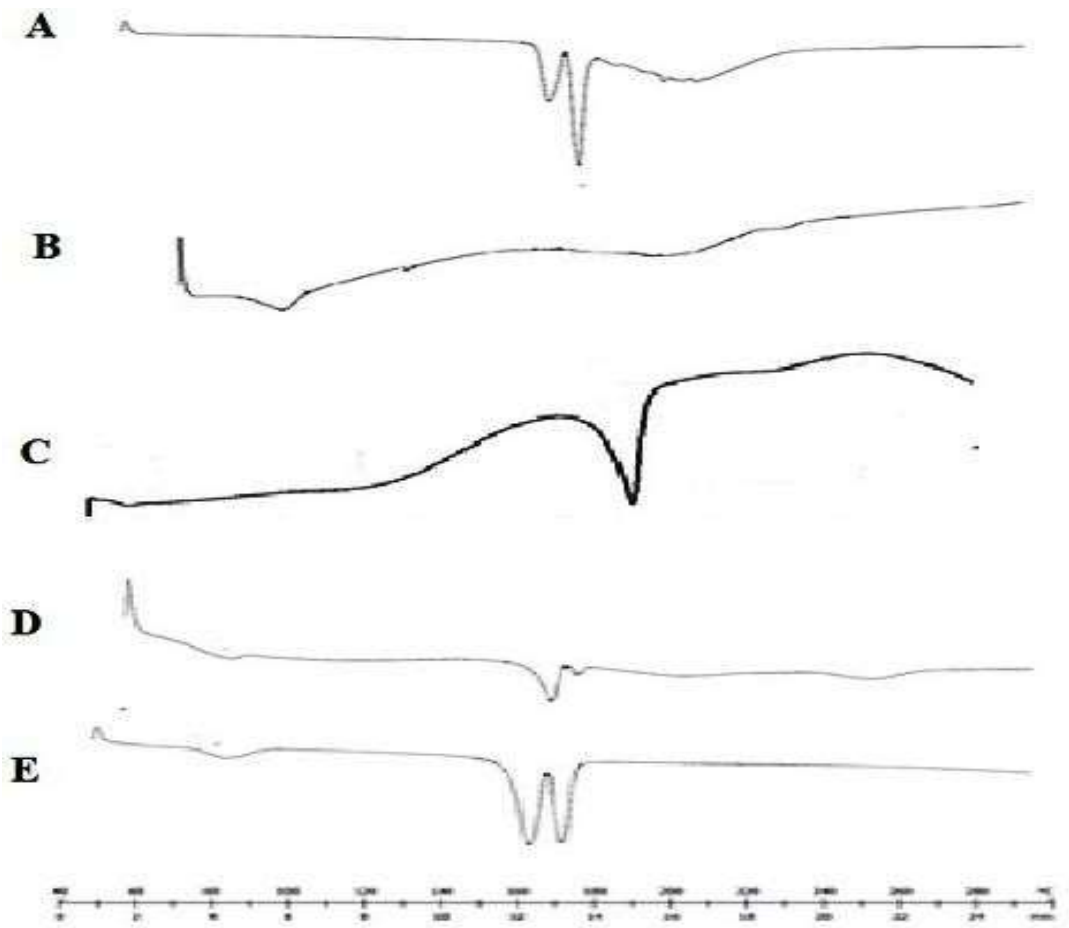

Figure 3. DSC curves of crude KT (A), Eudragit RS-100(B), polyvinyl alcohol (C), physicalmixture (D) and lyophilized nanoparticles KTN4 (E).

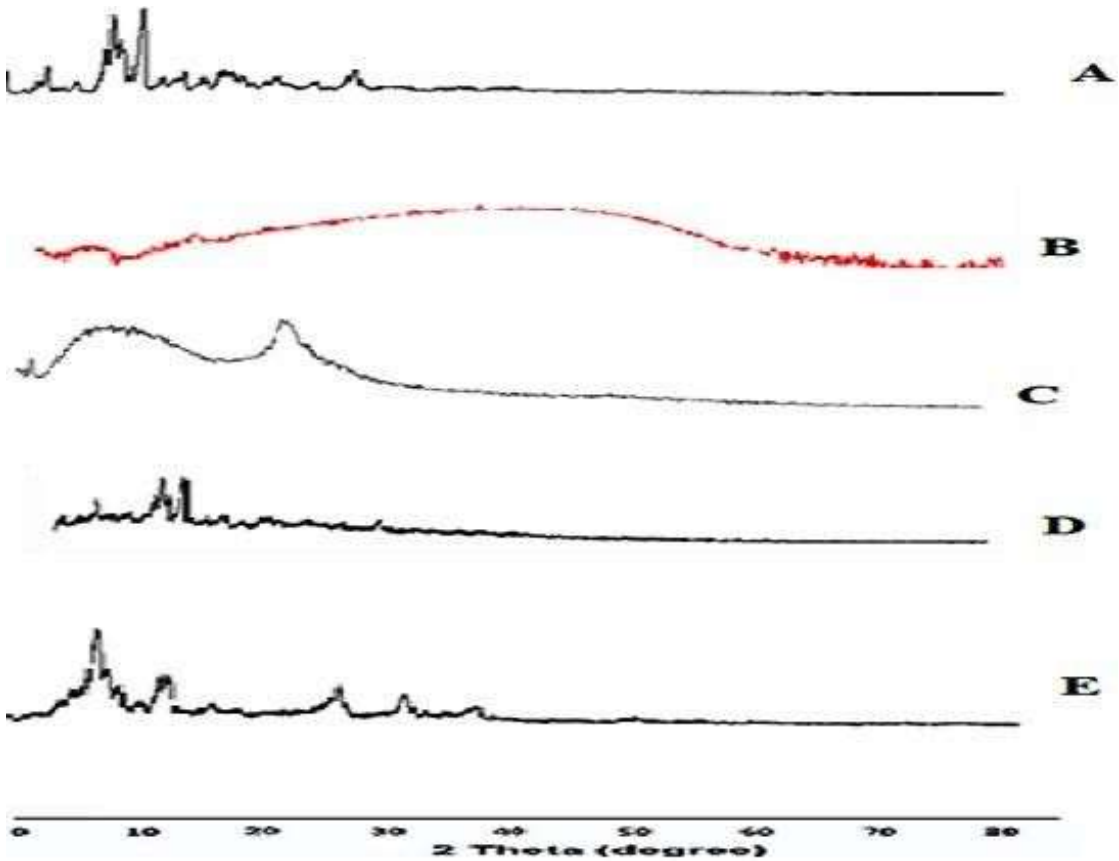

Figure 4. PXRD spectra of crude KT(A), Eudragit RS-100(B), Polyvinyl alcohol (C) physicalmixture (D)and

lyophilized nanoparticles KTN4 (E)

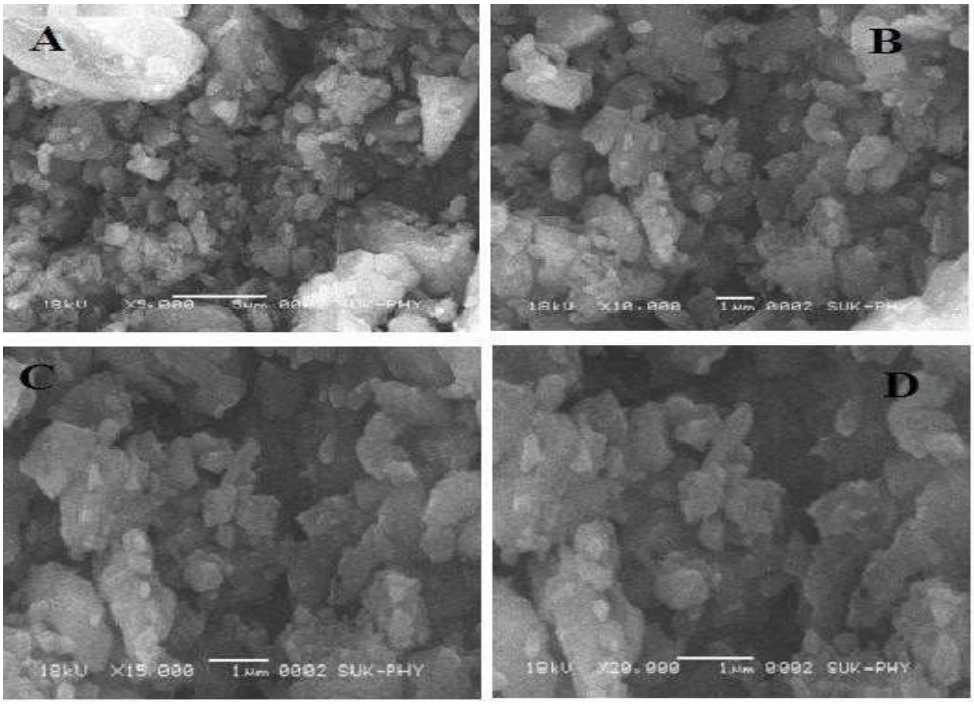

Figure 5. TEM images of KT loaded nanoparticles (Optimized batch) (A: at magnification x 5,000, B: at magnification x10, 000, C: at magnification x15 000, D: at magnification x20, 000).

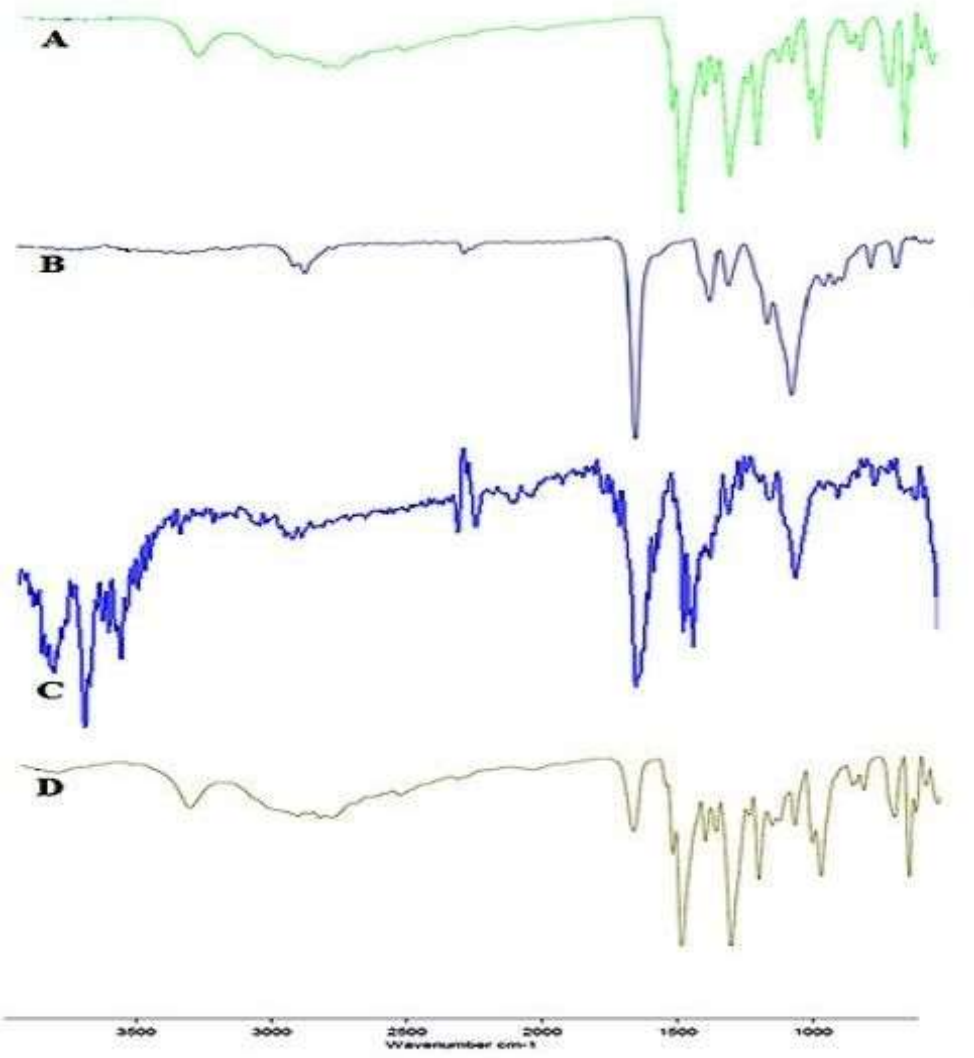

Figure 6. FTIR spectra of KT loaded nanoparticles (a), Xanthan gum (b), Physical mixtureof nanoparticles and Xanthan

gum (c) and KT matrix tablets (d)

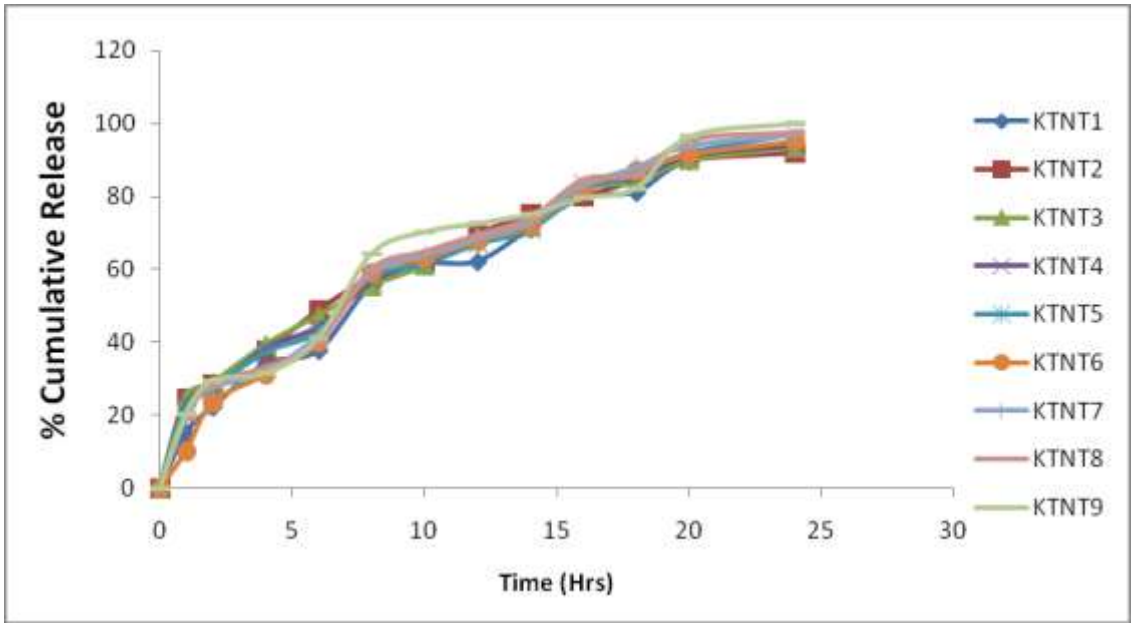

Figure 7. Comparative Drug release profile of Xanthan gum based KT nanoparticles loadedmatrix tablets.