Original Article

Chitosan Loaded Ketorolac Tromethamine Nanoparticles for Improved Ocular Delivery in Eye Inflammation

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ABSTRACT

Aim: Ketorolac tromethamine (KT) is highly effective in treating post-operative eye inflammation, allergic conjunctivitis as well other ailments. It is reported that USFDA has approved a 0.45% ophthalmic solution of KT (Acuvail, Allergan, Inc) for the treatment of pain and inflammation after cataract surgery. However, the bioavailable amount of an ocular dosage form is very low due to continuous defensive mechanism in the eye. Thus the aim of present study was to improve the bioavailability of KT via sustained release using the polymer matrix (Chitosan) as a carrier. **Materials and Methods:** Nanoparticles of Ketorolac tromethamine were prepared by ionotropic gelation method. Design expert software was used to evaluate the effect of chitosan and tripolyphosphate (TPP) concentration on particle size and entrapment efficiency of nanoparticles. Prepared nanoparticles were physico-chemically characterized for % yield, entrapment efficiency, particle size and Zeta potential, surface morphology, *in-vitro* drug release, release kinetics and stability studies. In accordance with the evaluation parameters and results obtained from factorial design, an optimized batch was designed and evaluated for above mentioned parameters. **Results:** The optimized batch thus prepared was having Percentage yield (66.4%), Percentage Entrapment Efficiency (61.65%), Particle size (153.9 nm), Zeta Potential (-21.8) and percentage drug release (94.368 ± 0.181 & 92.797 ± 0.150% in PBS and STF (pH 7.4) respectively). Results of release kinetic study revealed that drug dissolution followed Zero order release kinetics model. No physicochemical changes were seen when stored at accelerated conditions. **Conclusion:** It was concluded that the principle adopted behind this research work will provide impetus for future researchers to carry out such formulations of wider variety of drugs rendering highly economical utility.

Key words: Ketorolac tromethamine, Chitosan, Tripolyphosphate, Nanoparticles, Design expert.

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INTRODUCTION

Inflammation is the indication of cellular and vascular response of the host tissue to injury which may be inflicted by physical or chemical agents, invasion of pathogens, ischemia, and excessive (hypersensitivity) or inappropriate (autoimmunity) operation of immune mechanisms. Post-operative inflammation includes distracted aqueous-blood barrier, excessive blood flow in conjunctival vessels, miosis, elevated IOP, intervened by COX pathways.[1-2] Ocular inflammation most frequently hastens due to infection, allergens, surgical intervention or trauma.[3] Various ocular problems/diseases i.e. intra-operative miosis (during cataract surgery), postoperative inflammation, cystoid macular edema (CME) following cataract extraction, seasonal allergic conjunctivitis, ocular dis-

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comfort (pain and photophobia) after refractive surgery, Diabetic retinopathy (DR) and Diabetic macular edema (DME) are prevented/treated by various drugs belonging to NSAID class.[1-4] Eye-drops accounts for the 90% of currently accessible conventional ophthalmic formulations. The bioavailable amount of an ocular dosage form is very low due to continuous defensive mechanism in the eye. The instilled amount of drug is continuously wiped out from the retinal flora because of blinking and involuntary lachrymation. Also, the faster absorption of applied drugs is more massed by the anatomy, physiology and barrier functions of cornea.[5] Nanoparticles have been formulated as eye drops or injectables to surmount ocular obstacles faced after administration. Better drug pharmacodynamics and pharmacokinetics, immunogenicity, bio recognition and non-specific toxicity can be achieved to improve drug efficacy by loading drugs in the nanoparticles.[6-9] Chitosan nanoparticles are good drug carriers because of their good biocompatibility and biodegradability, and can be readily modified.[10-11] Ketorolac tromethamine (KT) belongs to pyrrolo-pyrrole group of NSAIDs. Its chemical name is (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1). It is highly effective in relieving pain after radial keratotomy (RK), photorefractive keratectomy (PRK), laser *in situ* keratomileusis (LASIK); acute pseudophakic cystoid macular edema (PCME) and to treat allergic conjunctivitis pertaining to inhibition of ocular PG synthesis.[12-13] Hence, the present worker conceptualized "Chitosan loaded Ketorolac tromethamine nanoparticles for improved ocular delivery in Eye inflammation" that would fulminate into improved therapy. The outcomes of research work, in reference, would contribute to the society in getting rid of such problems by recognizing ultimate ease and least negligence to maintain the drug therapy i.e. least possible frequency of administration, higher ocular residence time and thus sustained longer duration of action.

MATERIALS AND METHOD

Materials

Ketorolac tromethamine was procured from Panchsheel Organics Ltd, Indore. Chitosan (Medium grade; 400 KD) was purchased from Evonik Industries, Mumbai, MHA. Other chemicals i.e. Glacial acetic acid, Span–80, Ethanol, Sodium hydroxide, Sodium chloride, Sodium bicarbonate, Calcium chloride dihydrate, Sodium tripolyphosphate, Potassium dihydrogen phosphate were procured from various companies.

Methods

FTIR and TLC study

Drug (Ketorolac tromethamine)-excipient compatibility was checked by adopting IR spectroscopy and densitometric TLC analyses. Infra-red spectra of pure drug alone and with chosen ingredients were recorded on FTIR (Shimadzu IR Affinity^{-1}) spectroscopy at a resolution of 2 cm^{-1} ranged from 4000 to 400 cm^{-1} using KBr discs. Ketorolac tromethamine was analyzed densitometrically using combination of glacial acetic acid: acetone: dichloromethane (mobile phase) in ratio 1:1:9 % v/v, respectively. Obtained spots were detected at 322 nm.[14]

Preparation of Ketorolac tromethamine loaded Chitosan nanoparticles

Drug (Ketorolac tromethamine) laden nanoparticles were produced by ionotropic gelation method using chitosan and sodium tri-polyphosphate (Na-TPP). Prepared product (suspension) was centrifuged (Remi, Mumbai, India) for 15 min. at 12000 rpm. Sediment was freeze dried (Lyophilizer, Biogen-model no BGS214, India) for 48 h. The obtained nanoparticles were stored under dehydrated conditions for further studies (Figure 1).[15]

Experimental design

Design Expert (Version 9.0, Stat-Ease Inc., Minneapolis, MN) was used for optimization study of ketorolac tromethamine nanoparticles consisted of 2 independent factors i.e. amount of chitosan (X1) and sodium tri-poly phosphate (X2) which were evaluated, at 3 levels (-1, 0, 1 i.e. 100, 200 and 300 respectively) and 9 experimental trials were performed with reference to particle size and percent (%) entrapment as dependent variables (Table 1). All other processing variables were kept constant throughout the study.[16]

Physicochemical characterization of Ketorolac tromethamine nanoparticles

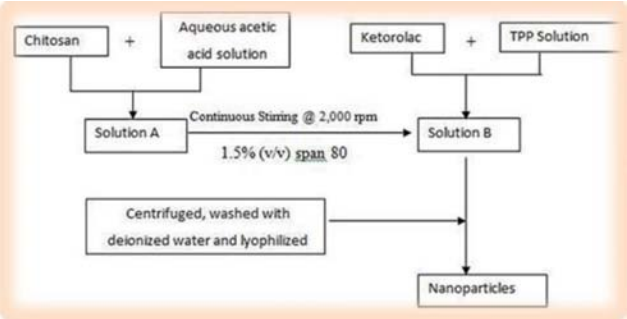

Figure 1: Ketorolac tromethamine loaded Chitosan nanoparticles.

Table 1: Independent and Dependent variables (Coded and actual values).

Variables			Coded values (Independent variables)			Actual values (Independent variables)		
Drug	Independent variables	Dependent Variables	Low	Medium	High	Low	Medium	High
Ketorolac tromethamine	amount of chitosan (X1)	particle size	-1	0	1	100	200	300
	sodium tri- poly phosphate solution (X2)	% entrapment	-1	0	1	100	200	300

The average diameter and zeta potential of drug-loaded nanoparticles were measured by dynamic light scattering method using Zetasizer nano zs (Malvern instrument ltd., Worcestershire, UK). Surface morphology was used to determine the shapes and distribution of particles and measured by SEM (XL series Quanta FEI 200F).

In-vitro Drug release

Drug release from drug-loaded nanoparticles was carried out by suspending the prepared nanoparticles in PBS (phosphate buffer saline, pH 7.4) in a conical flask (100 ml) and shaked on magnetic stirrer (150 cycles/min) at 37°C. Withdrawn samples were centrifuged at 12000 rpm and analyzed using UV spectrophotometry at 322 nm.

Ocular Irritancy test

The prepared nanoparticles belonging to optimized batch were evaluated for *in-vivo* performance in Albino rabbits. They were manipulated suitably for experimental conditions. Eyes were marked as test and control respectively. The control eyes received no sample while the test eyes received the nanoparticles, and observed for the ocular irritancy. The protocol was approved by Institutional Animal Ethical Committee.[17]

Accelerated (Physical) Stability studies

ICH (International Conference of Harmonization) guidelines were followed to carry out the stability study of optimized formulation. The optimized formulation was stored at accelerated conditions ($40^0 \pm 2^0$C/75%±5% RH) for six months respectively and reckoned, for released characteristics, at predetermined time period.[18]

RESULTS AND DISCUSSION

FTIR analysis

The FTIR spectra of pure drug resulted in characteristic peaks which resembled with those obtained with the combinations. In the spectrum of ketorolac tromethamine (Figure 2A), major peaks (3,625 cm-1; NH stretch); 1,157 cm^{-1}; C = O stretch (diaryl ketone); 1,625 cm^{-1}; C-C stretch (aromatic stretching); and 3,650 cm^{-1}; OH (acid); 2679 cm^{-1}; CH stretching vibration, 1172 cm-1; C–O–C and 1908 cm-1; NH_2, were observed in spectra obtained with chitosan (Figure 2B). Hence, drug polymer compatibility was confirmed by confinement of distinctive peaks of pure drug in its combination with chitosan.[19]

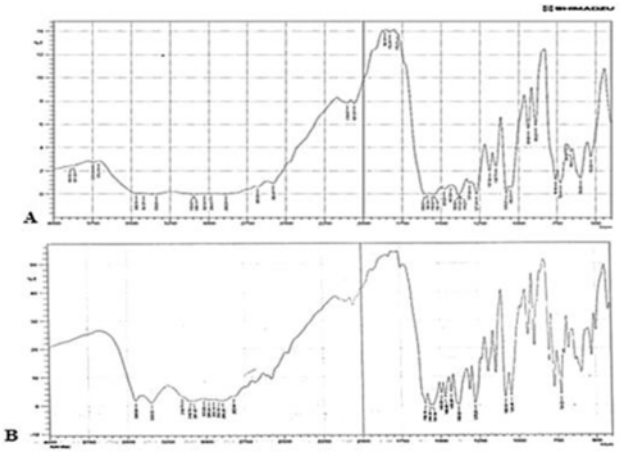

Figure 2: FTIR spectra of (A) Pure drug (Ketorolac tromethamine), (B) Ketorolac tromethamine and chitosan.

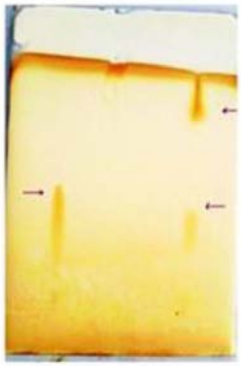

Figure 3: TLC image of ketorolac tromethamine (pure drug) and drug with Chitosan.

Thin Layer Chromatography (TLC) Method

Nearly similar R_f values of the drug alone and its combinations with selected polymer confirmed their compatibility. R_f value of pure drug i.e. ketorolac

Table 2: Summary of Regression Analysis Results for Particle size.

Source	Sum of Squares	df	Mean Square	F-value	p-value	Remark
Model	1915.28	5	383.06	710.34	< 0.0001	significant
A-Chitosan	1683.38	1	1683.38	3121.64	< 0.0001	
B-Sodium tri poly phosphate	212.42	1	212.42	393.90	0.0003	
AB	6.76	1	6.76	12.54	0.0383	
A^2	12.67	1	12.67	23.49	0.0168	
B^2	0.0672	1	0.0672	0.1247	0.7474	
Residual	1.62	3	0.5393			
Cor Total	1916.90	8				

Table 3: Summary of Regression Analysis Results for Entrapment efficiency.

Source	Sum of Squares	df	Mean Square	F-value	p-value	Remark
Model	490.48	5	98.10	26807.69	< 0.0001	significant
A-Chitosan	436.74	1	436.74	1.194E+05	< 0.0001	
B-Sodium tri poly phosphate	53.16	1	53.16	14528.42	< 0.0001	
AB	0.0676	1	0.0676	18.47	0.0232	
A^2	0.4449	1	0.4449	121.59	0.0016	
B^2	0.0697	1	0.0697	19.04	0.0222	
Residual	0.0110	3	0.0037			
Cor Total	490.49	8				

tromethamine was found to be 0.539 and with chitosan it was 0.538 (Figure 3). Similar results were shown by Dhiraj A. Khairnar *et al.* (2014).[20]

Formulation, Optimization and Evaluation

In the present investigation, selected independent variables were amount of chitosan and TPP while the particle size and percentage drug entrapment was selected as dependent variables. The selected independent variables were studied at different levels to observe their individual as well as interactive effects.

Particle size of prepared nanoparticles ranged between 155.5- 200.4 nm and quadratic model was best suited for the data which was validated by ANOVA. As mentioned in Table 2, the Model F-value is 710.34, which implies that model is significant. Moreover, the factor A had shown more effect on Particle size of nanoparticles with F-value of 3121.64 (p<0.0001) than factor B with F-value of 393.90 (p<0.05). The predicted R^2 of 0.9898 was significantly correlated with adjusted R^2 of 0.9977; i.e. the difference is less than 0.2. Signal to noise ratio greater than 4 is desirable, and in the present study, it is 75.719 that indicated an adequate signal.

Polynomial equation thus generated was as shown below (equation 1):

$$\text{Particle size (nm)} = 181.61 - 16.75A - 5.95B - 1.30AB - 2.5A^2 + 1.8B^2 \quad \text{Eq. 1}$$

As shown in Figure 4a, the particle size decreased significantly with increase in concentrations of both factors i.e. chitosan and TPP which was presented in the form of contour and 3D response surface plots. It is already reported that as the concentration of chitosan and TPP increased, particle size decreased accordingly.[21-22]

Second dependent factor was chosen as percent (%) drug entrapment. Entrapment efficiency of prepared batches (A1-B3) was found between 38.86%-61.91%. As shown in Table 3, the Model F-value is 26807.69, which implies that model is significant. Both factors A and B had similar effect on entrapment efficiency of nanoparticles with F-value of 1.194E+05 and 14528.42 respectively at p<0.0001. The predicted R^2 of 0.9998 was in correlation with adjusted R^2 of 0.9999; i.e. the difference is less than 0.2. Signal to noise ratio was 466.0; indicated an adequate signal.

Polynomial equation thus generated was as shown below (equation 2):

$$\text{Entrapment efficiency (\%)} = 49.61 - 8.53A - 2.98B - 0.13AB - 0.47A^2 + 0.19B^2 \quad \text{Eq. 2}$$

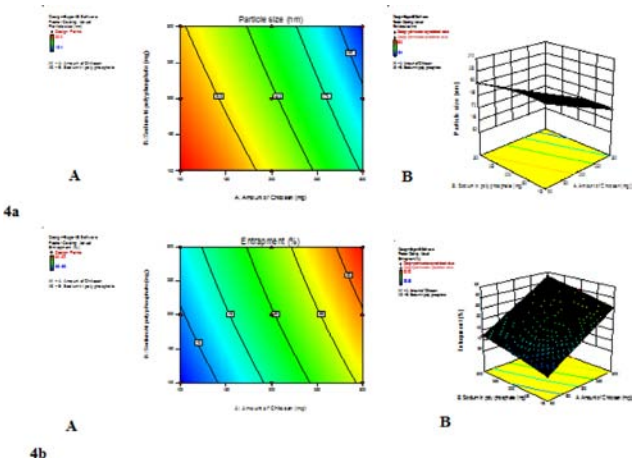

Figure 4: Contour (A) and 3D response surface (B) plots of showing the effect of Chitosan and sodium TPP on Particle size, 4b. Contour (A) and 3D response surface (B) plots showing the impact of Chitosan and sodium TPP on Entrapment efficiency.

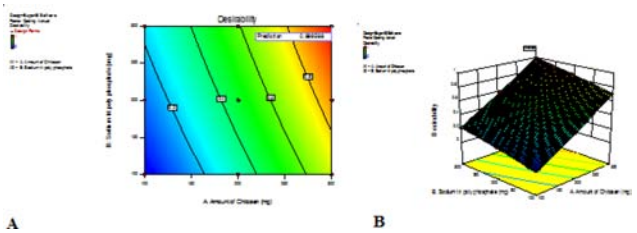

Figure 5: Desirability Contour and 3D graph of KT nanoparticulate batch (OKT).

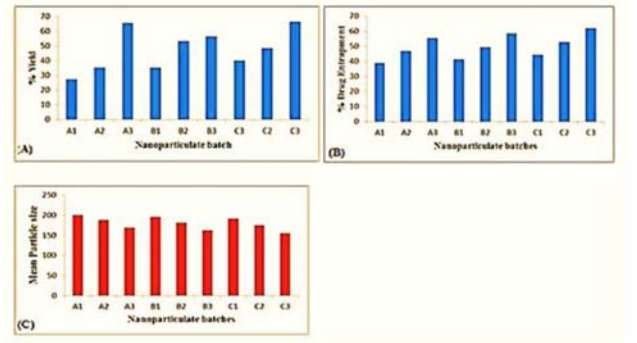

Figure 6: Evaluation Parameters for Ketorolac tromethamine nanoparticles (batches A1-C3), (A) Percentage (%) yield, (B) Percentage drug entrapment, (C) Mean Particle size.

From the polynomial equation, it was shown that when factors i.e. A and B increased, the drug entrapment into polymer was also increased. It is reported that a decrease in weight ratio of CS/TPP, decreases the encapsulation efficiency of nanoparticles pertaining to more compact solid-matrix structure that had led to the increasing amount of nanoparticles formation, resulting in the increased nanoencapsulation.[22] Moreover, the maximum polymer and surfactant (TPP) concentration give more encapsulation efficiency and vice-versa (Figure 4b). It may be due to fact that increased size of polymer can encapsulate more drug, but more surfactant also accelerate the encapsulation by increasing the binding contact between drug and polymer in emulsion stage.[23] Desirability function was used for optimization to obtain the levels of process parameters in which particle size was kept at minimum and entrapment efficiency at maximum. Based on the results obtained from predicted solution (Figure 5) given by optimization study, a checkpoint batch (OKT) was prepared and considered as optimized batch for further studies.

Physicochemical evaluation of KT nanoparticles

Percentage yield and Drug entrapment efficiency

Percentage yield of prepared nanoparticles (batches yield (58.9%) was obtained with batch C. Nanoencapsulation of therapeutic agents increases their targeting ability, specificity and efficacy. Moreover, they protect the drug from earlier degradation; improve bioavailability and cellular uptake and controlled drug release.[24-25] Percent (%) drug entrapment was found between 38.86%-61.91% with batches A1-C3.

Particle size analysis and Zeta potential

It is reported that particle size has profound effect on drug release. Smaller the nanoparticle size resulted in greater surface area which leads to quick drug delivery.[26] Mean particle size consisting of all batches were found in the range of 155.5- 200.4 nm. Nanoparticles comprised of batch C3 had smallest (155.5 nm) particle size. Nanoparticles with zeta potentials of less than −30 mV or greater than +30 mV are considered strongly anionic and strongly cationic, respectively and they show greater colloidal stability. Since most biological cells have negative zeta potential; thus zeta potential of nanoparticulate systems must be slightly negative so that they do not stick non-specifically to cells but interact through a receptor mediated interaction.[27] The zeta potential of prepared nanoparticles (batch A1-C3) ranged between (-9.58) to (-18.5) mV.

Percentage yield, entrapment efficiency and mean particle size data of prepared batches (A1-C3) has shown in Figure 6.

Surface Morphology

The Scanning Electron Microscope (SEM) is most versatile instrument available for examination and analysis of morphology and chemical characterization of nanomaterials. It is an important tool for characterization of particle morphology and its distribution. Ketorolac

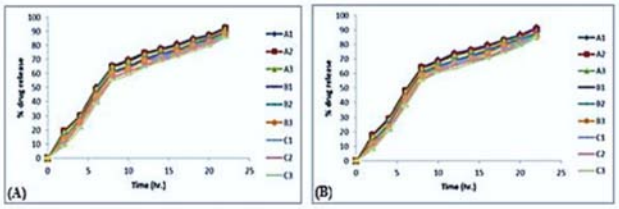

Figure 7: *In-vitro* drug release data of KT nanoparticles (batches A1- C3) in (A) pH 7.4 PBS, (B) Simulated Tear Fluid.

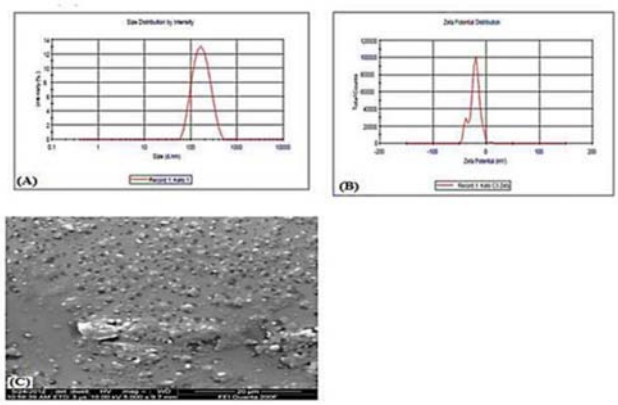

Figure 8: Evaluation Parameters for Optimized batch (OKT) of Ketorolac tromethamine (A) Particle size, (B) Zeta Potential, (C) Scanning Electron Microscopic image.

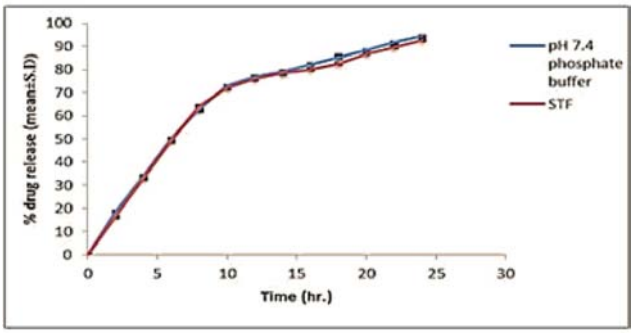

Figure 9: *In–vitro* release data of OKT in pH 7.4 PBS and STF (mean± Standard deviation).

tromethamine nanoparticles (batches A1-C3) were having rough surfaces with spherical in shape.[28]

In-vitro release study

The release rate decreased with increase in cross-linking density. A dense matrix of the nanoparticles might exhibit slower release rate of the drug.[29] Percentage drug release from Ketorolac tromethamine nanoparticles was

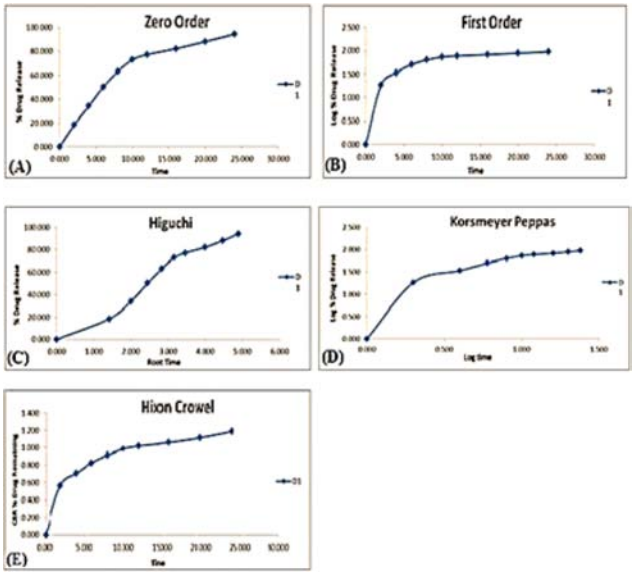

Figure 10: Release Kinetic graphs of OKT (A) Zero order graph, (B) First order graph, (C) Higuchi graph, (D) Korsmeyer peppas graph, (E) Hixon Crowel graph in STF.

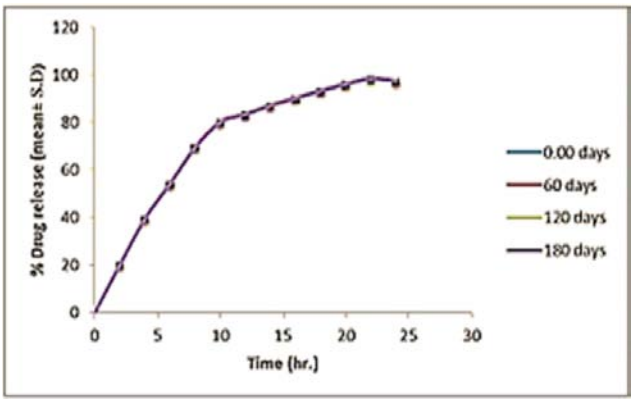

Figure 11: Drug release data of optimized batch (OKT) of Ketorolac tromethamine nanoparticles obtained during stability study (mean± S.D).

found to be in 90.23-96.87% and 89.22-95.65% in pH 7.4 PBS and STF respectively (Figure 7).

Evaluation Parameters for Optimized batch (OKT)

The optimized batch thus prepared was having Percentage yield (66.4%), % Entrapment Efficiency (61.65%), Particle size (153.9 nm), Zeta Potential (-21.8) and percentage drug release (94.368±0.181 and 92.797±0.150% in PBS and STF (pH 7.4) respectively) (Figure 8, 9). Results of release kinetic study revealed that drug dissolution followed Zero order release kinetics model (Figure 10).

Ocular Irritancy test

No irritation was observed.

Accelerated Stability studies

Nanoparticulate optimized batch was found to be almost absolutely stable at storage conditions. The percentage drug release from prepared optimized batch of ketorolac tromethamine was found to be 98.086±0.204% at 180 days (Figure 11).

CONCLUSION

It was concluded that the novel formulations being reported by the present worker possessed in-built advantage in having longer ocular residence time and thus enhancing the patient compliance besides significant ocular availability.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

ABBREVIATIONS

KT: Ketorolac tromethamine; **STF:** Simulated Tear Fluid; **TLC:** Thin Layer Chromatography; **FTIR:** Fourier Transmission Infra-Red; **CS:** Chitosan; Na-TPP: sodium tri-polyphosphate; **ICH:** International Conference of Harmonization; **OKT:** Optimized batch of Ketorolac tromethamine; **PBS:** Phosphate buffer Saline; **STF:** Simulated Tear Fluid; **RH:** Relative humidity, **Rf:** Retention factor.

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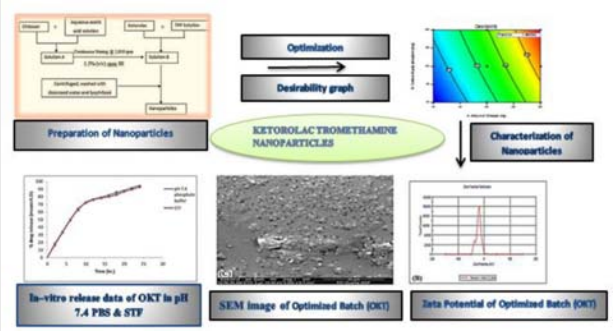
PICTORIAL ABSTRACT



SUMMARY

- Ketorolac tromethamine is used for post-operative eye inflammation.
- It is highly effective in relieving pain after radial keratotomy (RK), photorefractive keratectomy (PRK), laser *in-situ* keratomileusis (LASIK); and to treat allergic conjunctivitis.
- Nanoparticles of Ketorolac tromethamine thus prepared would penetrate readily through corneal surface to deeper tissue pertaining to nano size particles for enhanced therapeutic response.

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