IJPPR (2016), Vol. 7, Issue 3 *Research Article*

International Journal of Pharma Professional's Research

Received on 22 May, 2016; received in revised form, 02 June, 2016; accepted, 23 June, 2016; published 01 July, 2016

FORMULATION AND EVALUATION OF KETOROLAC TROMETHAMINE MICROPARTICLES FOR OCULAR DELIVERY

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Key words:
Ketorolac tromethamine, microparticle, Ocular Delivery

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ABSTRACT: The objective of the present work was to formulate and evaluate microparticles of Ketorolac tromethamine and produced sustained drug delivery for ocular delivery. In this 9 batches(A_1-C_3) of Ketorolac tromethamine microparticle was prepared with chitosan, Sodium Tri-polyphosphate and other ingredients by Ionotropic gelation technique. The prepared microparticles were evaluated for different parameters i.e % Drug yield, % Drug entrapment, Surface morphology, Zeta potential and in-vitro drug release for 24hrs in phosphate buffer 7.4 and simulated tear fluid. The best batch was performed stability studies for 6 months. The research concluded that Ketorolac tromethamine microparticles could be alternative for conventional dosage form.

INTRODUCTION:

Microparticles are a type of drug delivery systems in which the particle size ranges from 1 micron to few mm. This microencapsulation technology allows protection of drug from the environment, stabilization of sensitive drug substances, elimination of incompatibilities, or masking of unpleasant taste. Hence, microparticles play an important role as drug delivery systems aiming at improved bioavailability of conventional drugs and minimizing side effects [1].

Material and Method:

Ketorolac tromethamine was acquired as a gift sample from Knox life sciences, Baddi, H.P.

Formulation design:

Ketorolac tromethamine was studied for physicochemical characteristics. Microparticles of Ketorolac tromethamine were produced, by employing technology. Various ingredients were selected, for Ketorolac tromethamine, formulation design of Microparticles as represented in the table no 1.

Preparation of Drug loaded Microparticles:

Ionotropic gelation process: Ketorolac tromethamine loaded Microparticles were prepared using ionotropic gelation method. Drug and polymer, in different proportions,

were accurately weighed. The chosen polymer was dissolved in 100 ml of aqueous acetic acid solution while the drug was dissolved in the solution of sodium tri-polyphosphate at room temperature. Chitosan solution was added drop wise into the drug solution containing Na-TPP (Sodium Tri-polyphosphate), in the presence of 1.5% (v/v) span 80, under continuous stirring at 2000 rpm (using mechanical stirrer). The prepared suspension was centrifuged at 12000 rpm for 15 min. Supernatant was removed and the sediment was freeze dried for 48 hours. The obtained particles were kept in dehydrated conditions for further studies[2].

Evaluation of Microparticles:

The Microparticles produced with each drug i.e. Ketorolac tromethamine, was evaluated for various parameters i.e. % yield, entrapment efficiency, determination of particle size & Zeta potential, surface morphology, in-vitro drug release, release kinetics and stability studies.

Percentage yield (% yield)

The yield values were calculated as the weight of the microparticles recovered from each batch divided by total weight of drug and polymer used in the preparation of the particular batch[3].

$$\% \text{ Yield} = \frac{\text{Weight of microparticles obtained}}{\text{Weight of drug + polymer}} \times 100$$

Determination of drug entrapment efficiency

The formulations were dissolved in a minimum quantity of methanol individually and centrifuged at 1,500 rpm for 20 minutes. The sediments were separated and upper layers were filtered, suitably diluted and analyzed spectrophotometrically at respective wavelengths. Each experiment was repeated in triplicate. Percentage drug entrapment, for each class of Microparticles, was determined by the following formula:

$$\text{E. E.} = \frac{\text{Amount of drug actually present in microparticles}}{\text{Amount of drug actually used}} \times 100$$

Particle size and zeta-potential

The mean particle size of drug-loaded Microparticles and zeta potential (for Microparticles obtained with each drug) were determined by a **Malvern Zetasizer nano zs** (Malvern instrument ltd., Worcestershire, UK).

Surface morphology

Surface morphology was determined by scanning electron microscopy of each class of Microparticles. It determined whether particles had a uniform shapes or not and whether they were uniformly/ununiformly distributed. It also confirmed the obtained particle size in each case.[4]

In-vitro drug release from Drug-loaded Microparticles:

Drug-loaded Microparticles obtained with each drug were suspended in pH 7.4 phosphate buffer in a glass vial which was placed in a mechanical shaking bath (100 cycles /min) at the temperature adjusted to 37°C. At selected time intervals sample was removed and replaced with fresh buffer medium. Each withdrawn sample was then centrifuged at 15000 rpm (Ketorolac tromethamine microparticles**)** and supernatant was analyzed using UV spectrophotometry.[5]

Accelerated Stability studies:

The selected (optimized) formulation, in each case, was packed in amber-colored bottles which were tightly plugged with cotton and capped. These were then stored at 400±20C/75%±5% RH for 6 months and evaluated, for its physical appearance & drug contents, at specified intervals of time.[6,7]

Result and Discussion:

Table 1: Formulation design of Microparticles of Ketorolac tromethamine:

Formulation Code	Drug (mg)	Polymer (Chitosan) (mg)	Aqueous acetic acid solution, 100 ml (%)	Sodium tri-polyphosphate mg / 100 ml	Span 80 (1.5 % µl)
A_1	100	100	1	100	100
A_2	100	200	1	100	100
A_3	100	300	1	100	100
B_1	100	100	1	200	100
B_2	100	200	1	200	100
B_3	100	300	1	200	100
C_1	100	100	1	300	100
C_2	100	200	1	300	100
C_3	100	300	1	300	100

Percentage yield:

The maximum percentage yield was found to be 67.42% with batch C_3 (Ketorolac tromethamine),while minimum of 28.16% with batch A_1 (Ketorolac tromethamine).

Table 2: Percentage yield of Ketorolac tromethamine microparticles (batches A_1 - C_3)

Microparticulate Batches	Total amount of Ingredient (mg)	Practical yield(mg)	Percentage yield (%)
A_1	600	169	28.16
A_2	800	287	35.87
A_3	1000	658	65.8
B_1	800	286	35.75
B_2	1000	539	53.9
B_3	1200	682	56.83
C_1	1000	411	41.10
C_2	1200	593	49.41
C_3	1400	944	67.42

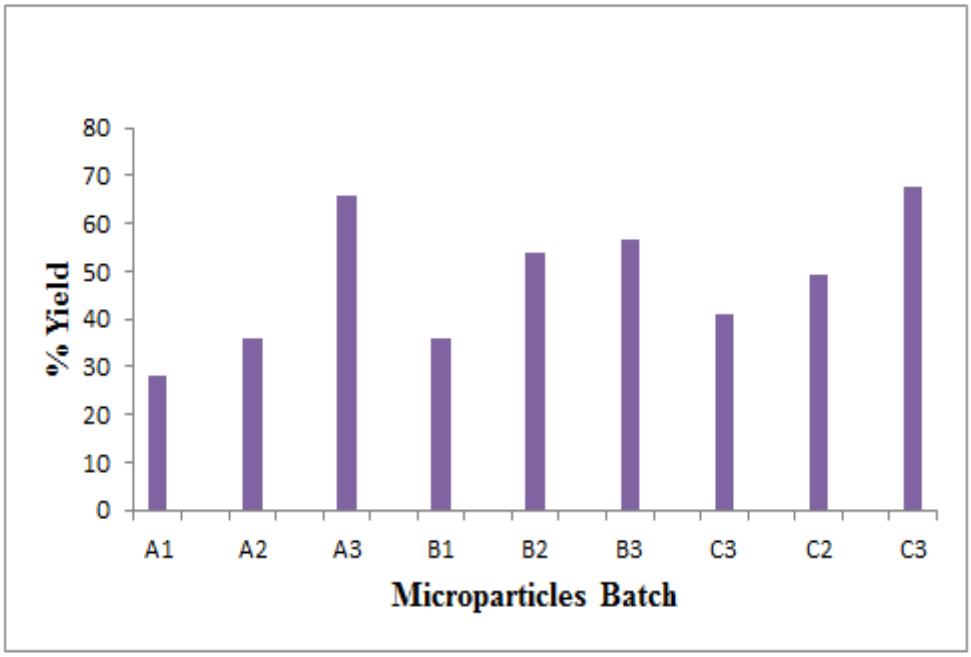

Fig. 1: Percentage (%) yield of Ketorolac tromethamine microparticles (batches A_1-C_3)

Drug entrapment efficiency:

The % drug entrapment of Ketorolac tromethamine microparticles (batches A1-C3) was determined. It ranged between (45.26%-63.49%) respectively.

Table 3: Percentage drug entrapment of Ketorolac tromethamine microparticles (batches A_1 - C_3)

Microparticulate Batches	% drug content
A_1	45.26
A_2	54.78
A_3	59.27
B_1	49.49
B_2	57.65
B_3	61.14
C_1	53.68
C_2	60.28
C_3	63.49

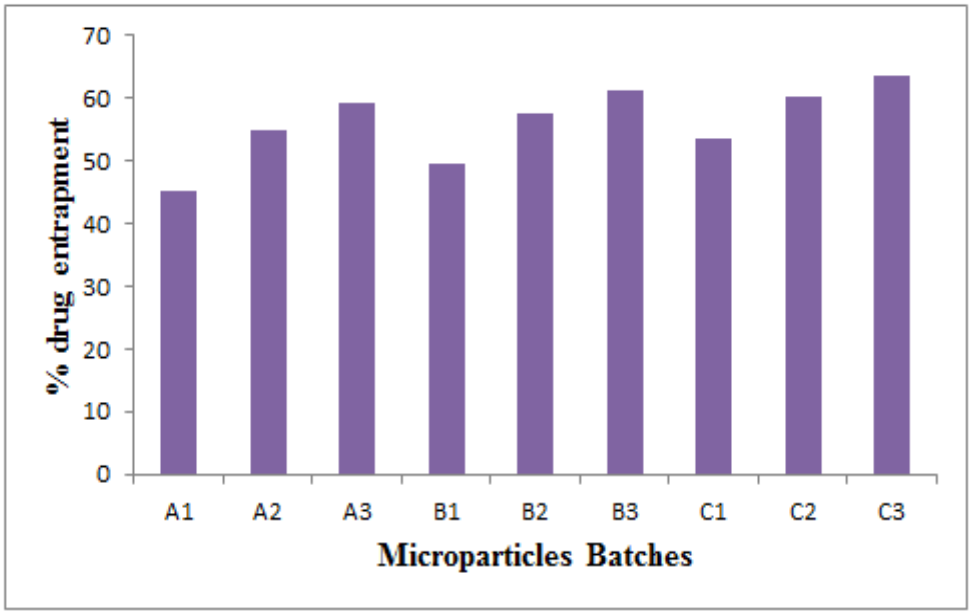

Fig. 2: Percentage drug entrapment of Ketorolac tromethamine microparticles batches (A_1-C_3)

Particle size analysis:

The analysis was performed for all nine batches prepared with Ketorolac tromethamine. The mean diameters of particles for all batches were found in the range of 152- 205 nm.

Table 4: Particle size analysis of Ketorolac tromethamine microparticles (batches A_1-C_3)

S. No	Microparticulate Batches	Mean particle size (µm)
1	A_1	201
2	A_2	189
3	A_3	168
4	B_1	196
5	B_2	182
6	B_3	161
7	C_1	192
8	C_2	176
9	C_3	155

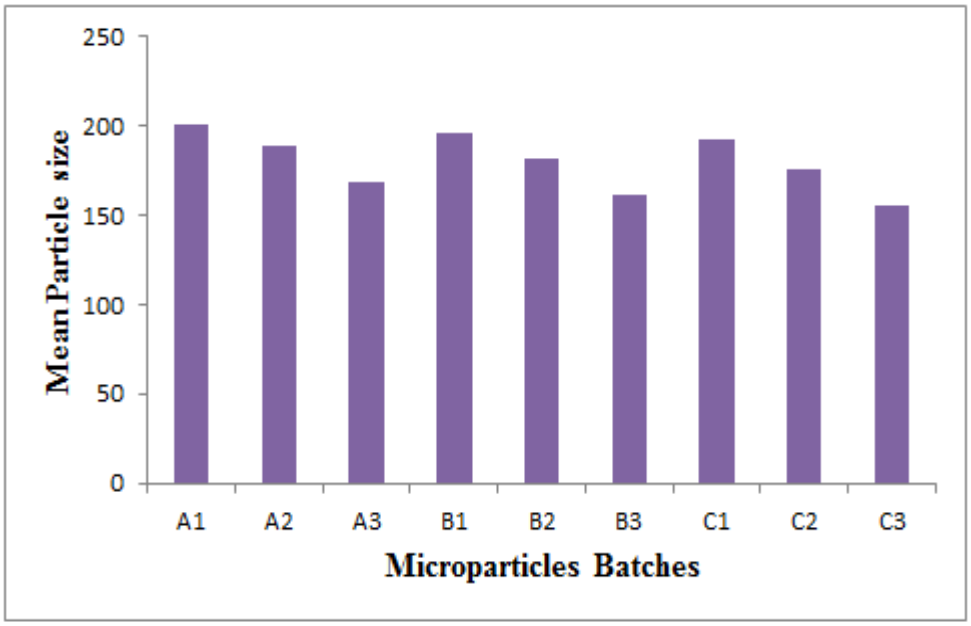

Fig. 3: Mean Particle size of Ketorolac tromethamine microparticles (batches A_1- C_3)

Zeta potential: The zeta potential of Ketorolac tromethamine (batch A_1-C_3) was determined. It ranged between [(-9.50 & -17.64)])] mV respectively.

S. No	Microparticulate Batches	Zeta Potential Mean (mV)
1	A_1	-10.28
2	A_2	-13.20
3	A_3	-12.60
4	B_1	-14.60
5	B_2	-15.40
6	B_3	-16.40
7	C_1	-13.80
8	C_2	-9.50
9	C_3	-20.50

Table 6: In –vitro comparative release study of Ketorolac tromethamine microparticles (batches A_1-C_3) in pH 7.4 phosphate buffer:

Time (hr.)	A_1	A_2	A_3	B_1	B_2	B_3	C_1	C_2	C_3
0	0	0	0	0	0	0	0	0	0
2	20.325	19.726	18.757	16.226	15.694	14.548	12.206	11.548	9.657
4	31.254	30.251	29.636	28.292	27.276	26.364	24.424	24.556	22.057
6	50.365	49.989	48.425	46.645	45.329	44.486	42.901	41.414	39.936
8	66.258	65.223	64.622	62.056	61.773	60.056	58.306	57.205	56.258
10	70.698	69.059	68.823	66.954	65.248	64.975	62.284	61.601	59.412
12	75.287	74.854	73.256	70.802	70.062	69.243	67.381	66.323	65.247
14	78.129	77.325	76.306	75.123	73.602	72.257	71.218	70.902	69.021
16	81.034	80.212	79.421	78.374	76.145	75.549	72.594	73.612	72.258
18	85.657	84.751	83.369	82.606	81.243	80.263	79.963	78.856	76.158
20	88.256	87.658	86.167	85.829	84.222	83.051	82.456	81.437	80.317
22	93.648	92.587	91.254	90.333	89.372	88.347	87.202	86.159	86.329
24	97.682	96.348	95.633	94.502	93.102	92.385	91.057	91.254	91.241

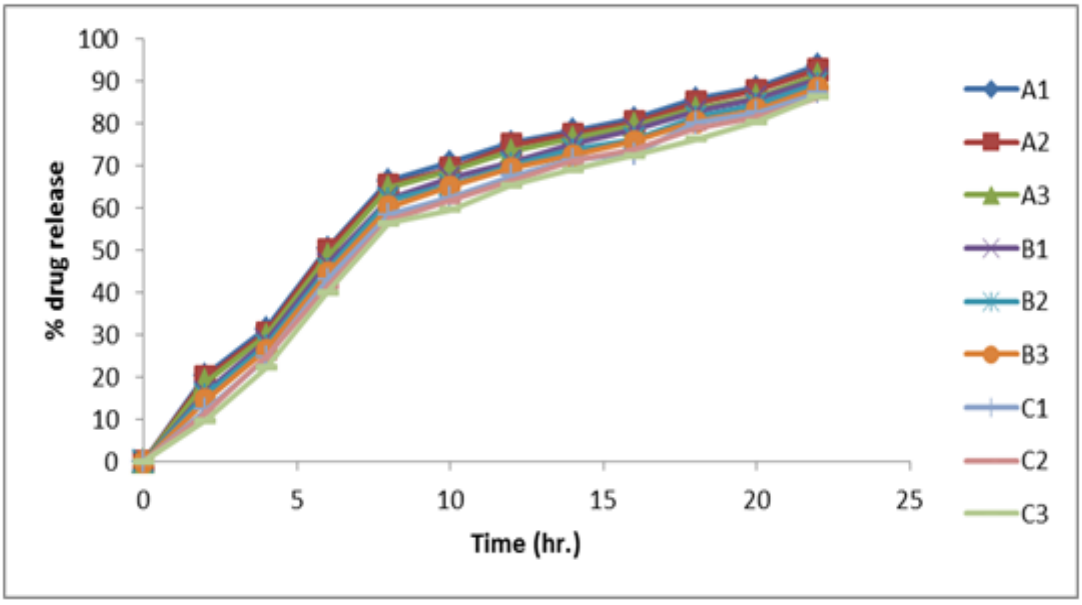

Fig. 4: Comparative % drug release of Ketorolac tromethamine microparticles (batches A1- C3) in pH 7.4 phosphate buffer

Table 4.25: In –vitro dissolution study of Ketorolac tromethamine microparticles batches (A_1-C_3) in simulated tear fluid:

Time (hr.)	A1	A2	A3	B1	B2	B3	C1	C2	C3
0	0	0	0	0	0	0	0	0	0
2	19.321	18.19	16.824	14.02	13.562	12.348	11.353	10.348	8.624
4	30.658	29.681	28.174	26.379	25.317	24.367	23.648	22.154	21.348
6	49.257	48.325	47.502	45.364	44.258	43.601	41.279	40.387	38.745
8	65.124	64.902	63.856	61.279	60.321	59.941	57.314	56.252	55.245
10	69.347	68.378	67.521	66.028	65.348	64.872	63.492	62.149	61.275
12	74.158	73.542	72.575	70.185	69.674	68.821	67.423	66.189	64.253
14	77.356	76.314	75.688	73.181	72.368	71.245	70.129	69.055	67.835
16	80.124	79.278	77.333	76.284	75.685	73.652	72.142	71.456	70.556
18	84.249	83.258	82.202	81.245	80.295	79.985	77.156	76.485	75.256
20	87.045	86.247	85.312	84.527	83.666	82.022	81.275	80.242	79.634
22	92.302	91.348	89.657	88.112	87.303	86.942	85.884	84.847	84.212
24	96.105	95.246	94.532	93.454	92.368	91.054	90.757	90.117	91.247

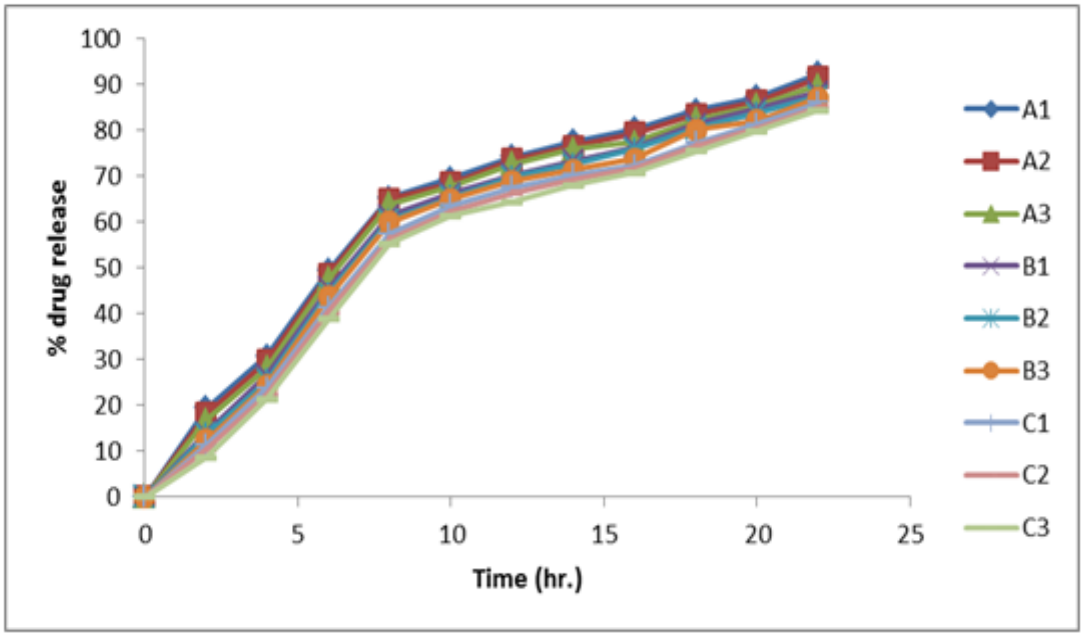

Fig. 5: Comparative % drug release of Ketorolac tromethamine microparticles (batches A_1- C_3) in simulated tear fluid.

Table 8: Stability data of Ketorolac tromethamine microparticle A_1 batch in simulated tear fluid.

Time (hr.)	0 days	60 days	120 days	180 days
0	0	0	0	0
2	19.321	19.201	19.031	18.589
4	30.658	30.328	30.214	30.045
6	49.257	49.167	49.087	48.854
8	65.124	65.034	64.982	64.852
10	69.347	69.127	68.898	68.733
12	74.158	74.038	73.857	73.543
14	77.356	77.126	76.998	76.882
16	80.124	80.004	79.788	79.55
18	84.249	84.029	83.674	83.432
20	87.045	87.015	86.632	86.459
22	92.302	92.122	91.878	91.662
24	96.105	96.095	95.747	95.548

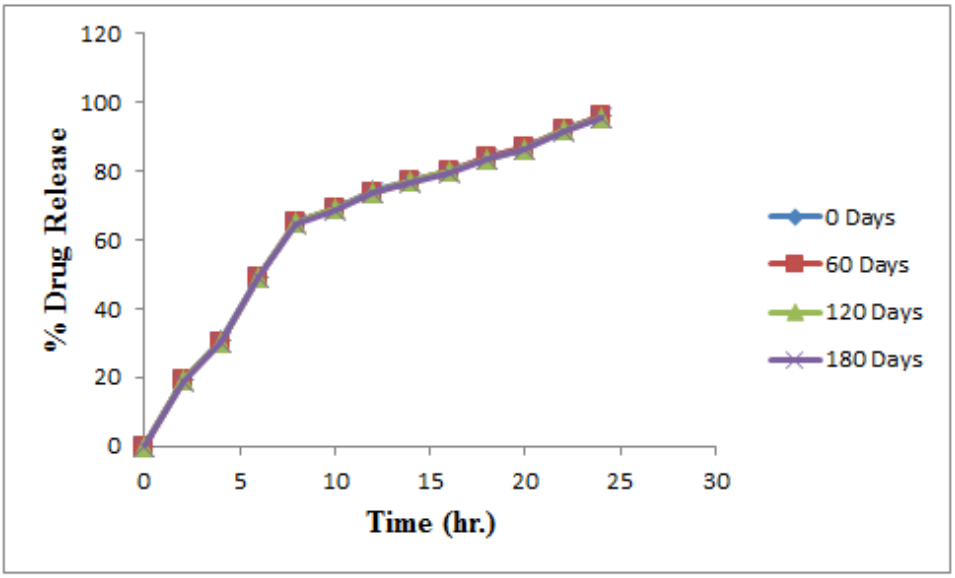

Fig. 5: Comparative release profile of Ketorolac tromethamine microparticles batch A_1 on stability studies (n=3)

Conclusion

In the Present study the Ketorolac tromethamine microparticles were evaluated for different parameters i.e % Drug yield, % Drug entrapment, Surface morphology, Zeta potential and in-vitro drug release for 24hrs in phosphate buffer 7.4 and simulated tear fluid. The latter revealed that A_1 batch from the nine formulations shows maximum sustained release (96.105%) in 24 hr. The A_1 batch was performed for stability studies for 6 months. The research, reference characterized that Ketorolac tromethamine microparticles could be alternative than conventional dosage for sustained action in ocular delivery.

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