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FORMULATION DEVELOPMENT OF KETOROLAC TABLETS COMPARED TO INNOVATOR FORMULATION AND EVALUATION VIA IN-VITRO BIO-EQUIVALENCE STUDY FOR PRODUCT INTERCHANGEABILITY

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ABSTRACT

Ketorolac Tromethamine (KT) is a non-steroidal anti-inflammatory drug that belongs to the class of Heteroaryl acetic acid derivatives. It is a non-selective cyclooxygenase (COX) inhibitor, being marketed in the racemate form. Most of its analgesic and COX inhibitory activity is retained in the S-isomer. Ketorolac is administered as its Tromethamine salt orally. Side by side there is a common psychology that high cost drug product manufactured by top pharmaceutical companies are better in comparison with the low cost products manufactured by small scale companies. These facts directed our interest to develop interchangeable product having same quality as innovator product. Assess the quality of developed formulation with special emphasis on physicochemical and dissolution study due to their enormous prominence in predicting bioavailability and product quality. In the present study Ketorolac Tablet 10 mg were prepared by using direct compression method with the excipients that are used in innovator formulation (Microcrystalline Cellulose, Lactose Monohydrade, Magnesium Stearate, Hypromellose, Titanium dioxide etc) by adjusting concentration of Microcrystalline Cellulose, Lactose Monohydrade & Magnesium Stearate. Formula number BF3 containing Microcrystalline Cellulose 58.25 %, Lactose Monohydrade 33.50% & Magnesium Stearate 0.5% was found to be the best formulation shows good physicochemical behavior and dissolution profile.

KEYWORDS: Ketorolac, Formulation, Direct Compression Method, Physicochemical, Dissolution profile.

INTRODUCTION

Ketorolac Tromethamine [(+/-)-5(benzoyl)-2,3- dihydro-1N-pyrrolizine-1-carboxylic acid tris hydroxymethylaminomethane salt] is a highly potent member of a new class of compounds of nonsteroidal anti-inflammatory drug (NSAID) available in intramuscular (IM) and oral formulations for the management of acute pain. The compound shows potent prostaglandin cyclooxygenase inhibitory activity. The agent elicited mild CNS and[1] cardiovascular activity only at doses far in excess of those required for analgesic and anti-inflammatory activity. A single 10 mg tablet given orally to human volunteers following surgery provided pain relief equivalent to that provided by 10 mg of morphine given intramuscularly. Ketorolac, when administered[1] intramuscularly or orally, is a safe and effective analgesic agent for the short-term management of acute postoperative pain and can be used as an alternative to opioid therapy.[2]

Development of interchangeable formulation is one of the best and ideal methods to improve patient complacence and bio availability and to gives immediate relief. In the present scenario along with the development of various drug technologies, this kind of developments are widely employed and show a satisfactory outputs. There are various methods to prepare improved formulation which are conventional methods like wet granulation technique, moulding technique, direct compression method etc.

The drugs which were used in the present study are comes under a non-steroidal anti-inflammatory drug that belongs to the class of Heteroaryl acetic acid derivatives and water soluble drugs. In order to improve the physicochemical behavior and pharmacokinetics like innovator product, by using direct compression method with the excipients that are used in innovator formulation (Microcrystalline Cellulose, Lactose Monohydrade, Magnesium Stearate, Hypromellose, Titanium dioxide etc) by adjusting concentration of Microcrystalline Cellulose, Lactose Monohydrade & Magnesium Stearate. Physicochemical analysis and comparative dissolution study has been conducted to evaluate the quality of individuals formulation.

MATERIALS AND METHODS

Pre compressed Parameters

Bulk Density: Blend was weighed and transferred to a measuring the cylinder. Then bulk volume was noted. Bulk density was calculated by using the following formula.

$$\text{Bulk Density} = \frac{\text{Mass of th Powder}}{\text{Bulk Volume}}$$

Tapped Density: Blend was weighed and transferred to the measuring cylinder and subjected to 100 tappings. Then volume was noted as tapped volume. Tapped density was measured by using the following formula

$$\text{Tapped Density} = \frac{\text{Mass of the Powder}}{\text{Tapped Volume}}$$

Carr's Index: Carr's index was calculated by using the following formula.

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

Hausner's Ration: Hausner's ratio is an index of ease of powder flow; it's calculated by following formula.

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Post Compression Parameters

Weight Variation

In a weight variation test twenty tablets were selected at random and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight.

Hardness test

The crushing strength (KgF) was determined with an Automatic Tablet Hardness Tester (8M, Dr Schleuniger, Switzerland). The force applied to the edge of the tablet was gradually increased by moving the screw knob forward until the tablet was broken. Ten tablets were randomly selected from each brand and the pressure at which each tablet crushed was recorded.

Disintegration test

Six tablets from each brand were employed for the test in distilled water at 37 °C using a Tablet Disintegration Tester (Model: VDT-2, Veego, India). As stated by Alderborn, the disintegration time (DT) was taken as the time when no particle remained in the basket of the system.

Wetting Time

In wetting time a piece of tissue paper folded twice was placed in small petri dish (i.d = 6.5cm) containing 10mL of water, a tablet was placed on the paper, and the time for complete wetting was measured. Three trails for each batch were performed and standard deviation was also determined.

Friability test

Ten tablets from each brand were weighed and subjected to abrasion by employing a Veego Friabilator (VFT-2, India), operated at 25 RPM for 4 minutes. The Friabilator was divided into two plastic chambers. During each revolution the tablets were made to fall from a distance of six inches to undergo shock. After 100 revolutions the tablets were weighed again. The loss in weight indicated the friability.

Dissolution test

The dissolution test was undertaken using Tablet Dissolution Tester (TDT-08L, Electrolab, India) in 12 replicates for each formulation involving USP apparatus-II (paddle) at 50 RPM. The dissolution medium was 600 ml of water which was maintained at 37 ± 0.5 °C. In all the experiments, 20 ml of dissolution sample was withdrawn at 10, 15, 30, 45 and 60 minutes and replaced with an equal volume to maintain an ideal sink condition. Samples were filtered through. This is the final solution. The solution was then assayed by UV spectrometry.

Assay

Weight accurately 10 tablets; in a 500 ml volumetric flask add 50 ml purified water. Shake until the tablets disintegrate. Add 200 ml HPLC grade Methanol and sonicate for 3-4 min, Cool and, dilute to volume with HPLC grade Methanol, centrifuge a portion of the suspension. Transfer 3 ml of this solution in to 50 ml volumetric flask and add 5 ml of internal standard and dilute to HPLC grade methanol – water 1:1. The solution will be approximately 20 mcg/ml of Ketorolac Tromethamine.

Comparative study

The uniformity of weight was analyzed with simple statistics while the dissolution profiles were analyzed by difference factor (f1) and similarity factor (f2).

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} X100$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{i=1}^{n} (R_t - T_t)^2 \right)^{-0.5} X100 \right\}$$

Where n is the number of time points, Rt is the dissolution value of the reference product at time t and Tt is the dissolution value for the test product at time t. Similarity factor (f2) has been adopted by FDA and the European Agency for the Evaluation of Medicinal Products by the Committee for Proprietary Medicinal Products (CPMP) to compare the dissolution profile. Two dissolution profiles are considered similar and bioequivalent, if f1 is between 0 and 15 and f2 is between 50 and 100.[5-13] **Table 4 & Figure 1** shows f2 values of different formulations in respect of the reference brand. It reveals for formulation BF1, BF2,

BF3, BF4 & BF5, f2 value were more than 50. So, their dissolution profile is similar to that of the reference product and can be used interchangeably.

RESULTS AND DISCUSSION

Ketorolac tablet 10 mg were prepared by using direct compression method with the excipients that are used in innovator formulation (Microcrystalline Cellulose, Lactose Monohydrade, Magnesium Stearate, Hypromellose, Titanium dioxide etc) by adjusting concentration of Microcrystalline Cellulose, Lactose Monohydrade & Magnesium Stearate. Tablet blend is prepared by simple geometric mixing in a polythen bag. The pre-compression property study was Tabulated in **Table 2,** Hausner's Index of all the formula lies between 0.76 - 0.86 which is indicate that their flow was excellent to fair which in acceptable range. Angle of repose lies between 16.35 - 19.84, indicating that they had an excellent flow. The post compression studies of tablets of Ketorolac are tabulated in **Tablet 3**. They reviled that all the parameters such Friability, Weight Variation, Hardness, Disintegration time, Wetting time, Assay all are with. In the acceptance criteria limits for individual tests. Up to Certain concentration With increase in concentration of Microcrystalline Cellulose & adjusting Lactose Monohydrade & Magnesium Stearate the Disintegration Time and Wetting time of tablet was decreased there after more or less remained same.

Considering physico-chemical analysis of all the formulation, it is observed that formulation BF3 showed best results among 5 formulations (**Table 2 & 3**) and as well as best similarity factor (**Table 4**).

Table 1: Formula of Ketorolac bio-equivalence tablet.

Ingredients	Quantities in mg per one tablet				
	BF1	BF2	BF3	BF4	BF5
Ketorolac Tromethamine	10	10	10	10	10
Microcrystalline Cellulose	100	110	120	130	140
Lactose Monohydrade	89.5	79	69	59.5	49
Magnesium Stearate	0.5	1	1	0.5	1
Hypromellose	3	3	3	3	3
Titanium dioxide	2	2	2	2	2
Propylene glycol,	1	1	1	1	1
Purified water*	qs	qs	qs	qs	qs
Total Weight	206	206	206	206	206

* Used as coating solvent and not appear in finished product.

Table 2: Pre-formulation studies of Bio-equivalence tablets of Ketorolac.

Formulation	Bulk density (g/cc) (Avg. ± S.D.)	Tapped density (g/cc) (Avg. ± S.D.)	Carr's index (Avg. ± S.D.)	Hausner's Index (Avg. ± S.D.)	Angle of Repose (Avg. ± S.D.)
BF1	0.31±0.01	0.38±0.02	13.73±0.11	0.86±0.01	17.58± 0.21
BF2	0.34±0.02	0.41±0.03	11.44±0.13	0.82±0.01	16.35± 0.16
BF3	0.31±0.05	0.38±0.01	13.73±0.16	0.86±0.01	19.84± 0.19
BF4	0.32±0.01	0.38±0.03	10.84±0.12	0.81±0.01	17.99± 0.23
BF5	0.31±0.03	0.34±0.01	6.87±0.12	0.76±0.01	17.54± 0.16

Table 3: Post Compression studies of bio-equivalence tablets of Ketorolac.

Test Performed	BF1	BF2	BF3	BF4	BF5
	Results (Avg. ± S.D.)				
Weight Variation (mg)	207.88	206.71	206.14	206.23	205.44
Hardness (Kg/cm2)	7.8 ±0.2	8.2 ±0.2	8.4 ±0.2	7.8 ±0.2	8.2 ±0.2
Friability (%)	0.11±0.05	0.09±0.05	0.08±0.05	0.04±0.05	0.03±0.05
Wetting time(sec)	36.3±0.6	30.4±0.4	30.7±0.3	50.5±0.1	56.3±0.6
Disintegration time (Min. Sec.)	5.0±0.1	5.3±0.2	6.8±0.2	8.1±.4	10.3±0.3
Assay	99.2±0.9	99.4±0.5	100.03±1.0	103.9±0.9	99.3±0.9

Table 4: Dissolution profile of formulated Ketorolac tablet and reference innovator sample

Time (MIN)		0	10	15	30	45	60	Similarity factor (f2)
FORMULATION	BF1	0	74.50	90.59	95.79	97.08	96.92	75
	BF2	0	77.12	88.29	99.15	99.59	98.37	72
	BF3	0	72.74	83.11	94.99	96.55	96.09	87
	BF4	0	66.75	81.61	90.09	92.90	91.88	64
	BF5	0	69.21	82.19	94.68	96.27	96.27	74
RI		0	75.71	84.47	94.34	96.37	95.54	--

RI= Reference Innovator

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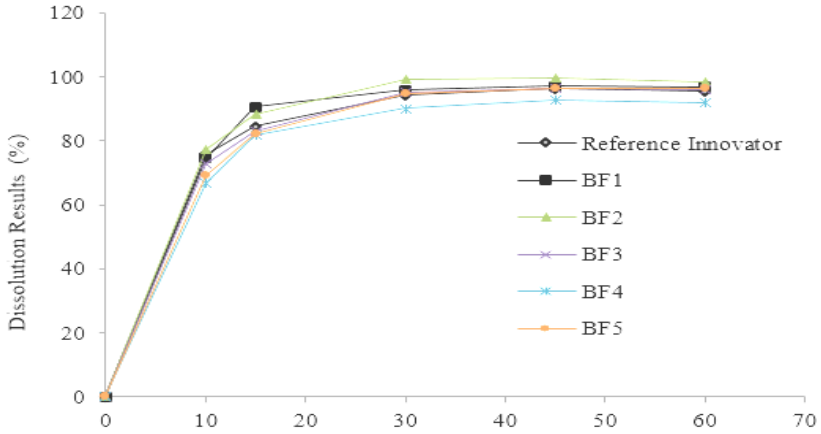

Figure 1: Graphical presentation of comparative dissolution study.

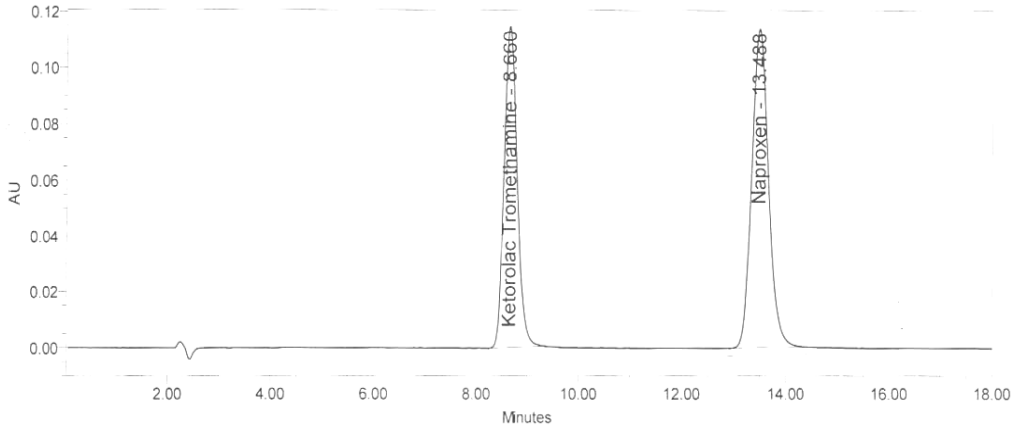

Figure 2: Chromatogram obtained from % Assay.

Table 5: Qualitative comparison of formulation.

Ingredients (Selected formulation BF3)	Ingredients (Innovator Toradol 10 mg Tablets)
Ketorolac Tromethamine	Ketorolac Tromethamine
Microcrystalline Cellulose	Microcrystalline cellulose
Lactose Monohydrade	Lactose
Magnesium Stearate	Magnesium stearate
Hypromellose, Titanium dioxide, Propylene glycol, Purified water	Film coating (Hypromellose, Titanium dioxide (E171) and Macrogol), Ink (shellac modified), Iron oxide black (E172) and Purified water)

CONCLUSION

The study describes direct compression technique for immediate release behavior by taking various concentrations of filler and diluent. Among all the formulations the best formulation (BF3) showed a similarity factor 87 and good physicochemical behavior both in granulation and post compression stage. For generic product **(**developed formulation BF3**),** the data (Table 4 & Figure 1) indicates that the product is likely to perform the same with the reference innovator since the computed f2 is within the acceptance level with high similarity factor among 5 formulation. Therefore, it can be anticipated that these BF3 formulation can be considered interchangeable. This study has showed that the formulation BF3 can likely to be bioequivalent to the reference innovator using Physico-chemical analysis and the Dissolution profile.

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