Research Article

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In-vitro assessment of quality control specifications for ketorolac tromethamine tablets marketed in Bangladesh

Abstract

This study aims to evaluate the quality parameters of the immediate release Ketorolac tromethamine (KT) 10 mg tablet of different local brands available in Bangladesh. The evaluation was done in compliance to various Pharmacopeial quality parameters, i.e., weight variation, friability, hardness, thickness, disintegration, potency, and dissolution. Six formulations of KT were prepared by direct compression method using different super disintegrants. Micrometric properties of the mixtures of the drug and the excipients prepared for formulation were evaluated. Quality evaluation of the six different formulations and randomly selected six different brands of KT 10-mg tablets purchased from the local market were performed according to Pharmacopoeia. The results were obtained by UV-Vis spectrophotometer and all the dissolution profiles were characterized by the zero order kinetics. All the brands of KT and developed formulations met the official specification with some fluctuations in the range. The marketed ketorolac tablet's potency ranged from 93% to 97% and formulated tablets is 91.15%. The values obtained from the tests were used to analyze the degree of conformance of commercially available drugs to the USP specification that represents the quality of both commercially available and formulated tablets. All the parameters comply with the USP specifications which ensure the safe usage of ketorolac tablets in Bangladeshi population that doesn't compromise with the quality.

Keywords: Ketorolac tromethamine, marketed tablet, immediate release, quality evaluation, pharmaceutical equivalency

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Introduction

Ketorolac is a non-steroidal anti-inflammatory drug (NSAID) known for its potent analgesic effects but limited anti-inflammatory efficacy. It also exhibits antipyretic properties. Like other NSAIDs, its primary mode of action is through the inhibition of prostaglandin production.[1] Ketorolac is administered in the form of its tromethamine salt, which belongs to the heteroaryl acetic acid derivative family.[2] It's a racemate, meaning it contains both S and R isomers, but the S-isomer is responsible for most of its analgesic and COX-inhibiting effects. It can be taken orally, intramuscularly, intravenously, or topically.[3]

This medication provides relief from mild to severe pain associated with conditions like renal colic, migraines, musculoskeletal pain, and sickle cell crises. It's often as effective as opioids such as morphine and codeine, as well as other NSAIDs and pain relievers. Additionally, it's commonly used to manage postoperative pain in patients undergoing major surgeries or ambulatory procedures.[4,5]

Ketorolac, when administered intramuscularly, can provide analgesia comparable to meperidine, morphine, or pentazocine. Clinical trials have occasionally demonstrated that even low doses of ketorolac can provide pain relief equivalent to or greater than established treatments like naproxen sodium and morphine.[2,6] Moreover, it has been found to reduce intraocular irritation and cystoid macular edema after cataract extraction and lens implantation. A 0.5% Ketorolac solution has also shown promise in treating conjunctivitis and other eye conditions caused by Candida albicans and Pseudomonas aeruginosa.[7,8]

Ketorolac serves as an effective alternative to opioid therapy for short-term relief of mild to severe pain. Traditionally, centrally acting opioids have been the primary choice for postoperative pain management. However, due to their adverse effects, including respiratory depression, agitation, ataxia, constipation, sedation, tolerance, and potential dependency, some healthcare professionals are opting to reduce the regular administration of opioids.[9] Instead, they turn to NSAIDs to provide adequate postoperative pain relief while minimizing the unfavourable pharmacological effects associated with opioids. During the initial postoperative period, the use of ketorolac, either alone or in combination with opioids, enhances the quality of analgesia while reducing opioid-related side effects.[10–12]

Different brands of KT tablets in Bangladesh serve as analgesics for severe pain relief. Variations in formulation properties and manufacturing methods affect the quality of these tablets. The tablet manufacturing process, such as direct compression, offers advantages over other methods due to its efficiency, reduced cycle time, and suitability for moisture-sensitive products.

Material and methods

Sample collection

Beximco Pharmaceuticals Ltd kindly gifted API KT.

Marketed samples of Ketorolac Tromethamine 10 mg tablets (20 tablets) were collected from various local pharmacies located in Farmgate, Dhaka. During the time of purchase, the samples' DAR numbers, batch numbers, manufacturing license numbers, expiry dates, and expiration dates were all scrutinized. Additionally, their physical attributes, manufacturing company, production date, and expiration date were examined.

Equipment

Electronic Balance (ATY 224, Shimadzu, Japan), Tablet Dissolution Tester (Electro lab, India), UV-VIS Spectrophotometer (UV-1280, Shimadzu, Japan), Tablet Disintegration Tester (VDTO-2, Electro lab, India), Tablet Hardness Tester (HT-50P, Thermonik, India), Friability Tester (Electro lab, India), Sonicator (power sonic-420, Hw ashin technology co, Korea), pH Meter (pH 211 Microprocessor pH Meter, Hanna instrument, Romania), Vernier Caliper (Series 530, Mitutiyo, Japan) were used in this study.

Apparatus

Test tubes, Test tube holders, Spatula, measuring cylinder, Beakers (250 ml, 500ml, 100ml), Mortar and pestle, Volumetric flasks (10ml, 50ml, 100ml), Glass rod, Pipette, Funnel, Wax paper, Filter paper, Stopwatch, Pipette filler, UV Pyrex cell were used in this study.

Preparation of granules

All the ingredients were dispensed as per the batch size of Table 1 and shifted through 30 mesh sieves separately except Magnesium stearate and Talc. These above ingredients were mixed at a geometric ratio and blended for 15 minutes in a large poly bag using tumbling action. Then, Magnesium stearate and Talc were mixed with the above blend by shifting through a 30-mesh sieve and blended for another 3 minutes. Finally, the blend was compressed using the single punch tablet machine (TSD-5 China).

Table 1 Ketorolac tromethamine tablet formulation

Ingredients	Quantity (mg)	Justification
Ketorolac Tromethamine	10	API
Microcrystalline cellulose (Avicel pH 02)	50	Bulking agent, Binder
Spray Dried Lactose	50	Diluent
Starch 1500	77	Binder, Disintegrants
Sodium Starch Glycolate (Primojel)	5	Super disintegrants
Magnesium Stearate	5	Lubricant
Purified Talc	3	Glidant
Total	200	

Table 2 Potency of formulated Ketorolac tablets

Abs.	Conc. (mcg/ml)	Total Vol(ml)	DF.	Avg. Wt. (mg)	Sample Taken(mg)	Drug in a Tbt(mg)	Strength(mg)	%Potency
0.913	18.26	100	5	192.5	192.5	9.13	10	91.3

Preformulating studies

Preformulation studies are primarily done to investigate the physical properties of the powder mixture and to establish its compatibility with other excipients.

Bulk density

Bulk density is calculated by the following formula (USP 29-NF-24, 2006a):

Bulk density = Weight of granules/Bulk volume

Tapped density

Tapped density is the ratio of total mass of powder to the tapped volume of the powder (USP 29-NF-24, 2006a), which can be determined by the following formula:

Tapped Density = Mass of the powder/Tapped volume of the powder

The angle of repose (θ)

The angle of repose, the measurement of friction forces in a loose powder, is defined as the maximum angle possible between the surface of the pile of powder and the horizontal plane (USP 29-NF-24, 2006b). It is defined as the maximum angle possible between the surface of the pile of powder and the horizontal plane. To measure the angle of repose, the powder was allowed to flow freely through a funnel with height adjusted in such a way that the tip of the funnel.

Methods

Analytical method

The study conducted quality tests on different brands of ketorolac tablets available in Bangladesh, and the specific tests performed on each brand, which involved examining 20 tablets.

Weight variation

An analytical electronic balance was used to weigh all thirteen of the tablets. The average weight of each tablet was determined and contrasted with its unique weight in order to determine the variation. The restrictions on weight variation for tablets (USP) were followed from the United States Pharmacopoeia.[13]

Average Weight of tablets are determined by:

Average Weight = (Total Weight of Tablets)/ (Number of Tablets)

The following formula was used to determine each tablet's percent weight variation:

% of Deviation = (Tablet Weight-Average weight) / (Average weight) × 100

Thickness

After taking 20 ketorolac tablets from each brand for the test, numbered T1, T2, T3..., T20, Thickness of each tablet was determined using a slide caliper. The measurements were calculated in (mm).

The formula for calculating average thickness is:

Average Thickness T= (T1+T2+T3+…+T20)/20

And formula used to compute % deviation was:

%Deviation= {(Individual tablet thickness-Average thickness) / Average thickness} ×100

Diameter

A slide caliper was used to measure the diameter of 20 ketorolac tablets. The shape of tablets was established by comparing their shape to FDA-approved specifications.

The average diameter and % deviation were estimated using the following formulas:

Average diameter D= (D1+D2+D3+…+D20)/20

And formula used to compute % deviation is:

%Deviation= {(Individual tablet diameter -Average diameter)/ Average diameter} ×100

Friability test

The friability of tablets was assessed using the Roche Friabilator. The 7 tablets weight loss percentage was utilized to measure friability. When placed on the friabilator, seven ketorolac tablets were precisely weighed, subjected to repeated spinning and shocks, and dropped six inches with each rotation. The weight of the pills was measured after 4 minutes of treatment, or 100 rotations, and compared to their starting weight before the treatment. The degree to which a tablet is friable is determined by how much material is lost by abrasion inside the machine as it rotates. If the pill loses less than or equal to 1% of its original weight, that is acceptable; less than 1% is not acceptable.[14] The differences in weight can be calculated by using the following formula:

% Friability = {(Initial weight − Final weight)/Initial weight} × 100

Disintegration

The disintegration test instrument was used to calculate the in vitro disintegration time. In accordance with USP guidelines, the disintegration equipment consists of six glass tubes, each of which is three inches in length and has a ten-number mesh at its base. This collection of six tubes is submerged in a fluid that symbolizes the disintegration process. To keep the liquid at 37° C, a thermostatic heating system is used. 28–32 rotations per minute are employed to move this mechanism up and down over a 5–6 cm span. Three ketorolac tablets were tested in this experiment using a disintegration tester. The amount of time that there weren't any particles on the device basket was used to calculate the disintegration time.[15]

Dissolution

Three tablets were subjected to a dissolve test in a volume of 900 ml of distilled water at 37ºC, 75 rpm and various predetermined intervals using a dissolution tester. At 5, 15, 30, 45, and 60 minutes the test sample (10 ml) was removed and replaced with fresh dissolving solution while remaining at the same temperature. Following the suitable dilution of the sample, it was filtered and detected using a UV-Spectrophotometer, with distilled water serving as a blank. The rate of release or dissolution was expressed as a percentage.[16]

Hardness

The hardness tester comprises of two jaws facing each other that can be moved in relation to one another. On a precisely calibrated hardness tester, three ketorolac tablets were stacked vertically. The tablet's hardness is therefore determined at the point of cracking. The strength of tablet crushing was measured in kilograms, with 4 to 8 kilograms/force (Kg/F) commonly being regarded as the acceptable tablet threshold.[17]

Hardness is calculated by:

Average Hardness= (Total Hardness of Tablets) / (No of Tablets)

Standard curve preparation

A standard curve was prepared from the solution of reference ketorolac powder. The UV spectrophotometer was then used to determine the absorbance of each solution at 323 nm. The absorbance value was then plotted on the Y-axis and the solution concentration (g/ml) on the X-axis to produce a linear standard curve.

Potency

The potency of a drug is determined by how much medication is contained in it. The average weight of the four tablets was determined. They were then crumbled into powder and measured afterward. The powder was thereafter dissolved in distilled water while being constantly stirred. The combination was then filtered to produce a clear liquid. To quantify the absorbance at 322 nm, a UV-visible spectrophotometer was used.[18]

%Potency can be determined by the following equation:

$$\left(\frac{\textit{Drug present in a single tablet}}{\textit{Strength}}\right) \times 100$$

Procedure of tablet formation

In a university laboratory, the process of creating five Ketorolac Tromethamine tablets using direct compression was conducted. Here's a simplified summary of the steps involved:

Tablet formulation: To prevent any material loss during production, measurements were taken for the API and excipients for 7 tablets. The necessary quantities were sourced from the university lab's stock.

Weighing and Crushing: All the ingredients, including the API and excipients, were accurately weighed using an electronic scale. Subsequently, these weighed components were placed in a mortar for crushing, resulting in a fine powder.

Mixing and homogenizing: The ingredients were meticulously mixed in the mortar and then crushed using a pestle to create a finely homogeneous powder.

Tablet compression: 200 mg of the powdered material was taken from the mortar and placed into the die punch of a direct compression machine. This punch had an 8 mm diameter, falling within the specified range of around 180 mg to 250 mg for an 8 mm die punch. The upper and lower punches of the machine compressed the powder to form tablets, with the entire process controlled by the machine's turret.

Collection of tablets: The tablets, which were formulated in this manner, were collected for further use or analysis.

This procedure outlines the key steps involved in producing Ketorolac Tromethamine tablets through direct compression within a university laboratory, ensuring precise measurements and compliance with specified size and weight criteria for the die punch.

Results and discussion

A standard curve was established to facilitate the measurement of various parameters related to Ketorolac tablets.

Weight variation test

Weight variation of marketed & formulated tablet

All six brands of Ketorolac tromethamine tested as per the USP weight variation test showing a standard deviation.

Weight variation of tablet

Using Formulation data 6 tablets were formulated in the Laboratory. Each tablet was weighed in the electronic measuring scale and the value was recorded. The weight of the 6 individual tablets and their average weight along with % deviations were calculated. The avg. weight of formulated tablets came out to be 203.8mg.

According to the study the average weight of marketed tablet was 163.6 and maximum weight was 185.7 and minimum was 137. Maximum and minimum % deviation was 13.5 and -16.3 respectively. These values were plotted on a graph and shown in Figure 1.

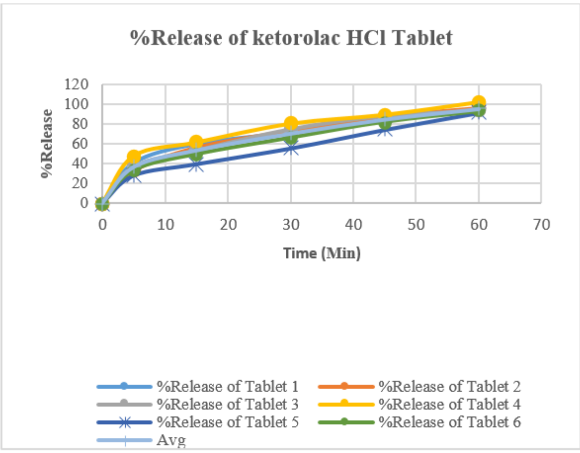

Figure 1 %Drug release profile of marketed ketorolac tablet.

In case of formulated tablet 5 tablets were taken and each tablet was weighed in electronic balance. According to finding the average weight of the tablets was 203.8 and maximum weight was 204.9 and minimum weight was 202.8. Maximum and minimum % deviation was 0.539 and -0.490 respectively. The USP guideline states that if the average tablet weight is between 130 mg- 324 mg, a weight variation of up to 7.5% is acceptable. From the above table it can be stated that both formulated and marketed drug met the USP specification.

Diameter

Diameter of marketed tablet

The diameter and shape of all six brands ketorolac tablets were determined using Vernier calipers. Average diameter is 7.63mm.

Diameter of formulated tablet

A vernier scale is used to measure 6 tablets (round shaped) diameter. In Figure 2, the results of the formulation of ketorolac tablets' average diameter 8mm. A maximum of 5% is permitted for tablets with a diameter less than 12.5mm.[15] From the calculated data in table 3.3 and 3.4 average diameter of the given 6 marketed tablets was 7.63 mm. And Maximum and minimum % deviation was 7.47 and -6.94 for all 6 tablets. Diameter of round-shaped formulated tablets was 8 with 0% deviation. So, it can be stated that diameter of both tablets was within range.

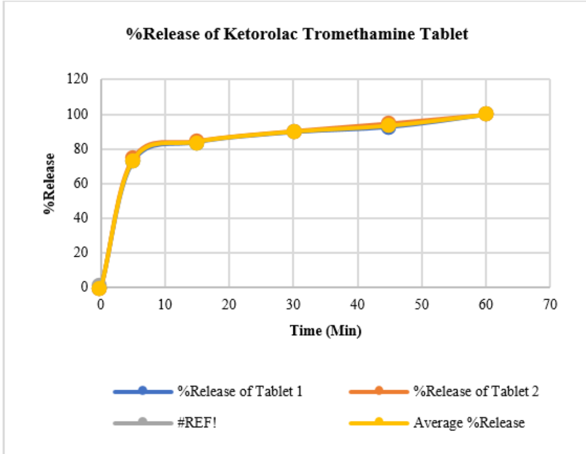

Figure 2 % Drug release profile of formulated Ketorolac tablets.

Thickness

Thickness of marketed tablet

Thickness of 6 Ketorolac tablets was estimated using Vernier calipers. Tablet thickness may change without changing tablet weight as a result of changes in granule density, pressure, and tablet compression speed.

Thickness of formulated tablet

The average thickness and % deviation of formulated ketorolac tablets was calculated.

Solid oral dosage forms, such as tablets, are defined by the features of the granules, such as flow property, particle size and rate of passage through the hopper. According to the experiment's findings, marketed tablets were 3.42 mm thick on average and % deviation Maximum and minimum % deviation was 11.1 and -9.36 for all 6 tablets. Above result was depicted in a graph of Figure 3. For formulated tablet average thickness was 3.9 and % deviation was 0. Comparison of marketed tablet thickness and formulated tablet thickness was shown in graphical representation in Figure 3. Maximum thickness should be controlled within 5% .[19] It can be said that both marketed and formulated tablet fell within this range.

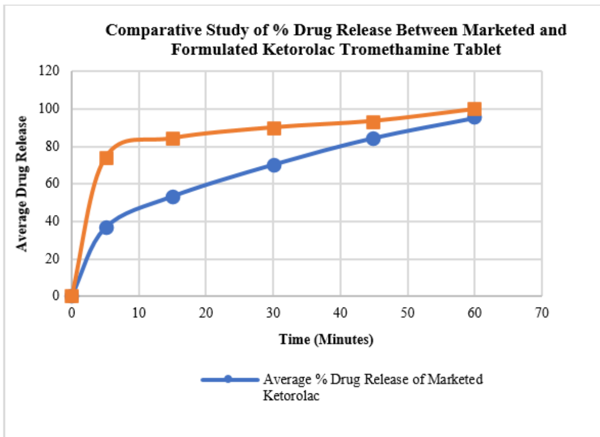

Figure 3 Comparative graph of % drug release for formulated and marketed tablet.

Hardness

Hardness of marketed and formulated tablet

Hardness testing is the scientific method used to evaluate the structural integrity and breaking point of tablets. The capacity of tablets to withstand mechanical shocks while being handled is directly related to their hardness. The figure below displays the results of the calculation for the typical hardness. Among five formulated tablet two tablets have undergone the hardness test and the test value is 3.61 and 3.65 kp.

A tablet hardness tester was used to measure the resistance of tablets to crushing. By turning the screw knob forward, the force imparted to the tablet's edge was gradually increased until the tablet cracked. The level of hardness may vary depending on the manufacturer. 3 marketed ketorolac tablets were taken and hardness was measured. The average hardness was 6.20 kp. And in formulated the hardness value was 3.63 Kp. A comparative of hardness for marketed and formulated tablet was shown in Figure 4.

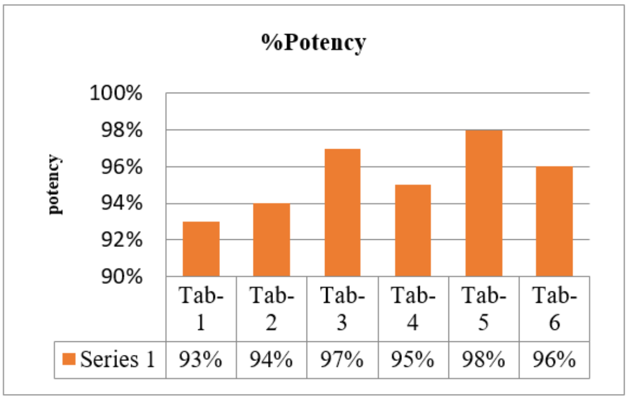

Figure 4 Comparative graph of % potency marketed tablet.

Friability test

Friability test of marketed tablet

Friability test is used to evaluate the durability of a tablet in terms of its ability to endure physical and mechanical pressures during transit and handle. The friability test results of Ketorolac tablets were found 0.0304%. In this experiment 7 ketorolac tablets were chosen at random using a digital balance. The friabilator was then employed to revolutionize the tablets. The weight of the tablets was measured and compared to the starting weight after 100 spins. Tablets must not have a %friability greater than one to fulfill USP specifications. Based on the requirements the tablet met USP requirements.

Disintegration time

Disintegration time of marketed and formulated tablet

The disintegration time of 3 Ketorolac tablets were taken and it was done separately in case of both formulated and marketed tablets. The time was found 2.51minutes for marketed tablet and 2.13 minutes for formulated tablets.

Coated tablets must have a disintegration period longer than 30 minutes or 1800 seconds according to the USP standard. Average disintegration time of marketed tablet was 2.51 minute and formulated tablet was 2.13 minute. A comparative graph was shown. The rate at which the tablets dissolved were all within acceptable limits. Each tablet thus complied with USP standards.

Dissolution

Dissolution of marketed tablet

The graphs below represent the average percentage of drug release and the rate of dissolution of ketorolac tablets (Figure 1).

Dissolution of formulated tablet

The Figure 2 below represents the results of estimating the average percentage of drug release and the rate of dissolution of ketorolac tablets. A comparative study of Dissolution time in between marketed and formulated tablet is illustrated in the following Figure 3.

Drugs dissolution value give the idea about drugs bioavailability and effectiveness. Here the drugs showed good dissolution profile. Around 78.09% drug dissolved in 5 minutes, 93.11 % in 30 minutes and 95.47% in 45 minutes. It shows an average drug release profile of 100.47% in 60 minutes in case of marketed tablets. In case of formulated drug 67.8 % dissolved within 5 minutes. After 30,45and 60 minutes it has dissolution value of 90%, 93.45% and 99.76% respectively. According to USP Specification dissolution of drug should not less than 75% after 45 minutes. Hence both marketed and formulated drug met the criteria. Here all the drugs showed good % release and dissolution profile. Figure 3 showed a comparative dissolution profile between average % release of marketed drug and formulated drug.

Potency

Potency of marketed tablet

The following Figure 4 summarizes the potency of the Ketorolac tablets were evaluated.

Potency of formulated tablet

The USP monograph specifies a 90.0%–110.0% range as the acceptable range for tablets. In this case, the marketed ketorolac tablet's potency ranged from 93% to 97% and formulated tablets is 91.15%. Both tablets met the USP criteria (Table 2).

Conclusion

Ketorolac is a potent non-steroidal anti-inflammatory medication used for pain relief, offering both pain management and fever reduction. It also serves as a viable alternative to opioid therapy for short-term pain control. Ensuring stringent quality control measures is crucial because patients consume this medication directly, and its quality is directly linked to various health concerns. To guarantee the highest level of safety and optimal therapeutic outcomes, quality control must be conducted meticulously. These evaluations allow us to identify problematic medicines while initiating steps to resolve them. This study focused on some specific brands of Ketorolac tromethamine 10 mg tablets available in the local market in Bangladesh, as well as comparing the quality criteria with another version which was manufactured using the resources provided by the B. Pharm project lab of the university. The test results indicate that the marketed product and the in-house product have very similar profiles for the required parameters. Conducting more of such studies is essential to raise public awareness and ensure the quality of pharmaceutical products.

The findings of this study underscore the importance of regularly reviewing and enhancing medication quality standards. By identifying their strengths and areas for improvement, pharmaceutical companies can strive to consistently provide customers with safe, effective, and high-quality products.

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Conflicts of interest

There is no conflict of interest.

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