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Research Article

Comparative *In Vitro* Evaluation of Conventional Ibuprofen Marketed Formulation

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Abstract

Ibuprofen is one of the most potent orally active antipyretic, analgesic and non-steroidal anti-inflammatory drug (NSAID) used extensively in the treatment of acute and chronic pain, osteoarthritis, rheumatoid arthritis and related conditions. This compound is characterized by a better tolerability compared with other NSAIDs. This study aimed at evaluating some quality control parameters to compare the quality, safety, and efficacy of three brands of ibuprofen tablets available in the Indian market. The organoleptic and physicochemical properties of three brands of ibuprofen tablets were assessed according to established methods. The ibuprofen tablet, brand Q exhibited highest dissolution efficiency up to 30 min (48.68±1.24) and lowest mean dissolution time (3.32±0.06) compared to other tablets. Moreover, this branded tablet showed highest % of drug content (99.21±0.17) compared to other tablets.

***Keywords*:** Ibuprofen, drug content, mean dissolution time, friability

Introduction

The relief of pain has been described as a universal human right but is not always easily achieved.[1] Opioid analgesics are effective, but have troublesome and potentially dangerous side-effects, and their potential for abuse may lead to regulatory and logistical difficulties. Non-steroidal anti-inflammatory drugs (NSAIDs) have fewer regulatory restrictions, but they too have important adverse effects which are more likely at higher dose or with longer courses.[2] NSAIDS are a group of unrelated organic acids that mostly affect gastrointestinal tract (GIT). Dyspeptic complaints,[3] upper GI bleeding,[4] and mucosal and duodenal ulcers,[5-7] are common adverse drug reaction associated with this group and may be life threatening.[8] In 2002, Aletaha found that about 72% of the patients with rheumatoid arthritis treated with NSAIDs received gastrointestinal (GI) protective therapy mainly with histamine antagonists and sucralfate.[9] Due to gastrointestinal side effects, the health and economic burdens related to these drugs are considerable.[1] A distinct relationship between effects and side effects exists, namely, rapid absorption beginning in the stomach in associated with intensive gastric-duodenal irritation and ulceration.[11] Epidemiological studies have clearly demonstrated a rank order of risk of ulcer complication for commonly used NSAIDs, with ibuprofen consistently associated with the lowest risk.[12-13]

Ibuprofen is the most commonly used and most frequently prescribed NSAID.[14-15] It was the first member of propionic acid derivatives to be introduced in 1969 as a better alternative to Aspirin (Fig. 1). Gastric discomfort, nausea and vomiting though less than aspirin or indomethacin, are still have most common side effects.[16]

It is non-selective inhibitor of cyclooxygenase-1(COX-1) and cyclooxygenase-2(COX-2).[17] Although its anti-inflammatory properties may be weaker than those of some other NSAIDs, it has a prominent analgesic and antipyretic role. Its effects are due to the inhibitory actions on cyclooxygenase, which are involved in the synthesis of prostaglandins. Prostaglandins have an important role in the production of pain, inflammation, and fever.[18]

Ibuprofen is supplied as tablets with a potency of 200 to 800 mg.[19] The usual dose is 400 to 800 mg three times a day.[20] It is almost insoluble in water having pKa of 5.3.[21] It is well absorbed orally; peak serum concentrations are attained in 1 to 2 h after oral administration. It is rapidly bio-transformed with a serum half-life of 1.8 to 2 h. The drug is completely eliminated in 24 h after the last dose and eliminated through metabolism.[22-23] The drug is more than 99% protein bound, intensively metabolized in the liver and is excreted unchanged.[24]

Post market surveillance or monitoring involves all activities undertaken to obtain more data and information about a product after it had been granted marketing authorization and made available for public use. The data and information so obtained could be employed for product improvement, development of standards and regulations. Regulatory agencies rely on limited information obtained during clinical trials and to some extent scientific literature as guides to granting marketing authorization of medicines for public use. It is therefore imperative to conduct post-market surveillance or monitoring of approved medicines in order

to adequately assess the quality therapeutic effectiveness and safety of medicines for the larger public. The aim of this study was to compare the physicochemical parameters and assay of the three brands of ibuprofen tablets.

Materials and Methods

Materials

Ibuprofen brands having label strength of 400 mg (Table 1) were purchased from a retail pharmacy in Bhilai, Chhattisgarh, India. All tests were performed within product expiration dates. The reagents used were potassium dihydrogen phosphate, sodium hydroxide, hydrochloric acid were obtained commercially and used as received.

Determination of drug content

The tablets were finely powdered and a quantity of powder equivalent to 100 mg of ibuprofen were accurately weighed and transferred to 100 ml of buffer solution (pH 7.2) and mixed thoroughly. The solutions were filtered, diluted with buffer solution (pH 7.2), and analyzed for the content of ibuprofen using UV-visible spectrophotometer (UV-1800 Shimadzu, Japan) at 221 nm. The drug content of each sample was estimated from their previously prepared standard curve.[25]

Uniformity of weight

The variation of the weight of individual tablets is a valid indication of the corresponding variation in the drug content[26]. The average tablet weight was determined by weighing 20 tablets individually using a digital analytical balance (Denver Instrument, TB 214, India).

Thickness and diameter measurement

20 tablets were taken and their thickness and diameter were determined individually by Vernier caliper (China). Mean and standard deviation were calculated.

Friability Test

Twenty tablets were weighed and subjected to friability test using a Roche Friabilator (India). After the given number of rotations (100 rotations/4 min) loose dust was removed from the tablets. Finally tablets were weighed. The loss in weight indicates the ability of the tablets to withstand this type of wear.[27] The percent friability was determined by using following formula:

$$\%F = \frac{W_1 - W_2}{W_1} \times 100$$

where, W_1 is the initial weight and W_2 represents final weight.

Hardness testing

The crushing strength of the tablets was determined using a Monsanto tablet hardness tester (Monsanto, Rolex tablet Hardness tester, Labtech, India).

Disintegration test

Disintegration time of six tablets per brand was determined in distilled water maintained at $37 \pm 0.5^{\circ}C$ using tablet disintegration apparatus (Lab Hosp, India). The disintegration time was taken to be the no particle remained on the basket of the system.

Preparation of standard calibration curve for Ibuprofen in phosphate buffer (pH 7.2)

10 mg of ibuprofen was taken in a 100 ml volumetric flask and makes up the volume with phosphate buffer (pH 7.2) and named it stock solution, its concentration was 0.1 mg/ml. From the above solution 0.1, 0.2, 0.4, 0.6, 0.8 and 1 ml was taken in 10ml volumetric flask and makes up the volume. Its concentration was 1, 2, 4, 6, 8, 10 µg/ml. Absorbance of the sample was taken at 221nm in a UV-visible spectrophotometer (UV-1800 Shimadzu, Japan). The average values of absorbance were plotted against respective concentrations (Fig. 2).

Dissolution test

Dissolution profiles of the ibuprofen tablets were determined in USP phosphate buffer solution (900 ml, pH 7.2, $37 \pm 0.5^{\circ}C$) using USP II dissolution test apparatus (TDL-08L, India). At appropriate time intervals, 5 ml samples were withdrawn and replenished with the same volume of fresh medium. The aliquots following suitable dilution were analyzed spectrophotometrically at 221 nm.

Statistical analysis

The differences in physicochemical properties were evaluated by one-way analysis of variance using Graph Pad Instat software. Differences were considered significant when $p < 0.05$.

Results and Discussion

Three ibuprofen brands having label strength of 400mg were purchased from a local retail pharmacy (India). All tests were performed within product expiration dates during study period. The compendia standards are weight variation, drug content, disintegration time, and dissolution, whereas hardness and friability are non compendia standards. However, friability is now included in the United State Pharmacopeia (USP, 1995). The uniformity of weight determination for three brands of ibuprofen tablets gave values that are within limits. There was different mean weight of all brands because of different excipient used in the different brands. For consumer requirement and also for packaging of tablets thickness and diameter parameters are also necessary for uniformity of tablets. The thickness and diameter of ibuprofen tablets were found to be within their permissible limit ($\pm$ 5%) (Table 2).

For assurance of uniform potency of tablets, weight variation is not sufficient. The potency of tablets is expressed in terms of

gram, milligrams, or micrograms of drug per tablet and is given as the label strength of the product. The BP specification is that the content of drug should not be less than 95% and not more than 105%. The potency of tablets was found to be 97.74 - 99.21% (Table 3). The result ascertains the presence and compendia quantity of ibuprofen in all the brands and so could not be judged as counterfeits without active pharmaceutical ingredients. However, statistically significant difference ($p < 0.05$) of drug content was observed in different tablet brands. The hardness of the tablets is an essential criterion in the determination of the ability of the tablets to resist chipping, abrasion, or breakage under conditions of storage, transportation, and handling. The hardness of the tablet was found to be 5.56-5.73 kg/cm^2 (Table 3). Brand R required least pressure before fracture while brand Q required highest pressure. The result of analysis of variance revealed significant difference ($p < 0.05$) in hardness of all the three brands at 95% confidence interval. This indicated that the tablet can withstand the rigors of transportation and handling. Another measure of tablet strength, its friability is often measured because tablet hardness is not an absolute parameter of strength since some tablets tend to cap on attrition, losing their crown portions when compressed into very hard tablets. The Pharmacopoeia (USP 30, NF 25) states that the friability value of tablets should be less than 1% and as such all the brands of ibuprofen had passed this friability specification 0.05-0.1% (Table 3). Analysis of variance revealed significant difference in friability ($F_{calculated} < F_{tabular}$ at 95% level) of all branded tablets.

Different formulation factors are known to be affect results of disintegration test. The disintegration test measures the time required for a tablet to disintegrate into particles when in contact with gastrointestinal fluids. This is necessary condition and could be the rate- determining step in the process of drug absorption. The type and amount of excipient used in tablet formulation as well as manufacturing process are all known to affect the disintegration. The BP 2003 stipulates a disintegration time of not less than 15 min for uncoated tablets and 30 minutes for coated tablets. The disintegration time of coated ibuprofen 400mg tablets was determined according to USP 2007. Film coated tablets pass the disintegration test if each of six tablets disintegrate in not less than 30 minutes in simulated gastric fluid. The result of the disintegration test is presented in Table 3. Result indicates that all brands of ibuprofen tablet passed the disintegration test. However, analysis of variance revealed significant difference in disintegration time ($F_{calculated} > F_{tabular}$ at 95% level) of branded tablets.

Dissolution of drug from oral solid dosage form is a necessary criterion for drug bioavailability (i.e., the drug must be solubilized in the aqueous environment of gastrointestinal tract to be absorbed). For this reason, dissolution testing of solid oral drug products has emerged assuring product uniformity. The results of dissolution tests in terms of dissolution efficiency and time to dissolve 50% drug ($t_{50\%}$) and 85% ($t_{85\%}$) drug and mean dissolution time are shown in Table 4. Mean dissolution time (MDT) reflects the time for the drug to dissolve and is the first statistical moment for the cumulative dissolution process that provides an accurate drug release profile. A higher mean dissolution time value indicates greater drug retarding ability. MDT was calculated from the following equation:

$$MDT = \left[\frac{\sum_{i=1}^{n} t_{mid} \times \Delta M}{\sum_{i=1}^{n} \Delta M} \right]$$

where i = dissolution sample numbers, n = number of dissolution times, t_{mid} = time at the midpoint between times t_i and t_{i-1}, ΔM = amount of drug dissolved between times t_i and t_{i-1} .The release profiles of the drug from various tablets are shown in Fig. 3. The dissolution efficiency (DE) is defined as the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.[28] DE was calculated from the following equation;

$$DE = \left[\frac{\int_0^t y \, dt}{y_{100} \, .t} \right] \times 100\%$$

Where, y is the drug percent dissolved in the time t.

Dissolution efficiency (DE) can have a range of values depending on the time interval chosen. However, while comparing a set of data a constant time interval should be selected. In the present study, DE_{30} min (Dissolution efficiency up to 30 min) were calculated from the dissolution profile of three brands of ibuprofen tablets and used for comparison. The time required for 50% ($t_{50\%}$) of drug dissolution ibuprofen from three brands of ibuprofen tablets P, Q and R were found to be 20.11, 13.93 and 15.46 min, respectively. Similarly, time required for 85% ($t_{85\%}$) of drug dissolution were found to be 43.84, 26.67, 35.87 min respectively (Table 4). Dissolution efficiency curve of tablets are presented in Fig. 4. From dissolution efficiency profile, it was observed that the dissolution efficiency increased in the following order P<R<Q.

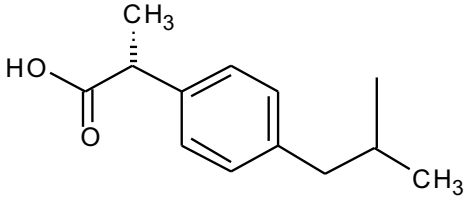

Fig.1: Structure of ibuprofen

Table 1. Label information on the Ibuprofen tablets evaluated

Code	Brand name	Batch No.	Manufacture date	Expiry date	Labeled strength (mg)	Manufacture
P	Ibuprofen 400	4188	Nov 2010	Oct 2012	400	Vikram Laboratories (P) LTD.
Q	Brufen 400	B– 411B	Sep 2009	Aug 2012	400	Abbott India Limited
R	Ibugesic 400	AO 2971	Dec 2010	Nov 2013	400	Cipla LTD

Table 2. Weight variation, thickness, and diameter of ibuprofen tablet

Code	Weight (mg) (Mean ± SD, n= 20)	Thickness (mm) (Mean ± SD, n= 20)	Diameter (mm) (Mean ± SD, n= 20)
P	0.515 ± 0.010	5.613 ± 0.099	12.428 ± 0.023
Q	0.557 ± 0.011	5.747 ± 0.070	14.122 ± 0.030
R	0.571 ± 0.005	5.876 ± 0.033	14.120 ± 0.025

Table 3. Drug content, hardness, friability, and disintegration time of branded tablets

Code	Drug content (%) (Mean ± SD, n= 3)	Hardness (Kg/cm^2) (Mean ± SD, n= 3)	Friability (%) (Mean ± SD, n= 6)	Disintegration time in simulated gastric fluid (Mean ± SD, n= 6)
P	97.74 ± 0.54	5.566 ± 0.11	0.11 ± 0.06	32.00±1.26
Q	99.21 ± 0.11	5.733 ± 0.20	0.05 ± 0.02	34.00±0.89
R	98.70 ± 0.17	5.333 ± 0.06	0.08 ± 0.03	33.83±1.16

Table 4. Characteristics of ibuprofen tablets

Code	$t_{50\%}$ (Mean ± SD, n= 3)	$t_{85\%}$ (Mean ± SD, n= 3)	MDT (Mean ± SD, n= 3)
P	20.11 ± 1.04	43.84 ± 0.97	4.33 ± 0.11
Q	13.93 ± 0.27	26.67 ± 1.23	3.32 ± 0.06
R	15.46 ± 1.23	35.87 ± 6.11	3.92 ± 0.19

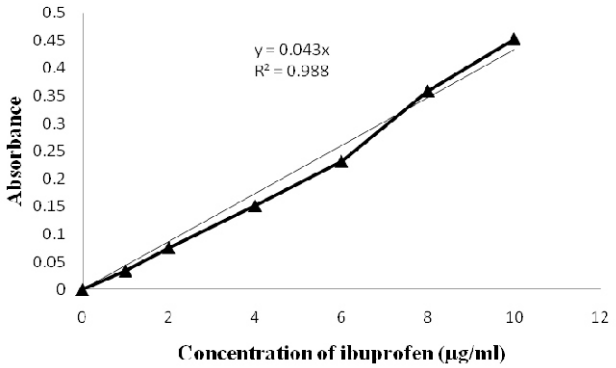

Fig. 2: Calibration curve of ibuprofen in phosphate buffer USP, pH 7.2

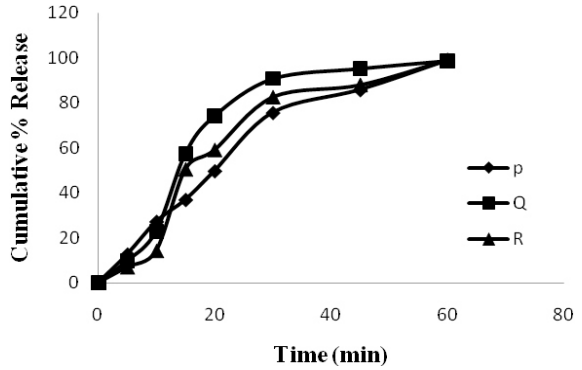

Fig. 3: Dissolution profile of three brands of ibuprofen tablets

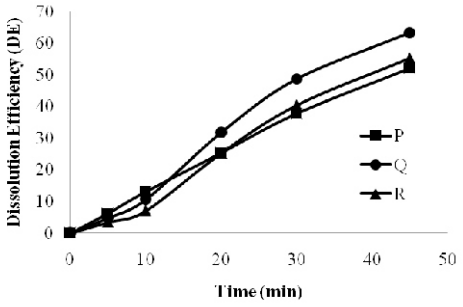

Fig. 4: Dissolution efficiency of three brands of ibuprofen tablets

Conclusion

In this study three brands of ibuprofen tablets evaluated and could be evaluated as being pharmaceutically and chemically equivalent and can be freely interchanged. The ibuprofen tablet, brand Q exhibited highest DE up to 30 min (48.68 ± 1.24) and lowest MDT (3.32 ± 0.06) compared to other tablets. Moreover, this branded tablet showed highest % of drug content (99.21 ± 0.17) compared to other tablets. This study highlights the need for constant market monitoring of new products to ascertain their equivalency to official standards.

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