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An *In-Vitro* Evaluation Study of the Quality Control of Different Brands of Ibuprofen 400 Mg Tablets Marketed in Sana'a Governorate

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ABSTRACT

The Yemeni drug market is open, and most of the companies that manufacture drugs are non- research bases, and consequently, it could be expected that some of those products are substandard. Ibuprofen is an over the counter antipyretic analgesic and non –steroidal anti-inflammatory drug. The ten samples of this study were collected from the Sana'a governorate. The solid dosage forms are considered worse in bioavailability. The purposes of this study are to evaluate the nine generic brands compared with the reference according to standard specifications. The method of analysis was carried out by spectrophotometer at 221 nm by using a phosphate buffer solution at pH 7.4 against blank. The method of analysis was valid and achieves reproducibility, accuracy, and linearity. The correlation coefficient was 0.999. The relative standard deviation percent (RSD %) at the lower limit was 1.7%. The results of the study showed that seven out of ten brands were failed to an agreement with Pharmacopoeias specifications in dissolution and uniformity contents test. The conclusion of this study reflected that seven brands of ten ibuprofen 400 mg tablets failed to meet specifications. Substandard, counterfeit and adulterate medicines available in large quantities that constitute 70%. So, the investigator advises the authority of the health to build large laboratories for research and development to solve the problems of drug quality and applied the advanced criteria such as bioavailability and bioequivalence studies and drug stability and toxicity studies.

INTRODUCTION

The Yemeni drug market is open, and most of the companies that manufacture drugs are non-research bases, and consequently, it could be expected that some of those products are substandard. There are more than 100 brands of ibuprofen in the Yemeni market that contained different strength and dosage forms; according to the annual report of the supreme board of drug and medical appliances[1]. Ibuprofen is a chiral propionic acid derivative belonging to the class of non-steroidal anti-inflammatory drugs (NSAIDs) with a short half-life (1.8 - 2h). It is used for relief of symptoms of rheumatoid arthritis, primary dysmenorrhea osteoarthritis and ankylosing spondylitis[2, 3]. The oral dose is 200 - 400 mg (5 - 10 mg/kg in children) every 4 - 6h to a maximum of 1.2 g per day in adults. The mode of action is believed to involve the reversible inhibition of the enzyme cyclooxygenase (COX) which is then responsible for the biosynthesis of prostaglandins (PGs) from arachidonic acid in the cellular membrane. PGs are the main cause of the feeling of the pain and raise the normal body temperature more than 37°C. The major side effects of NSAIDs are gastrointestinal irritation[2](Technical information, 2018). Others include nausea and dyspepsia. Ibuprofen, however, has the least of these side effects commonly associated with NSAIDs[4]. Avery serious adverse drug reaction of ibuprofen can be fatal such as thrombocytopenia[5]. It is also very cheap and readily available as an over-the-counter (OTC drugs) preparations.

Physicochemical properties as follow: Ibuprofen is the racemate of (+) and (-) ibuprofen (optical rotation = 0). It is a colorless crystalline powder with a melting point of 74- 77 °C, very slightly soluble in water (<1mg/ml) and readily soluble in most organic solvents, boiling point 157 °C, density 1.029/cm^3, refractive index 1.5500, pKa 4.45[6]. Furthermore, Alvarez et al[7], 2011 proved that ibuprofen BCS class II which defined as low solubility high permeability, while EMEA[8] considered ibuprofen BCS class II and IV, which defined as low solubility and low permeability.

Ibuprofen tablets formulation contains excipients such as diluents, binders, disintegrates, lubricants, coloring matter, and flavoring substances which should be used in quantities that do not affect stability, dissolution rate, release, and bioavailability. The above additives lead to decrease solubility and hence decrease bioavailability[9]. Moreover, small differences in the manufacturing process could consistently alter the disintegration, dissolution and consequently the bioavailability of the active ingredients in a product[10].

Therefore, it ranks as one of the most commonly prescribed NSAIDs in most of the countries with many new medicines products released into the market regularly, it is increasingly difficult to keep track of the safety of every product and this failure to keep track of medicinal product has led to an influx of counterfeit or substandard products[4]. Counterfeit medicine is defined by the World Health Organization[11] as one, which is deliberately and fraudulently mislabeled concerning identifying and/or source.

A modern study carried out by Khan and Khar (2015)[12] mentioned that globally, every country is the victim of substandard or spurious drugs, which results in a life-threatening, the financial loss of consumer and manufacturer and loss in trust on the health system. The adverse effects of fake and adulterated drugs are so serious and can give rise to treatment failure which at times may be serious enough to result in death.

Florence et al[13], (2009) summarized the reasons adduced for the availability of counterfeit drugs in Nigeria include: inadequate laws; ineffective enforcement of existing laws; Non-health professionals in drug business; lose control system; high cost of drugs; agreed; ignorance and corruption. And so consequently, the Yemeni market is similar to the Nigerian market.

Previous studies

Asaifi et al[14], 2018, and Al-mekhlafi[15], 2019 studied the drug quality control on five brands of ibuprofen tablets and eleven brands of amoxicillin capsules that marketed in the ROY. The conclusion of both the studies is, four and six brands failed in both of the studies respectively. Also, Adedibo et al[16], reported that the sub-Saharan Africa countries market is flooded with fake and adulterated drugs to such an extent that only 30% of drugs available in these countries can be said to be genuine in terms of contents and efficacy. It is very clear, that ibuprofen tablets quality control study, face different challenges: firstly, ibuprofen is a racemic mixture with the lower melting point, secondly, the excipients that added to the formulation, thirdly, climatic factors such as temperature and humidity during storage conditions that lead to drug degradation. And also, substandard drugs and adulterated medicines may be led in some times to very risky and maybe sometimes lead to death. Over more, the CGMP, and post-marketing surveillance are still far away in our country. The previous reasons justify to check the quality of ten brands of ibuprofen medicines in the Yemeni market and to ensure the desired level of efficacy, safety, and quality.

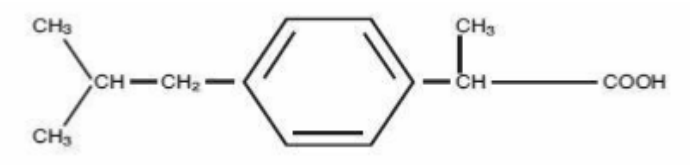

Figure No. 1: Ibuprofen Chemical Structure

MATERIALS AND METHODS:

Collection of samples:

The samples of study collected randomly from retail Pharmacy in Sana'a governorate which included ten different brands as follow: 1 one British; 2 three brands their original from United Arab Emirates (UAE); 3 two brands are Indian, 4 one brand is Syrian 5 one brand in Germany, 7 one locally, and 8 one brand Italian as reference and as mentioned below:

Table No. 1 different brands of ibuprofen 400 mg tablets included in the studies

Sample code	Batch no	Sample code	Batch no	Sample code	Batch no
Ibupfn 01	011	Ibupfn 05	70	Ibupfn 09	19120
Ibupfn 02	0143	Ibupfn 06	20030213	Ibupfn 10	17550
Ibupfn 03	3427	Ibupfn 07	A 730		
Ibupfn 04	17ID10	Ibupfn 08	212020		

Reagents

All reagents used were of analytical grade purchased from the local market; BDH, Germany from local agent.

Standard phosphate buffers pH 7.2: composition of phosphate dihydrogen phosphate/NaOHanalar.

Ibuprofen reference raw material was kindly supplied by local manufacturer: Modern Pharma.

Preparation of buffer solution

Dissolve 6.805 g of dihydrogen phosphate, and 1.833 g of sodium hydroxide into 1000 ml of purified water, adjust pH to 7.2 by 2 N NaOH.

Design calibration curve

Weigh accurately 20 mg of ibuprofen reference material by analytical balance (Model: HM 2000, Japan) dissolved in 100 ml volumetric flask (stock solution) and from the stock solution prepare 6-point different concentrations (2, 4, 8, 10, 12, 16). The work standard solution ranged between 2 –16 µg/ml, and measure the absorbance using a UV spectrophotometer (UV – 550, Jusco, Japan) at 221 nm.

The calibration curve was constructed and the results showed to achieve accuracy, reproducibility, and linearity. The relative standard deviation percent at lower and upper concentrations were 1.70% and 0.052 respectively. The correlation coefficient (r^2) was 0.999. The average of the results represented in Fig 2.

Physicochemical tests:

Uniformity of weight variation

The British Pharmacopeia[17]method was adapted by using twenty randomly selected tablets from each batch and the allowance ± 5%.

The hardness tests

The hardness of 5 tablets randomly selected from each batch was determined on a tablet hardness tester (Pharma Test, Model: PTB 111, Germany).

Friability test

Five tablets previously freed from dust were weighed together before rotation in a friabilator (Erweka, Germany) and rotate for 4 minutes at 25 rpm. Thereafter, the dusted were removed and reweighed.

$$\% \text{ friability} = (W1 - W\,2/W\,1) \times 100$$

Where W 1 the initial weight, W2 the weight of tablets after rotation.

Disintegration time test

The British Pharmacopeia[17] method for determination of disintegration time for uncoated tablets was adopted using a disintegrating apparatus (Pharma test, Model: DIST 3, Germany)

and the medium was phosphate buffer solution at 37 ±1 °C. Six tablets were placed in each six open-ended transparent tubes for determination of the test, a device to raising and lowering the basket is 30 cycles per minute.

Dissolution test

USP[18] apparatus 1 method was used to determine the dissolution test (Pharma test, Model: PTWS 1220, Germany). The medium was phosphate buffers solution at pH 7.2 and 37 ±1 °C and heated by auto-heater. Different samples analysis during 60 minutes.

Uniformity of content

The quantity of ibuprofen was determined in each batch according to USP[18]. A standard solution was prepared by dissolving pure ibuprofen in phosphate buffer, and the same solvent for sample solution of ibuprofen tablets (n = 20) for each batch. The amount of ibuprofen in each product was calculated using the regression equation of the calibration curve.

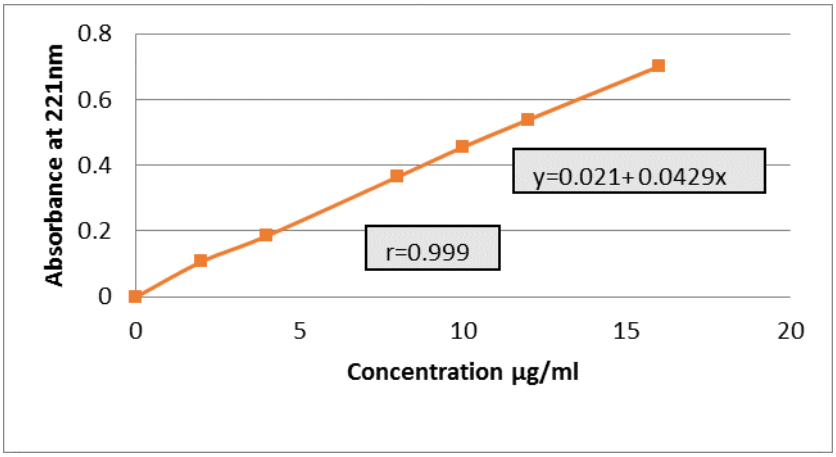

Figure No. 2: Calibration curve of Ibuprofen

RESULTS AND DISCUSSION

RESULTS:

This study included ten brands of ibuprofen 400 mg tablets that were available in Sana'a Governorate'sYemeni market. The brands of the study and they are original had been mentioned in the previous under samples collection and Table 1. The spectrophotometer was used to determine the qualitative and quantitative analysis at 221 nm. The method of analysis was valid (see methodology). The tablet's products were examined according to British

Pharmacopoeia[17] and the United States Pharmacopoeia[18]in physical essential examinations for tablets such as weight variations, and uniformity contents, hardness, disintegrations, dissolutions, and friability tests.

The physicochemical results were illustrated in Table 2. Three brands that coded Ibupfn 01, Ibupfn 03 and Ibupfn 06 of ten occurred agreement with standard criteria in physical and chemical assays. Other brands that coded Ibupfn 4, 5, 7, 8, 9 and 10 failed in quantitative analysis and at the same time failed in dissolution test except no 2 passed the test. The hardness occurred between 4 – 9 Kgf, all the brands within the limit except no 06 that slightly increased (Table 2). Disintegration time test; the results of this test range between 2.81 – 9. Friability test measured the least force that affects the tablets, according to the limit allowance ≤1%, and hence all the brands passed this test as occurred in Table 2. Weight variation: the average of the weight ranged between 0.541 – 1.163. the average weight variation in all the brands seemed comparable with ± 5% except Ibupfn 01 and 6.

DISCUSSION

Hardness tests

The results of hardness (crushing strength) represented in Table 2, the range of the results occurred between 4-9.30 for all brands. Whereas the two brands that coded Ibupfn 3 and 6had lower and upper limits respectively. The limit of this unofficial parameter ranged between 4-8 kilograms force (kgf). The crushing strength for all brands was within the limit, except no 6 that slightly increase over the limit. These results reflect that compression force, disintegrate and binders were available in the components of formula in a compromised amount. Whereas the no 6 that had value 9 kilos may be due to the increase in the aforementioned amount. And hence, all the brands did not fracture (crushing) during handling, packaging, shipping, and transportation.

Weight variation

Table 2 showed that ten brands gave good results in this official physical test. The results occurred in the average ±5% according to the British Pharmacopeia (BP, 1998) which specifies that not more than two individual weights should deviate from the average weight by more than 5% and none should deviate by 10%. These results reflected that the flowability from the Hooper of the machine was homogeneity due to the best granulation that

achieved the balanced between the components of the formula and the fluid of granulator. Andhence good maintained and calibrated the machine according to the standard.

Disintegration time and friability tests

The disintegration time is the official test according to Pharmacopeias. The results of all brands in the disintegration time range between 2.81 and 9.30 minutes (Table 2). All the brands were within the allowance limit according to BP, (2008)i. e, the components of the tablets were in a balanced amount.

Dissolution tests:

Table 3 represented, the results of dissolution behaviors for ten various brands of ibuprofen tablets, the brands that coded Ibupfn no2, 3, 4, and 6had passed the test compared to reference no 1, whereas the other brands that coded Ibupfnno 5, 7, 8, 9, and 10 failed to meet the criteria of the dissolution profiles (Figure 3) according to USP 24[18]. Again, the brands that failed in dissolution profiles as mentioned above, and at the same time, failed in quantitative analysis, judged as substandard and adulterated. The failure in this test could be attributed to different factors: first, physical properties of ibuprofen due to lower melting point and racemate of (+) and (-) ibuprofen, whereas BCS is class II and class IV, besides, polymorphisms, five grades, increase the particle size diameter of raw materials, complexation, and co-precipitation. Second, the lack experienced in drug manufacturing processes such as mixing, granulation processes or increase solvents of granulation, and drying of granules. The third, the excipients that added to active ingredients such as a binder, a lubricant such as magnesium stearate, and compressibility force. All factors mentioned above lead to decrease solubility and hence decreased bioavailability and therapeutic effectiveness may be failed. The predict of bioavailability and bioequivalence studies were unfortunately very worse in this situation. Finally, our results agree with the study conducted by Florence et al[12], (2009), who studied the physicochemical properties of 19 brands of ibuprofen tablets in the Nigerian market. The results of this study represent that 15 brands of the samples failed in the official dissolution test.

Uniformity content:

Table 2 and Figure 4 show brands that coded Ibupfn no 1, 3, 6 passes the contents uniformity test, whereas the brands that coded Ibupfn no 2, 4, 5, 7, 8, 9 and 10 failed to meet specifications. The results of these brands in the quantitative analysis were in this order(higher to lower) as illustrated in Table 2:86.50, 87.76%, 82.23, 73.40, 82.80, 78.30and 86.46. Again, these seven brands that failed in uniformity contents ensured that these brands were considered adulterated since starting manufacturing as discussed aforementioned. It could be concluded that the results of the present study were the worst in the Yemeni market at all. The conclusion of our results indicated that 70% of these samples were not agreed with BP and USP24[18]criteria in physical and chemical assays. And hence they reflect bad quality, poor CGMP, substandard and adulterated drugs. Our findings also similar to the reported studies that conducted by Florence et al[12] (2009), Gawazina et al[4], (2017), and Asaifi et al[14](2018) who studied nineteen, fourteen and five samples of ibuprofen tablets, the results of the total samples that failed in physicochemical tests were sixteen (84.21), twelve (85.71) and four (80%) respectively. If we take the average of our findings together with the aforementioned studies, the unofficial medicines reached to 79.98%.

The conclusion of these studies

There are comparable between our findings in this study and that conducted by Adedibuet al[16], in sub-Saharan Africa as mentioned previously, that the fake, adulterated, and substandard medicines are available in Yemeni marketing that constitutes 70 to 80 %. Moreover, this study reflects that CGMP and post-marketing surveillance are still far away in our country. So, the investigator advises the authority of health to build large quality control laboratories for research and development to face challenges that jeopardize drug quality and apply restricted regulation besides advanced criteria during medicines registration such as bioavailability and bioequivalence studies and also drug stability and toxicity studies.

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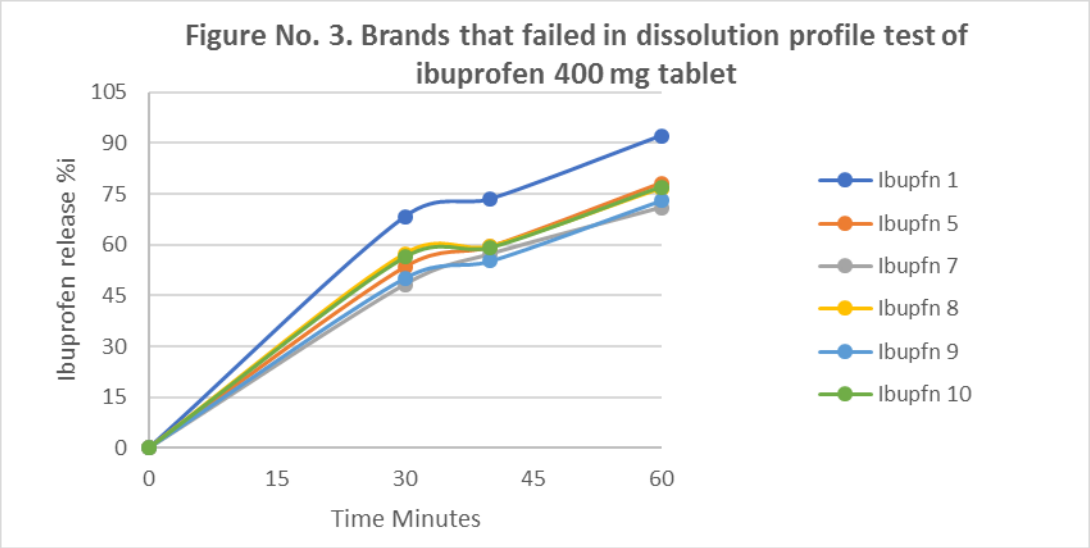
Table No. 2: Results of different brands of ibuprofen 400 mg tablets

	Essential tests						
Sample Code	WV Av ± 5%	Hardness Limit 4 - ≤ 8 kgf/cm	Disin Time min≤ 15	dissoln after 60 m≥ 85%	Friability test ≤ 1%	Assays Limit:95 -105%	Results
Ibupfn 01	0.800	04.76 ± 0.60	02.81	92	0.37	96.96	CPY
Ibupfn 02	0.601	07.20 ±01.62	08.49	85	0.31	**86.50**	N.CPY
Ibupfn 03	0.691	04.67 ±0.36	03.06	85.20	0.70	95.95	CPY
Ibupfn 04	0.541	06.90 ±01.52	09.55	85.4	0.38	**87.76**	N. CPY
Ibupfn 05	0.555	07.20 ± 01.62	03.16	**71**	0.90	**82.23**	N. CPY
Ibupfn 06	1.163	09.30 ± 0.16	06.10	85	01.00	100	CPY
Ibupfn 07	0.591	06.90 ± 01.52	05.41	**69**	0.55	**73.40**	N. CPY
Ibupfn 08	0.565	07.50 ± 01.96	04.51	**76.6**	0.40	**82.80**	N. CPY
Ibupfn 09	0.663	07.20 ± 01.62	08.00	**73**	0.19	**78.30**	N. CPY
Ibupfn 10	0.592	07.30 ± 01.50	03.19	**77**	**0.78**	**86.46**	N. CPY

Ibuprofen tablets, WV: weight variation, N: not, CPY: Comply

Table No. 3: Dissolution rate of various brands of ibuprofen tablets

Sample code	**% of drug release after 30 minutes**	**% of drug release after 40 minutes**	**% of drug release after 60 minutes**
Ibupfn 01	68.18	73.44	92
Ibupfn 02	60.22	65.23	85
Ibupfn 03	53.40	59.4	85.20
Ibupfn 04	61.48	66.7	85.40
Ibupfn 05	48.30	57.3	**71**
Ibupfn 06	62.30	67.04	85
Ibupfn 07	54.50	68.11	69
Ibupfn 08	57.35	59.50	**76.6**
Ibupfn 09	50.14	55.18	**73**
Ibupfn 10	56.30	59.10	**77**



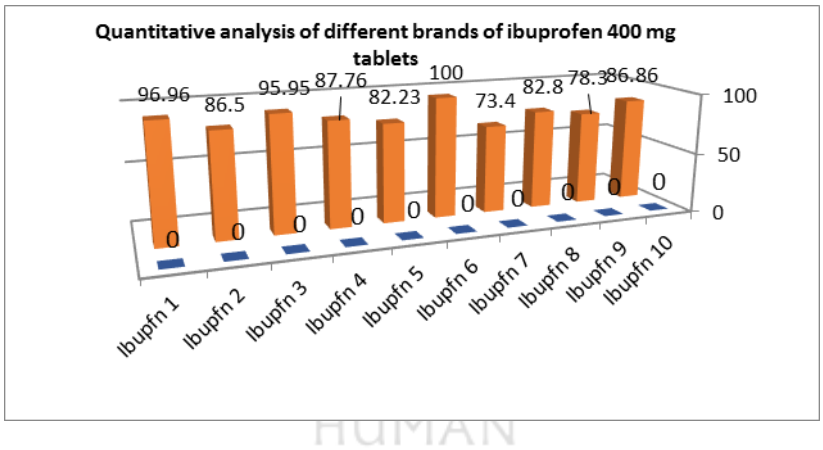


Figure No. 4: Quantitative analysis of different brands of ibuprofen 400 mg tablet

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