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Generic versus innovator: Analysis of the pharmaceutical qualities of paracetamol and ibuprofen tablets in the Nigerian Market.

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The physicochemical equivalence of twenty-two brands of paracetamol and nine brands of ibuprofen tablets sourced from retail Pharmacy outlets in the Nigerian market to their respective innovator brands were investigated. The uniformity of weight, friability, crushing strength, disintegration and dissolution times and assay of active paracetamol ingredient were used as assessment parameters. All the brands of paracetamol and ibuprofen tablets complied with the official specifications for uniformity of weight. However, five brands of paracetamol failed the friability test, one brand of paracetamol and two brands of ibuprofen failed the disintegration test and three brands of paracetamol and four brands of ibuprofen failed the assay of active ingredients. The study shows that not all the brands of paracetamol and ibuprofen tablets are physico-chemically equivalent to their innovator brands. There is therefore the need for constant market surveillance to ascertain their compliance with official standards and equivalence to the innovator products.

Keywords: Generic, innovator brand, paracetamol, ibuprofen, physicochemical equivalence

INTRODUCTION

Reports have shown that various substandard drugs are available in markets worldwide [1, 2]. Treatment failure and drug resistance are frequently reported in developing countries [3,4] largely as a result of the prevalence of substandard or counterfeit drugs particularly in African and Asian countries [5]. In a random quality testing conducted in Nigeria, 48% of the samples of different categories of drug products were found to be outside the British Pharmacopoeia (BP) specifications for drug assay and about 40% of these products were manufactured in India [6]. Another study also reported that most of the bulk active ingredients produced by China and India are used in the manufacture of counterfeit pharmaceuticals worldwide [1]. Hence, the WHO has suggested a rapid alert system for the relevant authorities in Asian countries to combat the global threat posed by counterfeit pharmaceutical products [7].

In Nigeria, the prevalence of substandard and counterfeit drugs in the market has resulted in the belief that innovator pharmaceutical products are more effective, being in most cases, imported and relatively expensive [2]. However, a large percentage of the population lack the purchasing power to afford these branded products. As a result generic drugs, many of which are manufactured in Asia, have offered opportunities for significant cost savings over innovator drug products. Inadequate surveillance and monitoring, as well as lack of adequate information to the public have contributed to the flourishing market of these substandard drug products. In Nigeria, the National Agency for Food and Drug Administration and Control (NAFDAC), an agency of the Federal Ministry of Health, was established to regulate and control the manufacture, importation, exportation, distribution, advertisement, sale and use of drugs. An important land mark in the renewed fight against substandard pharmaceuticals by NAFDAC was the prohibition of the importation of some generics

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including paracetamol tablets and syrups [8]. This restriction has proved to be effective in encouraging pharmaceutical companies in the country to embark on local production of these drug products. The generic manufacturers do not incur the cost of drug discovery, bear the burden of proving the safety and efficacy of the drugs through clinical trials and may also receive the benefit of the previous marketing efforts of the innovator company. Thus the prices of generic products are significantly lower than those of innovator brands [9]. However, generic drug products must satisfy the same standards of quality, efficacy and safety as those applicable to the innovator products [2].

Paracetamol is a well known analgesic and antipyretic agent while ibuprofen is a commonly used anti-inflammatory agent for conditions such as rheumatoid arthritis [10]. With the prevalence of several brands of paracetamol tablets and ibuprofen tablets in the Nigerian market, there is the need to evaluate the chemical and pharmaceutical equivalence of these generic products with the innovator products. The present study was aimed at investigating the equivalence of 22 brands of paracetamol and 9 brands ibuprofen to their respective innovator brands.

MATERIALS AND METHODS

Twenty three brands of paracetamol tablets (A – W) and ten brands of ibuprofen tablets (A—J) were obtained from different retail pharmacy outlets in Nigeria. The pharmacy outlets were selected randomly and the brands available in each outlet were noted. Most outlets visited had more than five brands of paracetamol and more than three brands of ibuprofen tablets available. The origin and type of tablets of the various brands are shown in Table 1.

Identification test

The B.P. (1998) method for the identification of paracetamol tablets was used to ascertain the presence of paracetamol in the tablets. Five (5) tablets were crushed into powder and the amount of sample containing 0.5g of paracetamol was transferred into a 50 ml beaker. About 20 ml of acetone was added and then filtered. The filtrate was evaporated to dryness at 105˚C and 0.1 g of the residue was transferred into a second beaker. Concentrated hydrochloric acid, (1 ml) was added with heating to boiling on a hot plate for about 3 min, followed by 10 ml of water and then left to cool. On addition of 0.05 ml of 0.0167 M potassium dichromate, a violet colour that did not change to red was observed, confirming the presence of paracetamol.

The B.P (1998) method for the identification of ibuprofen was used for the identification of ibuprofen in the various brands. A quantity of powdered tablets containing 0.5 g of ibuprofen was extracted with 20 ml of acetone. This was filtered and the filtrate was evaporated to dryness in a current of air, without heating. The ibuprofen extract obtained was washed and recrystallized from petroleum spirit and the melting point of the dried extract was found to be about 75 ˚C

Determination of tablet properties

Twenty (20) tablets from each brand selected randomly, were weighed individually using an analytical balance (Mettler PE 360 Delta range, Switzerland). The average weights and percentage deviation from the average weight were calculated to determine the weight uniformity.

The crushing strength of the paracetamol was determined at room temperature (27 ± 2ºC) using a EH01 hardness tester (DBK Instruments, London, England) while the friability test was carried out using a 40FTA01 friabilator (DBK Instruments, London, England) operated at 25 rpm for 4 min.

The disintegration times of the tablets were determined in distilled water at 37 ± 0.5 ºC using the 4070A02 Tablet Disintegration Test Apparatus (DBK Instruments, London, England).

The dissolution test on the paracetamol tablets was carried out using the Dissolution test apparatus (DBK Instruments, London, England) fitted with a basket rotated at 50 rpm in 900 ml

of 0.1M HCl maintained at 37±0.5◦C. Samples (5 ml) were withdrawn and replaced with equal amounts of fresh medium. The samples were diluted and the amount of paracetamol released was determined by UV spectrophotometry at 243 nm, on 7804C UV/Visible spectrophotometer (Jenway, Essex, England). Dissolution tests on the ibuprofen tablets were similarly carried out using 900 ml of phosphate buffer, pH 7.2 with the rotation speed set at 100 rpm. The amount of ibuprofen released was determined spectrophotometrically at 221 nm. All tests were done in triplicates or more and results are expressed as mean ±SD.

Assay of active ingredient

The assay of paracetamol was carried out using the B.P. (1998) method. For this purpose, twenty tablets were weighed and powdered and a quantity of the powder containing 0.15 g of paracetamol was added to 50 ml of 0.1M sodium hydroxide, diluted with 100 ml of water and shaken for 15 min. Sufficient amount of water was added to make up to 200 ml, followed by mixing and filtration. Ten ml of the filtrate was diluted to 100 ml with water and 10 ml of 0.1M NaOH was added to 10 ml of the resulting solution. After diluting to 100 ml with water, the absorbance of the resulting solution was measured at the maximum at 257 nm.

Titrimetric assay of ibuprofen was carried out according to the B.P. (1998) method. Twenty tablets of ibuprofen were weighed and powdered and a quantity of the powdered tablets containing 0.5 g of ibuprofen was extracted with 20 ml of chloroform. The solution was allowed to stand for 15 min, filtered and the residue washed with three quantities each of 20 ml chloroform. The combined filtrates were evaporated to dryness and then dissolved in 100 ml of ethanol (96 % v/v). This was then titrated with 0.1M NaOH V.S. using phenolphthalein solution as indicator.

Statistical Analysis

Statistical analysis was done to compare the properties of the various generics with their innovator brands using the analysis of variance (ANOVA) on a computer software GraphPad Prism© 4 (Graphpad Software Inc., San Diego, CA, USA). At 95% confidence interval, $p \leq 0.05$ was considered significant.

RESULTS AND DISCUSSION

All the brands of paracetamol and ibuprofen tablets used for the study were within their shelf life at the time of investigation. All brands of paracetamol tablets tested were manufactured in Nigeria and registered by NAFDAC. Only one brand of ibuprofen which is the innovator product, Brand A, was manufactured in Nigeria while the others were imported either from USA, UK or India. Three (3) of the products from India were not registered by NAFDAC. Ibuprofen is not on the list of drug products prohibited for importation into Nigeria by NAFDAC and hence many of the brands are still imported. All the samples passed the B.P. (2008) identification test [10] showing that the products contained the labelled therapeutic ingredients.

The physicochemical properties of the tablets presented in Table 2 shows that all the brands of paracetamol and ibuprofen tablets passed the weight uniformity test. The results of the crushing strength and friability tests for paracetamol tablets shows that most brands of paracetamol tablets showed acceptable crushing strength of ≥ 4 Kilogram Force (KgF) or 39.2 Newton (N) [11]. However, brands K and L had significantly ($p \leq 0.05$) higher crushing strength values while brands B, I, P, T and U had significantly ($p \leq 0.05$) lower values than the innovator product, brand A. Brands D, G, N, T and W failed to meet the specification on friability [10].

The disintegration time of tablets determines to a large extent, the surface area of contact between the solid and liquid in the dissolution process and could be the rate-determining step in the process of drug absorption [2]. The results of the disintegration test presented in Table 2 shows that all brands of paracetamol tablets except brand C conformed to the B.P. (2008) specifications [10]. Brand C showed a significantly ($p \leq 0.01$) high disintegration time

(59 min) in comparison to the innovator product, brand A. There was generally a good balance between the mechanical and release properties of all the brands of paracetamol tablets studied. Even the brands of paracetamol with relatively high crushing strength (>100 N) gave disintegration times of less than 5 min. On the other hand, eight out of the ten brands of ibuprofen tablets disintegrated within the B.P. (2008) limit of 60 min for coated tablets. Brands C and D showed disintegration times of 100 min and 75 min respectively while the innovator brand, A, gave the shortest disintegration time of 4 min.

The results of the assay of paracetamol and ibuprofen content in each brand presented in Table 3, show that most of the brands of paracetamol tablets contained 95 - 105 % of the labelled amount of active ingredient specified except brands E, I and K which showed significantly ($p<0.05$) higher values than the innovator brand A and did not meet pharmacopoeial specifications. Similarly, seven of the ten brands of ibuprofen tablets examined met the B.P. (1998) requirement on the content of the active ingredient. Brands C, D and E showed significantly ($p<0.05$) lower values of ibuprofen content. This could result from the use of inappropriate amount of active ingredient or poor formulation and manufacturing practices.

The dissolution profiles of the various brands of paracetamol and ibuprofen tablets are presented in Figures 1 and 2 respectively while the dissolution parameters are presented in Table 4. The B. P. (1998) specifies that not less than 70% of the labelled amount of paracetamol should be released within 45 min [10]. All brands of paracetamol passed the dissolution test implying that they are likely to exhibit good bioavailability and thus give good therapeutic responses. Brands E, J, M and S showed faster disintegration (< 2 min) but relatively slower dissolution rates in comparison to the innovator brand, A. This shows that the disintegrated particles may have retained the active drug within their hard core and did not release the drug into the dissolution medium.

When all the tablet properties are considered, nine out of the 23 brands of paracetamol tablets did not comply with one or more pharmacopoeial requirements. Only eleven (11) brands of paracetamol showed physicochemical equivalence to the innovator Brand A.

The B.P. (1998) specifies that for ibuprofen tablets, at least 80% of the active drug should be released within 60 min of the *in vitro* dissolution test. The results showed that six (6) brands of ibuprofen tablets passed the dissolution test. Brands D, E and G released less than 80% of the active drug while brand C did not release the active drug after one hour. All four brands were sugar-coated and the drug release from coated tablets has been shown to be affected by the type and thickness of the coating materials. Brand C which was not registered by NAFDAC, was shown to contain 68% of ibuprofen and showed a disintegration time of 100 min. This brand did not comply with all the requirements and thus may not elicit the desired therapeutic effects. It is also noteworthy that Brand D, which was registered by NAFDAC, did not meet the requirements on disintegration and dissolution test. This indicates the need for constant market surveillance to ensure that the quality of drug in the market complies with specifications at all times. There is need for careful evaluation of the various generics manufactured worldwide, to ensure the compliance to official standards.

CONCLUSION

The results showed that 11 brands of generic paracetamol tablets were chemically and physically equivalent to the innovator brand while only 5 ibuprofen brands showed the same behaviour as the innovator brand. The brands of ibuprofen manufactured in India did not compare favourably with the innovator product and thus cannot serve as suitable substitutes. There is need for constant monitoring of locally produced and imported generic drugs in the market in order to ascertain their level of compliance with official standards.

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Table 1: Country of origin of the different brands of paracetamol and ibuprofen tablets evaluated.

PARACETAMOL				IBUPROFEN				
Brand	**NAFDAC registration**	**Country of origin**	**Dosage form**	**Brand**	**NAFDAC registration**	**Country of origin**	**Type of Coating**	**Strength of tablet (mg)**
A	Yes	Nigeria	Caplet	A	Yes	Nigeria	Sugar	400
B	Yes	Nigeria	Tablet	B	Yes	England	Sugar	200
C	Yes	Nigeria	Caplet	C	No	India	Sugar	200
D	Yes	Nigeria	Tablet	D	Yes	India	Sugar	200
E	Yes	Nigeria	Tablet	E	No	India	Sugar	200
F	Yes	Nigeria	Tablet	F	Yes	U.S.A	Sugar	200
G	Yes	Nigeria	Tablet	G	No	India	Sugar	400
H	Yes	Nigeria	Tablet	H	Yes	India	Film	400
I	Yes	Nigeria	Tablet	I	Yes	India	Film	400
J	Yes	Nigeria	Caplet	J	No	India	Sugar	400
K	Yes	Nigeria	Tablet					
L	Yes	Nigeria	Caplet					
M	Yes	Nigeria	Tablet					
N	Yes	Nigeria	Tablet					
O	Yes	Nigeria	Tablet					
P	Yes	Nigeria	Caplet					
Q	Yes	Nigeria	Tablet					
R	Yes	Nigeria	Tablet					
S	Yes	Nigeria	Tablet					
T	Yes	Nigeria	Tablet					
U	Yes	Nigeria	Tablet					
V	Yes	Nigeria	Tablet					
W	Yes	Nigeria	Tablet					

Table 2: **Physicochemical properties of twenty three brands of paracetamol 500 mg tablets and ten brands of ibuprofen (mean ± Standard deviation, n = 3)**

Paracetamol					Ibuprofen		
Brand	**Uniformity of weight (g)**	**Friability (%)**	**Crushing strength (N)**	**Disintegration time (min)**	**Brand**	**Weight (g)**	**Disintegration time (min)**
A	0.56 ±0.02	0.05 ± 0.00	93.35 ± 6.71	4.34 ±1.25	A	0.64±0.01	4.00 ± 0.34
B	0.58 ±0.01	0.64 ± 0.07	63.35 ± 8.86	1.12 ± 0.49	B	0.40±0.01	9.00 ± 0.10
C	0.54 ±0.01	0.18 ± 0.03	110.50 ± 23.92	59.04 ±30.49	C	0.40±0.02	100.00 +2.51*
D	0.58 ±0.00	4.25 ± 0.04*	88.05 ± 5.87	1.42 ± 0.28	D	0.39±0.01	75.00 ± 0.70*
E	0.54 ±0.02	0.41 ± 0.01	110.78 ± 28.34	1.46 ± 0.56	E	0.52±0.02	27.00 ± 0.28
F	0.76 ±0.01	0.09 ± 0.01	124.43 ± 11.23	5.44 ± 0.74	F	0.51±0.02	10.00 ± 0.10
G	0.53 ±0.01	1.15 ± 0.06*	81.98 ±16.58	1.28 ± 0.01	G	1.01±0.01	47.00 ±0.55
H	0.57 ±0.02	0.11 ± 0.00	121.30 ± 2.85	3.05 ± 0.70	H	1.03±0.01	17.00 ±0.42
I	0.56 ±0.01	0.97 ± 0.02	51.78 ±8.37	0.82 ± 0.13	I	0.57±0.01	34.00 ± 0.35
J	0.54 ±0.01	0.02 ± 0.02	113.00 ±16.69	1.23 ± 0.43	J	0.92±0.02	26.00 ± 0.11
K	0.56 ±0.02	0.18 ± 0.00	157.53 ± 10.56	11.12 ± 4.61			
L	0.57 ±0.02	0.19 ± 0.01	137.80 ±11.04	2.76 ± 0.34			
M	0.57 ±0.02	0.31± 0.05	66.48 ± 9.92	1.00 ± 0.42			
N	0.54 ±0.02	1.44± 0.10*	85.70 ± 4.51	4.92 ± 0.55			
O	0.57 ±0.02	0.19± 0.00	112.73 ± 15.43	2.26 ± 0.66			
P	0.52 ±0.02	0.38± 0.02	54.68 ±11.28	2.91 ± 0.70			
Q	0.57 ±0.02	0.77± 0.03	90.95 ± 10.27	1.68 ± 0.43			
R	0.57 ±0.00	0.49± 0.01	79.58 ± 21.96	1.42 ± 0.48			
S	0.54 ±0.04	0.24± 0.03	85.63 ± 15.97	1.51 ± 0.35			
T	0.56 ±0.01	8.00 ±0.11*	52.18 ± 16.91	13.12 ± 6.76			
U	0.55 ±0.01	0.48 ± 0.01	112.60 ± 7.65	1.80 ± 0.50			
V	0.61 ±0.01	0.97 ±0.03	69.10 ±15.66	5.14 ± 0.88			
W	0.61 ±0.01	0.97 ±0.03	69.10 ±15.66	5.14 ± 0.88			

* - Brands that failed to comply with Pharmacopoeial requirements

Table 3: Chemical contents of paracetamol and ibuprofen in the brands of tablets (mean ± standard deviation, n = 3).

Paracetamol		Ibuprofen	
Brand	**%w/w**	**Brand**	**%w/w**
A	102.03 ±2.03	A	100.61±0.02
B	107.35 ±1.47	B	103.66 ±0.04
C	105.30 ±0.59	C	68.97 ±0.04*
D	95.84 ±4.17	D	87.67 ±0.02*
E	112.96 ±2.62*	E	84.25 ±0.04*
F	96.34 ±2.72	F	103.90 ±0.04
G	100.98 ±1.39	G	95.86 ±0.00
H	96.92 ±3.21	H	102.20 ±0.00
I	130.39 ±4.99*	I	103.00 ±0.04
J	95.50 ±1.96	J	101.00 ±0.04
K	138.24 ±2.95*		
L	104.79 ±2.12		
M	104.55 ±0.71		
N	104.81 ±0.76		
O	104.55 ±1.22		
P	104.47 ±0.53		
Q	98.14 ±3.23		
R	103.92 ±2.77		
S	100.20 ±2.72		
T	105.06 ±0.71		
U	95.50 ±1.96		
V	104.55 ±0.71		
W	105.06 ±0.71		

* - Brands that failed to comply with Pharmacopoeial requirements

Table 4: Dissolution parameters of the twenty three brands of paracetamol tablets and ten brands of buprofen tablets (mean ± standard deviation, n = 3).

Paracetamol				Ibuprofen			
Brand	**t_{50} (min)**	**t_{80} (min)**	**% drug released after 45 min**	**Brand**	**t_{50} (min)**	**t_{80} (min)**	**% drug released after 60 min**
A	3.88±0.18	7.65±0.21	101.50±0.71	A	6.00 ± 0.21	10.50 ±0.71	99.63 ±0.30
B	2.75±0.35	5.00±0.00	113.50±4.95	B	9.00 ± 0.35	46.50 ±4.95	94.44 ±2.10
C	17.00±0.71	27.50±0.71	107.44±1.29	C	0.00 ± 0.00	0.00 ±0.00	0.00 ±0.50*
D	2.00±0.00	4.38±0.18	129.50±2.12	D	42.00 ±0.18	72.00 ±2.12	70.19 ±0.22*
E	20.00±4.24	34.50±6.36	97.65±7.40	E	40.00± 2.36	97.65 ±2.40	70.37 ±1.55*
F	4.00±0.00	7.75±0.35	112.00±15.56	F	8.20 ±0.85	69.00 ±1.56	98.15 ±0.71
G	10.00±2.12	26.00±8.49	102.65± 9.33	G	49.50± 4.55	24.00 ± 3.20	61.67 ±1.12*
H	9.50±0.71	24.50±0.71	104.25±0.64	H	14.30 ±0.25	78.25 ± 0.68	92.78 ±0.35
I	9.25±0.35	17.00±1.41	106.56±1.29	I	22.50 ±1.45	38.50 ± 1.10	88.89 ±1.10
J	25.00±7.07	41.00±4.24	87.40±7.09	J	13.00± 2.36	25.00 ±1.20	99.44 ±2.10
K	29.00±8.49	45.00±7.07	82.40±16.09				
L	20.25±8.84	31.00±9.90	106.70±16.50				
M	25.00±1.41	39.75±4.60	88.99 ±8.69				
N	24.50±2.12	38.00±1.41	91.96±4.50				
O	7.00±1.41	13.00±4.24	103.34±3.22				
P	25.00±1.41	41.50±2.12	85.36±4.19				
Q	23.00±7.07	40.00±7.07	86.72±9.33				
R	19.00±4.24	38.00±2.83	89.23±5.80				
S	22.00±5.66	43.50±2.12	81.49±0.64				
T	7.50±0.71	14.50±2.12	115.18±4.50				
U	3.50±0.71	6.50±0.71	113.00±2.83				
V	28.50±4.95	37.25±3.89	81.49±14.81				
W	5.25±1.06	10.25±2.47	118.00±18.38				

* - Brands that failed to comply with Pharmacopoeial requirements

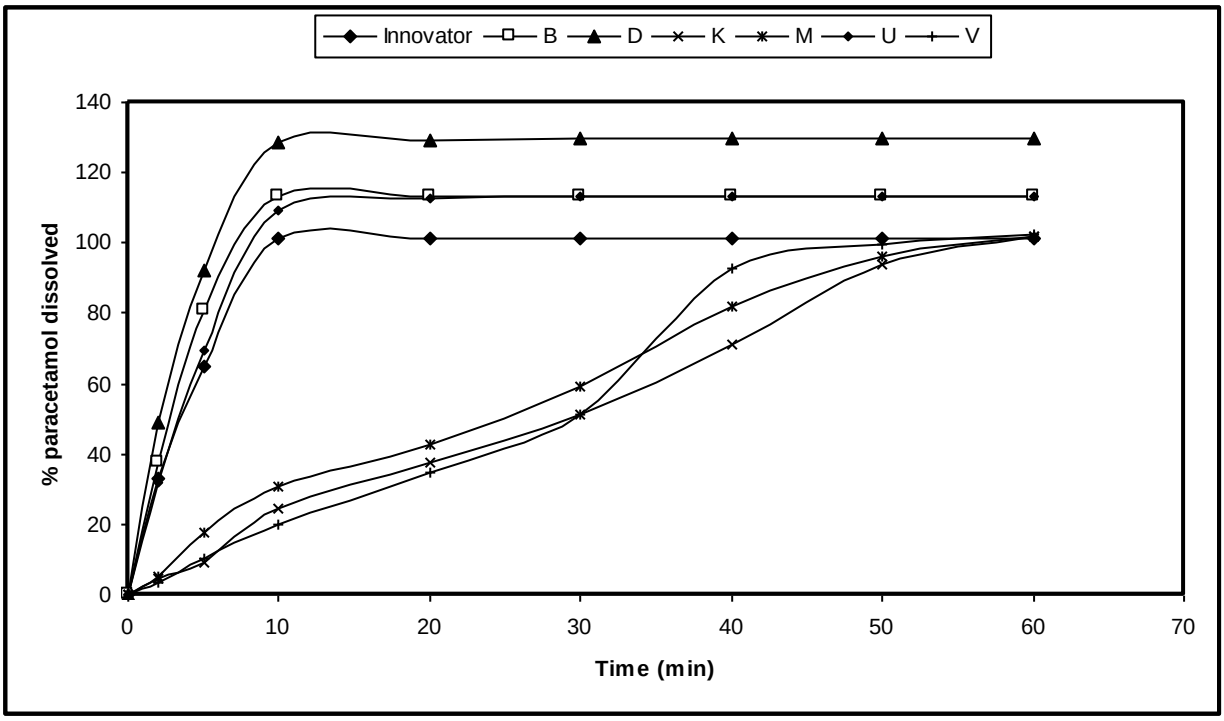

Figure 1: **Dissolution profiles of paracetamol released from innovator brand and brands B, D, K, M, U and V.**

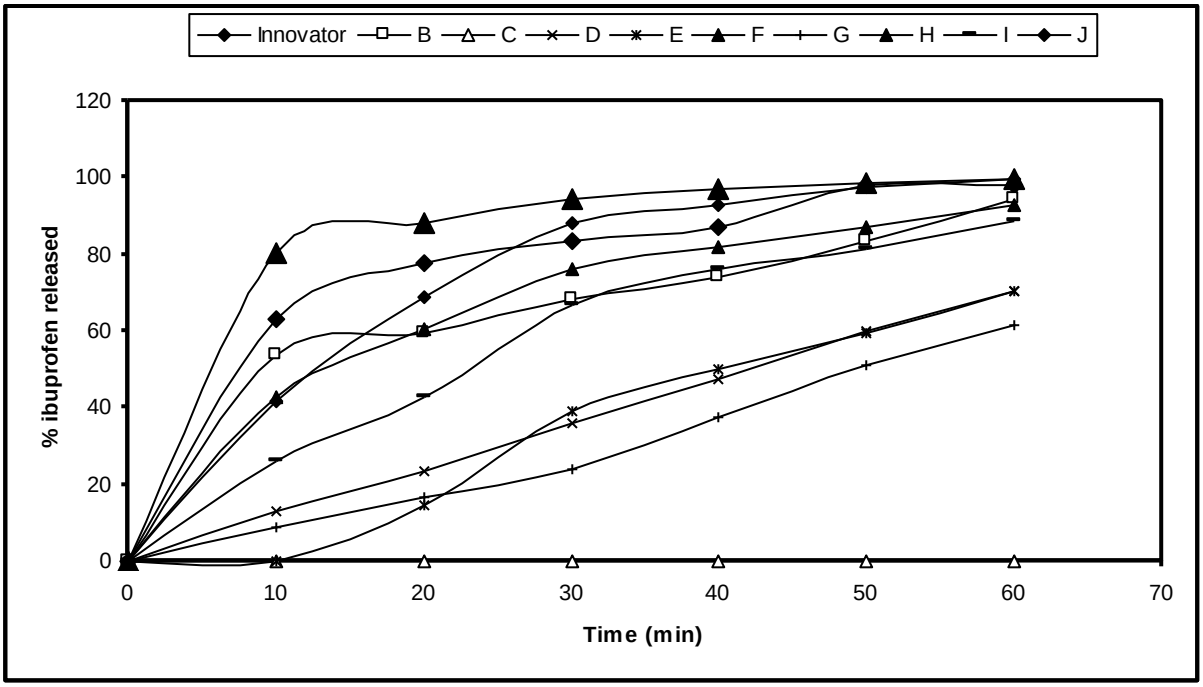

Figure 2: **Dissolution profiles of ibuprofen released from innovator brand and brands B, C, D, E, F, G, H, I and J.**