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ASIAN JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN: 0976-3376

Asian Journal of Science and Technology
Vol. 08, Issue, 06, pp.4936-4943, June, 2017

RESEARCH ARTICLE

COMPARING DISSOLUTION KINETICS WITH TRADITIONAL *IN VITRO* STUDY APPROACH FOR DIFFERENT COMMERCIAL BRANDS OF IBUPROFEN AND PARACETAMOL TABLETS

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ARTICLE INFO

Article History:
Received 04th March, 2017
Received in revised form
11th April, 2017
Accepted 21st May, 2017
Published online 30th June, 2017

Key words:

Ibuprofen, Paracetamol,
Dissolution kinetics,
Dissolution modelling and
Similarity factor.

ABSTRACT

The objective of this study was to compare between the in traditional *in vitro*testing and dissolution kinetics of selected commercial brands of ibuprofen and paracetamol tablets. Ibuprofen (400 mg/Tab) and paracetamol tablets (500 mg/Tab) from the Gulf Cooperation Council (GCC) pharmaceutical market were evaluated for hardness, friability, uniformity of weight, disintegration and dissolution profiles. The study indicated that there is a correlation between the different in vitro tests proposing that tablets with higher hardness value, slow disintegration time will show slower dissolution rate. The results indicated a significance difference between different brands in hardness, disintegration time and dissolution. This difference was more prominent for ibuprofen brands compared to paracetamol brands. The similarity test supported this findings where f2 for all comparisons for the ibuprofen tablets were less than 50. Dissolution kinetics indicated that the first order equation was best equation to give the goodness of fit and therefore to represent the dissolution data. The dissolution kinetics confirmed the difference between different brands of both ibuprofen and paracetamol tablets. The use of dissolution kinetics proved to be a good tool in studying the interchangeability of generic drugs. The study raise a valuable question about the interchangeability of different brands as this in vitro difference may suggest a more serious in vivo difference in their bioavailability.

INTRODUCTION

The most desirable and convenient method of drug administration is the oral route and the most favoured dosage forms include tablets, capsules and solutions because of their ease of manufacture and administration. For example, the oral dosage formulations represent 84% of the sales for the 50 most sold products in the USA and Europe (Abrahamsson, 2003). Ibuprofen is the most commonly used and most frequently prescribed NSAID (Abrahm, 2005 and Bradbury, 2004). It was the first member of propionic acid derivatives to be introduced in 1969 as a better alternative to Aspirin. It is non-selective inhibitor of cyclooxygenase-1(COX-1) and cyclooxygenase-2(COX 2) (Chavez, 2003). 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 (Wahbi, 2005).

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Ibuprofen is supplied as tablets with a potency of 200 to 800 mg (Roberts, 2001). The usual dose is 400 to 800 mg three times a day (Ritter, 1983). It is almost insoluble in water having pKa of 5.3 (Herzfeld, 1983). 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 (Ross, 1990 and Antal, 1986). The drug is more than 99% protein bound, intensively metabolized in the liver and is excreted unchanged (Katzung, 1998). Chemically, Paracetamol (PCM) is N-(4-hydroxyphenyl) ethanamide. It is widely used as analgesic and anti-pyretic (The United States pharmacopeia, 2008). Paracetamol is a non-steroidal anti-inflammatory drug (NSAID) and is prescribed most frequently. It is also commonly used as analgesic and antipyretic agent in the relief of fever, headaches, other minor aches and pains. Paracetamol is generally safe for human use at recommended doses. Overdoses of paracetamol can cause potentially fatal liver damage and in rare individuals, a normal dose can do the same (Daly, 2008). The safety and efficacy of a pharmaceutical dosage form can be guaranteed when its quality is reliable (Chowdary, 2001). The efficacy of pharmaceutical dosage

forms generally depends on their formulation properties, and manufacturing methods, hence it is likely that the quality of dosage form may vary (The Pharmaceutical Codex, 1994 and Yogananda, 2009). Dissolution test is one of the in vitro tests usually employed to assess the quality of oral pharmaceutical solid dosage forms such as tablets and capsules. In vitro dissolution tests can be used to guide formulation developments, identify critical manufacturing variables, monitor formulation quality from batch to batch, predict the in vivo performances and also serve as a surrogate for bioavailability and bioequivalence (Olaniyi, 2001 and Bamigbola, 2009). Different modelling approaches for dissolution of drugs from dosage forms (theories and methods) are well described in the literature (Higuchi, 1963; Wagner, 1969; Kitazawa, 1974; El-Yazigi, 1981 and Abdou, 1989). One of the important outcomes of this modelling approach was the ability to estimate, not only the concentration of dispersed or agglomerated particles, but also the apparent rate constant. The comparison between the dissolution modelling results and indications and those derived from the traditional dissolution representation would be helpful in studying possible variation between generic drugs. 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. 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. Therefore, the aim of this study was to compare the physicochemical parameters with the dissolution modelling of selected commercial brands of ibuprofen and paracetamol tablets from the GCC market.

MATERIALS AND METHODS

Materials

Five commercial ibuprofen (400 mg/Tab): Brand 1-Ibu, Brand 2-Ibu, Brand 3-Ibu, Brand 4-Ibuand Brand 5-Ibu and five commercial paracetamol (500 mg/Tab): Brand 1-Para, Brand 2-Para, Brand 3-Para, brand 4-Para and brand 5-Parawere selected from the GCC market. All batches for every drug were selected to have a close expiry date. Distilled water and phosphate buffer (pH = 7.2) which was prepared according to the USP [12] were used as the dissolution medium for ibuprofen and paracetamol tablets respectively. All chemicals used in the preparation of phosphate buffer were from analytical grade. Standard ibuprofen and paracetamol (Sigma, USA) was provided by Spimaco (Spimaco, KSA). Distilled water was used as the dispersion medium for the disintegration test for both ibuprofen and paracetamol.

Methods

Hardness test: Four tablets for each selected brand of ibuprofen and paracetamol were determined using a TBH 125 Erweka hardness tester (Erweka GmbH, Germany). The load required to break the tablet into two halves was estimated for each tablet. The results collected for ibuprofen and paracetamol will be compared will be compared across different brands.

Friability Test: Twenty tablets from each brand of ibuprofen and paracetamol were subjected to the combined effects of abrasion and shock using a digital Friabilator (Lab Aids, India) rotating at 25 rpm/min dropping and rotating over 4 minutes. The bulk weight of the tablets before and after the rotation was measured and the percentage of loss was calculated across different brands.

Disintegration test: The disintegration test measures the time required for a tablet to disintegrate into particles when in contact with distilled water. The disintegration times of six tablets per brand for both ibuprofen and paracetamol were determined in distilled water at 37 ± 20°C using the VEEGO disintegration apparatus (VEEGO, India) and was determined according to [12]. The average of the disintegration time for 6 tablets was calculated and compared across different brands.

Uniformity of weight: Twenty tablets selected at random was weighed individually and the average weight was calculated to estimate the weight uniformity. The percentage deviation of each tablet from the average weight was calculated and compared across different brands.

Dissolution test: Dissolution studies for ibuprofen commercial tablets were conducted using a PT-DT70 model dissolution apparatus (PharmaTest, Germany). A USP/NF paddle method was used at a rotational speed of 50 rpm. Phosphate buffer (pH = 7.2) which was prepared according to the USP/NF method was used as the dissolution medium for ibuprofen. The dissolution medium (900 mL) was filtered and degassed through a 0.45 μm Millipore membrane (Millipore, Bedford, MA, Ireland) and then equilibrated to 37.0 ± 0.5 °C. Different brands of ibuprofen tablets (n = 4-6) were added to the dissolution apparatus and samples (5 mL) was collected at 5, 10, 20, 30, 45 and 60 minutes time intervals. Ibuprofen concentrations were determined using the UV spectrophotometer. Dissolution studies for paracetamol commercial tablets were done using a PT-DT70 model dissolution apparatus (PharmaTest, Germany). A USP/NF paddle method was used at a rotational speed of 100 rpm. Distilled water was used as the dissolution medium for paracetamol tablets. The dissolution medium (900 mL) was filtered and degassed through a 0.45 μm Millipore membrane (Millipore, Bedford, MA, Ireland) and then equilibrated to 37.0 ± 0.5 °C. Different brands of paracetamol tablets (n = 4-6) were added to the dissolution apparatus and samples (5 mL) was collected at 5, 10, 15, 20, 25 and 30 minutes time intervals. Paracetamol concentrations were determined using the UV spectrophotometer.

UV spectrophotometer analysis: Collected samples from the dissolution at different time intervals will be analyzed at λ=221 nm using an Agilent UV-spectrophotometer (Agilent technologies, USA) with cell path of 10 mm. Ibuprofen and paracetamol concentrations were determined at the maximum absorbance (λ=221 and 249 nm for ibuprofen and paracetamol respectively) using a validated ultraviolet spectrophotometric assay using an Agilent UV-spectrophotometer (Agilent technologies, USA) containing a 10 mm UV flow cells. Calibration curves were established using five concentrations for each of ibuprofen and paracetamol solutions by diluting 1 mL, 2 mL, 3 mL, 4 mL and 5 mL from the stock solution (phosphate buffer with pH=7.2 and distilled water for ibuprofen and paracetamol respectively) into a 100 mL of the

same buffer to a final concentration 0.44 mg/L and 0.60 mg/L for ibuprofen and paracetamol respectively. Beer's Lambert law was used to establish the absorbance-concentration relationship. Curves were linear (R^2> 0.999) and intercepts were not significantly different from zero (P > 0.06) for both drugs.

Comparison between dissolution profiles using the similarity factor f2: Comparison between different dissolution profiles for each of ibuprofen and paracetamol commercial tablets was conducted using the similarity factor (f2) which was determined according to the following equation (Moore, 1996).

$$f2 = 50\ Log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n} W_t\,(R_t - T_t)^2\right]^{0.5} X\ 100\right\}$$

where:

n is the number of sample points
W_t is the optional weight factor
R_t is the reference assay at time point t
T_t is the test assay at time point t

Assessing the goodness of fit for different dissolution kinetics

Dissolution data for both ibuprofen and paracetamol tablets were modelled by SigmaPlot software (version 13.0, Systat Software, Inc., USA) using different equations: the zero-order rate equation, the first-order equation, the Higuchi square root equation and the Hixson- Crowell cube root law. The zero-order rate equation describes the systems where the release rate is independent of the concentration of the dissolved species (The United States Pharmacopeia, 2005). The first-order equation describes the release from systems where dissolution rate is dependent on the concentration of the dissolving species (Baveja, 1988). The Higuchi square root equation, describes the release from systems where the solid drug is dispersed in an insoluble matrix and the rate of drug release is related to the rate of drug diffusion (Najib, 1985). The Hixson- Crowell cube root law describes the release from system where there is a change in surface area and diameter of the particles or tablets (Dortunc, 1997 and Buckton, 1988). Discrimination between these models was determined using the following statistical parameters which were calculated from SigmaPlot software (version 13.0, Systat Software, Inc., USA): the Akaike Information Criterion (AIC) which is an approximately unbiased estimator of the expected Kullback-Leibler information of a fitted model, which can be used as a discrepancy measure between the actual and the fitted model (Gabrielsson, 2000), the F value which gauges the contribution of the independent variables in predicting the dependent variables, and the coefficients of determination, R^2.

Dissolution kinetics for different ibuprofen and paracetamol tablets: The best model which gives the best goodness of fit will be used to model the dissolution data for all ibuprofen and paracetamol tablets. In particular, the dissolution rate constants will be calculated from the estimated model parameters using a SigmaPlot software (version 13.0, Systat Software, Inc., USA) and will be compared among all brands.

RESULTS AND DISCUSSION

Hardness Test: The hardness of the selected commercial ibuprofen and paracetamol tablets was tested and is shown in Figure 1. The instrument was not able to test the hardness of Brand 1-Ibu from the ibuprofen tablets and Brand 3-Para, brand 4-Para, brand 5-Parafrom the paracetamol tablets due to their shape.

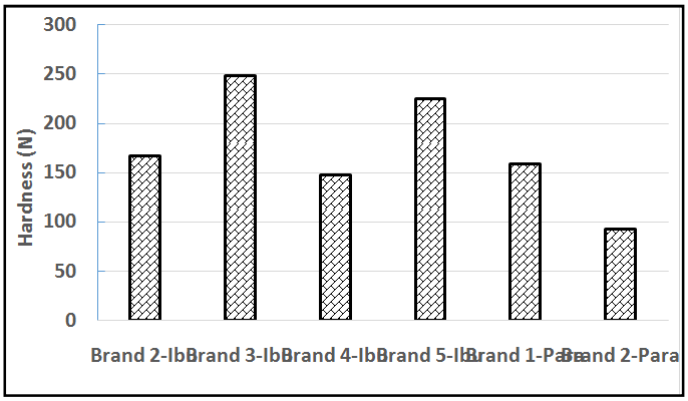

Figure 1. Hardness of the selected commercial ibuprofen and paracetamol brands measured (in N) using a TBH 125 Erweka hardness tester hardness tester

The results for ibuprofen tablets indicated that Brand 4-Ibu required the least force before fracture while Brand 3-Ibu required highest force. Force measurement ranged from 147.9 N to 248.3 N showing a variation in the average force needed to break the tablet. The result of analysis of variance revealed significant difference (p< 0.05) in hardness of all the four brands at 95% confidence interval. The for paracetamol tablets results indicated that Brand 1-Para required a higher force (159.1 N) before fracture compared toBrand 2-Parawhich required a lower force (92.4 N). The result of analysis of variance revealed significant difference (p< 0.05) in hardness between the two brands tested at 95% confidence interval. The difference in hardness for both ibuprofen and paracetamol selected commercial tablets may affect the disintegration and the dissolution of these tablets and therefore may suggest a level of variation in the vivo deposition of the drug from these tablets.

Friability Test: The friability of the selected commercial ibuprofen and paracetamol tablets was tested and is shown in Figure 2. The results indicated that all brands have shown a friability of less than 0.2% w/w indicating no significant difference in these commercial tablets in their friability except for the paracetamol Brand 2-Para where the friability was about 0.84% w/w.

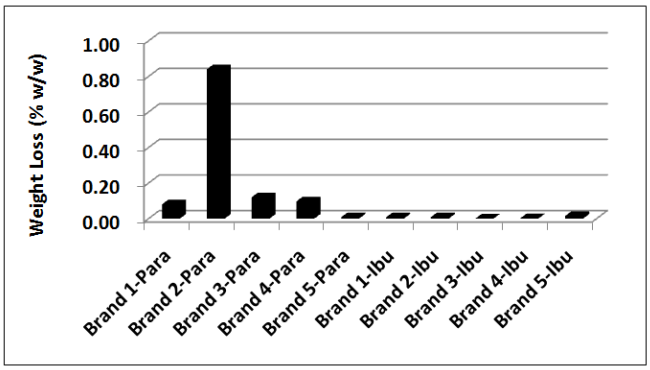

Figure 2. The percentage of weight loss (in % w/w) for all the selected commercial ibuprofen and paracetamol brands after a friability test measured using a digital Friabilator rotating at 25 rpm/min dropping and rotating over 4 minutes

The US Pharmacopoeia [12] states that the friability value of tablets should be less than 1% which mean that the selected commercial ibuprofen and paracetamol tablets conformed to the pharmacopoeia's standard and there was no difference between all brands in friability.

Disintegration Test: The disintegration time of all the selected commercial brands of ibuprofen and paracetamol tablets was conducted and is shown in Figure 3. Disintegration time for different brands of ibuprofen tablet ranged from 1.5 to 10.8 minutes with Brand 5-Ibu had the fastest disintegration time while Brand 3-Ibu had the slowest disintegration time. Disintegration time for different brands of paracetamol tablets ranged from 2.6 to 7.6 minutes with Brand 1-Para had the fastest disintegration time while brand 5-Para had the slowest disintegration time. All tablets passed the USP disintegration test which indicates that the disintegration time should be less than 30 minutes, however, results indicates that there is a significant difference in the disintegration time for different brands of ibuprofen tablet and the different brands of paracetamol tablets ($p< 0.05$). The disintegration time could be the rate-determining step in the process of drug absorption. Therefore, this difference in disintegration time between different brands could reflect other consequences. The type and amount of excipient used in tablet formulation as well as manufacturing process are all known to affect the disintegration.

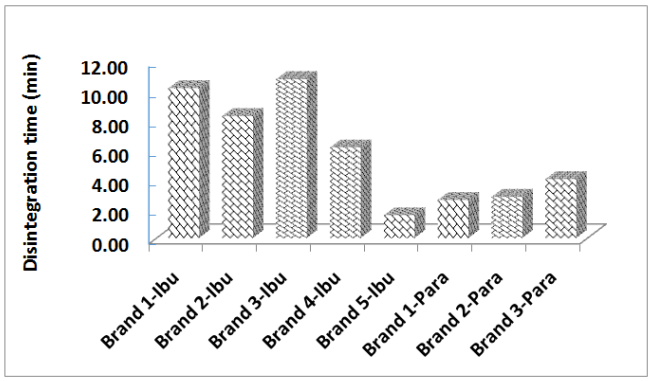

Figure 3. The disintegration time for all the selected commercial ibuprofen and paracetamol brands measured determined in distilled water at 37 ± 0.5°C using a VEEGO disintegration apparatus according to USP method

g) while Brand 2-Ibu had the smallest average weight (0.4990 g). All ibuprofen and paracetamol passed the uniformity test with no tablet outside the upper and the lower weight limits except for the Brand 1-Ibuand Brand 1-Parafrom the ibuprofen and the paracetamol brands respectively having one tablet each with average weight above the upper limit. Therefore all tablets conformed to the US pharmacopoeia indicating no difference across different brands in this test.

Dissolution test: Dissolution studies for four ibuprofen tablets were conducted and the 5-mL samples were collected, filtered, analyzed using the UV spectrophotometer and is shown in Figure 4. The dissolution process for these commercial ibuprofen tablets appeared to follow a biphasic pattern that was characteristic of a rapid dissolution phase at the initial stage of the profile and a slower dissolution phase at the later stage of the profile. The results indicated different dissolution profiles for the commercial ibuprofen brands and in particular, Brand 1-Ibushowed a slow dissolution profile compared to other brands.

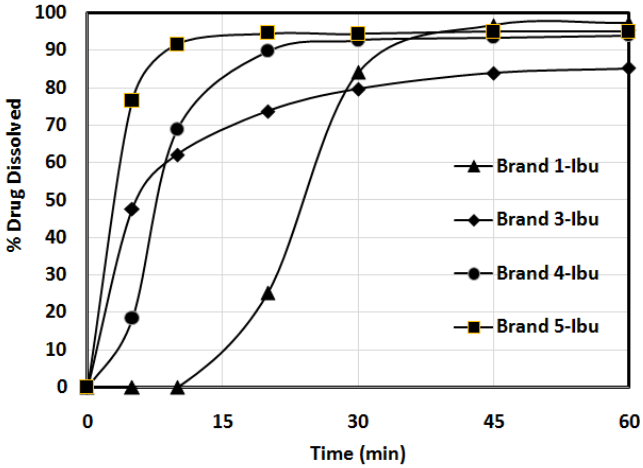

Figure 4: Dissolution profile of selected commercial ibuprofen brands measured in phosphate buffer (pH=7.2) at 37 ± 0.5○C, using a PT-DT70 model dissolution apparatus and the USP paddle method at 50 rpm

For example, the ibuprofen in Brand 1-Ibutablets did not start dissolving except after 10 minutes, then reached 25.2 % w/w after 20 minutes which is the slowest percentage dissolved

Table 1. Uniformity of weight data for all the selected commercial ibuprofen and paracetamol brands

S. No	Tablet Brand	Average Weight (g)	Lower limit (g)	Upper limit (g)	No of Tablets outside limits	Pass/Fail
1	Brand 1-Ibu	1.0171	0.9662	1.0679	1	Pass
2	Brand 2-Ibu	0.4990	0.4740	0.5239	none	Pass
3	Brand 3-Ibu	0.6195	0.5885	0.6504	none	Pass
4	Brand 4-Ibu	0.6632	0.6300	0.6963	none	Pass
5	Brand 5-Ibu	0.6356	0.6038	0.6674	none	Pass
6	Brand 1-Para	0.5616	0.5328	0.5898	1	Pass
7	Brand 2-Para	0.6615	0.6284	0.6943	none	Pass
8	brand 3-Para	0.5540	0.5260	0.5820	none	Pass
9	brand 4-Para	0.6428	0.6107	0.6749	none	Pass
10	brand 5-Para	0.5933	0.5636	0.6229	none	Pass

Uniformity of Weight: The uniformity of weight test for all brands of ibuprofen and paracetamol tablets was conducted and is shown in Table 1. There was a difference in the average mean weight of ibuprofen compared to less variation in the average weight of paracetamol due to different excipients. For example, Brand 1-Ibuhad the largest average weight (1.0170

compared to 73.8, 89.8 and 94.5 % w/w for Brand 3-Ibu, Brand 4-Ibu and Brand 5-Iburespectively.After 30 minutes of dissolution, the percentage of ibuprofen dissolved was 79.7, 84.2, 92.8 and 94.4 % w/w for Brand 3-Ibu, Brand 1-Ibu, Brand 4-Ibu and Brand 5-Ibu respectively indicating the start of a plateau of the dissolution except for Brand 5-Ibu where its

plateau was reached after 15 minutes of dissolution indicating the fastest dissolution compared to other brands. Dissolution studies for four paracetamol tablets were conducted and the 5-mL samples were collected, filtered, analyzed using the UV spectrophotometer and is shown in Figure 5. The dissolution process for these commercial paracetamol tablets appeared to follow a biphasic pattern that was characteristic of a rapid dissolution phase at the initial stage of the profile and a slower dissolution phase at the later stage of the profile.

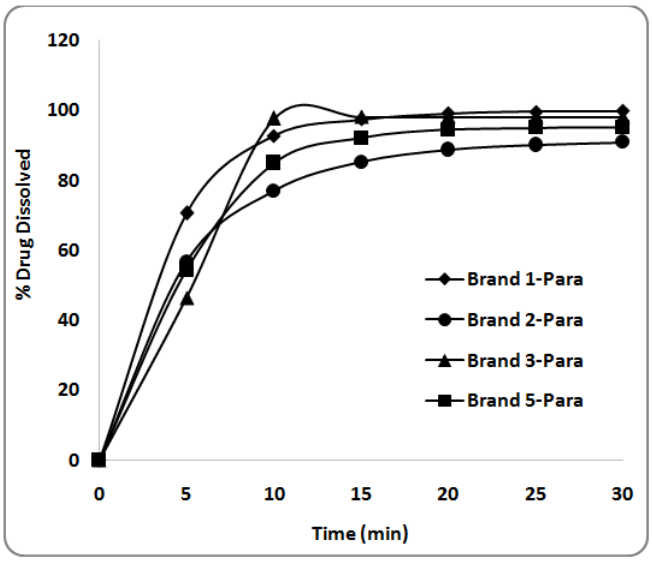

Figure 5. Dissolution profile of selected commercial paracetamol brands measured in distilled water at 37 ± 0.5°C, using a PT-DT70 model dissolution apparatus and the USP paddle method at 50 rpm

drug dissolved at the early part of the dissolution profile while this became less prominent at the last part of the dissolution profile, however, it can be noted that the difference in the percentage of dissolved drug was less in the case of paracetamol compared to ibuprofen tablets as it is more prominent.

Comparison between dissolution profiles using the similarity factor (f2): Similarity factor (f2) was calculated for every pair of brands for the commercial ibuprofen tablets and is shown in Figure 6. The similarity factor (f2) for all the pairs ranged from 14.1 to 41.7 indicating different dissolution profiles and that they were not lyoequivalent (if f2 < 50, then dissolution profiles are different) (Moore, 1996).

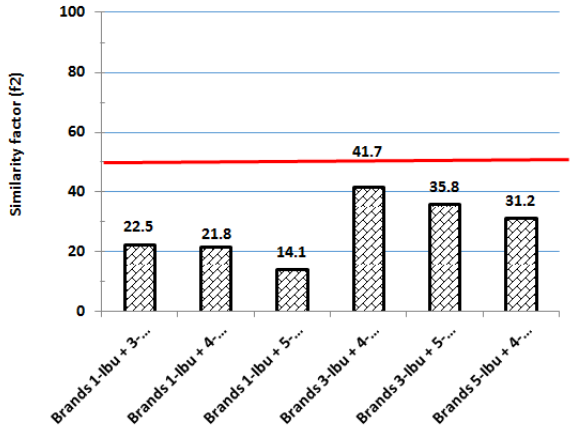

Figure 6: Similarity factor (f2) calculated for all the dissolution profiles of the selected commercial ibuprofen brands where the horizontal line at f2=50 represents the minimum value for similar dissolution profiles

Table 2. Statistical parameters used to assess the goodness of fit of the different equations for Ibuprofen tablets estimated using SigmaPlot 13.0 software

Brands	Statistical Parameters	Zero Order Equation	First Order Equation	Higuchi Equation	Hixson-Crowell Equation
Brand 1-Ibu	R^2	0.8752	0.9225	0.8115	0.9145
	F	35.0527	59.47	21.52	53.50
	AIC	52.3358	-9.6394	55.2217	1.5425
Brand 3-Ibu	R^2	0.6018	0.8248	0.8572	0.7541
	F	7.56	23.55	30.01	15.34
	AIC	54.2524	-16.0849	47.076	-0.2982
Brand 4-Ibu	R^2	0.6088	0.7702	0.8164	0.7150
	F	7.78	16.76	22.24	12.55
	AIC	57.887	-6.2866	52.59	6.8472
Brand 5-Ibu	R^2	0.3398	0.5340	0.6200	0.4605
	F	2.57	5.73	8.16	4.27
	AIC	59.8329	-2.3305	55.9659	9.8039

The results indicated difference in the percentage of paracetamol dissolved after 5 and 10 minutes across different brands but less variation after 15 minutes where the dissolution is approaching a plateau. For example, about 76.9% w/w of the paracetamol was dissolved at 10 minutes for the Brand 2-Para while it was 84.9% w/w, 92.6% w/w and 97.6% w/w for Brand 5-Para, Brand 1-Para and Brand 3-Para respectively. After 20 minutes of dissolution, the percentage of paracetamol dissolved was 88.7, 94.3, 98.0 and 99.1 % w/w for Brand 2-Para, brand 5-Para, brand 3-Para and Brand 1-Para respectively indicating the start of a plateau of the dissolution except for Brand 2-Para where its plateau was not reached within 30 minutes indicating the slowest dissolution compared to other brands. Although both ibuprofen and paracetamol commercial tablets showed difference in the percentage of

Similarity factor (f2) was calculated for every pair of brands for the commercial paracetamol tablets and is shown in Figure 7. The similarity factor (f2) for all the pairs ranged from 47.2 to 63.8. The f2 similarity values were 47.2 and 47.6 for brand 3-Para-Brand 2-Paraand the Brand 1-Para-Brand 2-Para pairs of paracetamol tablets indicating that they were not lyoequivalent(f2 < 50) compared to a similarity value of 51.4, 55.5, 59.3 and 63.8 for the following paracetamol pairs: Brand 1-Para-Brand 3-Para, Brand 1-Para-Brand 5-Para, Brand 5-Para-Brand 3-Para and Brand 5-Para-Brand 2-Para respectively indicating a similar dissolution profile (f2 > 50). The similarity factor results for both ibuprofen and paracetamol commercial tablets was consistent to what was seen in the previous section (3.5) as the results indicated a significant prominent difference in the dissolution profiles of

ibuprofen commercial tablets while in the case of paracetamol tablets, the difference in dissolution profile was not the case for all brands.

using the Higuchi equation for Brand 4-Ibu. Having smaller AIC values, higher F and R^2 values indicate that the first order equation is the best model among all selected models to

Table 3.Statistical parameters used to assess the goodness of fit of the different equations for paracetamol tablets estimated using SigmaPlot 13.0 software

Brands	Estimated parameters	Zero Order Equation	First Order Equation	Higuchi Equation	Hixson-Crowell Equation
Brand 1-Para	R^2	0.6923	0.9748	0.8474	0.8554
	F	7.03	193.30	27.76	29.57
	AIC	57.2176	-13.494	50.2077	4.7644
Brand 2-Para	R^2	0.6738	0.8894	0.9073	0.8233
	F	10.33	23.29	48.96	23.29
	AIC	54.0365	-15.8527	45.2264	-0.1704
Brand 3-Para	R^2	0.6237	0.6658	0.8439	0.6564
	F	8.29	9.96	27.04	9.55
	AIC	57.3111	1.3988	51.1505	10.6619
Brand 5-Para	R^2	0.6631	0.8691	0.8942	0.8058
	F	9.8421	33.20	42.28	20.75
	AIC	55.3100	-10.571	47.2	3.2079

***Assessing the goodness of fit for different dissolution kinetics*:** Dissolution profiles data for different ibuprofen brands were modelled using the four equations (zero order, first order, Higuchi and Hixson-Crowell Equations) from SigmaPlot software (version 13.0, Systat Software, Inc., USA). The estimated statistical parameters to assess the goodness of fit for the different parameters for every equation are shown in Table 2. Results indicated that the zero order equation and the Hixson-Crowell equations produced smaller F and R^2 values and higher AIC values compared with the first order and the Higuchi equations for all ibuprofen tablets.

represent the dissolution data of all the ibuprofen tablet brands. In the same way, dissolution profiles data for different paracetamol tablet brands were modelled using the four equations (zero order, first order, Higuchi and Hixson-Crowell Equations) from SigmaPlot software (version 13.0, Systat Software, Inc., USA). The estimated statistical parameters to assess the goodness of fit for the different parameters for every equation are shown in Table 3. Results indicated that the zero order equation produced smaller F and R^2 values and higher AIC values compared with the first order, the Hixson-Crowell and the Higuchi equations for all paracetamol tablets.

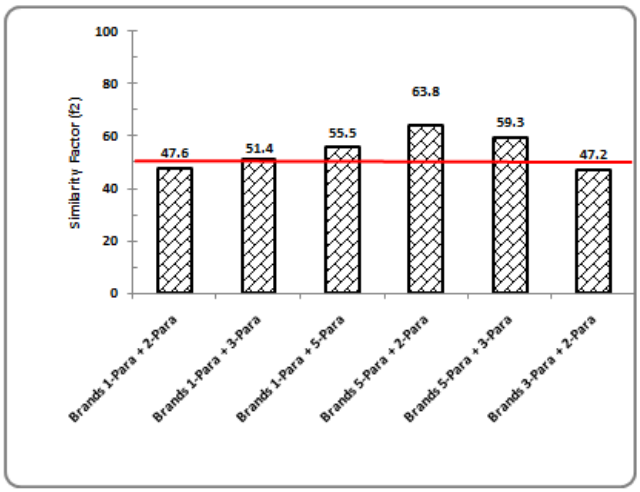

Figure 7. Similarity factor (f2) calculated for all the dissolution profiles of the selected commercial paracetamol brands where the horizontal line at f2=50 represents the minimum value for similar dissolution profiles

Results indicated that both the first order and the Higuchi equations produced larger F and R^2 values, however, modelling the dissolution data using the first order equation produced smaller always AIC values for all ibuprofen tablets. For example, the AIC was -9.6394 using the first order equation compared with 55.2217 using the Higuchi equation for Brand 1-Ibu, -16.0849 using the first order equation compared with 47.076 using the Higuchi equation for Brand 3-Ibu, -2.3305 using the first order equation compared with 55.9659 using the Higuchi equation for Brand 5-Ibu and -6.2866 using the first order equation compared with 52.59

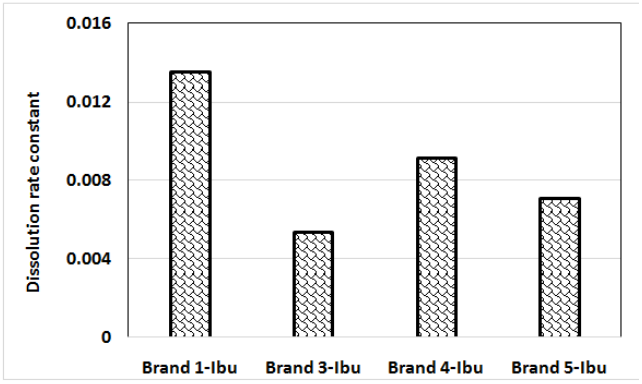

Figure 8. Dissolution rate constants for all the dissolution profiles of the selected commercial ibuprofen brands estimated using the first order equation with SigmaPlot 13.0 software

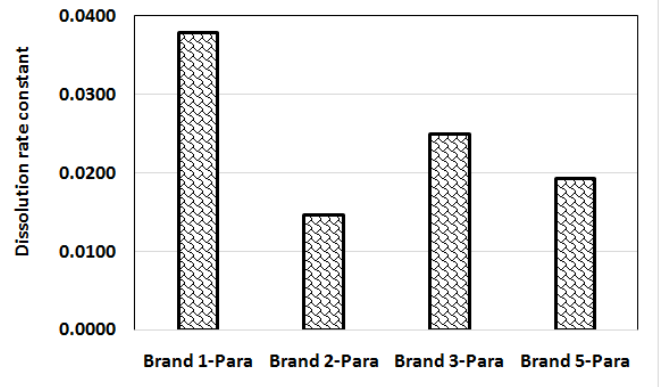

Figure 9. Dissolution rate constants for all the dissolution profiles of the selected commercial paracetamol brands estimated using the first order equation with SigmaPlot 13.0 software

The F and R^2 values resulted in conflicting results between the first order, the Hixson-Crowell and the Higuchi equations, however, modelling the dissolution data using the first order equation produced always smaller AIC values for all paracetamol tablets. For example, the AIC was -10.571using the first order equation compared with 47.2 using the Higuchi equation for Brand 5-Para, -13.494 using the first order equation compared with 50.2077 using the Higuchi equation for Brand 1-Para, 1.3988 using the first order equation compared with 51.1505using the Higuchi equation for Brand 3-Para and -15.8527 using the first order equation compared with 45.2264 using the Higuchi equation for Brand 2-Para. Having smaller AIC values and reasonably higher F and R^2 values indicate that the first order equation can be selected as the best model among all selected models to represent the dissolution data of all the paracetamol tablet brands.

Estimated dissolution rate constants from the modelled data: In the previous section, the first order equation was found to give the best goodness of fit for the dissolution data. Therefore, it was used to calculate the dissolution rate constants through the use of the SigmaPlot software (version 13.0, Systat Software, Inc., USA)by dividing the estimated slopes of the linear log equations by (-2.303). Dissolution rate constants were calculated and are shown in Figure 8 and 9 for ibuprofen and paracetamol tablets respectively. The calculated dissolution rate constants showed variation within the different brands of ibuprofen and paracetamol tablets. The results indicated that Brand 1-Ibuhad the largest dissolution rate constant (0.0135^{-1}) among the ibuprofen tablets while Brand 1-Parahad the largest dissolution rate constant (0.0379 min^{-1}) among the paracetamol tablets. Variation in the drug dissolution rate constants seen among ibuprofen tablets and paracetamol tablets was confirmed by the use of modelling.

Calculating the dissolution rate constant from the estimated parameters using the first order equation modelling for ibuprofen tablets gave conflicting results to the apparent trend seen by the traditional representation of dissolution (ie. % dissolved per time) as seen in Figure 4 for ibuprofen tablets. Results from Figure 4 indicated that Brand 3-Ibu was the slowest brand in dissolution rate while Brand 5-Ibuwas the fastest, while the modelling calculation of the dissolution rate constants indicated that Brand 1-Ibuwas the fastest brand in dissolution rate while Brand 3-Ibuwas the slowest brand in dissolution (in consistence with the traditional representation of dissolution data). However, the calculated dissolution rate constants from the estimated parameters using the first order equation for paracetamol tablets gave results consistent with the trend seen by the traditional representation of dissolution (ie. % dissolved per time) as seen in Figure 5 for paracetamol tablets. Figure 5 indicated that Brand 1-Para was the fastest brand in dissolution rate while Brand 2-Parawas the slowest (after 10 minutes), in consistence with the modelling calculation of the dissolution rate constants indicating that Brand 1-Para was the fastest brand in dissolution rate while Brand 2-Parawas the slowest brand in dissolution. The conflicting results in the ibuprofen tablets could be explained by different directions. One explanation is the poor goodness of the fit and the possibility that the data could be modelled using another equation for the ibuprofen tablets. Another explanation could be that different parts of the dissolution data could have different dissolution rate and therefore having one dissolution rate constant for the whole dissolution could not be appropriate. Having only seven data collection points over the dissolution could add up to the two explanations. The comparison between traditional dissolution representation and that extracted from the modelling needs more investigation considering these explanations and using different drugs.

Conclusion

Selected brands of ibuprofen and paracetamol tablets were evaluated in terms of hardness, friability, uniformity of weight, disintegration and dissolution and whether they can be freely interchanged. The results indicated a correlation between the hardness test, disintegration test and the dissolution test results for the ibuprofen tablet brands. For example, Brand 3-Ibuhadthe highest hardness of 258.1 N, a slow disintegration and dissolution rate. A similar correlation between the disintegration and dissolution results can be applied to the paracetamol brands where Brand 2-Para had a slow disintegration and dissolution profile but lower hardness value. This was consistent with its friability where Brand 2-Para had shown a high percentage of loss in weight after the friability test (0.8% w/w). More importantly, the hardness test, disintegration time test, and dissolution study indicated a significant difference between the different brands under study. This difference was consistent in all tests conducted (except for the friability) and in addition was more prominent in the case of ibuprofen brands compared to the selected paracetamol brands. In particular, dissolution study indicated a variation in the in vitro dissolution profiles for the different four commercial ibuprofen brands. This was confirmed by the similarity factor f2results where all f2 comparison values were below 50 while most of the comparisons were above 50 for the paracetamol tablets (except between Brand 1-Para-Brand 2-Para and Brand 3-Para-Brand 2-Parapairs of tablets).

Statistical analysis of the modelled dissolution data for both ibuprofen and paracetamol tablets indicated that the first order equation could represent the best goodness of fit compared with the zero order, the Higuchi and the Hixson-Crowell equations. The modelled data provided evidence for a difference in dissolution rate constants for both ibuprofen and paracetamol tablets. However, care should be taken to correlate direct relationship between the calculated dissolution rate constants from the modelled estimated parameters and the traditional representation of dissolution data due to possible error in applying one model for all brands and the possibility of multiple dissolution rate constants over different parts of the dissolution. The use of modelling of dissolution data proved to be a useful tool in testing any difference among generic brands of ibuprofen and paracetamol. The difference in the dissolution profile may have more serious in vivo consequences and in particular for drugs which are poorly-water soluble drugs where the dissolution could be the determining factor of the drug bioavailability. The results of this study which contribute to the post market surveillance, raise a question about the interchangeability between different brands of commonly used drugs such as the ibuprofen. The difference in the in vitro evaluation between the original brand and their generic counterparts and among generics themselves suggest that regulatory bodies in the GCC region should adopt more rigorous regime to ensure less variability between different brands which will lead safe and efficient interchangeability between these brands.

Acknowledgement

Authors would like to acknowledge Spimaco for providing ibuprofen and paracetamolpure active ingredients as well as providing their labs to conduct the dissolution study.

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