

Assessment of Dissolution Performance of Immediate Release Ibuprofen Products: Screening of Products Available on the Palestinian Market

Naser Shraim ^{*1}, Tasneem Hamawi ², Sawsan Hummaid ², Bara'ah Adeli ², Asma Radwan ¹, Fairouz Abu Shaikha ¹

¹Department of Pharmacy, College of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine. ²Pharmacy program, College of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine

*Corresponding author: shraim.n@gmail.com

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Abstract

Dissolution testing has emerged as an essential quality-control tool to monitor batch-to-batch consistency during drug development. The aim of this study was to assess the dissolution performance of drug products containing ibuprofen as active pharmaceutical ingredient available on the Palestinian market. Ibuprofen is one of the most widely used analgesic, antipyretic and anti-inflammatory over the counter (OTC) medication. Dissolution tests were performed using simulated intestinal fluid (pH 7.2) in accordance to the specifications in the United States Pharmacopoeia (USP). *In vitro* dissolution profiles of nine immediate-release ibuprofen formulations (A-I) were evaluated and compared. Percent of drug released was determined by spectrophotometric method. Comparison of dissolution profiles was done using similarity (f_2) and difference (f_1) factors. In the present work dissolution in basic media (7.2 phosphate buffer) was tested using a rotating paddle apparatus. The results obtained showed that the average drug release after 60 minutes of products A-I exceeded 90%. All of the tested products passed the dissolution test and met specifications in the USP. The results were above the Q value = $80 + 5\%$ which is recommended in the USP. Similarity and difference factors -when applied for both dosage forms tablets and liquid capsules - showed that there were no significant differences of all tested products compared to branded version of ibuprofen except product A (local tablet dosage form) compared to its counterpart brand. Pertaining pharmacoeconomic aspects, our data revealed that customer prices of ibuprofen products varied widely.

Keywords :Dissolution, Quality control, Ibuprofen, Palestine

Introduction:

The quality assessment of pharmaceutical products is a basic responsibility of Quality control (QC) unit. QC is concerned with the finished product and any signs of defects or deviations from set of standards in pharmacopoeias (1, 2). Dissolution testing is considered as a valuable QC tool to monitor batch-to-batch consistency during drug development. However; dissolution testing can be used for optimization of formulations and monitoring drug stability over time (3, 4). It is also useful in providing pharmaceutical product quality information following post-approval changes to the product such as changes in formulation, changes to the manufacturing process or the site of manufacture, and in process scale-up(3, 5). Nowadays, the use of generic

medicines has increased and many countries which have enforced rules to provide safe, effective, and good quality medications for their population (1, 6). Besides, dissolution testing is also employed as an alternative tool for the assessment of *in vivo* bioequivalence. *In vivo* bioequivalence studies are conducted in healthy volunteers. These studies are costly, time consuming and involve subjecting healthy volunteers to risks of side effects. However, today regulatory agencies like the United State Food and Drug Administration (FDA) and the European Medicines Agency (EMA) allow the replacement (waiver) of *in vivo* bioequivalence studies by *in vitro* dissolution testing especially for highly soluble drug substances (i.e., Class I and III). Accordingly, the *in vitro* dissolution test is used to predict the *in vivo* absorption of the

drug product, by means of *in vivo/in vitro* correlations (IVIVC)(7-10).

Ibuprofen (IBP) is a non-steroidal drug derived from propionic acid and is widely used as an anti-inflammatory analgesic, and has been approved as a nonprescription drug since 1983(11). It has a pK_a value of 4.5 and is poorly soluble in water ($0.078 \mu\text{g/mL}$)(12-14). According to the Biopharmaceutical Classification System (BCS), IBP had been classified as a class II drug (low solubility and high permeability); therefore, drug dissolution may be a rate limiting step in the drug absorption process (15). IBP is well absorbed orally; peak serum concentrations are attained in 1 to 2 hours after oral administration. It is rapidly bio-transformed with an elimination half-life of 1.8 to 2 hours. The drug is almost entirely eliminated by hepatic metabolism within 24 hours after the last dose(16).

Many studies and reports were published in the literature assessing and comparing the *in vitro* QC tests and particularly dissolution performance of pharmaceuticals in Palestine and worldwide (1, 17-20). To the best of our

knowledge there were no previous studies conducted in Palestine evaluating the *in vitro* dissolution performance of solid dosage forms containing IBP. Therefore, the main objective of the current study was to assess the dissolution performance of solid oral dosage forms containing IBP as active pharmaceutical ingredient (API) available on the Palestinian market. In addition, the current work aimed to compare the dissolution profiles and the percentage of released IBP over specified time points of these products.

Methods and Materials

Chemicals:

Potassium dihydrogen phosphate, sodium hydroxide, and IBP powder were obtained from An-Najah National university laboratory central stores. The tablets and liquid capsules were obtained from the local commercial pharmacy as any patient can buy them from any pharmacy. Tablets have strength of 400 mg, while liquid capsules strengths are 200 and 400 mg. Table 1 reports a list of all tested products.

Table(1): A list of the tested products available on the Palestinian market.

Product	Dosage form	Manufacture	Price*	Strength(mg)	Expiry date
A	Tablet	Local	1.43	400	2/17
B	Tablet	Israel	1.43	400	9/15
C	Tablet	Local	1.43	400	1/17
D	Tablet	Local	1.43	400	3/19
E	Tablet	Israel	0.71	400	12/17
F	Tablet	Imported***	**	200	1/16
G	Liquid capsule	Imported	5.57	400	1/16
H	Liquid capsule	Local	1.71	400	1/17
I	Liquid capsule	Imported***	4.57	200	11/15

* USD \$ /10unit, ** data are not available, *** reference product (brand)

Methods

Spectrophotometric analysis of IBP: All UV spectrophotometric measurements were performed using a UV-vis spectrophotometer (Jenway7315, Staffordshire, UK). Determination of the percentage of dissolved IBP was achieved based on the Beer's plot.

Calibration curves were constructed for buffer medium in standard solutions. A stock solution of IBP was prepared by mixing 25 mg of IBP powder with 0.5 – 1 mL acetone and sufficient quantity of distilled water to make the solution 250 mL. The working standard solutions of serial concentrations (i.e., 2, 5, 10, 15, 20 and 25 $\mu\text{g/mL}$) were

made by diluting the stock solution of IBP with phosphate buffer. Five calibration curves were made using linear regression of the absorbance at $\lambda_{\max} = 221$ nm versus the nominal concentration.

Dissolution testing

In general the United States Pharmacopoeia (USP) 2014 procedures were employed for dissolution testing of the various products under simulated intestinal fluid (SIF) i.e., buffer pH 7.2. Adjustment of pH values were made using (Jenway 3520) pH meter that was previously calibrated appropriately. Using a rotating paddle apparatus Dissolution tester (Hsiang Tai Machinery Industry Co Ltd, Taiwan). Type II dissolution apparatus was employed and the paddles were rotated at 50 rotations per minute (rpm). Samples were withdrawn, filtered using a 1.0 μm polyethylene micro-membrane filter, diluted as appropriate and measured at 221nm. Sampling points were set at 5, 10, 15, 20, 30, 45 and 60 minutes. Compendial specifications in the USP sets the QC acceptance criterion for dissolution testing when tolerances release not less than 85% of the labeled quantity of IBP in 60 minutes (Q value = 80 + 5%) in all tested products.

Rupture time

Rupture time test for gelatin capsule considered an easy way for qualifying and quantifying the film strength of the gel capsule. It gives indications on the dissolution rate, it is also a straightforward

descriptive test designed to measure critical points of physical failure in the sample. Meaningful test data can be used for new product development, quality control and production efficiency. Liquid capsules contain drug materials carried by liquid vehicle encapsulated with a gelatin shell. The shell should disintegrate in the presence of fluid so that the contents are released. The contents of soft capsules are usually solution or suspension of the active ingredients in non-aqueous liquids. Once the shell ruptured, drug release occur, in which, drug release percentage jumps for zero or low drug release to more than 60% drug release, giving its peak. Dissolution of the capsule shell normally starts at the ends of the capsule, tiny holes may be formed which continually grow, causing rupture of the gelatin capsule (21, 22).

Dissolution comparison

The difference factor (f_1) is proportional to the average difference between the two profiles, whereas f_2 (similarity factor) is inversely proportional to the average squared difference between the two profiles (23, 24). According to FDA guide, generally f_1 values up to 15 (0-15) and f_2 values greater than 50 (50-100) ensure sameness or equivalence of the two curves (25). The values of f_1 and f_2 factors for test products versus reference were calculated from the means of percent dissolved at each time point according to equations provided below (26).

$$f_2 = 50 \cdot \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

$$f_1 = \left\{ \left[\sum_{t=1}^n |R_t - T_t| \right] / \left[\sum_{t=1}^n R_t \right] \right\} \times 100$$

Where R_t and T_t are the percentages of drug dissolved at each time point for the reference and test products, respectively. An f_1 value greater than 15 indicates non-similarity, and an f_2 value greater than 50 indicates significant similarity between the two analyzed products

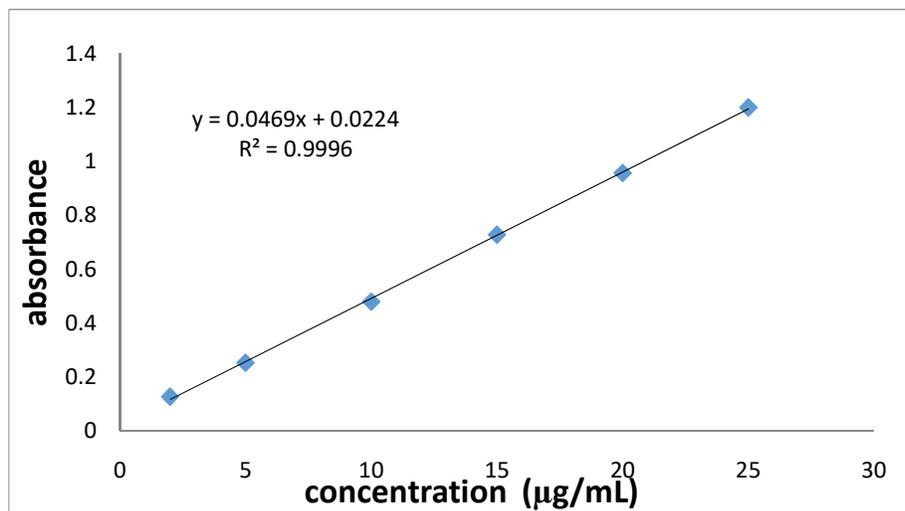
Results and Discussion

The work described in this study focused on the evaluation of the *in vitro* dissolution profiles of nine local pharmaceuticals containing IBP as API that are commercially available on the Palestinian market. These drug products are being formulated as tablets, caplet, and liquid capsule. The dissolution tests were performed using SIF (pH 7.2) in accordance to specifications in the USP (2).

There is an increasing need to evaluate the *in vitro* performance of available products containing IBP since it is among the most commonly used medicines as a pain killer. Dissolution testing of drug products plays an important role as a QC tool to monitor batch-to-batch consistency of drug release from a dosage form and as an *in vitro* surrogate for *in vivo* performance (27).

Linearity range

A linear relationship within the studied concentration range (2-25 $\mu\text{g/mL}$) was obtained. The linear regression equation of the calibration curves made of standard solutions in phosphate buffer solution is presented in Figure 1.

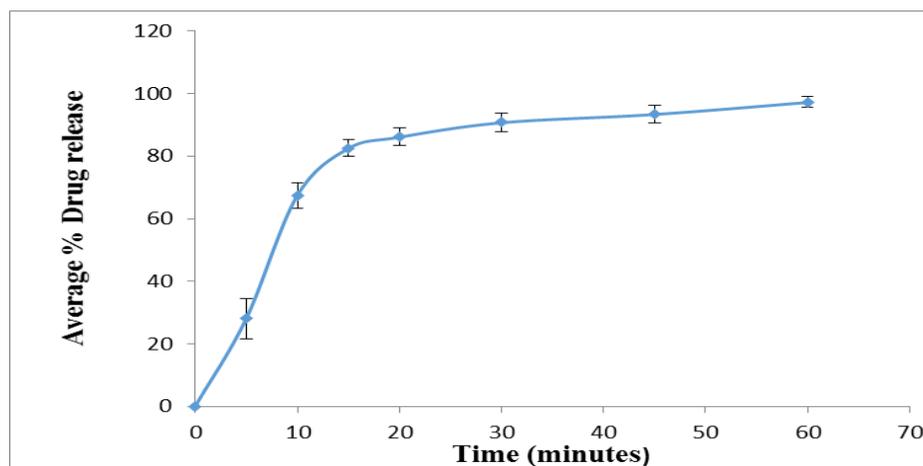


Figure(1): Average calibration curve in phosphate buffer solution.

Dissolution testing

As expected, all tested products (A-I) met pharmacopeial specifications in the first stage (S1). The USP guidelines require *in vitro* dissolution such that no unit is less than 85% (Tolerances, Q value = 80% of the labeled amount) dissolved within 60 min in 900 mL phosphate buffer pH 7.2 under dissolution

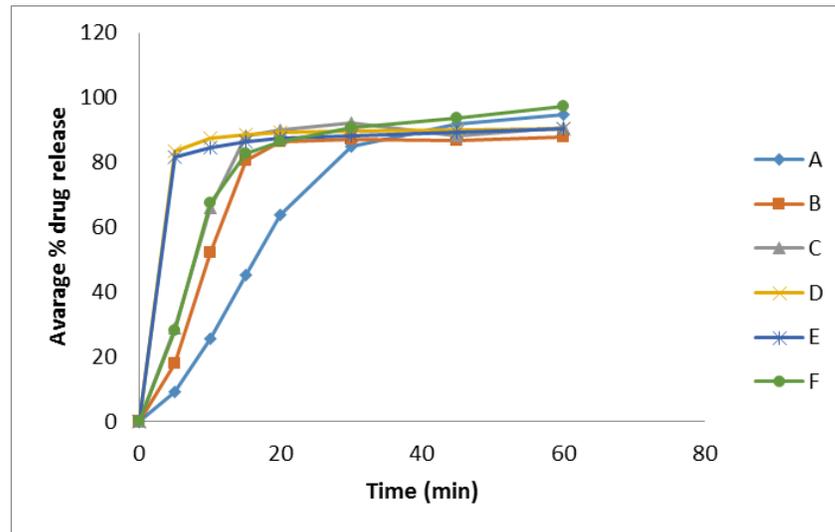
conditions described previously. In addition, all pharmaceutical products were subjected to dissolution testing and the average drug release percentage was determined after 5, 10, 15, 20, 30, 45 and 60 min. Figure 2 exemplified the % drug released –time profile of a selected product.



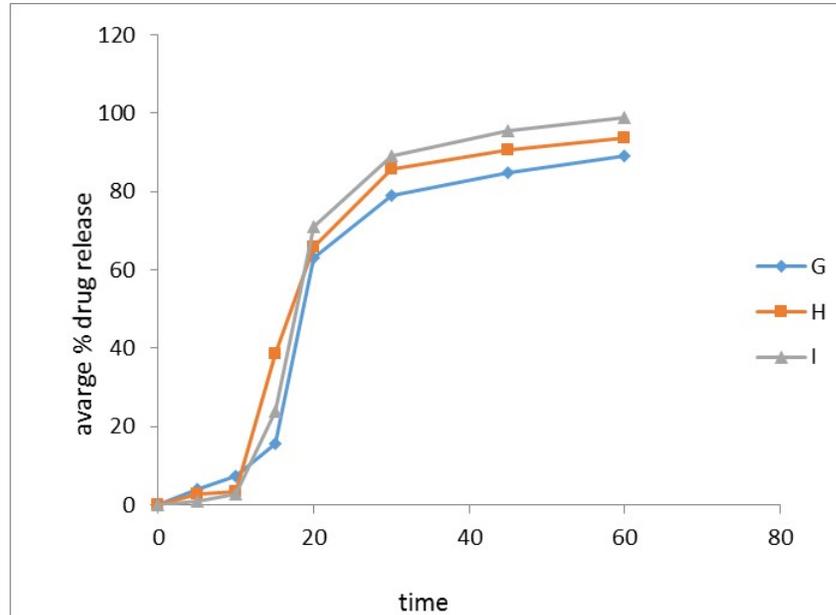
Figure(2): A representative drug release profile of product F, the data are represented by average drug release with SD.

Our data showed that there was a clear evident that product D and product E have the shortest dissolution time with fastest pattern of drug release, in which both products released more than 80% of the labeled drug substance within 5 min. and attained 95% after 60 min. Whereas product B, product C and product F required 15 min

to release about 85% of the drug of interest. However, product A reached the 80% within 30 min from starting the dissolution testing. Figure 3 and Figure 4 demonstrated the average drug release-dissolution profiles for tablet dosage forms (A-F) and liquid capsule (G-I) products respectively.



Figure(3): Average drug release of tablet dosage form A - F.



Figure(4): Average drug release of liquid capsule dosage forms G, H and I.

The variations in the dissolution time for the same drug material of release during the first 60 min. time interval refers to many factors. Some are within the dosage form

manufacturing: milling, mixing and compression force. These factors highly affect the dissolution time and rate. Tablets were prepared by direct compression method,

in the first step, drug was milled in ball mill for specific time, and then it is mixed with other excipients using double cone blender for certain time, the blended powder was directly compressed using rotary tablet punching Machine. Each step can affect the dissolution rate and drug release. Milling time has negative effect on dissolution, as the milling time increased, dissolution time decreased; due to higher dissolution, this may be due to micronization of the drug particles (3, 5, 28, 29). The dissolution properties of tablet contains excipients, were found to be affected by the type of excipient used. Some will increase the dissolution rate and increase the disintegration of the tablet, making the dissolution time shorter. Lubrication mixing time place an important role on rate process. It can be concluded that the mixing time has positive effect on dissolution time, as the pre lubrication mixing time increase dissolution time increase due to low dissolution. As we increase the lubrication mixing time, more uniformly binder mix in the powder, so hardness of the tablet increase, so ultimately release of the drug decrease(29, 30). Besides, the compression force and speed are considered influential factors. Increasing the compression force will reduce the surface area and the porosity, resulting in a highly compact hard tablet that needs prolonged time to disintegrate, dissolve and release the drug particles leading to increase dissolution time (31).

Rupture time

Based on release profile obtained for Product G, H and I, the rapture times for these products ranged between the 15 and 20 min after testing. These results are somehow controversial to the expectations since; some products with tablet forms were capable to release their contents within less than 15 min. However, rupturing of gelatin shell depends on different factors such as agitation, temperature and dissolution medium. These factors have insignificant influence since

they were set constants. More importantly, the shell composition is seen to play a key point that affects the rupture time of gelatin capsule. Different type of capsules shells are presents, (gelatin, gelatin/polyethylene glycol, hydroxypropyl methylcellulose (HPMC)) (22). It was reported that the maximum extent of drug dissolution was significantly increased when HPMC were used, the dissolution time is significantly reduced, indicating a faster dissolution rate of the drug. The addition of micro-fine cellulose to the formulation as filler reduced the dissolution time. Whereas the addition of lactose monohydrate did not enhance drug dissolution (32). Giving a delayed dissolution time in liquid capsules can be explained by that dissolution time of liquid capsules is a multi-factorial process; so more than factor can be involved

Data Analysis according to difference and similarity factor

Tablet products that were subjected to comparative analysis (A - F), the reference product used to calculate f_1 and f_2 was product F (Advil® as tablet form). Since average drug release of more than 85% attained within 15 min for products C, D and E, only two products among the six products (A, and B) necessitate comparison using f_1 and f_2 values. Hence, there is no valuable need to calculate f_1 and f_2 values for product C, D, and E. The analysis of product A to Advil revealed that there is a significant difference between dissolution profile of A compared to F, the values of f_1 and f_2 were 24 and 31 respectively. However, looking back to average percentage release of drug results of product A and product F, it is noticeable the reasonable difference between these two profiles. Whereas, product B showed f_1 to be 9 and f_2 to be 54 which indicates that there is no difference between product B and product F in its dissolution profile. Table 2 summarizes the calculated values of f_1 and f_2 .

Table(2): Similarity and difference values of tested products compared to reference (brand) products.

	Product A	Product B	Product G	Product H
f_1 value	24	9	10	13
f_2 value	31	54	56	53

For liquid capsule products, the tested products were Product G, and product H, while the reference was product I (Advil® in the capsule form). The obtained results showed that comparing product G with Advil® provided a calculated f_1 value of 10 and f_2 value of 56. These findings reflect similarity between the two profiles. Likely, product H when compared to Advil®, was found to be similar such that f_1 was equal to 13 and f_2 was equal to 53.

Limitations

The content of the active ingredient of each tested product is not assessed against the label claim. In addition, the dissolution tests were performed on pH 7.2 only and other media with different pH values were not used for granting biowaiving purposes. Besides, *in vitro* dissolution test might be an indicator to investigate the interchangeability of products. The study has not been assisted by other methods like *in vivo* bioequivalence study for better conclusion.

Conclusions

The obtained results showed that the average drug release after 60 minutes of tested products were above the Q value = 80 + 5% which is reported in the USP and therefore they passed the dissolution test and met the specifications of the USP. On the pharmaco-economic side, it was observed that there is wide range of prices set of IBP products.

CONFLICT OF INTERESTS

The authors report no conflicts of interest in this manuscript

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