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Article

Interchangeability of medications and biopharmaceutical implication of taking drugs with fluids other than water: ibuprofen case study

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The aim of this study was to compare the dissolution properties of ibuprofen solid oral dosage forms commercially available in Bosnia and Herzegovina and to estimate the influence of dissolution medium composition on the drug release. Eight products (A-H) were subjected to *in vitro* dissolution test using experimental conditions described in USP42–NF37. Dissolution properties of one selected product were examined in the presence of alcohol (22.2% v/v) and fruit juice (22.2% v/v). Products marked B-H complied with the pharmacopeial criteria. Dissolution profile of product B was similar with dissolution profiles of products D, E, F and G and similarity was also found between products A-D, C-G, D-G and E-F. Drug release from most of the examined preparations fitted best to the Weibull kinetic model. In the presence of alcohol in the medium, higher amount of ibuprofen was dissolved. Contrary, ibuprofen dissolved in the presence of fruit juice was significantly lower. Differences in the dissolution profiles of investigated preparations suggest that their interchangeability should be additionally considered and demonstrated with *in vivo* bioequivalence studies. Presence of different substances in the medium can affect dissolution properties of ibuprofen, emphasizing the importance of the patient's compliance.

Keywords: Ibuprofen. Dissolution test. Alcohol. Fruit juice. Tablets. Capsules.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most frequently used medications with analgesic, anti-inflammatory and antipyretic activity. Due to their effectiveness and widespread use, variety of formulations from different manufacturers can be found on the market, mainly in the form of solid oral dosage forms such as tablets and capsules (Bacchi *et al*., 2012). Considering that the drug release from solid dosage forms and the dissolution of active substance are mandatory for a substance to be absorbed in the small intestine, these processes can be limiting factors for the absorption and therefore, directly affect bioavailability and therapeutic effects of the drug (Dressman, Krämer, 2005).

In vitro dissolution test is one of the key biopharmaceutical tests widely employed in the pharmaceutical industry, starting from drug development and quality control to approval of generic drugs (Dressman, Krämer, 2005; FDA, 1997). Furthermore, dissolution properties of a certain drug can be used for prediction of *in vivo* behavior of active pharmaceutical ingredient which can significantly reduce the risks for human subjects and generally, the duration of bioequivalence studies (Cardot, Beyssac, Aldic, 2007). Results of *in vitro* dissolution test can be used to calculate parameters necessary for establishment of correlation between *in vitro* and *in vivo*

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conditions, such as mean dissolution time (MDT) and dissolution efficiency (DE) (Suarez-Sharp *et al.*, 2016).

In the case of generic products, manufacturing process and the formulation must provide that drug release of generic and the reference product occurs in the same way at predefined experimental conditions. Therefore, interchangeability of generic drug products is promoted by an appropriate *in vitro* drug release assessment as a prerequisite which ensures the same pharmacological drug effect (Medina *et al.*, 2014).

Ibuprofen is considered as one of the most tolerable drugs from the NSAIDs class (Bjarnason, 2013), frequently used in the management of mild to moderate pain, fever and inflammation in various conditions such as headache, dysmenorrhea, dental pain, postoperative pain, musculoskeletal and soft tissue disorders (Martindale 39, 2017). Recommended oral daily dose of ibuprofen is between 1200 and 1800 mg, divided into several doses. The ibuprofen daily dose may be increased if necessary up to 2.4 g in the UK or up to 3.2 g in the USA. Depending on the patient condition, recommended initial drug dose for most indications is 200-400 mg every 6 to 8 hours. However, to treat acute migraine and severe rheumatoid diseases higher doses are recommended (ALIMS 2022, Martindale 39, 2017). In order to ensure the adequate dose of the drug, immediate-release preparations available on the market of Bosnia and Herzegovina contain between 200 mg and 800 mg of ibuprofen. Besides from immediate-release dosage forms, modified-release preparations containing 800 mg of the drug are also available and they are intended for once- or twice-daily dosing (ALIMS, 2022). Ibuprofen is a poorly water-soluble drug and its pKa is in the range of 4.5 to 4.6. Hence, the drug exhibits pH-dependent solubility which causes variability in its therapeutic efficacy (Potthast *et al.*, 2005). Ibuprofen solubility in ethanol is higher than in water (Friuli *et al.*, 2018). Two enantiomers of ibuprofen are identified. Pharmacodynamically active are a racemic mixture and the S(+)-isomer dexibuprofen (Hao, Wang, Sun, 2005). According to the Biopharmaceutical Classification System (BCS), ibuprofen belongs to Class II, which indicates that its low solubility can affect the bioavailability after oral use (Potthast *et al.*, 2005). Also, as a general rule, the *in vivo* dissolution of a BCS Class II drug within the gastrointestinal tract is the main determinant for its *in vivo* performance and it is considered as the rate-limiting step for the systemic absorption. Given that an inadequate and insufficiently discriminative *in vitro* dissolution methodology might lead to a false positive bioequivalence decision, in order to make biowaiver extension feasible, robust and biopredictive *in vitro* dissolution methods coupled with mathematical modelling could be potential solutions (Hofmann *et al.*, 2020; Hofsäss, Dressman, 2019; Kubbinga, Langguth, Barends, 2013; Lennernas *et al.*, 2017).

Commercially available preparations usually contain a racemic mixture, although drug products containing dexibuprofen are available in some countries (Martindale 39, 2017; Potthast *et al.*, 2005). The patient information leaflets (PILs) of ibuprofen tablets indicate that ibuprofen tablets should be taken with sufficient water during a meal in order to reduce the risk of gastrointestinal complaints. However, these recommendations are not followed by many patients. Contrary, as to mask unpleasant taste of drugs they often take drugs with juices, tea, milk, coffee and other beverages and, as a consequence, this practice can result in various interactions altering drug dissolution and absorption (Almukainzi *et al.*, 2021).

The intake of drugs with food and/or beverages other than water may directly or indirectly affect oral absorption of drug by changes made in gastrointestinal tract environment. The mechanisms of food interaction with drugs can be multiple depending on various factors such as drug properties and its dosing regimen, categories of food etc (Deng *et al.*, 2017). The interactions between drugs and beverages different from water are of a great concern given that many people take drugs with juice, milk, tea or even alcohol beverages (Koziolek *et al.*, 2019). Alcohol is particularly problematic because many drugs interact with it pharmacokinetically and also at a pharmacodynamic level, which can lead to serious side effects (Friuli *et al.*, 2018). Also, unspecific interactions between ethanol and drug that may occur due to changes of physiology of gastrointestinal tract upon alcohol consumption contribute to its overall effect (Koziolek *et al.*, 2019). The content of ethanol in different alcohol drinks ranges from about 4% in beers, to 20% and 40% in cocktails and undiluted spirits, respectively (Friuli *et al.*, 2018).

Similarly, the presence of fruit juices in gastrointestinal tract can influence its microenvironment and these alternations may impede or improve absorption depending on many factors (Jaruratanasirikul, Kleepkaew, 1997). Also, when fruit juice is taken instead of water in order to administer drugs, inhibition of enzymes and the uptake transporters involved in drug disposition may take place (Deng *et al*., 2017).

The objective of the present paper was to investigate and compare the dissolution properties of eight ibuprofen generic immediate-release solid dosage forms containing 400 mg of the drug obtained from the local market. In addition, in order to simulate various gastrointestinal conditions one drug product was selected and the influence of fruit juice and ethanol added to dissolution medium on ibuprofen dissolution characteristics was assessed.

MATERIAL AND METHODS

Sodium hydroxide, potassium dihydrogenphosphate, ethanol (Lach:Ner, Ltd, Czech Republic) and ibuprofen of analytical grade (Sigma Aldrich, USA) were used in the study. Eight preparations of ibuprofen marked A-H were purchased from the local pharmacy. Preparations A-G were film-coated tablets with immediate release of ibuprofen, and preparation H was in the dosage form of soft capsules. All products contained 400 mg of ibuprofen and were within their expiration dates. Characteristics of examined products are shown in Table I.

TABLE I - Characteristics of examined preparations

Product	Product description	Excipients	Manufacturer
A	Round, biconvex, white to off-white, with a score line.	Microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate (type A), stearic acid, talc, polysorbate 80, Eudragit L 30 D, titanium dioxide.	Local
B	White to off-white, oval shaped, biconvex.	Microcrystalline cellulose, croscarmellose sodium, lactose hydrate, colloidal silicon dioxide, magnesium stearate, sodium lauryl sulfate, magnesium stearate, hypromellose, talc, titanium dioxide.	Foreign
C	Dark pink, round shaped, biconvex.	Pregelatinized starch, lactose hydrate, povidone, microcrystalline cellulose, croscarmellose sodium, talc, colloidal silicon dioxide, magnesium stearate, macrogol 6000, titanium dioxide, hypromellose, 30% polyacrylate dispersion, carmoisine (E122).	Local
D	Biconvex, round, purple colored.	Lactose monohydrate, corn starch, povidone, microcrystalline cellulose, dimethicone, croscarmellose sodium, colloidal silicon dioxide, talc, hypromellose, macrogol 6000, titanium dioxide, carmoisine 85 (E122), cochineal red 80 (E124).	Foreign
E	White to off-white, oblong shaped, biconvex with a score line.	Corn starch, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, hypromellose, titanium dioxide, macrogol.	Foreign
F	Round shaped, biconvex, white to off-white with a score line.	Microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate (type A), stearic acid, talc, polysorbate 80, Eudragit L 30 D, titanium dioxide.	Local
G	Dark pink, round shaped, biconvex.	Lactose monohydrate, pregelatinized starch, povidone, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, talc, magnesium stearate, macrogol 6000, titanium dioxide, hypromellose, 30% polyacrylate dispersion, carmoisine 85 (E122).	Local

TABLE I - Characteristics of examined preparations

Product	Product description	Excipients	Manufacturer
H	Oval shaped, pale yellow, soft gelatin capsules, transparent, filled with liquid content.	Potassium hydroxide, macrogol 400, purified water, gelatin, sorbitan sorbitol solution, sodium ethylparaben, sodium propylparaben.	Local

Apparatus

As stated by The United States Pharmacopeia (USP42-NF37, 2019), the dissolution studies were conducted using apparatus 2 (Erweka DT 720) in 900 mL of phosphate buffer solution (PBS), pH = 7.2. The stirring speed of the paddles was 75 rpm, and temperature of the medium was maintained at 37±0.5 °C. For every drug product, the test was carried out in six replicates. As a drug with acidic characteristics, ibuprofen exhibits pH-dependent solubility (Potthast *et al*., 2005). In order to estimate the influence of medium composition on dissolution properties of ibuprofen from solid oral dosage forms, one product was subjected to dissolution testing in the medium where 200 mL of PBS was replaced with ethanol (96% v/v) and fruit juice. Fruit juice used in the study was obtained from the local market (Fruit drops, apple juice; ingredients: water, apple fruit juice from concentrate 15%, glucose-fructose syrup, sugar, citric acid, flavor, trisodium citrate, sulfite ammonia caramel, sucralose). By adding ethanol and fruit juice, pH of the medium changed from 7.2 to 7.1 and 5.24, respectively. Other experimental conditions of the test remained identical.

In all conducted studies, 5 mL of dissolution samples were taken after 10, 20, 30, 45 and 60 minutes. In order to maintain sink conditions, withdrawn volumes were instantly substituted with the same volume of preheated dissolution medium. Samples were filtered through 0.22 µm membrane filters (Chromafil® Xtra PTFE-20/25, Macherey-Nagel, Germany).

Concentrations of dissolved drug in the filtrates were determined by utilizing spectrophotometric methods (r^2=0.9979 for PBS; r^2=0.9996 for PBS with ethanol; r^2=0.9995 for PBS with fruit juice) at absorption maximum of 264 nm, using dissolution medium from the test as blank (UV-1800 spectrophotometer, Shimadzu, Japan). Amount of drug dissolved from examined dosage forms were compared to the acceptance criterion given by USP, which is not less than 80% of labeled amount of ibuprofen dissolved in 60 minutes.

Data analysis

Acquired dissolution profiles of ibuprofen from different products were compared by employing model-independent and model-dependent approaches. Model-independent comparison was executed by calculating similarity factors (f_2) by using equation (1):

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

where n is number of sampling time points, Rt and Tt are the amount of drug dissolved at time t from reference and test product, respectively. Dissolution profiles are considered to be similar if the f_2 values range between 50 and 100 (FDA, 1997).

Model-dependent analysis was carried out by employing four kinetic models: first order kinetics, Higuchi model, Korsmeyer-Peppas model and Weibull model, as presented in Table II. Furthermore, obtained results were analyzed statistically by Tukey's test of multiple comparison (CI = 95%) where p values less than 0.05 were considered to be significant.

TABLE II - Mathematical models used for data fitting (Lokhandwala, Deshpande, Deshpande, 2013)

Model	Equation
First order kinetics	$\log Q = \log Q_0 - Kt/2.303$
Higuchi model	$Q = K_H\, t^{1/2}$
Korsmeyer-Peppas model	$Q = K_{KP} t^n$
Weibull model	$Q = Q_0 [1 - e^{-k(t-T)}]$

Q = amount of drug released in time t; Q_0 = initial drug amount in the dissolution medium; K, K_H, K_{KP}, k = constants of dissolution rate; n = dissolution exponent; T = lag time.

RESULTS

Results of *in vitro* dissolution test (Table III) are presented as the average amount of ibuprofen dissolved from six replicates ± standard deviation (SD). Results indicate that products B-H meet the requirements given by USP (USP42-NF37, 2019), where the amount of dissolved ibuprofen was between 86.14 ± 1.81% and 101.42 ± 1.69%. Product A released 79.18 ± 1.25% of the drug after 60 minutes of the test, which does not comply with the acceptance criterion. Dissolution profiles of all eight preparations are shown in Figure 1.

TABLE III - Amount of drug dissolved instead of released (%) from examined products at the end of the test (60 min)

Product	Amount of drug dissolved (%) ± SD	Meet the criteria of USP
A	79.18 ± 1.25	No
B	88.12 ± 1.26	Yes
C	95.39 ± 9.92	Yes
D	86.14 ± 1.80	Yes
E	88.97 ± 0.69	Yes
F	97.52 ± 2.41	Yes
G	89.03 ± 0.24	Yes
H	101.42 ± 1.69	Yes

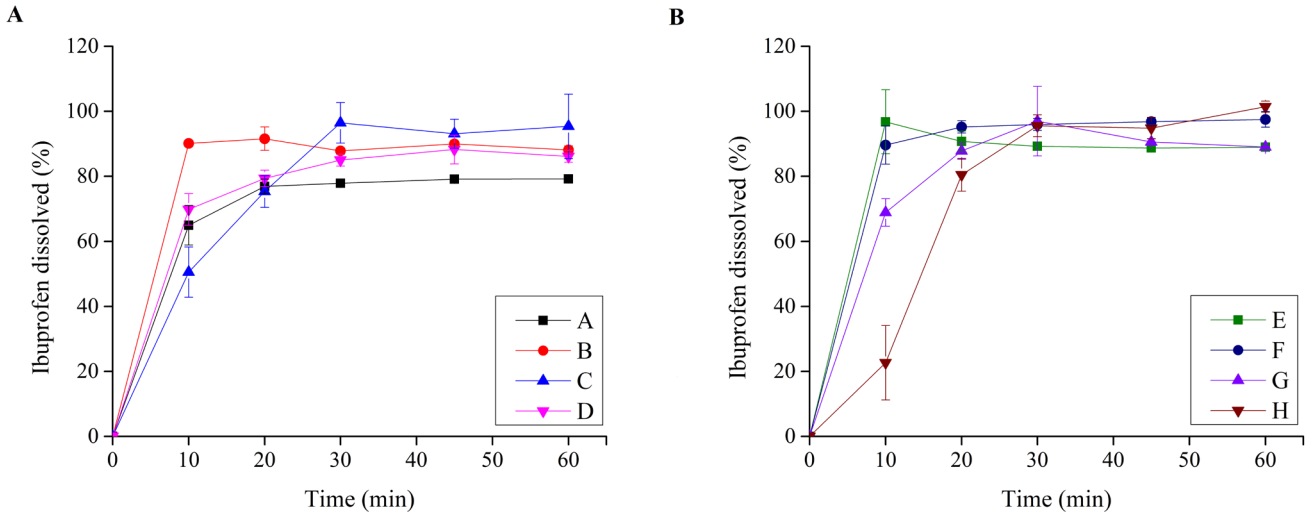

FIGURE 1 – Dissolution profiles (mean ± SD; n = 6) of commercially available tablets and soft capsules containing 400 mg of ibuprofen: A) products A-D; and B) products E-H.

The shortest dissolution time was observed for products B, E and F with more than 85% of the labeled drug amount dissolved within the first 10 minutes of the test. Somewhat slower dissolution rate was noticed in the case of products C and D, where more than 85% of the drug was dissolved after 30 minutes. The highest amount of ibuprofen was dissolved from product H, but the obtained increment was insignificant in comparison with the results obtained with C and F products.

Based on the correlation coefficients acquired by model-dependent approach, it has been shown that dissolution profiles from the majority of examined products fitted best to the Weibull kinetic model (Table IV), which is generally used for describing the release profiles of matrix type drug delivery carriers (Lokhandwala, Deshpande, Deshpande, 2013). As previously reported, the Weibull model also provided the best dissolution kinetics curve adjustment in the case of nine formulations of meloxicam tablets (Simionato *et al.*, 2018), supporting the results obtained in our study.

TABLE IV - Correlation coefficients (R^2) obtained by fitting dissolution data in kinetic models

Product	First order kinetics	Higuchi model	Korsmeyer-Peppass model	Weibull model
A	0.7691	0.6924	0.9918	**0.9952**
B	**0.7597**	0.4975	n/a	n/a
C	**0.9638**	0.8841	0.9283	0.9581
D	0.9123	0.7761	0.9916	**0.9943**
E	**0.6880**	0.4351	n/a	n/a
F	0.9942	0.6792	0.9974	**0.9976**
G	0.9290	0.7033	0.9551	**0.9688**
H	0.8652	0.8752	0.1334	**0.9884**

In order to compare ibuprofen release patterns from the drug products studied here, FDA adopted criterion – model independent approach using similarity factor (f_2) was also utilized. Calculated similarity factors suggest that dissolution profile of product B was similar to the profiles of products D, E, F and G. Also, similarity was found for pairs of products A-D, C-G, D-G and E-F (Table V). Statistical analysis of the obtained results was also carried out and similarity of dissolution profiles of the abovementioned product pairs was also confirmed.

TABLE V - Similarity factors for dissolution profiles of tested products

Products	f_2	Products	f_2	Products	f_2	Products	f_2
A-B	42.92	B-C	37.03	C-E	34.52	D-H	34.00
A-C	44.23	**B-D**	**50.30**	C-F	37.22	**E-F**	**59.02**
A-D	**61.02**	**B-E**	**76.00**	**C-G**	**50.98**	E-G	46.16
A-E	39.87	**B-F**	**60.82**	C-H	46.24	E-H	24.03

TABLE V - Similarity factors for dissolution profiles of tested products

Products	f_2	Products	f_2	Products	f_2	Products	f_2
A-F	37.35	**B-G**	**50.80**	D-E	45.75	F-G	49.98
A-G	47.83	B-H	27.10	D-F	44.77	F-H	27.60
A-H	33.05	C-D	49.36	**D-G**	**60.11**	G-H	27.60

In comparison with the model independent approach, statistical analysis of the results revealed similarity of dissolution profiles of additional pairs of products, i.e. C-E, C-F, C-H, D-E, E-G and F-H ($p<0.05$). It is considered that the similarity between dissolution profiles shown by using Tukey's test of multiple comparison is more sensitive compared to the limit value of f_2, which is 50 (Wang *et al.*, 2016).

By utilizing experimental conditions given by USP, 79.18 ± 1.25% of ibuprofen was dissolved from product A within 60 minutes. After adding ethanol in the dissolution medium, kinetic model that best described ibuprofen dissolution pattern remained unchanged (Weibull kinetic model, $R^2 = 0.9987$). Also, the obtained dissolution profile was similar to dissolution parameter of ibuprofen tablets assessed using PBS as dissolution medium ($f_2 = 58.32$). However, the amount of ibuprofen dissolved after 60 minutes significantly increased ($p = 0.0004$) and was 89.79 ± 0.17% of the labeled amount (Figure 2), suggesting that the presence of ethanol in dissolution medium affected its dissolution from tablets.

On the other hand, in the presence of apple fruit juice, the amount of ibuprofen dissolved was significantly lower ($p < 0.0001$) and reached 21.27% at the end of the experiment (Figure 2). In addition, dissolution profiles obtained in medium with and without fruit juice were not similar, as calculated f_2 value was 12.26.

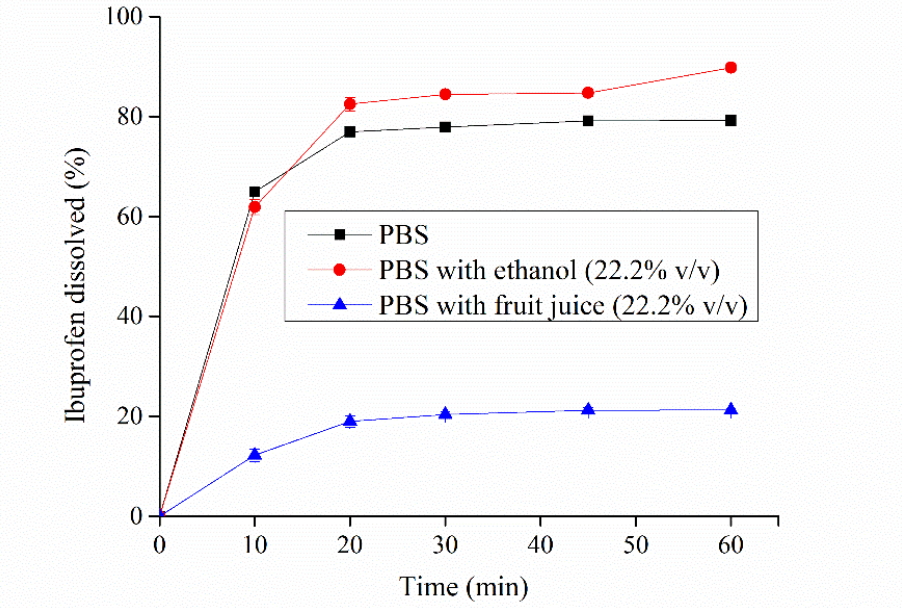

FIGURE 2 – Dissolution profiles (mean ± SD; n = 6) of ibuprofen tablets in PBS, PBS containing ethanol (22.2% v/v) and PBS containing fruit juice (22.2% v/v).

DISCUSSION

Eight ibuprofen solid oral dosage forms were within their shelf life when examined on their *in vitro* dissolution profiles in order to detect if there exist any differences among them. The dissolution process is basically consisted of two consecutive steps that are controlled by the affinity between the solvent and the drug. Liberation of drug molecules from solid phase is the first step. The following step involves the transport of solutes into bulk solution from the solid-liquid interface. Hence, dissolution process of solid dosage forms starts with its wetting and dissolution medium penetration into the drug formulation. Although after this usually disintegration or deaggregation into granules or particles occurs, for drug dissolution that finally takes place, this step is not prerequisite. However, multiple factors affect the drug dissolution rate of solid dosage forms, with factors related to product formulation and its manufacturing process being recognized as very important (Lee, Raw, Yu, 2008). Based on the FDA guidance for the pharmaceutical industry, a two-point dissolution assessment, one to include a dissolution range (a dissolution window) and the other one at a later time point (30, 45, or 60 minutes) to ensure 85% dissolution, is recommended to characterize the quality of the product containing poorly water soluble drugs or slowly dissolving (BCS class II) (FDA, 1997). All products except from the products A and D released ibuprofen greater than 85% in 30 min, suggesting that they are rapidly dissolving products. Ibuprofen tablets B, E and F exhibited very rapidly dissolving behavior as the drug released was more than 85% in 15 min. Interestingly, the results obtained with products A and F were somehow controversial to the expectations since these products contained the same excipients (Table I) and similar dissolution properties were participated. However, the variation in drug dissolution time and rate depends on many factors, such as excipients type and quantity, dosage form manufacturing process (milling, mixing and compression force), size of drug particles. Thus, it is possible that products A and D differs in content of excipients (e.g. product D may contain more disintegrator and/or less lubricant; micronized drug particles or lower compression forces were used during tablet compression) (Akdag *et al*., 2020; Lee, Raw, Yu, 2008). In line with our results, earlier study by Bertocchi *et al.* (2005) revealed that even identical formulations of diclofenac sodium exhibited rather dissimilar release profiles. Furthermore, as can be seen from Table I, each of the investigated tablet formulations contained microcrystalline cellulose, colloidal silica and titan dioxide, magnesium stearate was employed as lubricant in all of the formulations except for the products A and F in which stearic acid was used. The only tablet formulation without stearates was product E. Disintegrators used were cross carmellose sodium and sodium starchglycolate. Taking into account that these excipients belong to the group of superdisintegrators, very rapid drug dissolution was expected, but it did not occur. However, this finding could be explained by improper formulation technique which led to disintegration into coarse particles preventing the drug from diffusing into solution (Eraga *et al*., 2015). It should be noted that despite the fact that brand E was the only product without solubilization/wetting agent, almost complete ibuprofen dissolution occurred in the first 10 min suggesting the mutual influence of many factors involved in drug dissolution process. Also, it should not be forgotten that ibuprofen exhibits pH-dependent solubility. Despite the medium used was the same for each drug product, different excipients or their amount in tablet formulations could affect medium pH, reflecting on ibuprofen solubility. In brief, in the case of ibuprofen tablets brands the wide range of dissolution profiles obtained for ibuprofen oral dosage forms could be due to either one or combination of these factors.

Interestingly, drug dissolution rate from product H was the lowest, which was not presumed, taking into consideration that soft capsules usually exhibit faster drug dissolution than tablets (Gibson, 2009). However, similar findings supporting our results were already reported (Shraim *et al*., 2018). Hence, as observable from Figure 1B, the lowest dissolution rate obtained with soft capsules can be ascribed to the delayed rupture time of the capsule shell which is considered as a multi-factorial process (Hom, Veresh, Miskel, 1973). Furthermore, exposition of gelatin to certain storage conditions that may took place before purchasing the product or during the experiment can be a reason for cross-linking of

gelatin. This in turn can lead to a formation of rubbery partially water-insoluble gelatin film acting as a barrier limiting ibuprofen release (Marchais *et al.*, 2003; Singh *et al.*, 2002). Another possible explanation for this finding could be the excipients used in the product formulation or the capsule shell, which behave differently in different dissolution media (Almukainzi *et al.*, 2021).

Most medicines tested in our study complied with the pharmacopoeial specifications and achieved 80% dissolution in 60 min. However, calculated f_2 values illustrate that substitution among the drug products themselves can be risky. Brand B showed the greatest possibility for mutual interchangeability, as its dissolution pattern was similar to the profiles obtained for brands D, E, F and G. On the other hand, dissolution properties of product A were different from all the other brands, except from ibuprofen tablets D. These differences in dissolution properties between different ibuprofen oral solid dosage forms derived from the dosage form formulation and/or the employed manufacturing process may consequently have an influence on drug effectiveness and side-effects profiles (Dressman, Krämer, 2005). By taking the proper drug formulation orally, the drug reaches in a solution form the upper part of gastrointestinal tract, which represents a site of its absorption. Taking into consideration that earlier studies demonstrate that 99% of ibuprofen is absorbed from the small intestine, and hence, its complete dissolution in the intestinal fluids, differences in drug release and *in vitro* dissolution properties may reflect on ibuprofen absorption in biological environment. Therefore, non-equivalent preparations of ibuprofen usually differ by drug absorption rate (C_{max}) rather than the amount of the drug absorbed (AUC) (Tubic-Grozdanis, Bolger, Langguth, 2008). Differences between the results analyzed by using statistical tests and calculating similarity factors were also shown when dissolution profiles of different products of other NSAIDs, such as diclofenac sodium (Bertocchi *et al.*, 2005), meloxicam (Simionato *et al.*, 2018) and aceclofenac (Soni, Chotai, 2010) were assessed.

Based on previous findings on both pharmacokinetic and pharmacodynamic interactions between alcohol and NSAIDs (Barron, Perry, Ferslew, 1992; Fraser, 1997; Minocha *et al.*, 1986), influence of ethanol on biopharmaceutical properties of ibuprofen was evaluated in this study. Ethanol has a role of a cosolvent for ibuprofen (Martindale 39, 2017). More precisely, ethanol is miscible with water in all ratios, leading to a decrease of the dielectric constant value. As a result, the presence of ethanol in aqueous dissolution medium leads to higher solubility of nonpolar and/or lipophilic drugs in comparison with drug solubility in pure aqueous medium and thus, a higher drug release. Although pH of dissolution medium has a direct effect on solubility of drugs with weak acidic or basic properties, pH of the medium was not significantly affected after adding ethanol. For that reason, a significantly higher ($p = 0.0004$) solubility of ibuprofen in ethanol containing medium can be mostly ascribed to the decreased dielectric constant rather than the change of pH. In accordance with the fact that differences in the amount of ibuprofen dissolved in the medium with and without ethanol were observed, pharmacopeial requirements also were not fulfilled in both cases. However, based on the calculated similarity factors, similarity of dissolution profiles of ibuprofen in PBS and PBS with ethanol was not found ($f_2 = 42.10$). Presented results are in a good agreement with earlier findings. Friuli *et al.,* (2018) recently investigated dissolution properties of ibuprofen in water-ethanol solutions (4%, 20% and 40% v/v), where it was shown that the presence of ethanol in concentrations of 20-40% leads to higher amount of ibuprofen dissolved compared to water only. Fagerberg *et al.*, (2012) have shown that the presence of ethanol (20% v/v) in dissolution media such as phosphate buffer (pH 6.8) and fasted state simulation intestinal fluid (FaSSIF) lowers the dose number (D_0) of other drugs from NSAID group, such as indomethacin and naproxen. Higher dissolution rate obtained in the case of ethanol intake can result in a changed absorption process, i.e. possibly unexpected and problematic drug bioavailability increment. Particularly, BCS class II drugs (e.g. ibuprofen) are at risk, as they exhibit poor solubility and high permeability under normal physiological conditions causing the absorption limited by solubility and/or dissolution issues. Another issue should be also mentioned - as the presence of ethanol in the gastrointestinal tract may affect the amount of dissolved-undissolved drug inside the stomach there is

a possibility that serious gastrointestinal complications occur (Friuli *et al.*, 2018).

Given that all NSAIDs have acidic properties and exhibit pH dependent solubility, significant change of pH of the medium could be the potential cause for significantly lower drug dissolution in the presence of fruit juice. Namely, the addition of fruit juice to PBS (pH 7.2) decreased pH to 5.24. Further pH reduction was observed upon tablet disintegration, as pH value measured at the end of the study was 4.78, confirming that tablet formulation excipients also had a significant influence on product dissolution properties. Significant decrease of ibuprofen dissolved from different oral dosage forms upon pH reduction from 7.2 to 4.5 was reported by Rivera-Leyva *et al.* (2012). Also, our findings are in line with the phenomenon reported for diclofenac in similar study by Dutta *et al.* (2011). Namely, in the presence of fruit juice, amount of diclofenac dissolved from tablets with sustained release was significantly lower compared to the results in the dissolution medium without fruit juice. Almukainzi *et al*., (2021) found that the disintegration time of ibuprofen tablets was significantly prolonged in different beverages in comparison with water. In addition to their finding, our study suggests that not only desintegration time of solid dosage form was changed, but also drug dissolution was reduced in presence of fruit juice in dissolution medium. According to the results obtained in the present study, the investigated ibuprofen solid oral dosage forms should not be taken with fluids other than those specified within the corresponding summary of product characteristics (SmPC).

To conclude, low solubility of ibuprofen can limit the absorption of the drug and affect bioavailability after oral administration. Some of commercially available preparations of ibuprofen on the market of Bosnia and Herzegovina show significant differences in the drug release. These differences suggest that interchangeability of these products should be additionally evaluated by testing on more samples obtained from different drug batches and further demonstrated with *in vivo* bioequivalence studies. Presented results also show that taking ibuprofen with fruit juice or alcohol, significantly affects the drug release which can lead to different outcomes, from the absence of therapeutic effects to unexpected drug bioavailability increment and hence increased risk of side effects. Therefore, to provide safe and effective treatment, patients should always be advised to follow instructions given in the PIL.

REFERENCES

Akdag Y, Gulsun T, Izat N, Oner L, Sahin S. Comparison of dissolution profiles and apparent permeabilities of commercially available metformin hydrochloride tablets in Turkey. Dissolution Technol. 2020;27(1):22-9.

ALIMS, 2022. Register of Medicinal Products of Bosnia and Herzegovina. Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina. 2022 Febrary, http://www.almbih.gov.ba/_doc/registar2022/Registar2022.pdf. (accessed 2022 July 20).

Almukainzi M, Alobaid R, Aldosary M, Aldalbahi Y, Bashiri M. Investigation of the effects of different beverages on the disintegration time of over-the-counter medications in Saudi Arabia. Saudi Pharm J. 2021;29(7): 699-705.

Bacchi S, Palumbo P, Sponta A, Coppolino MF. Clinical pharmacology of non-steroidal anti-inflammatory drugs: a review. Antiinflamm Antiallergy Agents. Med Chem. 2012;11(1):52-64.

Barron SE, Perry JR, Ferslew KE. The effect of ibuprofen on ethanol concentration and elimination rate. J Forensic Sci.1992;37(2):432-5.

Bertocchi P, Antoniella E, Valvo L, Alimonti S, Memoli A. Diclofenac sodium multisource prolonged release tablets—a comparative study on the dissolution profiles. J Pharm Biomed Anal. 2005;37(4):679-85.

Bjarnason I. Gastrointestinal safety of NSAIDs and over-the-counter analgesics. Int J Clin Pract Suppl. 2013;178:37-42.

Cardot J-M, Beyysac E, Alric M. In Vitro-In Vivo Correlation: Importance of dissolution in IVIVC. Dissolution Technol. 2007;14(1):15-9.

Deng J, Zhu X, Chen Z, Fan CH, Kwan HS, Wong CH, et al. A review of food-drug interactions on oral drug absorption. Drugs. 2017;77(17):1833-55.

Dressman J, Krämer J. Pharmaceutical dissolution testing. Boca Raton: Taylor & Francis; 2005.

Dutta M, Nath AK, Uddin MZ, Hossain M.A, Morshed MM, Kawsar MH. Effect of fruit juice on the dissolution of diclofenac sodium sustained release matrix tablets. IJPSR. 2011;2(12):3109-13.

Eraga SO, Arhewoh MI, Chibuogwu RN, Iwuagwu MA. A comparative UV− HPLC analysis of ten brands of ibuprofen tablets. Asian Pac J Trop Biomed. 2015;5(10):880-4.

Fagerberg JH, Al-Tikriti Y, Ragnarsson G, Bergström CA. Ethanol effects on apparent solubility of poorly soluble drugs in simulated intestinal fluid. Mol Pharm. 2012;9(7):1942-52.

FDA, 1997. Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms. Food and Drug Administation, Center for Drug Evaluation and Research (CDER), U.S. Department of Health and Human Services.

Fraser AG. Pharmacokinetic interactions between alcohol and other drugs. Clin Pharmacokinet. 1997;33(2):79-90.

Friuli V, Bruni G, Musitelli G, Conte U, Maggi L. Influence of dissolution media and presence of alcohol on the In vitro performance of pharmaceutical products containing an insoluble Drug. J Pharm Sci. 2018;107(1):507-11.

Gibson M, Pharmaceutical preformulation and formulation, 2nd ed. USA: IHS Health Group, 2009.

Hao H, Wang G, Sun J. Enantioselective pharmacokinetics of ibuprofen and involved mechanisms. Drug Metab Rev. 2005;37(1):215-34.

Hofmann M, García MA, Al-Gousous J, Ruiz-Picazo A, Thieringer F, Nguyen MA, et al. In vitro prediction of in vivo absorption of ibuprofen from suspensions through rational choice of dissolution conditions. Eur J Pharm Biopharm. 2020;149:229-37.

Hofsäss MA, Dressman JB. The discriminatory power of the BCS-Based biowaiver: A retrospective with focus on essential medicines. J Pharm Sci. 2019;108(9):2824-37.

Hom F, Veresh S, Miskel J. Soft gelatin capsules I: Factors affecting capsule shell dissolution rate. J Pharm Sci. 1973;62(6):1001-6.

Jaruratanasirikul S, Kleepkaew A. Influence of an acidic beverage (Coca-Cola) on the absorption of itraconazole. Eur J Clin Pharmacol. 1997;52(3):235-7.

Koziolek M, Alcaro S, Augustijns P, Basit AW, Grimm M, Hens B, et al. The mechanisms of pharmacokinetic food-drug interactions - A perspective from the UNGAP group. Eur J Pharm Sci. 2019;134:31-59.

Kubbinga M, Langguth P, Barends D. Risk analysis in bioequivalence and biowaiver decisions. Biopharm Drug Dispos. 2013;34(5):254-61.

Lee SL, Raw AS, Yu L. Dissolution testing. In: Krishna R, Yu L, editors. Biopharmaceutics applications in drug development. Boston, MA: Springer US; 2008. p. 47-74.

Lennernas H, Lindahl A, Van Peer A, Ollier C, Flanagan T, Lionberger R, et al. In vivo predictive dissolution (IPD) and biopharmaceutical modeling and simulation: future use of modern approaches and methodologies in a regulatory context. Mol Pharmaceutics. 2017;14(4):1307-14.

Lokhandwala H, Deshpande A, Deshpande E. Kinetic modeling and dissolution profile comparison: an overview. Int J Pharm Bio Sci. 2013;4(1):728-37.

Marchais H, Cayzeele G, Legendre JY, Skiba M, Arnaud P. Cross-linking of hard gelatin carbamazepine capsules: effect of dissolution conditions on in vitro drug release. Eur J Pharm Sci. 2003;19(2-3):129-32.

Martindale 39, 2017: The Complete Drug Reference. 39th edition. London: Pharmaceutical Press; 2017.

Medina JR, Salazar DK, Hurtado M, Cortés AR, Domínguez-Ramírez AM. Comparative in vitro dissolution study of carbamazepine immediate-release products using the USP paddles method and the flow-through cell system. Saudi Pharm J. 2014;22(2):141-7.

Minocha A, Barth JT, Herold DA, Gideon DA, Spyker DA. Modulation of ethanol-induced central nervous system depression by ibuprofen. Clin Pharmacol Ther. 1986;39(2):123-7.

Potthast H, Dressman JB, Junginger HE, Midha KK, Oeser H, Shah VP, et al. Biowaiver monographs for immediate release solid oral dosage forms: ibuprofen. J Pharm Sci. 2005;94(10):2121-31.

Rivera-Leyva JC, García-Flores M, Valladares-Méndez A, Orozco-Castellanos LM, Martínez-Alfaro M. Comparative studies on the dissolution profiles of oral ibuprofen suspension and commercial tablets using Biopharmaceutical Classification System criteria. Indian J Pharm Sci. 2012 Jul;74(4):312-8.

Shraim N, Hamawi T, Hummaid S, Adeli Ba, Radwan A, Shaikha F. Assessment of dissolution performance of immediate release ibuprofen products: Screening of products available on the Palestinian market. Palest Med Pharm J. 2018;3(1):31-8.

Simionato LD, Petrone L, Baldut M, Bonafede SL, Segall AI. Comparison between the dissolution profiles of nine meloxicam tablet brands commercially available in Buenos Aires, Argentina. Saudi Pharm J. 2018;26(4):578-84.

Singh S, Rao KR, Venugopal K, Manikandan R. Alteration in dissolution characteristics of gelatin-containing formulations. Pharmaceutical technology. 2002;26(4):36-54.

Soni T, Chotai N. Assessment of dissolution profile of marketed aceclofenac formulations. J Young Pharm. 2010;2(1):21-6.

Suarez-Sharp S, Li M, Duan J, Shah H, Seo P. Regulatory experience with In Vivo In Vitro correlations (IVIVC) in new drug applications. AAPS J. 2016;18(6):1379-90.

Tubic-Grozdanis M, Bolger MB, Langguth P. Application of gastrointestinal simulation for extensions for biowaivers of highly permeable compounds. AAPS J. 2008;10(1):213-26.

USP42-NF37, 2019. The United States Pharmacopeia 42, The National Formulary 37, The United States Pharmacopeial Convention, Rockville.

Wang Y, Snee RD, Keyvan G, Muzzio FJ. Statistical comparison of dissolution profiles. Drug Dev Ind Pharm. 2016;42(5):796-807.

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