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Dissolution of pain-relief drugs: Does beverage choice matter?

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A B S T R A C T

Oral administration continues to be the most common route for drug delivery with the majority of approved medicines being tablets and capsule dosage forms. Standardised pharmacopeial media are typically used to test tablet dissolution in vitro, however patients use non-standard beverages to take with their medicines. Information about the dissolution of drugs in beverages consumed by patients has not been reported in the literature. Our aim was to investigate if the choice of beverage influences the dissolution of common pain relief tablets. The prevalence and type of alternative beverages used by patients to take their tablets was investigated in an online survey. The rate of dissolution of the common pain relief tablets, aspirin and acetaminophen, was measured in 15 different dissolution media including pharmacopeial dissolution media, simulated gastrointestinal fluids, and the common alternative beverages used by patients to take their tablets (including water, tea, coffee, soft drink and beer). The concentration of drug dissolved in each beverage over time was determined using either UV–vis spectroscopy or HPLC. The rate of dissolution of aspirin and acetaminophen tablets was in some cases significantly affected by the composition of the dissolution media. Factors such as mineral content, carbonation, and pH contributed to differences in the rate of dissolution for both aspirin and acetaminophen. The rate of dissolution of aspirin was significantly lower in some beverages compared to pharmacopeial media. When translated to the in vivo setting, these differences have the potential to alter the pharmacokinetics and bioavailability of orally administered medicines and so their efficacy.

1. Introduction

Dissolution testing to quantify the release of active pharmaceutical ingredient over time from an orally administered medicine in vitro is an essential part of product development and quality control [1–3]. The in vitro rate and extent of drug release from solid, immediate release oral dosage forms is also used in bioequivalence studies to determine whether a manufactured generic product exhibits a similar rate of dissolution, and therefore expected in vivo pharmacokinetics, compared to the innovator product [3,4]. The choice of dissolution media has important implications for drug release [5] and so specific pharmacopeial media have been mandated as the conventional dissolution media to ensure consistent in vitro product testing [6]. The ability to predict the in vivo behavior of medicines has received increasing attention and biorelevant dissolution media have been employed in dosage form development that include components found in the human small intestine (e.g. bile salts and phospholipids) in both the fed and fasted prandial states [7] and so are thought to more-closely mimic in vivo conditions encountered by dosage forms [3,8]. Such biorelevant media are useful for establishing IVIVC (in vitro in vivo) correlations as part of product lifecycle management [8] and in research to develop new formulations for the future using Quality by Design approaches where prediction of clinical performance is a key input [9]. However, these media employed for dissolution testing during product development are not the same as that consumed by patients. Consequently, there is a discrepancy between the media used in the development and testing of oral medicines and their in vivo application when used by patients. These differences in dissolution may have critical implications for the efficacy of medicines leading to unpredicted outcomes in patient therapy.

Patients are advised to take their oral tablets, including common pain relief tablets like aspirin or acetaminophen, with water to aid in the swallowing process. However, it is not certain whether patients follow
these guidelines and use water as the beverage used to take their medicines. The influence of beverage composition on the process of tablet disintegration, the physical breakdown of tablet composition in a liquid medium, has been studied previously. Chuong et al. found that there was a delay in tablet disintegration when milk was used to take pain medications compared to when water was used [10]. However, despite the fact that dissolution is a key step to achieving the appropriate bioavailability of an oral medicine, there is a paucity of literature available on the influence of beverage composition on dissolution. A recent study investigated the dissolution rate of innovator and generic pain relief products in several dissolution media [4]. There was a significant difference between the dissolution of naproxen in phosphate buffer, a cola drink and grapefruit juice with grapefruit juice having the lowest rate of dissolution [4]. Similarly, for gastro-resistant aspirin tablets, the presence of glucose in the dissolution medium due to the addition of sweet beverages resulted in a reduced rate of dissolution compared to buffer only [11]. Therefore, investigating the rate of dissolution of drugs in the beverages used to consume medications can provide important insights for drug absorption, bioavailability estimation and so efficacy of the medicines delivered using oral dosage forms.

Acetylsalicylic acid, also known as aspirin, is one of the most commonly used pain relief medications. In 2021, aspirin was on the World Health Organization (WHO) Model List of Essential Medicines and so is an important medication in the basic health system [12]. Aspirin is a weakly acidic, white crystalline substance and the solubility and partition coefficient of aspirin are pH dependent, where environmental changes in pH will influence its solubility [13]. Therefore, it is important to investigate the difference in the rate of dissolution of aspirin in different dissolution media and determine whether the choice of beverage when taking aspirin tablets might potentially affect its absorption in vivo. Acetaminophen, also known as paracetamol, is a non-opioid analgesic that is a preferred alternative to aspirin with patients who cannot tolerate aspirin, as well as in adolescents [14]. The solubility of acetaminophen is dependent on the polarity of the solvent as well as the temperature of the dissolution environment [15]. Therefore, the variation in the composition between different types of beverages may contribute to solubility changes of acetaminophen, and hence, affect the rate of dissolution and subsequent biological effect.

In this study, we aimed to firstly understand the prevalence of non-adherence to the use of water by patients when taking their medication using an open online survey. We then determined the rate of dissolution of two pain relief drugs formulated as immediate release tablets, aspirin and acetaminophen, in 15 dissolution media. The dissolution media were selected based on the beverages identified by survey participants, as well as simulated gastrointestinal fluid. The dissolution profiles were compared to those in the pharmacopeial media via similarity test to determine whether there was a difference in the dissolution rate between the pharmacopeial media and the beverages used to take pain medications [16]. The hypothesis for this study was that the rate of the dissolution of both drugs will be dependent on the composition of the dissolution media.

2. Materials and methods

2.1. Materials

Aspirin tablets (100 mg per tablet) were purchased from Mayne Pharma, VIC, Australia. Acetaminophen (paracetamol) tablets (500 mg per tablet) were purchased from Panamax®, VIC, Australia. Purified water was obtained from a MilliQ water purification system sourced from Merck Millipore, VIC, Australia. Tap water was collected from Monash University, VIC, Australia. Juice (Golden Circle cordials, orange), coffee (Essentials instant coffee, granulated), tea (Taylors of Harrogate Yorkshire tea bags), cola (Coca-Cola® Classic soft drink), and soda water (Woolworths supermarket brand) were purchased from local supermarkets in Melbourne Australia in August 2022. Beer (Victoria Bitter) was purchased from BWS, VIC, Australia. Fasted State Simulated Intestinal Fluid/Fed State Simulated Intestinal Fluid/Fasted State Simulated Gastric Fluid (FaSSF/FaSSF/FaSSGF) powder (58 g, 25 L size) was purchased from Biorelevant.com Ltd, London, United Kingdom. Acetaminophen API (98.0%) and aspirin API (99.5%) were purchased from Sigma-Aldrich, Darmstadt, Germany. Glacial acetic acid (100%) was purchased from EMSURE®, Billerica MA, USA. Hydrochloric acid (32%) was purchased from RCI Labscan Limited, NSW, Australia. Potassium di-hydrogen phosphate (99.0%) was purchased from Ajax Finechem, Auckland, New Zealand. Sodium acetate trihydrate (99.0%) was purchased from Sigma-Aldrich, Darmstadt, Germany. Sodium hydroxide (99.0%) was purchased from Merck KGaA, Darmstadt, Germany. Sodium chloride (99.7%), sodium lauryl sulfate also known as sodium dodecyl sulfate (98.0%) and sodium phosphate monobasic anhydrous (98.0%) were purchased from Chem-Supply, Gillman, SA, Australia. Acetonitrile (ACN) (HPLC grade) was purchased from Ajax Finechem, Auckland, New Zealand.

2.2. Investigation of beverages consumed when taking pain relief tablets

A survey was conducted to ascertain the beverage that people choose to consume when taking their pain relief tablets. The protocol was approved by Monash University Human Research Ethics Committee (No. 35702) prior to the commencement of the study. The survey instrument used was Survey Monkey and it was distributed via Twitter, LinkedIn and Facebook over the period of October 2022 to January 2023. As this survey was administered via an open link on the internet, responses are expected to be from the wider population beyond Australia. The only restriction was that all participants were requested to be older than 18. No demographic information was collected and responses were anonymous. The participants were asked to answer one question “What beverage did you last use when taking tablets? (Please do not respond if under 18 years of age)”. A sample size calculator (Qualtrix) was used to determine that 385 responses were needed to get results that are representative of the population with a 95% confidence level and a 5% margin of error.

2.3. Dissolution of aspirin tablets

Dissolution testing was carried out using a RC-6 Dissolution Tester dissolution apparatus. The dissolution testing set up was according to the US Pharmacopoeia (USP) protocol [17]. Aspirin (3 x 100 mg tablets) were added to the dissolution vessel containing 600 mL of the selected dissolution media. This volume was selected as a volume that might typically be used in in vitro dissolution testing protocols, and is not intended to represent a biorelevant volume of liquid. The pH of the selected dissolution media was measured at room temperature using a pH meter and provided a range of pH environments (Table 1). The preparation process and nutritional information of the dissolution media is provided in the supporting material (Table S1). The dissolution media were pre-filtered before use in every experiment. The theoretical maximum drug concentration in each vessel was 0.5 mg/mL. The paddle apparatus was selected for this experiment and the stirring speed was 50 rpm according to the USP dissolution test [18]. The temperature of the water bath was set to 37 °C to simulate the human body temperature. Samples were collected from three separate vessels at the following time intervals: 2, 5, 10, 20, 40, and 60 min. Each sample solution was filtered via disposable 0.45 μm filters into 1.5 mL Eppendorf tubes to remove undissolved drug particles. The collected supernatant was diluted 1 in 10 (v/v) with the prepared and filtered mobile phase solution and the amount of drug dissolved was quantified using HPLC. For several samples studied with UV–vis spectroscopy, the collected supernatant was diluted 1 in 10 (v/v) with the same solution that acted as mobile phase solution from HPLC.
2.4. Quantification of aspirin using UV-vis spectroscopy

Pure aspirin (20 mg) was weighed to prepare a standard stock solution. The concentration range of the standard solutions were prepared between 20 μg/mL and 250 μg/mL. The standards (200 μL) were applied into the 96 well plate and the absorbance of the standard solution was determined via UV-vis spectroscopy. The total amount of aspirin contained in the tablets was confirmed prior to the dissolution experiments by dissolving one aspirin tablet into a 50 mL volumetric flask with absolute ethanol. The aliquot taken from the volumetric flask was further diluted with absolute ethanol and USP buffer. The concentration of the aspirin dissolved in the sample solution was then determined with reference to the standard curve. The mass of aspirin in a nominal 100 mg tablet was 123.4 ± 4.2 mg (n = 3 ± SD), which was used as the 100% dissolution value for the dissolution studies.

2.5. Quantification of aspirin using HPLC

The mobile phase solution consisted of 25% B of ACN and 75% A of phosphoric acid in H\(_2\)O (25:75 v/v) at 1.0 mL/min flow rate. The column temperature was set to be 40 °C and the injection volume was 10 μL. A standard curve of aspirin was prepared in mobile phase at a concentration of 1 mg/mL. The stock solution was further diluted with the mobile phase mixed with the designated dissolution media, to provide standards at different concentrations ranging from 10 μg/mL to 250 μg/mL. The HPLC method for aspirin was validated for precision and accuracy at three times within the same day using three independent standard samples ranging in concentration from 10 μg/mL to 250 μg/mL. The accuracy of the assay was 99.2% (Table S5). The selectivity of the method was confirmed by no interfering peaks being identified in the chromatograms at the retention time of the drugs investigated.

2.6. Dissolution of acetaminophen tablets

The dissolution testing for acetaminophen was identical to the method used for the aspirin assay. Pure acetaminophen (20 mg) was weighed and added into a 20 mL volumetric flask for stock solution preparation. The volumetric flask was then filled with mobile phase (ACN and phosphoric acid in H\(_2\)O (25:75 v/v)). Standard solutions were prepared in the concentration range from 20 to 250 μg/mL. To determine the mass of one acetaminophen tablet, 1 tablet (500 mg) was dissolved into a 50 mL volumetric flask with mobile phase containing ACN and phosphoric acid in H\(_2\)O (25:75 v/v)) and the concentration determined by HPLC to determine the mass of acetaminophen present. The mass of acetaminophen in a nominal 500 mg tablet was 525.8 ± 27.5 mg (n = 3 ± SD), which was used as the 100% dissolution value for the dissolution studies.

2.7. Quantification of acetaminophen using HPLC

The HPLC method that was used for the determination of the amount of acetaminophen in the dissolution media was adapted from the same reference as aspirin using a C18 column (4.6 × 75 mm\(^2\), 3.5 μm, 100 Å Waters Symmetry®, UK) [19]. The UV detector was set to 226 nm for the detection of acetaminophen. The HPLC method for acetaminophen was validated for precision and accuracy at three times within the same day using three independent standard samples ranging in concentration from 10 μg/mL to 250 μg/mL. The accuracy of the assay was 97.2% (Table S5). The selectivity of the method was confirmed by no interfering peaks being identified in the chromatograms at the retention time of the drugs investigated.

2.8. Solubility of aspirin and acetaminophen in different dissolution media

Excess amounts of aspirin and acetaminophen API (~20 mg) was dispersed in 1 mL of dissolution media to achieve a saturated solution and incubated at 37 °C. After 48 h, a 200 μL aliquot was collected and diluted to 1 mL with mobile phase solution (ACN: water (pH = 2.5), 25:75, v:v). The sample was centrifuged and the supernatant analysed for drug content using the respective HPLC methods described here.

2.9. Similarity test between the dissolution profile of drugs in pharmacopoeial media and dissolution media

The dissolution profiles over time for each drug in the different media were compared by conducting similarity tests based on criteria outlined by the US Food and Drug Administration (FDA) [20]. The similarity factor (f\(_s\)) was calculated according to Equation (1) to represent the extent of similarity measured in the percentage (%) of dissolution between the dissolution profiles [21]. The difference factor (f\(_d\)) was also calculated according to Equation (2) to compare the differences between the testing dissolution profiles and the profile obtained using the corresponding USP buffer for each drug [22].

\[
f_s = 50 \log \left(100 \times \frac{1 + \frac{1}{n} \sum_{i=1}^{n} (R_i - T_i)^2}{\sum_{i=1}^{n} R_i} \right)^{-0.5}
\]

\[
f_d = \left( \frac{\sum_{i=1}^{n} (R_i - T_i)}{\sum_{i=1}^{n} R_i} \right) \times 100
\]

where \(n\) is the number of time points and \(R_i\) and \(T_i\) are the mean percentages of drug released in the reference medium (USP dissolution buffers, Table S1) and the tested dissolution media, respectively at time \(t\).

Statistical comparisons were made using a Student’s t-test (Prism Version 9) with \(p < 0.05\) being considered significant.
3. Results

3.1. Survey of the preference of beverage when taking pain relief tablets

A total of 389 valid responses were collected from the survey. The majority of respondents stated the beverage they used to consume their pain relief tablets was water (81.0%) (Fig. 1 and Table S3). Of the survey participants, 2.8% stated that they did not take any beverage with their tablets, while 16.2% of those surveyed chose to take their pain relief tablets with other kinds of beverages such tea, coffee or juice instead of water. Tea was the most common beverage used to take medicines other than water (4.1% of the total population). There was 1.3% of the total number of responses that reported alcohol was the most recent beverage that was taken along with tablets. Carbonated beverages (cola and soda water) were consumed with tablets by 2.3% of those surveyed.

3.2. Similarity test among dissolution media

Comparison tests were performed to determine the similarity and difference between the in vitro dissolution profiles for acetaminophen and aspirin in pharmacopeial dissolution media and other types of beverages as dissolution media. The threshold scores of 15 for difference ($f_1$) and 50 for similarity ($f_2$) are presented as a black solid line in Fig. 2A-D. Values for $f_1$ between 0 and 15 indicate similar dissolution profiles, with 0 being identical profiles and $f_2$ between 50 and 100 indicate similarity with 100 being identical profiles [20]. The values for the difference factor $f_1$ for the dissolution of acetaminophen showed that among the 14 dissolution media tested, FaSSF, FaSIF, FeSSF, beer, flat coke and juice exhibited minor statistical variance compared to pharmacopeial media (Table S1). Notably, when examining the difference factors for acetaminophen in Fig. 2A, it is apparent that the dissolution profiles for purified water and tap water were the most different compared to the pharmacopeia media ($f_1 > 15$). Comparing the dissolution profiles for pharmacopeial media and tap water in Fig. 3, the rate and extent of dissolution for acetaminophen in the pharmacopeial media was much higher compared to the tap water.

The similarity factor $f_2$ values in Fig. 2B for the dissolution of acetaminophen indicated that only FaSSFG had a statistically similar dissolution profile compared to pharmacopeial media (Fig. 4), where the $f_2$ value was greater than 50.

For the dissolution of aspirin in different beverages, all of the beverages investigated were significantly different compared to pharmacopeial media (Fig. 2C and D). Among the dissolution media that were tested, the dissolution profile for flat (degassed) cola was the most statistically different compared to the profile for pharmacopeial media (Fig. 5). The two dissolution profiles for aspirin are distinctly different with a maximum of 70% of aspirin dissolved after 60 min in flat coke compared to 95% for the pharmacopeial media.

Broadly, the results indicate that aspirin is less soluble in the dissolution media tested in the present study compared to acetaminophen (Table S2). Aspirin had the lowest solubility in coffee (1.2 mg/mL), whilst for acetaminophen, the lowest solubility was found to be in the soda beverage (5.2 mg/mL). For both drugs, solubility was highest in water with a near-neutral pH compared to the beverages tested. In cola, the most acidic of the beverages tested (pH 2.3), the solubility of acetaminophen was almost double that of aspirin (6.1 compared to 3.9 mg/mL for acetaminophen and aspirin, respectively).

3.3. Influence of pH on the rate of dissolution

The beverages chosen to include in this study represented a range across the pH scale from 1.00 to 7.22 (Table 1). As acetaminophen and aspirin can be dissolved in several dissolution media, the rate of dissolution for both drugs at the 5 min time point as well as 60 min time point were selected to compare the influence of the beverage pH. We did not observe a significantly change in pH of the dissolution media over the duration of the dissolution testing. When examining the dissolution profile for acetaminophen at the 5 min time point and 60 min time point (Fig. 6A&B), there was no apparent correlation between the pH of the dissolution media and the amount of drug dissolved, although there was a trend for the beverages with higher pH values to have a lower amount of drug dissolved. Similarly, for aspirin (Fig. 6C&D), there was no obvious correlation between pH of the beverages tested and dissolution. Notably, for more than half of the beverages tested, aspirin tablets had dissolved less than 80% of the drug after 60 min (Fig. 6D). We can confirm that there was no degradation observed in the tea, cola and water media, however we note that there was an additional peak apparent in the chromatogram when coffee was used as a dissolution media after 60 min that was equivalent to an approximately 24% degradation of aspirin (Table S6).

3.4. Influence of carbonation on the rate of dissolution

The dissolution profile of aspirin and acetaminophen in standard cola and flat cola were selected to investigate the significance of carbonation to the alteration of the rate of dissolution. By examining the dissolution profiles in Fig. 7A, it can be observed that acetaminophen tended to dissolve in carbonated cola at the same rate as flat cola. After 5 min, the extent of dissolution of acetaminophen in cola was slightly lower than flat cola. For aspirin, there was a trend for the carbonated dissolution media to have a higher extent of dissolution, with a higher percentage of drug dissolved for most time points for aspirin compared to the non-carbonated solutions however the differences were not statistically significant (p = 0.1469 for aspirin profile based on the unpaired, two tailed t-test) (Table S4).

3.5. Influence of minerals on the rate of dissolution

The dissolution of both of drugs in purified water and tap water were compared in Fig. 8 shows that the maximum amount of acetaminophen dissolved at 60 min appeared slightly higher in tap water compared to purified water (Fig. 8A) however the variation was not statistically significant. The dissolution test profile for aspirin in purified water and tap water were the same, and aspirin fully dissolved after 60 min in both cases (Fig. 8B).
4. Discussion

In vitro dissolution testing for orally administered drugs is used to provide information to test the bioequivalence of medicines and to predict bioavailability. However, the effect of the composition of the different beverages used by patients to take their medicines on dissolution requires further investigation. The aim of the work was not to conduct a formal similarity test because the quality and uniformity of these dosage forms has already been established as the tablets were purchased from a retail outlet. Our aim was to conduct a study to investigate any differences in dissolution depending on a patient’s beverage choice when taking oral pain medications.

Based on the responses collected from a survey conducted as part of the current study, it can be concluded that water was the most commonly consumed beverage with tablets (as is generally instructed) with 81% of respondents stating this beverage. This was consistent with...
the findings of Hens et al. [23] who investigated the liquids that patients used to consume oral dosage forms and found that 92% of the adult Dutch population swallow their tablets with water. However, there were 16.2% (Table S3) of survey responses that declared that a beverage other than water was used to consume their medication. Among the other alternatives to water, tea (4.1%) and coffee (3.3%) were the most...

Fig. 6. Influence of pH of the 15 dissolution media tested on (A) acetaminophen dissolved at 5 min time point and (B) acetaminophen dissolved at 60 min time point after the start of the dissolution experiment (C) aspirin dissolved at 5 min time point and (D) aspirin dissolved at 60 min time point. The dotted lines on the figures indicate the pKa value of the drugs. Data points are mean (n = 3).

Fig. 7. Comparison between the dissolution profiles for (A) acetaminophen in carbonated cola (square symbol) and flat cola (triangle symbol), and (B) aspirin in carbonated cola (square symbol) and flat cola (triangle symbol). Data points are mean (n = 3) ± standard deviation.

Fig. 8. Comparison of dissolution in tap water containing minerals compared to demineralized ‘purified’ water (A) acetaminophen dissolved in purified water (shown with triangle symbol) and tap water (shown with square symbol) at 60 min (B) aspirin dissolved in purified water (shown with triangle symbol) and tap water (shown with square symbol) at 60 min. Data points are mean (n = 3) ± standard deviation.
popular choices to be taken with the pain relief tablets (Table S3). Both tea and coffee beverages are rich in caffeine, which has been shown to enhance the pain relief effect of common analgesics [24]. Consequently, beverage choice could impact the apparent in vivo efficacy of orally administered tablets, with a potential risk of insufficient dose in the case of analgesics. A further important aspect, as discussed by Hens et al. [23], is the volume of liquid used to take oral medicines. The majority (84%) of the patients in the study by Hens et al. [16] took their oral medication with less than a full glass of water and 3.4% did not use any liquid to consume their oral tablets. Once consumed, oral medications also encounter fluids in the gastrointestinal tract that can have the effect of diluting beverages consumed with oral medicines. It is known that the resting volume of fluid in the stomach is highly variable between patients [25] and so it is difficult to predict the extent of dilution that can occur. The differences in fluid volume in the stomach have also been shown to impact gastric emptying and subsequent transit and drug absorption [26]. Together, the consumption of different beverages and non-standard volumes, will contribute to inter-subject variability in bioavailability and so the resulting drug effect from oral medicines.

The variety of beverages to include in the dissolution study was also chosen to represent a range of pH, extent of carbonation and mineral content. The differences (and lack of ‘similarity’) indicated in Fig. 2 led to a desire to look more closely for correlations in behavior based on the properties of the fluids used as dissolution media. The pKa values for both aspirin and acetaminophen are different, where aspirin has a pKa greater than 6.0. The three media were tap water, purified water and FaSSGF media. We anticipate that the level of ionization will however be low and so this effect will be minimal also. However, for the media that have a higher pH, salt formation is possible. We anticipate that calcium and magnesium are the ions most likely to form a salt with dissolved drugs. And that the likelihood of formation depends on concentration of the aspirin added to the media. In the present study the concentration of aspirin added was 0.5 mg/mL and so we do not anticipate that salt formation would occur to any appreciable extent.

Based on the results from Fig. 8A, the extent of dissolution of acetaminophen was reduced for both tap and purified water compared to pharmacopeial media, but despite tap water having a greater ionic strength [37], the difference in dissolution profiles was only modest, and there was no clear change to dissolution rate profile, just a slightly greater extent. This supports a change to the solubility of the drug rather than to a mechanism of dissolution. For aspirin, the two dissolution profiles in Fig. 8B were almost overlapping, indicating that the presence of minerals in the dissolution media had no effect on dissolution rate for aspirin. Therefore, overall, it appears that no single chemical factor apparently dictates the differences in dissolution evident in Fig. 2.

Another important aspect to consider is the buffering capacity of the dissolution media. We compared the buffer compacity of beverages used in this study to pharmacopeial media and found that the beverages were within the range of the USP media. Any change to beverage composition by the addition of ingredients (e.g. drug) will contribute to a change in pH, which has been discussed above. This makes prediction of dissolution behavior using systematic changes in media (as arrived at for pharmacopeial media or FaSSGF/FaSSIF/FaSSIF) fraught with potential misleading conclusions, and so the importance of studying the actual beverages that patients use to administer their oral tablets.

The greatest differences in dissolution profiles for acetaminophen compared to the pharmacopeial media, when analysed for Similarity Index, were tap and purified water. This illustrates the value at least in studying dissolution in media other than pharmacopeial media – especially water as the most common liquid used to take these common medications. It is also valuable to investigate other beverages as substantial differences in dissolution, and so bioavailability, could occur with liquid beverages used by patients, as seen for most of the selected beverages here. While pharmacopeial media play a useful role in a quality control context in determining deviations from specifications of manufactured tablets, the results likely have little relevance to the in-use behavior [9], yet are also used as the basis for bioequivalence studies. An additional complicating factor not accounted for in these experiments (due to its highly variable nature) is the presence of resting gastric media.
in the fasted stomach. The liquid present in the fasted stomach is reported to be only 35 mL [38] meaning that in consideration of our experiments here, the gastric fluid would be diluted with 600 mL. This large dilution factor with beverage means that it is unlikely that the existing stomach content will make a profound difference to the trends in dissolution observed in the beverages alone. It remains for industry to decide the limits of investigating bio-relevance – whether to add an aliquot of simulated fasted gastric fluid in consideration of these relative volumes, or a higher level of gastric components to ensure that a complete picture can be revealed about how dissolution may be affected by the gastric environment.

The results here suggest that water, not pharmacopoeial media, should be considered as an appropriate media in which to use for dissolution studies. It could also be argued that for low solubility lipophilic drugs such as those used here, a lipid-containing medium such as milk may be a more appropriate media to better reflect in vivo dissolution conditions and provide biologically relevant information. Beverages such as milk have received significant interest recently for their promising application in administering medications to pediatric populations [39] and so there is scope to investigate this beverage further with respect to drug dissolution.

5. Conclusion

The rate of dissolution of two pain relief drugs, aspirin and acetaminophen, in a range of different dissolution media including common beverages has been investigated and compared with pharmacopoeial media. The rate of dissolution was affected by the dissolution media, although it was not possible to attribute the differences to one characteristic of the media (carbonation, pH or ionic strength). When carbonated beverages were used as the dissolution media, the rate of dissolution was slightly elevated. Tap water and purified water showed the greatest differences in dissolution rate compared to pharmacopoeial media. The choice of beverages to be taken along with the pain relief tablets affects the rate of dissolution of the drugs, thus potentially impacting the rate of absorption and therapeutic effectiveness of pain-relief medicines, an issue that should be considered to a greater extent during product development and bioequivalence testing.

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CRediT authorship contribution statement

Shouyuan Huang: Data curation, Investigation, Methodology, Writing – original draft. Malinda Salim: Conceptualization, Data curation, Project administration, Supervision, Writing – review & editing. Bryce W. Barber: Data curation, Supervision, Writing – review & editing. Anna C. Pham: Data curation. Arlene McDowell: Conceptualization, Formal analysis, Supervision, Writing – review & editing. Ben J. Boyd: Conceptualization, Formal analysis, Funding acquisition, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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