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Original article

Investigation of the effects of different beverages on the disintegration time of over-the-counter medications in Saudi Arabia

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ABSTRACT

Full disintegration of Oral solid dosage forms is critically important to achieve reliable clinical performance of the drug. Tablets/capsules are supposed to be taken with a full glass of water; however, many patients do not follow this recommendation as they administer their medications with beverages other than water. This study aims to assess the impact of different commonly consumed beverages in Saudi Arabia on the disintegration times of common over-the-counter (OTC) medication tablets and capsules in the Kingdom of Saudi Arabia. Five immediate release OTC drugs were chosen: Fevadol®, Solpadeine®, Ralaxon®, Artiz ®, and Brufen®. The disintegration times of these medications were assessed using a disintegration test in five beverages: Coca-cola, arabic coffee, orange juice, buttermilk and an energy drink. Times were compared to the disintegration time in water under two temperature conditions (37 °C and 5 °C). All beverages significantly increased the disintegration times of fevadol, solpadeine, and relaxon in comparison with water. The same was found for burfen, except that arabic coffee did not significantly increase disintegration time ($p > 0.05$). The disintegration time of artiz tablets was also significantly influenced by all beverages, except for Coca-cola and the energy drink, which had no significant impact on the disintegration time. The tested beverages should not be used as substitutes for water when ingesting medications. Patients should be advised to avoid consuming beverages other than water with therapeutic products. Increasing public awareness of drug-beverage interactions is needed.

1. Introduction

Among all dosage forms that exist today, oral solid dosage forms (OSDFs), including tablets and capsules, are the most widely used. OSDFs have many advantages, such as their self-administration, compactness, dose accuracy, long shelf life, and ease of manufacturing (Almukainzi et al., 2014; Almukainzi et al., 2019).

The bioavailability of OSDFs depends on many factors, including the drug's formulation and its physicochemical characteristics, and patient's physiological conditions (M. Almukainzi et al., 2016). The ability of OSDFs to disintegrate completely and quickly enough into gastric media is a significant factor for in vivo drug availability. Full disintegration of a tablet/capsule is critically important to achieve reliable clinical performance of the dosage form (Almukainzi et al., 2010, 2011). The process of disintegration could be simply defined as the breaking up of solid materials when placed in a liquid medium, and it is the prerequisite step for drug dissolution (M. Almukainzi et al., 2014). The contents of OSDF can dissolve and be absorbed to be bioavailable only if it disintegrates; therefore, disintegration has a direct impact on the therapeutic effect of the medication (Eraga et al., 2015; Zuo et al., 2013a). For example, the time to reach peak concentration of ibuprofen tablets differs significantly in delayed drug disintegration, as in a disease state and/or concomitant food admiration (Almukainzi et al.,

Abbreviations: OTC, Over the counter; OSDFs, Oral solid dosage forms; IR, Immediate release; Spss, Statistical Package for the Social Sciences; SD, Standard deviation; USP, United States Pharmacopeia; DT, Disintegration time; QC, Quality control; QbD, Quality by design; BCS, Biopharmaceutics classification system.

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2016; Chuong et al., 2010). Thus, disintegration must be assessed and ideally quantified using a specifically designed compendial disintegration test (Fig. 1) (USP, 2020). The United States Pharmacopoeia (USP) adopted the disintegration test in 1950, and since then, it has been the apparatus used to perform the vast majority of disintegration testing procedures for OSDF (Al-Gousous & Langguth, 2015). The disintegration test is a useful quality control (QC) tool for tablets and capsules to determine if the drug disintegrates within the predetermined time (disintegration time) under given experimental conditions (Almukainzi et al., 2010, 2011; USP, 2020). This test is also the most appropriate performance test for quality by design (QbD) as a dissolution substituent test to determine drug release in certain scenarios, such as highly soluble drugs and biopharmaceutical classification system (BCS) class 1 drugs (Almukainzi et al., 2019; Grube et al., 2019; Zuo et al., 2013a). Disintegration is most commonly studied in water for the most immediate release (IR) or simulated gastric medium for delayed release (USP 2020).

Therefore, OSDF medications should be taken with a full glass of water rather than any other beverages. However, many patients do not follow this recommendation. Instead, they tend to take any accessible beverages, such as juices, coffee and soft drinks, when they swallow their OSDF medications (Chuong et al., 2010). There are many adverse results of drug-beverage interactions, some of which interfere with metabolism or excretion (Farkas & Greenblatt, 2008; Jaruratanasirikul & Kleepkaew, 1997). Others are related to altering drug disintegration and dissolution and hence absorption (Eraga et al., 2015; Priya Patel, Hina Bagada, 2013; Rana et al., 2017; Zuo et al., 2013a).

Some published studies have shown the effects of different beverages, particularly beer and wine (Zuo et al., 2013a), a major delay in disintegration was observed in 40% ethanol as disintegration media compared to water (Bisharat et al., 2019). Furthermore, some beverages, mainly cola drinks, demonstrated prolonged gastric emptying, which can affect the rate and extent of drug absorption (Kondal & Garg, 2003; Nomani et al., 2019).

The data available on the impact of beverage interactions with disintegration are limited, and the findings of these studies cannot be generalized for different reasons. The excipients added to the tablets and capsule may affect the disintegration behavior. Furthermore, technologies such as spray drying, molding, and lyophilization, which are used for the manufacturing of tablets, can affect the disintegration time (van der Merwe et al., 2020). Importantly, many of the previously studied medication brands used in published studies are not available in Saudi Arabia.

In Saudi Arabia, arabic coffee, soft drinks, energy drinks, and butter fermented milk (Laban) are the most frequently consumed drinks (Islam et al., 2020; Jalloun & Alhathlool, 2020; Nada & Sami, 2018; Naser et al., 2018; Otaibi, 2017; Subaiea et al., 2019). Therefore, there is an urgent need to study the impact of these beverages on OTC medication disintegration in Saudi Arabia.

The study aims to assess the impact of different commonly consumed beverages in Saudi Arabia on the disintegration times of most common OTC medication tablets and capsules that are locally available.

2. Materials and methods

The merits of the study proposal and its alignment with national regulations were evaluated and exempted by the Institutional Review Board (Registration Number 20–0194) of Princess Noura University, Riyadh, Saudi Arabia.

2.1. OSDF medication used:

The following five IR OTC medications were chosen: paracetamol 500 mg tablet (Fevadol) manufactured by Spimaco, batch no: 122699, expiry: March 2024; paracetamol 500 mg, codeine phosphate 8 mg, caffeine 30 mg capsule (Solpadeine) manufactured by Smithkline Beecham, batch no: S45 W, expiry: March 2024; Chlorzoxazone 250 mg, paracetamol 300 mg capsule (Ralaxon) manufactured by Jamjoom Pharma, batch no: XB0035, expiry: February 2023; cetirizine HCl 10 mg tablet (Artiz) manufactured by Tabuk Pharmaceutical, batch no: 0NR263, expiry: April 2023; ibuprofen 400 mg tablet (Brufen) manufactured by Abbott, batch no: 17289XV, expiry: November 2022 (Table 1). All medications were purchased from local pharmacies.

2.2. Study media

All tests were performed in deionized water and compared with six test beverages, including Coca-cola, an energy drink (Code red),

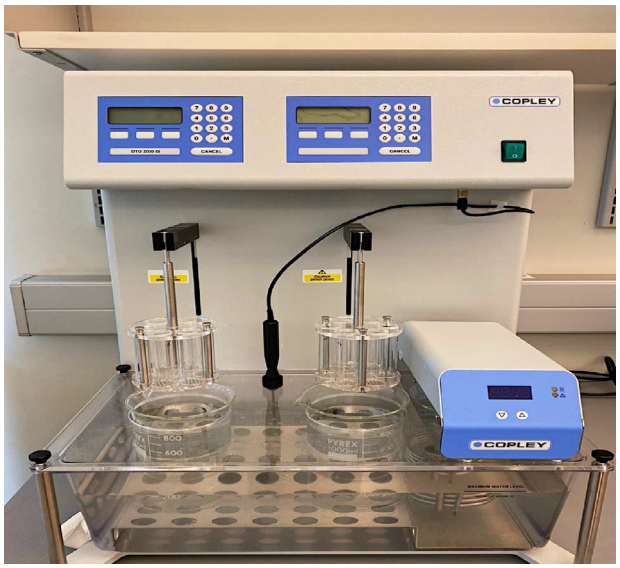

Fig. 1. Disintegration Tester DTG2000 IS.

Table 1
OTC medications used in this study.

Brand name	Active ingredients	Dosage form	Excipients
Fevadol	Paracetamol 500 mg	Tablet	No information available in the leaflet
Solpadein	Paracetamol 500 mg, caffeine 30 mg, codeine 8 mg	Capsule	Maize starch, Magnesium stearate, Titanium dioxide (E 171), erythrosine (E127), Patent blue V (E131), Quinoline yellow (E104), Gelatin, Shellac, Propylene glycol(E1520), Iron oxide black (E 172) and ammonium hydroxide (E527).
Brufen	Ibuprofen 400 mg	Tablet	No information available in the leaflet
Relaxon	Chlorzoxazone 250 mg, Paracetamol 300 mg	Tablet	Colloidal silicon dioxide, Crospovidone, Magnesium stearate, Sodium lauryl sulphate Titanium dioxide, Allura red, Tartrazine and Gelatin
Artize	Cetirizine HCL 10 mg	Tablet	Lactose, Cellulose, Providone, Magnesium stearate Silicon dioxide, HPMC Talc, polyethylene glycol and E171, Simethicone emulsion

arabic coffee (Bajah), orange juice (Almarai), and low-fat Laban (Almarai). All beverages were purchased from a local supermarket.

2.3. Methods

The disintegration test was performed using a Disintegration Tester Series DTG 2000 (Copley)® DTG2000 IS, United Kingdom (Fig. 1) with the capacity to test two different tablet batches, each of six tablets/capsules simultaneously.

The standardization of the apparatus was performed according to the USP guideline ⟨701⟩, which states that the thermostatic arrangement for heating the fluid should be 35–39 °C and that the basket ascends and descends at 29–32 cycles per minute in an immersion fluid until the tablet disintegrated completely so that the fragments fall out of the stainless-steel mesh.

Each of the six tablets or capsules of the same drug was dropped into the basket tubes of the disintegration apparatus, then the beaker was filled with 800 ml of beverage media. All disintegration times were determined in distilled water or the six beverages at two temperatures, 37 ± 2 °C and 5 ± 2 °C. Notable, arabic coffee was tested at 37 ± 2 °C and 43 ± 2 °C, since coffee is commonly consumed while hot. The time at which no residue remained on or attached to the screen of the test apparatus, i.e., the OSDF passed through the 2 mm diameter wire mesh, was recorded as the disintegration time for each tablet/capsule.

The above procedure was repeated using the different beverages as the disintegration media.

2.4. Statistical analysis

For each batch, the disintegration times for 6 tablets/capsules were determined, and the average disintegration time (±standard deviation) was calculated. The mean disintegration time was calculated in water as a control medium to be compared with the mean disintegration time of the product in each beverage. Univariate analysis of variance for data analysis and the Bonferroni test as the post hoc test were performed to identify which beverage and temperature differences were statistically significant. IBM SPSS Statistics version 20 was used to perform the statistical analysis. Population differences were considered significant at $p < 0.05$.

3. Results

The average disintegration time (±standard deviation) of all tested products in water and the different beverages are summarized in Table 2.

3.1. Fevadol

The mean disintegration times of the fevadol tablets are presented in Table 2 and in Fig. 2, A. univariate analysis of variance and Bonferroni tests showed that all alternative beverages and cold temperatures significantly increased the disintegration time of fevadol tablets, whereas disintegration time was significantly decreased at 43 °C ($P \leq 0.000$).

3.2. Solpadein

The mean disintegration times of the Solpadein capsules are presented in Table 2 and in Fig. 2, B. The univariate analysis of variance test showed that all the beverages and cold temperatures significantly increased the disintegration time of solpadein compared to water, whereas disintegration time was significantly decreased at 43 °C ($P \leq 0.000$). Bonferroni tests showed that orange juice, butter milk, Code red, and arabic coffee significantly increased the disintegration time of solpadein ($P \leq 0.000$). The disintegration time in Coca-cola at both temperatures (37 and 5 °C) also increased the disintegration time compared to that of water ($P = 0.018$).

3.3. Brufen

The mean disintegration times of Brufen are presented in Table 2 and in Fig. 2,C. The univariate analysis of variance showed that all the beverages and cold temperatures significantly increased the disintegration time of Brufen, whereas 43 °C significantly decreased the disintegration time ($P \leq 0.000$). The Bonferroni test showed that all the beverages significantly increased the disintegration time of Brufen, except the arabic coffee ($P = 1$).

3.4. Artize

The mean disintegration times of the Artize tablets in water compared to other beverages are presented in Table 2 and in Fig. 2, D. Although the univariate analysis of variance test showed that both temperature and media significantly influenced the disintegration time, Bonferroni tests showed that only Laban and orange juice significantly increased the disintegration time of Artize tablets ($P \leq 0.003$), while the arabic coffee slightly increased the disintegration time ($P = 0.011$). Coca-cola and Code red did not significantly increase the disintegration times of Artize tablets ($P = 1$).

3.5. Relaxon

The mean disintegration times of the Relaxon capsules in water compared to other beverages at the tested temperatures are presented in Table 2 and in Fig. 2 (E). The univariate analysis of vari-

Table 2
Disintegration times of all tested products in all tested media.

	Media											
	Water		Coca-cola		Code red		Orange juice		Laban		Arabic coffee	
Temp. (°C)	37 °C	5 °C	37 °C	5 °C	37 °C	5 °C	37 °C	5 °C	37 °C	5 °C	37 °C	43 °C
Mean(SD) of Fevadol	3.74 (0.48)	9.63 (0.53)	5.97 (0.39)	11.83 (1.02)	6.91 (0.72)	12.53 (03.21)	14.79 (1.71)	26.25 (1.72)	10.53 (0.54	28.94 (0.98)	4.66 (0.51)	2.36 (01.19)
Solpadein	9.05 (0.75)	19.33 (0.41)	13.38 (0.66)	19.13 (1.22)	14.85 (1.79)	25.12 (1.91)	15.35 (2.51)	30 (13.41)	16.18 (0.11)	37.45 (1.17)	10.98 (0.90)	7.66 (0.75)
Brufen	7.36 (2.45)	12.94 (2.69)	13.14 (1.66)	23.05 (1.89)	16.44 (2.10)	21.24 (0.70)	20.53 (5.45)	26.43 (1.44)	15.45 (1.70)	30.84 (1.89)	10.25 (1.13)	7.54 (2.41)
Artize	8.05 (1.95)	12.78 (1.6)	8.98 (1.53)	11.21 (0.640)	9.24 (2.23)	13.58 (1.61)	12.63 (1.34)	17.70 (1.72)	15.45 (1.70)	30.84 (1.89)	8.14 (1.65)	7.45 (1.65)
Relaxon	14.23 (4.47)	29.62 (5.40)	8.69 (0.41)	13.24 (0.07)	5.40 (0.08)	19.29 (0.46)	10.35 (0.38)	15.4 (0.58)	9.59 (1.12)	16.95 (0.20)	9.87 (0.97)	7.00 (0.48)

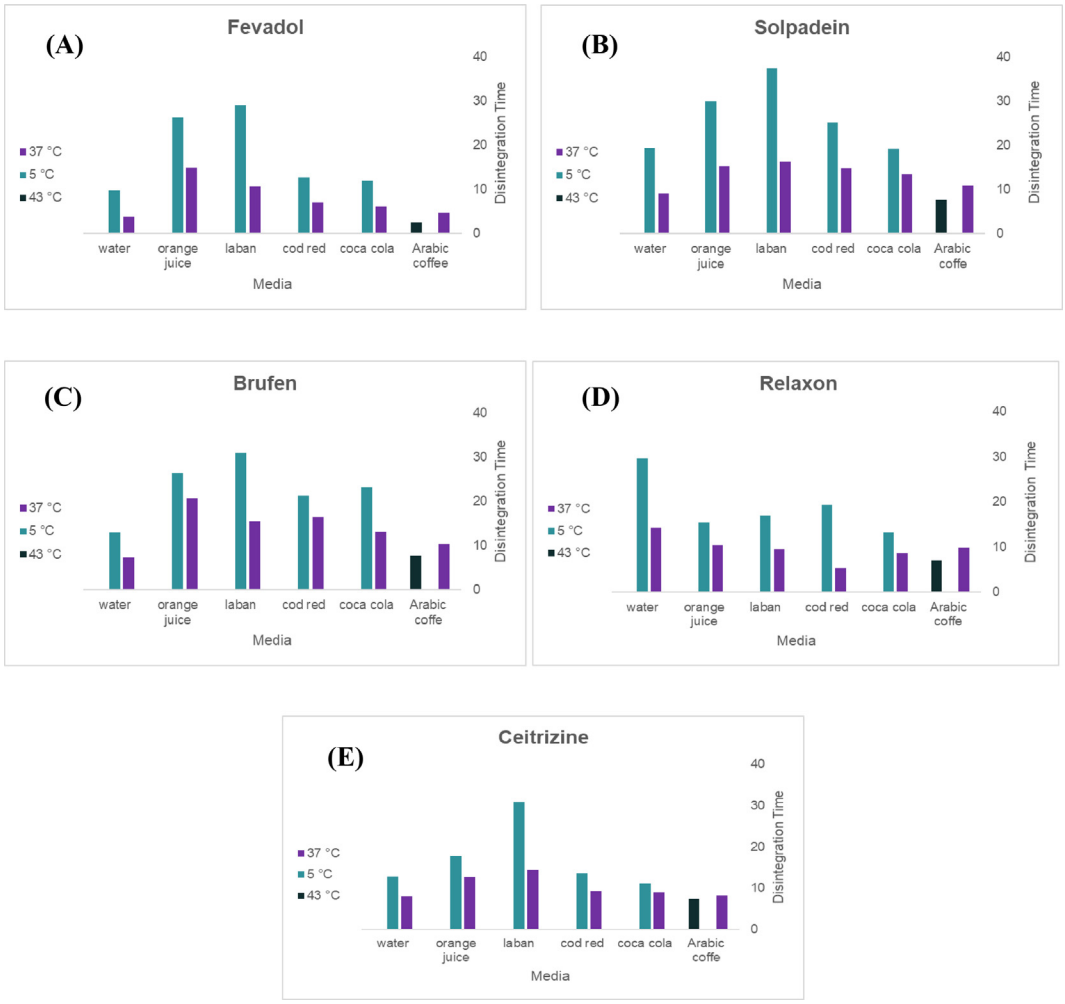

Fig. 2. The effect of the beverages (media) and temperatures on the disintegration time (DT) of the test product. A: Fevadol, B: Solpadein, C: Brufen, D: Relaxon, and E: Artize.

ance and Bonferroni tests showed that all the beverages and the 43 °C temperature significantly decreased the disintegration time, whereas the cold temperature (5 °C) increased the disintegration time, $P \leq 0.000$.

4. Discussion

The Saudi population consumes OTC medication on a large scale, where paracetamol, ibuprofen and solpadeine are among the top consumed OTC medications (Al-Ghamdi et al., 2020; Raja et al., 2020). Many OTC leaflets do not provide instructions about the type of liquid that should be used with OSDF administration; therefore, it can be assumed that any available beverage, including coffee, juices, or milk, can be administered with OTC medications (Al-Aqeel, 2012). Some patients prefer to take milk with their medication to minimize the risk for gastric irritation, while others take sweet beverages, such as juices or soft drinks to mask the unpleasant taste of their medications (Chuong et al., 2010; Yoshida et al., 2019).

The present study was designed to assess how different beverages impact the disintegration times of most common OTC medication tablets and capsules. The disintegration test was performed in buttermilk, Coca-cola, an energy drink, orange juice and arabic coffee, then compared to water. The beverages used in this study are among the top consumed drinks in Saudi Arabia. Cola drinks are widely consumed beverages worldwide (Nomani et al., 2019). Studies have shown that a high proportion of Saudi adults consume a high amount of soft drinks daily (Islam et al., 2020; Nada & Sami, 2018; Otaibi, 2017). Likewise, energy drinks, particularly Code Red, were found to be the top consumed energy drinks in Saudi Arabia compared to other types of energy drinks (Alrasheedi, 2016; Alsunni & Badar, 2011; Subaiea et al., 2019). Coffee is widely consumed worldwide, and traditional arabic coffee is the most widespread coffee in Saudi Arabia (Alfawaz et al., 2020; Jalloun & Alhathlool, 2020; Naser et al., 2018). Arabic coffee is a slightly roasted dry coffee bean mixed with spices such as cardamom, cloves and saffron. Buttermilk (Laban) is a fermented dairy product that is commonly consumed in Saudi Arabia (Béal et al., 2019; Wilson, 2017).

Our study showed that all beverages significantly delayed the disintegration time of fevadol tablets, solpadein capsules and brufen tablets. The same observation was found in Artize tablets, as all beverages delayed their disintegration time, but significant delays were found in buttermilk and orange juice (Table 2). In concurrence with our findings, a study from Nigeria aimed to assess the impact of orange juice, Coca-cola, energy drinks, and other beverages on the disintegration time of paracetamol uncoated tablets (Eraga et al., 2015). The researchers of the study found that all beverages significantly delayed the disintegration time of paracetamol (Eraga et al., 2015). Another study compared the disintegration times in water of three IR pain-relief tablets (ibuprofen, tramadol HCl, and the combination of hydrocodone bitartrate-

acetaminophen) with the disintegration in milk, orange juice, and Coca-cola using the USP disintegration apparatus (Chuong et al., 2010). The study found that Coca-cola and milk delayed the disintegration of all three products, while orange juice delayed the disintegration time of hydrocodone bitartrate–acetaminophen tablets and ibuprofen tablets (Chuong et al., 2010).

Among all other beverages used in our study that delayed the disintegration test, buttermilk (laban) and orange juice showed the most significant delay in disintegration times of all tested products. Similar to our findings, a study compared the disintegration times in different beverages of three IR pain-relief tablets (diclofenac, aceclofenac, and tramadol HCl) with disintegration in water. The results of the study showed that the disintegration times were delayed significantly in fruit juices and butter milk (Priya Patel, Hina Bagada, 2013). Another published study investigated the influence of buttermilk, in addition to other beverages, on the disintegration time of three immediate release pain reliever tablets: nimesulide, mefenamic acid, and aceclofenac(Rana et al., 2017). The study found that all studied tablets had significantly delayed disintegration time in buttermilk (Rana et al., 2017). A possible explanation for this delay might be the high viscosity and low surface tension of the laban and juice (Anwar et al., 2005; Chuong et al., 2010; Garin et al., 2014). Several studies have reported that an increase in media viscosity and a decrease in surface tension cause a profound delay in drug disintegration time (Radwan et al., 2014; Schramm, 1994; Zaheer & Langguth, 2019). Similarly, a study showed that food, particularly, milk content induced a strong delays in disintegration of IR tablets in-vitro and in-vivo (Abrahamsson et al., 2004). The prolonged DT in the butter milk (laban) could be also explained by the presence of protein (casein), and fat which can form a film around the tablets that cause significant rigidity and slow down the water penetration into the tablet (Abrahamsson et al., 2004).

These results showed that beverage intake may affect drug absorption by altering drug liberation (disintegration and dissolution) (Van Leeuwen et al., 2016). A study examined the effect of different juices on paracetamol dissolution (Deepak et al., 2019). The study found that the maximum drug dissolution in orange juice did not exceed 29% of the drug, compared to 98% of the drug at 120 min (Deepak et al., 2019).

In contrast to the other tested products, all beverages used as disintegration media sped up the disintegration of relaxon capsules compared to water, except arabic coffee. Although relaxon contains paracetamol, similar to fevadol and solpadin, the drug also contains chlorzoxazone, which is a weak basic drug. The change in pH in the beverage media used, especially in acidic beverages (Béal et al., 2019; Reddy et al., 2016), may also impact drug disintegration. For example, ketoconazole and itraconazole are weakly basic compounds and both are ionized only at a low pH. The absorption in humans was significantly increased when the drugs were taken with Coca-cola, which has a pH of 2.5 (Chin et al., 1995; Jaruratanasirikul & Kleepkaew, 1997). Another possible explanation for this observation could be the inactive ingredients used in the product and/or the components of the capsule shell, which do not behave the same in different media; therefore, the change in DTs induced by the beverages depends on the tablet composition (Abrahamsson et al., 2004; Cole et al., 2004; Tuleu et al., 2007; Zaheer & Langguth, 2019). As mentioned above, beverages may cause a delay in the DTs due to their high viscosity. Zaheer et al studied the role of excipients in minimizing the delay in DTs in high viscous media that induced by the food effect (Zaheer & Langguth, 2019). The study found that the DTs of the IR tablets in fed-state conditions differed significantly according to the type, amount and combination of the excipients used in the OSDF formulation. Interactions between the active component and capsule shell materials have also been reported to affect capsule disintegration (Glube et al., 2013).

Limited studies have systematically studied the effect of temperature on OSDF disintegration. To study the effect of temperature on disintegration, we used temperatures relevant to the purpose of the study (5 °C, 37 °C and 43 °C). The *in vitro* disintegration with the USP compendial disintegration apparatus was performed at 37 °C to mimic physiological body temperature (Al-Gousous & Langguth, 2015). The 5 °C temperature was chosen to simulate beverages that are usually ingested cold (orange juice, energy drinks and Coca-cola). However, a temperature of 43 °C was used to simulate elevated gastric temperatures due to fever or ingestion of a hot drink such as arabic coffee. Our study found that a cold temperature of 5 °C significantly decreased the disintegration time of all tested OSDFs used in the study. However, the high temperature, 43 °C, showed a decrease of the disintegration time. Temperature may affect the viscosity of the media (Haynes et al., 2012). This finding is supported by Basaleh et al., who investigated the effect of temperature on the disintegration of tablets using an image analysis technique and a compendial disintegration apparatus (Basaleh et al., 2020). The study found that the disintegration times of the tested tablets were reduced by increasing the temperature of the disintegration medium, where the extent of the temperature effect was variable between formulations (Basaleh et al., 2020). Excipients, particularly the binders, may also play a role in the tablet's formulation. The major determinant of tablet hardness is binding activity. As the temperature increases, the binding affinity is minimized; hence, the tablets can hydrate faster, forming looser and more porous plugs, which in turn lead to more rapid disintegration, and vice versa (Basaleh et al., 2020; Eraga et al., 2015). Combined effects from excipient-beverage interactions and the change in beverage viscosity by temperature may account for this observation.

Intragastric temperature returns to normal body temperature within 30 min of ingestion of cold drinks (Sun et al., 1988). Sun et al showed that the in vivo rate of gastric emptying slowed statically significantly after the cold drinks (4–5 °C) ingestion compared to the drinks ingested at 37 °C. The findings of this study may have major clinical impact. When beverages consumed with OSDF medications are ingested cold, their disintegration times exceed 15 min, which is the average gastric emptying time when fluid is taken with an OSDF in the absence of food (Table 2) (Zuo et al., 2013b). More importantly, OTC medications in IR perpetrations are designed and expected to release drugs instantaneously to take action in acute conditions. Administration of OSDFs with cold beverages other than water may decrease the OSDF onset of action. In contrast, studies conducted at room temperature can be expected to overestimate the disintegration times of OSDFs consumed with hot beverages.

Available evidence indicates that the package insert of Saudi-marketed drugs generally conveys limited and incomplete information (Al-Aqeel, 2012; Almukainzi, 2021; Almukainzi et al., 2020). Al-Aqeel et al examined the presence of information relevant for the safe and appropriate use of medication on package insert leaflets in Saudi Arabia. The researcher found that only 18% of the leaflets specified the type of beverages that should be ingested with the OSDF (Al-Aqeel 2012). Our previous study has examined the OSDFs administration manner and the adherence of patients to the instruction of administration criteria, and we found that 26% of the participants were frequently taking beverages other than water with their OSDF medication (Almukainzi, 2021). It is recommended that every package insert of OSDF medications should provide information related to consuming different beverages with medications to assure positive effects. In addition, the pharmacist's role in patient awareness is important to improve drug intake, assure positive effects and avoid negative impacts.

5. Conclusion

The study has shown that both the type and temperature of beverages that are commonly consumed with OSDFs affect the disintegration time of tested OTC products. OTC medications are designed to have a prompt onset of action; hence, any factor that affects drug disintegration may impact the onset of action and/or absorption. OTC medication in OSDF is recommended to be taken with a glass of water at room temperature. Increasing public awareness of drug-beverage interactions is needed to enhance drug efficacy.

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.

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