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ORIGINAL ARTICLE

Impact of Simulated Gastrointestinal Fluid: Viscosity, Surface Tension, and pH on the Dissolution and Rheology Assessment of Viscosity of Two Commercial Candesartan Cilexetil Products

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ABSTRACT

Objectives: The aim of this study was to ivnestigate the effect of simulated gastrointestinal viscosity, surface tension, and pH on the dissolution rate of two commercial candesartan cilexetil (CC) products.

Materials and Methods: *In vitro* dissolution of two commercial CC products and immediate release of 16 mg of CC were applied under two conditions: (1) the requirements of the United States Pharmacopeia (USP) and (2) conditions physiologically related to the gastrointestinal tract mimicking viscous food intake. The solubility of CC in different simulation fluids was also measured. The dissolution media's viscosity, surface tension, and pH were also measured. The viscosity of the gel layer was measured during CC dissolution.

Results: The CC dissolution rate was highest in the USP medium. It was found that the media type affected CC dissolution. The non-USP media exhibited a slower dissolution rate than the USP specification. The highest viscosity media lowered the dissolution rate in one of the CC products. Acidic pH showed a significant decrease in dissolution for both CC products. The solubility of CC was affected by solvent type (p value < 0.001).

Conclusion: Higher viscosity media slow the dissolution rate of a product, where a gel layer forms on the tablet surface.The results show variation in the dissolution media. This may reveal differences in the dissolution rates of the same drug in different products and media. Considering, viscosity's effect on dissolution might improve patient outcomes when treated with different products.

Keywords: Immediate release, dissolution, viscosity, simulated gastrointestinal fluid, gel

INTRODUCTION

The dissolution test is a tool that is conducted for measuring the *in vitro* performance of solid oral dosage forms and is performed during the design and optimization of tablet formulations as a comparative tool.[1] The data obtained from *in vitro* dissolution can be highly correlated with *in vivo* biopharmaceutical specifications.[2] Consequently, the generated data are used to predict the *in vivo* performance of oral drug products.[3] Therefore, the media used in *in vitro* dissolution studies should simulate the anticipated *in vivo* dissolution conditions, which sequentially mimic the physiological conditions in the gastrointestinal tract (GIT).[4]

Viscosity, surface tension, pH, and ionic strength of dissolution media are crucial conditions that affect drug dissolution.[5] In addition, several previous studies documented the effects of various dissolution conditions on the dissolution of poorly soluble drugs.[6,7]

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Solubility along with the dissolution of class II drugs can be affected by the complex luminal environment throughout GIT, including pH, buffer capacity, ionic strength, surface tension, osmolality, food intake, viscosity, GI motility, and volume available for drug dissolution.[8] When selecting a proper test method in a well-controlled environment, the dissolution test remains sensitive and affected by the finished product composition, material properties (including material source), and manufacturing process of the tested drug.[9] Hence, the choice of an appropriate medium for the evaluation of the dissolution of BCS class II drugs, which simulates the physiological conditions of GI fluids, is crucial for better predicting *in vivo* oral performance and differences in bioavailability among different formulations.[10,11]

The limited dissolution of highly permeable/low-soluble drugs, classified as class II drugs according to BCS, makes them less likely to be absorbed in the oral cavity.[7] Moreover, the physiological conditions of GIT may influence the speed of drug dissolution; for example, increasing the viscosity and surface tension of the dissolution medium may affect drug liberation from its pharmaceutical dosage form.[8] Therefore, testing the effects of these conditions on the dissolution of BCS class II drugs is important.

Candesartan cilexetil (CC) is an angiotensin II receptor blocker of BSC class II drugs.[12] CC is commonly used for the treatment of heart failure, hypertension, diabetic nephropathy, and myocardial infarction.[13] CC was previously used as a model drug for class II drugs due to its low solubility in water (lower than 8 x 10^{-8} M) and low bioavailability.[14] Therefore, the aim of this study was to investigate the effects of different parameters including viscosity, surface tension, and pH, on the dissolution of two CC tablets.

MATERIALS AND METHODS

Materials

CC powder was obtained from Dar Al Dawa Pharmaceuticals (Amman, Jordan). Two commercial 16 mg CC immediate-release tablets were collected from the Jordanian market; CC product 1 (AstraZeneca Company, UK, batch number: GTIN 07321839721397, production date: 01-2019) and CC product 2 (United Pharmaceuticals Manufacturing Co., Amman, Jordan, batch number: M073 JPD, production date: 01-2018). Table 1 presents the excipients and pharmaceutical uses of the two CC products.

Tween® 20 was purchased from Tedia Company (OH, USA), sodium lauryl sulfate (SLS, 94%) from Laboratory Rasayan (Gujarat, India), hydroxypropyl methylcellulose (HPMC; M = 69.49) from AZ Chem for Lab Chemicals (Pretoria, South Africa), and acetonitrile (CH3CN, 99.9%) from Sigma-Aldrich (Germany). Sodium acetate anhydrous (CH_3COONa, 99%, Guangdong Guangzhou Sci-Tech Co., Ltd, Guangzhou, China), sodium hydroxide (NaOH, 99%, EMD Millipore Corporation, Fairburn, Georgia), glacial acetic acid (CH_3CO_2H, 99.8%, Scharlab, Barcelona, Spain), hydrochloric acid (HCl, 37% *w/w*, Fisher, Shanghai, China), ethanol (EOH, Fisher, Shanghai, China), sodium tri-phosphate (Na_3PO_4, 98%, Fisher, Shanghai, China), and potassium dihydrogen phosphate (KH_2PO_4, 99.9%, Fisher, Shanghai, China). All chemical reagents used in the preparation of dissolution media were analytical grades.

Dissolution media

The contents of the compendial United States Pharmacopeia (USP) medium buffer and the four non-compendial dissolution media were prepared to investigate the effects of low pH (0.1N HCl), low surface tension (0.4% *w/v* SLS), and high viscosity (0.1 and 0.2% *w/v* HPMC).

Preparation of the CC calibration curve

Calibration curves for CC in the CC-USP, HCl, SLS, 0.1% HPMC, and 0.2% HPMC media were prepared according to previously documented procedures,[15] which were briefly described as follows: 100 mg of CC was weighed into a 100 mL volumetric flask, 10 mL of acetonitrile was added, and the flask was sonicated for 10 min. An additional volume of acetonitrile was added to the mixture to reach a final volume of 100 mL. The resulting standard stock solution (1 mg/mL) was used to prepare the final standard concentrations of 2, 5, 6, 10, 20, and 35 µg/mL by diluting the stock solution in plain USP medium (CC-USP) as well as in the other investigated media, including HCl, SLS, 0.1% HPMC, and 0.2% HPMC. The calibration curves were prepared three times, and the mean of the resulting curves was obtained.

The concentration of the dissolved drug in the media was measured using an ultraviolet (UV)-Vis spectrophotometer-1800 (SHIMADZU) scanned over a range of 200-400 nm to detect the maximum wavelength absorbance (λ_{max}). The absorbance

Table 1. Excipients of two commercially available CC tablets as issued on a leaflet by the manufacturers. product 1 (AstraZeneca Company, UK, batch number: GTIN 07321839721397, production date: 01-2019) and product 2 (United Pharmaceuticals Manufacturing Co., Amman, Jordan, batch number: M073 JPD, production date: 01-2018)

Pharmaceutical function	Product 1	Product 2
Disintegration enhancer Thickening agent	Carmellose sodium	
Disintegration enhancer Compression molding Adhesion agent		Microcrystalline cellulose*
Flow enhancer Direct-compression excipient	Lactose monohydrate	Lactose monohydrate
Dissolution enhancer	HPMC	HPMC
Direct-compression excipient Disintegration enhancer Diluent	Maize starch	Maize starch
Wetting agent Penetration enhancer	Macrogol	Polyethylene glycol
Colorant Ultraviolet absorber	Iron oxide (E127)	Ferric iron oxides

UV: Ultraviolet, CC: Candesartan cilexetil

was measured against 1 mL of acetonitrile in 100 mL of each prepared medium. The measured absorbance was plotted against drug concentrations to determine absorptivity using the Beer-Lambert equation.[16]

Hardness testing

Randomly selected tablets of CC products 1 and 2 (n= 10) were tested for hardness using an automated hardness tester (electrolab, India). The mean and standard deviation (SD) of the force were recorded in Newton (N).

In vitro dissolution testing

Dissolution testing was conducted in 900 mL of the investigated media to which the tablets were added. In all experiments, the temperature was fixed at 37 ˚C ± 0.5 using USP apparatus II (paddles) rotating at 50 rpm. Samples were withdrawn from the media at specific time intervals (15, 30, 45, 60, 75, 90, 105, and 120 min). Samples (3 mL) were first passed through a 0.22 µm syringe filter, and the amount of dissolved CC in the media was analyzed using a UV-Vis spectrophotometer at λ_{max} 254 nm. According to USP requirements, immediate-release dosage forms require the release of not less than 80% of the claimed amount after 45 min.[17] The dissolution rate of CC (expressed as dissolution percentage; %) was calculated by establishing calibration curves for each medium, with Milli-Q water used as a control. The applied tests were repeated six times for each product, and the raw material was dissolved in the investigated media. The same control and number of replicates were used in the solubility study, surface tension measurement, viscosity measurements, pH measurements, and ionic strength measurements.

Solubility of CC

The solubility of CC in the investigated media was measured as previously described (Hassan et al.,[15]). Briefly, CC was added in excess of 15 mL of each medium. The mixtures were kept at 37 ˚C for 24 h and then filtered through a 0.2 µm syringe filter. The filtrates were collected, and UV absorbance was measured using a UV-Vis spectrophotometer at λ_{max} 254 nm.[18]

Surface tension measurements

The surface tension of dissolution media containing drugs was measured using a micro-roughened platinum plate tensiometer (Tensiometer Attension®, Biolion Scientific, Sweden). The measurements were performed on the surface of Platinum plates immersed in 40 mL of the investigated media, which were placed in a round vessel made of Pyrex (with 50 mm diameter) and then incubated in a water bath for three minutes at 37 ˚C.

Viscosity testing of the dissolution media and gel layer formed on the tablet surface

The viscosities of dissolution media and the gel layer formed on the surface of the tablets undergoing dissolution were measured at 37 ˚C using Rheometer DVT3 (Brookfield, USA), coupled with a 4-mm diameter cone and plate geometry of 1˚. Tablets were first placed in dissolution vessels containing dissolution media. After 15 min, the formed gel layer on the tablets was carefully removed using a spatula. Viscosity measurements were performed at a shear rate of 75 s1, speed of 10 rpm, and strain stress of 0.01-10%.

pH and ionic strength testing

The pH of the media was measured using a pH meter (Mettler Toledo, USA) calibrated before each measurement. The ionic strength of the media was calculated using the following equation:

$$I = \frac{1}{2}\sum_{1}^{n} c_i z_i^2 \qquad (1)$$

Where I is the ionic strength, in the number of species in the solution, c_i is the molar concentration of ion I, z_i is the charge number of ions, and Σ refers to the summation symbol (the sum of overall ions in the solution).[7]

Statistical analysis

Data analysis was conducted using GraphPad Prism version 7. One-Way analysis of variance and Two-Way analysis of variance followed by the Tukey test were used ti differentiate and compare the dissolution profiles of CC products 1 and 2 in the tested media. Data were presented as mean ± SD. A p value lower than 0.05 (p value <) was deemed statistically significant.

RESULTS

CC calibration curves

The calibration curves of raw CC were obtained in all dissolution media with λ_{max} of 254 nm. The plotted curve was linear for all three replicates in a concentration range of 2 to 35 µg/mL. Results: Mean correlation factor R^2 = 0.9997 and mean slope (ε) of 27.5 $mg^{-1}.0.1L^{-1}.cm$.

CC hardness test

Products 1 and 2 had a significantly higher index of hardness (92.0 ± 3.7 N; p value < 0.01) compared to products 2 (56.6 ± 4.9 N).

Solubility, surface tension, viscosity, and ionic strength of raw CC in dissolution media

Table 3 presents the solubility of raw CC in different dissolution media and its physicochemical properties. The highest solubility was observed in CC-USP medium (20.9 ± 0.5 µg/mL), followed by SLS (14.7 ± 0.3 µg/mL) and 0.1% HPMC (13.9 ± 0.4 µg/mL) media. Lower solubility was observed in 0.2% HPMC (5.6 ± 0.3 µg/mL) and HCl (3.7 ± 0.2 µg/mL) media.

The highest surface tension was achieved using Milli-Q® water (72.0 ± 0.0 mN/m). The surface tension of the CC-dissolved media was comparable between the investigated media, ranging from 34.8 and 34.7 mN/m in HCl CC-USP media, respectively, followed by 33.2 mN/m in 0.1% and 0.2% HPMC, and then 30.20 mN/m in SLS media.

The highest viscosity was observed in the 0.2% HPMC medium, which was ten times higher than the viscosity of the Milli-Q® water, which was used as a control (8.0 ± 0.8 vs. 0.8 ± 0.1 cP 0.2% HPMC, Milli-Q® water respectively). The viscosity

decreased as the HPMC concentration decreased to 0.1% (5. 5 ± 0.3 cP). The CC-USP, HCl, and SLS media exhibited similar viscosities (1.2 ± 0.1, 1.2 ± 0.1, 1.2 ± 0.1 cP, respectively), which were approximately eight times lower than that of the 0.2% HPMC medium.

The ionic strength of the HCl media was the highest (0.1 mM), whereas the other media, except Milli-Q® water, had relatively similar ionic strengths of 0.06-0.07 mM. The results are presented in Table 2.

In vitro dissolution of Product 1

Figure 1 shows the dissolution profiles of product 1 tablets in the investigated media. CC dissolution was significantly affected by the dissolution media employed. While using the CC-USP medium, product 1 met the recommended USP release rate at 45 min post-dissolution of 106.9 ± 6.2%, whereas the USP requirements were not observed in the other dissolution media. As an example, low dissolution was observed in the SLS medium (51.80 ± 4.72% after 45 min), followed by that observed in the HCl medium (30.6 ± 8.96% after 45 min). Almost no release was detected when HPMC was used as a viscosity enhancer at a 0.2% *w/v* concentration. However, the rate of CC release was slightly increased to 12.16 ± 7.79% after 120 min when the concentration of HPMC was reduced to 0.1% *w/v*.

The differences in CC release rate using different dissolution media were marked immediately after 15 min post-dissolution. The CC-USP medium achieved a dissolution of 65.86 ± 13.77% in 15 min, followed by the SLS medium (24.1, ± 6.61%; *p* value < 0.001). Compared with the CC-USP medium, the rate of release was slower (*p* value < 0.001) in HCl medium with a release rate of 21.77 ± 6.48% after 15 min.

In vitro dissolution of product 2

Figure 2 illustrates the dissolution profiles of product 2 tablets in the investigated media. The dissolution profiles were significantly affected by the media employed. At 45 min, the highest CC dissolution was recorded in the CC-USP medium (100.5 ± 6.19%), followed by the 0.1% HPMC medium (97.36 ± 6.77%). However, dissolution was significantly lower in SLS (56.0 ± 1.8%), 0.2% HPMC (32.3 ± 9.2%, %; *p* value < 0.001), and HCl media (24.0 ± 1.7%, %; *p* value < 0.001).

Viscosity of the gel layer temporarily formed on dissolved tablets

A clear gel layer was formed on the surface of the tablets containing product 1 but not those containing product 2. The viscosity of the gel layer (Figure 3) was highest when using Milli-Q® water (5.15 ± 0.31 CP). The viscosity of the gel layer decreased to 4.25 ± 0.16 CP, and 3.66 ± 0.14 CP when using 0.2% HPMC and 0.1% HPMC media, respectively. The viscosities of the gel layers formed in the CC-USP medium (1.53 ± 0.16 CP) and the HCl medium (1.66 ± 0.46 CP) media were comparatively similar and low.

DISCUSSION

CC is a BCS class II drug that is typically characterized by low solubility and high permeability, which limit its oral bioavailability.[13,14] Therefore, the *in vitro* dissolution testing of CC is important for predicting its *in vivo* absorption and bioavailability. Consequently, optimization of the experimental parameters of the *in vitro* dissolution testing when compared to *in-vivo* conditions was needed. Comparing the two commercial CC products is not the primary aim of this study; on the contrary, it aims to identify new validated methods that are not usually applied in QC analysis to determine the physicochemical properties of the products.[19,20]

Dissolving the investigated commercial CC tablets in USP medium met the USP compendial requirements. However,

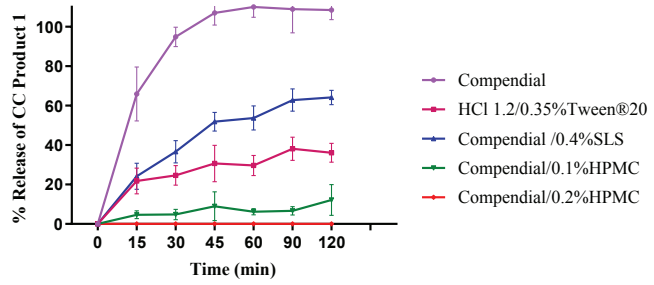

Figure 1. Dissolution profiles of candesartan cilexetil CC-product 1 (AstraZeneca Company, UK, batch number: GTIN 07321839721397, production date: 01-2019) were obtained at a rotation speed of 50 rpm and 37 °C, (n= 6). Dissolution was performed using CC-USP, HCl, SLS, 0.1% HPMC, and 0.2% HPMC media

CC: Candesartan cilexetil, USP: United States Pharmacopeia, HCl: Hydrochloric acid, SLS: Sodium lauryl sulfate, HPMC: Hydroxypropyl methylcellulose

Table 2. Composition of the media (components per 100 mL) used for dissolving candesartan and cilexetil

Media	pH	Phosphate buffer at pH 6.5		Tween® 20 (g)	HCl (mL)	SLS (g)	HPMC (g)
		Na2HPO4-7H2O (g)	NaH2PO4H2O (g)				
CC-USP	6.5	0.96	0.88	0.35			
HCl	1.2			0.35	8.3		
SLS 0.4% w/v	6.5	0.96	0.88	0.35		0.4	
0.1% HPMC	6.5	0.96	0.88	0.35			0.1
0.2% HPMC	6.5	0.96	0.88	0.35		0.2	

CC: Candesartan cilexetil, USP: United States Pharmacopeia, HCl: Hydrochloric acid, SLS: Sodium lauryl sulfate, HPMC: Hydroxypropyl methylcellulose

changes in the dissolution media conditions such as the viscosity and the surface tension were not responded in the same pattern when using different types of investigated media. Surfactants are usually used in the preparation of dissolution media to enhance the drug wetting and dissolution process.[21] When the surfactant concentration was increased, micelles were formed, and their stability was generally related to the critical micelle concentration (CMC).[22] The rationale for selecting specific surfactants for *in vitro* testing is essential to understand their interaction with drug molecules and other ingredients in dissolution media and excipients.[23,24] A 0.5 *w/w*% tween® 20 sample had a surface tension of 3.7 mN/m,[22] whereas the surface tension of SLS was 39.4 mN/m at an estimated CMC of 0.58 *w/v*%.[25] Differences in surface tension and CMC between the two surfactants used to explain the rheological behavior and wetting of dissolved drugs.[25] The USP medium includes tween® 20, which may enhance the dissolution of CC. The addition of 0.4% SLS to the USP medium was performed to further reduce surface tension and simulate gastric fluid conditions, which were approximately 30 mN/m.[26,27] However, the addition of SLS did not increase the rate of CC dissolution in the tablet products. This result can be attributed to the interaction between the anionic SLS and the cations present in the buffer, which may result in the formation of insoluble material that lowers the effect of SLS.[28] Moreover, the addition of more components may disrupt the water structure, reducing the cohesive dielectric constant and cohesive energy, leading to lowering solvent polarity[28] and, as a result, causing a reduction in drug dissolution. Generally, the viscosity of the dissolution media plays an essential role in the dissolution of drugs.[5] It was found that CC tablets and the raw material used in this study exhibited different dissolution patterns. The dissolution of CC in product 2 was comparable to that of raw CC in the CC-USP medium. On the other hand, the dissolution of CC in product 1 was comparable to that of raw CC in the CC-USP and 0.1% HPMC media but was slower in 0.2% HPMC, which has a higher viscosity level. The recorded viscosity of raw CC in the 0.2% HPMC medium was approximately eight times higher than that of the CC-USP medium, which may explain the slow dissolution of raw CC in the 0.2% HPMC medium. High viscosity can inhibit drug dissolution by reducing the dissolution rates.[29] Therefore, the passage of the drug through the surrounding medium is impeded, increasing the resistance to drug diffusion.[30] Viscosity may vary according to food content and the different parts of the GIT, which affects the diffusion of the drug into the surrounding media.[31] The variation between commercial drugs

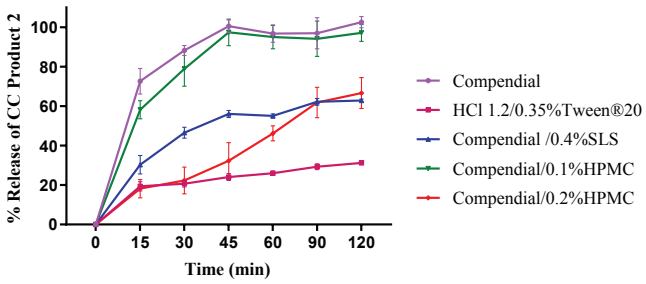

Figure 2. Dissolution profiles of candesartan cilexetil (CC-product 2: United Pharmaceuticals Manufacturing Co., Amman, Jordan, batch number: M073 JPD, production date: 01-2018) were obtained at a rotation speed of 50 rpm and 37 °C (n= 6). Dissolution was performed using CC-USP, HCl, SLS, 0.1% HPMC, and 0.2% HPMC media

CC: Candesartan cilexetil, USP: United States Pharmacopeia, HCl: Hydrochloric acid, SLS: Sodium lauryl sulfate, HPMC: Hydroxypropyl methylcellulose

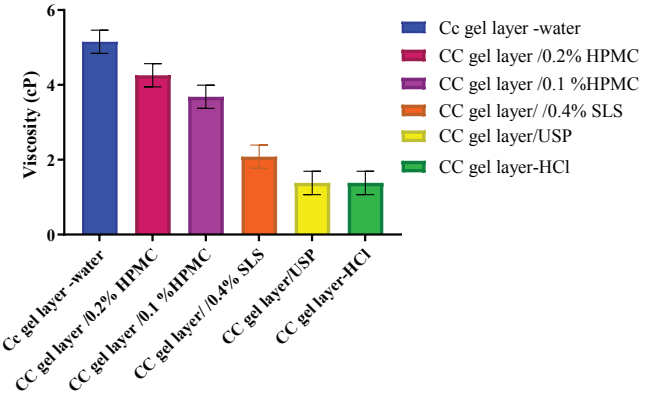

Figure 3. The viscosity of the gel layer formed on the surface of commercially available tablets of candesartan cilexetil (product 1: AstraZeneca Company, UK, batch number: GTIN 07321839721397, production date: 01-2019) after 15 min dissolution in various media at 37 °C and 50 rpm.

CC: Candesartan cilexetil, USP: United States Pharmacopeia, HCl: Hydrochloric acid, SLS: Sodium lauryl sulfate, HPMC: Hydroxypropyl methylcellulose

Table 3. Solubility, surface tension, viscosity, and ionic strength of raw CC in different media at 37 °C. Data are presented as mean ± SD. Milli-Q water was used as a control. The tests were repeated six times for each product, and the raw material was dissolved in the investigated media

Dissolution media	pH	Solubility (µg/mL)	Surface tension mN/m	Viscosity (CP)	Ionic strength (mM)
Milli-Q® water	6.99	1.7 ± 0.6	72.0 ± 0.0	0.8 ± 0.1	0.00
CC-USP	6.5	20.9 ± 0.5	34.7 ± 0.0	1.2 ± 0.1	0.06
HCl	1.2	3.7 ± 0.2	34.8 ± 0.8	1.2 ± 0.1	0.10
SLS	6.5	14.7 ± 0.3	30.20 ± 0.1	1.2 ± 0.1	0.07
0.1% HPMC	6.5	13.9 ± 0.4	33.2 ± 0.9	5.5 ± 0.3	0.06
0.2% HPMC	6.5	5.6 ± 0.3	33.2 ± 0.3	8.0 ± 0.8	0.06

CC: Candesartan cilexetil, USP: United States Pharmacopeia, HCl: Hydrochloric acid, SLS: Sodium lauryl sulfate, HPMC: Hydroxypropyl methylcellulose

and non-compendial requirements could be related to different compositions and sources of raw materials.[20] Therefore, an explanation of the food breeds that may reduce the availability of drugs should be noticed in the product leaflets.

Typically, the first step in drug dissolution is wetting followed by gelling the tablet.[4] The formed gelling layer is stagnant and is expected to dissolve to enhance the release of drugs from the tablet.[26] In this study, gel layers were formed in the tablets containing product 1 after 15 min of dissolution. Tablets of product 2 disintegrated quickly, probably as a result of the existence of microcrystalline cellulose. In addition, a harder tablet may increase the probability of dissolution failure.[32] On the other hand, higher compression forces are employed to attain tablet hardness, which results from an increase in interparticle bonding.[33] Hardness can be affected by processing techniques such as direct compaction, hot melt extrusion, or fused melting deposition, as well as by affecting intermolecular interactions, causing an increase in the tablet's hardness.[34] Furthermore, disintegration can be somehow related to tablet hardness. A harder tablet may increase the probability of dissolution failure; therefore, it takes longer for the tablet to interact with the medium to form the presumed gel layer.[35] In addition, the ionic strength of the media affects the formation and viscosity of gel layers formed on the surface of tablets.[8] High ionic strength increases the electrolyte concentration, thus increasing the spaces between water molecules as a result of the salting-out effect, which decreases gelation.[36] This will support the current findings that lower viscosity of the formed gel layers was observed in media of higher ionic strength (HCl and SLS) compared to the viscosity of gels formed in media of lower ionic strength (Milli-Q water, 0.1 and 0.2% HPMC).

The pH of the dissolution media plays an important role in drug ionization throughout the GIT.[37] In fasting conditions, the pH of the stomach can reach 1.2 or lower.[11]

When CC (pK_a = 4.66) is taken under fasting conditions with a low stomach pH, CC will be expected to exist in its unionized form, and thereby, it will precipitate. This was obvious in the current study, as the observed solubility of CC in the HCl medium was five to six times lower than that in the CC-USP medium, which affected the dissolution results for both products. It is worth mentioning that the leaflets of CC products lack instructions for avoiding the intake of tablets in the fasted stomach. This could be revised in the future to enhance the effects of CC.

CONCLUSIONS

The *in vitro* dissolution of two commercial products of immediate-release tablets containing CC in USP and non-USP media with various physiological properties was studied. Both products were consistent with the compendial requirement for immediate release according to USP, whereby more than 85% of the claimed amount was released after 45 min. However, the dissolution of tablets varied when using different media conditions. A higher-viscosity media slowed the dissolution rate of one CC product. It was found that a gel layer could form on tablets, thereby reducing the dissolution rate. The present results showed that variations in the pharmacopeia requirements of dissolution media may not only exhibit differences in the dissolution of the same drug in different products but can also show different dissolution profiles between these products in the investigated media. The findings of this study should be taken into consideration when revising the instructions in the published leaflets of the investigated CC tablets.

Ethics

Ethics Committee Approval: Not required.

Informed Consent: Not required.

Authorship Contributions

Concept: A.F., F.B.H., M.G., G.B.N., J.M., L.-N.M., S.G., Design: A.F., F.B.H., M.G., G.B.N., J.M., L.-N.M., S.G., Data Collection or Processing: A.F., F.B.H., G.B.N., L.-N.M., Analysis or Interpretation: A.F., M.G., J.M., L.-N.M., Literature Search: A.F., F.B.H., M.G., G.B.N., J.M., L.-N.M., S.G., Writing: A.F., F.B.H., G.B.N., L.-N.M.

Conflict of Interest: The authors have no conflicts of interest to declare.

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