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

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ABSTRACT
Objectives: The effect of simulated gastrointestinal viscosity, surface tension and pH on dissolution rate of a two commercial products of candesartan cilexetil (CC) were illustrated.
Materials and methods: In-vitro dissolution of two commercial CC products immediate release of 16 mg CC were applied under two conditions: (1) the requirements of the United States Pharmacopeia (USP), (2) a conditions that is physiologically related to gastrointestinal tract (GIT) mimicking viscous food intake. Solubility of CC in different simulated fluid was measured. Viscosity, surface tension and pH of the investigated dissolution media were also detected. The viscosity of the gel layer was measured during dissolution of CC .
Results: Dissolution rate of CC was highest in USP medium. It was found that the media type affected the CC dissolution. Non USP media exhibited slower dissolution rate compared to USP specification. Highest viscosity media slower the dissolution rate in one of CC products. Acidic pH showed a significant lowing in dissolution for both CC products. Solubility of CC was affected by solvent type.
Conclusions: Higher viscosity media slower the dissolution rate of one product, where a gel layer was formed on the tablet surface leading to slow the dissolution rate. The current results showed a variation in dissolution media. That may reveal differences in the dissolution rates of the same drug in different products and different investigated media. Taking this into consideration; the effect of viscosity on the dissolution might lead to better patient's outcomes when treated by different products.
Keywords: immediate release; dissolution; viscosity; simulated gastrointestinal fluid, gel

INTRODUCTION

Dissolution test is basically a tool that is conducted for measuring the in-vitro performance of solid oral dosage forms and 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 the in-vivo biopharmaceutical specifications[2]. Consequently, the generated data will be used for prediction the in-vivo performance of oral drug products[3]. Therefore, the employed media in the in-vitro dissolution studies should simulate the anticipated in-vivo dissolution conditions, which sequentially mimic the physiological conditions in the GIT [4].
Viscosity, surface tension, pH and ionic strength of dissolution media are crucial conditions that affect the drug dissolution [5], in addition, several previous studies documented the effect of various dissolution conditions for the dissolution of poorly-soluble drugs[6,7].
The solubility along with the dissolution of class II drugs can be affected by the complex luminal environment throughout the GIT, including: pH, buffer capacity, ionic strength, surface tension, osmolality, food intake, viscosity, GI motility, and volume available for drug dissolution[8]. Although, when selecting a proper test method in a well-controlled environment, dissolution test still sensitive and affected by the finished product composition, material property (including material source), and the manufacturing process of the tested drug[9]. Hence, the choice

of an appropriate medium for evaluation of the dissolution of BCS class II drugs, which simulates the physiological conditions of GI fluids, is crucial regarding a better predict for in-vivo oral performance and differences in bioavailability among different formulations[10].
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, physiological conditions of the GIT may influence the speed of drug dissolution; for example, increasing the viscosity and surface tension of the dissolution medium may impact drug liberation from its pharmaceutical dosage form[8]. Therefore, testing the effect of these conditions on the dissolution of the 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 in 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 8×10^{-8} M), with low bioavailability[14]. Therefore, in this study the effect of different parameters including: viscosity, surface tension and pH on the dissolution of two CC tablet will be investigated. The designated CC tablets are provided by different manufacturers and available in the local Jordanian market.

MATERIALS AND METHODS

Materials
CC powder was kindly donated by Dar Al Dawa Pharmaceuticals (Amman, Jordan). Two commercial CC immediate-release tablets of 16 mg CC were collected from the Jordanian market; CC Product 1: AstraZeneca Company, UK, batch no. GTIN 07321839721397, production date: 01-2019, and CC Product 2: United Pharmaceuticals Manufacturing Co., Amman, Jordan, batch no. M073 JPD, production date: 01-2018. Table 1 showed the excipients and the pharmaceutical use of the two products of CC.
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 (Na3PO4, 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.
Preparation of dissolution media
The contents of the compendial USP medium buffer and the four non-compendial dissolution media were prepared to investigate the effect 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), are presented in Table 2.

Preparation of 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 previous documented procedures[15], which briefly described as follows: 100 mg of CC was weighed into a 100 mL volumetric flask, then 10 mL of acetonitrile was added then 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 in the preparation of the final standard concentrations of 2, 5, 6, 10, 20, and 35 µg/mL by diluting the stock solution in the plain USP medium (CC-USP) as well as in the other investigated media including HCl, SLS, 0.1% HPMC, and 0.2% HPMC. The generating calibration curves were prepared three times and the mean of the resulted curves was obtainable.
The concentration of the dissolved drug in the media was measured using UV-Vis spectrophotometer-1800 (SHIMADZU), scanned over a range of 200 to 400 nm to detect the maximum wavelength absorbance (λ_{max}). The absorbance was measured against a blank of 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 their hardness by 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 in which the tablets of the products 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 the USP requirements, the 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 corresponding medium with Milli-Q water was used as a control. The applied tests were repeated six times for each product and the raw material dissolved in the investigated media. The same control and number of replicates were used in the solubility study, the surface tension measurement, viscosity tests, pH and ionic strength testing.

Solubility study of CC

The solubility of CC in the investigated media was measured as previously described (Hassan et al., 2015). Briefly, CC was added in an excess amount to 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 the UV absorbance was measured using a UV-Vis spectrophotometer at λ_{max} 254 nm[18].

Surface tension measurement

The surface tension of the dissolution media containing drugs was measured by a micro-roughened platinum plate tensiometer (Tensiometer Attension®, Biolion scientific, Sweden). The measurements were made 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) then incubated in a water bath for three minutes at 37˚C.

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

The viscosities of dissolution media and the gel layer that was formed on the surface of the tablets undergoing dissolution were measured at 37ºC using Rheometer DVT3 (Brookfield, USA), coupled with a 4 mm diameter cone and plate geometry of 1°. Tablets were first placed in the dissolution vessels containing dissolution media. Then after 15 min of immersing, the formed gel layer on the tablets was carefully removed using a spatula. Viscosity measurement was performed at a shear rate of 75 s-1, 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:

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

where I refers to the ionic strength, n the number of species in the solution, c_i the molar concentration of ion *I*, z_i refer to 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 software version 7. The difference between groups was determined by one-way analysis of variance and two-way analysis (ANOVA) followed by the Tukey test to compare the dissolution profiles of CC Products 1 and 2 in all tested media. Data were represented as mean ± standard deviation (SD) and (p-value < 0.05) was deemed statistically significant

RESULTS

CC calibration curves

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

CC Hardness test

Product 1 tablets had significantly higher index of hardness (92.0 ± 3.7 N; p-value < 0.01) compared to product 2 (56.6 ± 4.9 N).

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

Table 3 represents the solubility of raw CC in the different dissolution media and the physicochemical properties of the dissolution media. The highest level of solubility was found 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. The lower solubility was found in 0.2% HPMC (5.6 ± 0.3 µg/mL) and HCl (3.7 ± 0.2 µg/mL) media.

The highest level of surface tension was attained using Milli-Q® water (72.0 ± 0.0 mN/m). The surface tension of the CC dissolved media was comparable in 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 0.2% HPMC medium, with 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 with lowering HPMC concentration 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 other media, except Milli-Q® water, had relatively similar ionic strengths of 0.06 to 0.07 mM.

vitro dissolution of Product 1
Figure 1 shows the dissolution profiles of Product 1 tablets in the investigated media. The CC dissolution was significantly affected by the employed dissolution media. 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 seen in the other dissolution media. As an example, the 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 using HPMC as a viscosity enhancer at 0.2% w/v concentration. However, the rate of CC release was slightly elevated to 12.16 ± 7.79% after 120 min when the concentration of HPMC was reduced to 0.1% w/v.
The difference in CC release rate using different dissolution media was marked immediately after 15 min post-dissolution. The CC-USP medium achieved dissolution of 65.86 ± 13.77% at 15 min, followed by SLS medium (24.1, ± 6.61%; p- value < 0.001). Compared to 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**.**

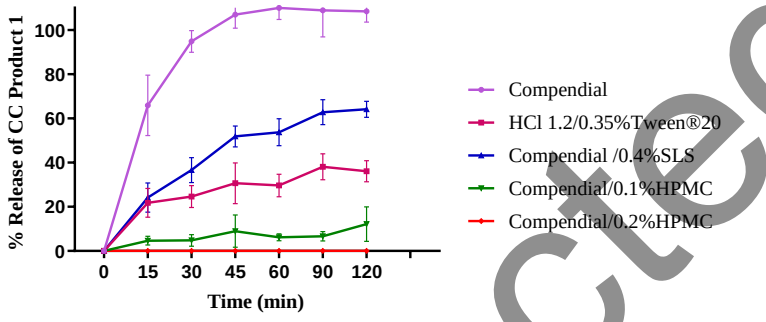

Figure 1. Dissolution profiles of candesartan cilexetil CC - Product 1 (AstraZeneca Company, UK, batch no. GTIN 07321839721397, production date: 01-2019) attained at a rotation speed of 50 rpm at 37°C, (n = 6). The dissolution was performed using CC-USP, HCl, SLS, 0.1% HPMC, and 0.2% HPMC media.

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 employed media. At 45 min, the highest levels of dissolution of CC was recorded using the CC-USP medium (100.5 ± 6.19%), followed by the 0.1% HPMC medium (97.36 ± 6.77%). However, the dissolution was significantly lower in both SLS (56.0 ± 1.8%), 0.2% HPMC (32.3 ± 9.2%), and HCl media (24.0 ± 1.7%).

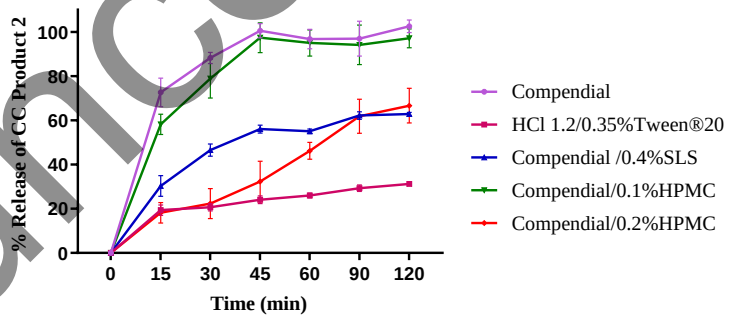

Figure 2. Dissolution profiles of candesartan cilexetil (CC - Product 2: United Pharmaceuticals Manufacturing Co., Amman, Jordan, batch no. M073 JPD, production date: 01-2018) attained at a rotation speed of 50 rpm at 37°C (n = 6). The dissolution was performed using CC-USP, HCl, SLS, 0.1% HPMC, and 0.2% HPMC media.

Viscosity of the gel layer temporarily formed on dissolved tablets

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

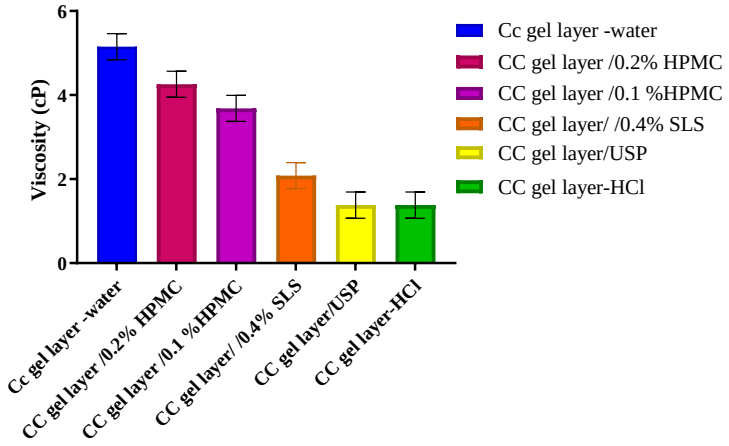

Figure 3 Viscosity of the gel layer formed on the surface of commercially available tablets of candesartan cilexetil (Product 1: AstraZeneca Company, UK, batch no. GTIN 07321839721397, production date: 01-2019), after 15min dissolution in various media at 37°C and 50 rpm.

DISCUSSION

Candesartan cilexetil (CC) is a BCS class II drug 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 the in-vivo absorption and bioavailability of CC. Consequently, optimization for the experimental parameters of the in-vitro dissolution testing when comparing to in-vivo conditions were needed. Comparing between the two commercial CC products is not the primary aim of this study, on the contrary, it aims to find a new validated methods which not usually applied in a quality control analysis to determine physicochemical properties of the product [19, 20].

The dissolution of the investigated commercially tablets of CC in the USP medium met the USP compendial requirements. However, changing of 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 preparation of dissolution media, to enhance drug wetting and dissolution process[21]. When increasing surfactant concentration, a micelles were formed, their stability is generally related to the critical micelle concentration (CMC)[22]. The rationale for selecting specific surfactants for in-vitro testing is essential to understand its interaction with drug molecules and other ingredients in dissolution media and excipients[23,24]. A 0.5 w/w% of Tween® 20 has a surface tension of 3.7 mN/m [22], while the surface tension of SLS is 39.4 mN/m at an estimated CMC of 0.58 w/v%.[25]. The 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 enhanced the dissolution of CC. The addition of 0.4% SLS to the USP medium was performed for further reducing of the surface tension and simulates of the gastric fluid conditions, which was approximately found to be 30 mN/m[26,27]. However, the addition of SLS did not increase the rate of CC dissolution in the tablet products. It could be attributed to the interaction between the anionic SLS and the cations present in the buffer which may result in forming insoluble material that lower the effect of SLS[28]. Moreover, the addition of more components may disrupt the water structure which will reduce cohesive dielectric constant and cohesive energy, leading to lowering solvent polarity[28] and as a result may cause reduction in the dissolution. Generally, the viscosity of the dissolution media has an essential role in the dissolution of drugs[5]. It was found that CC tablets and raw material in this study exhibited different dissolution patterns using different media. The dissolution of CC in product 2 was comparable only to that of the raw CC in the CC-USP medium. On the other hand, the dissolution of CC in product 1 is comparable to both raw CC in the CC-USP and the 0.1% HPMC media but was slower in 0.2% HPMC, which has a higher level of viscosity. 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 process of raw CC in the 0.2% HPMC medium. High viscosity can inhibit the drug dissolution by reducing the dissolution rates [29]. Therefore, impeding of the drug passage through the surrounding medium, and increasing the resistance to drug diffusion[30]. Viscosity may vary according to food contents and different parts of the GIT, which will affect the diffusion of the drug into the surrounding media[31]. The variation between the commercial drugs upon variation in

non compendial requirements could be related to the different composition 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 .

Usually, the first step in drug dissolution is wetting followed by gelling of the tablet[4]. The formed gelling layer is stagnant and expected to dissolve in order to enhance the release of drugs from the tablet[26]. In this study, gel layers were formed in tablets of product 1 after 15 min of the dissolution process. Tablets of product 2 disintegrated quickly, probably as a result of existence of microcrystalline cellulose. Moreover, a harder tablet may elevate the probability of dissolution failure[32]. On the other hand, higher compressions forces are employed to attain tablet hardness which result from increase in interparticle bonding[33]. Hardness can be affected by processing techniques, such direct compaction, hot melt extrusion or fused melting deposition, as well as affecting the intermolecular interaction causing the increase in the tablet hardness[34]. Furthermore, disintegration can be somehow related to the tablet hardness. Harder tablet may elevate the probability of dissolution failure; therefore, it will take longer time to interact with the medium to form the presumed gel layer[35]. In addition to that, the ionic strength of the media affects the formation and the viscosity of gel layers which formed on the surface of tablets[8]. High levels of ionic strength would increase the concentration of electrolytes, thus increasing the spaces between water molecules, as a result of the salting-out effect which will decrease gelation[36]. That will support the current findings where 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).

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

When CC (pK_a =4.66) taken under fasting condition with the low pH of stomach, CC will be expected to exists in its unionized form and thereby it will precipitate. This was clearly 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 affects the dissolution results in both products. It is worth mentioning that the leaflets of the CC products are lacking of any instructions for avoiding intake of tablets in the fasted stomach, which could be the revised in the future to enhance effect of CC.

CONCLUSIONS

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

Author Contributions:

Conceptualization, O.T..; methodology, O.T., R.S., R.H..; software, S.A.; validation, S.A. and O.T.; formal analysis, R.S..; investigation, M.A. and S.A.K; resources, S.B..; data curation, H.A..; writing—original draft preparation, O.T. and R.S..; writing—review and editing, H.A.; visualization, R.H..; supervision, O.T.; project administration, O.T..; funding acquisition, O.T. All authors have read and agreed to the published version of the manuscript." Please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

Conflicts of Interest: "The authors declare no conflict of interest."

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Table 1. Excipients of two commercially available tablets of candesartan cilexetil as issued on the leaflet by the manufacturers. Product 1 (AstraZeneca Company, UK, batch no. GTIN 07321839721397, production date: 01-2019) and Product 2 (United Pharmaceuticals Manufacturing Co., Amman, Jordan, batch no. 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 (MCC)*
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 (PEG)
Colorant UV absorber	Iron oxide (E127)	Ferric iron oxide

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

Media	**pH**	**Phosphate buffer pH 6.5**		**Tween®20 (g)**	**HCl (mL)**	**SLS (g)**	**HPMC (g)**
		Na_2HPO_4-7H2O (g)	$NaH_2PO_4H_2O$ (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

Table 3. Solubility, surface tension, viscosity, and ionic strength of raw candesartan cilexetil 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 dissolved in the investigated media

Dissolution media	**pH**	**Solubility (µg/mL)**	**Surface tension mN/m**	**Viscosity ($_C$P)**	**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