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Effect of thickener on disintegration, dissolution and permeability of common drug products for elderly patients

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ABSTRACT

Dysphagia is a very common problem suffered by elderly patients. The use of thickeners during administration in these patients helps to prevent difficulties with swallowing larger solid dosage forms. However, there are several indications when the thickeners may influence disintegration and dissolution processes of solid dosage forms, potentially affecting therapeutic efficacy. In this paper the effects of a commonly used thickener on tablet disintegration, dissolution and subsequent absorption of 6 formulated drugs frequently used in elderly patients (Aspirin, Atenolol, Acenocumarol, Candesartan, Ramipril and Valsartan) in two different administration conditions (intact tablet and crushed tablet) are reported. Disintegration times were determined using a modified disintegration test device. The presence of thickener leads to a pseudoplastic behavior with clearly increased viscosity values. The thickener was also shown to significantly affect the release processes (dissolution and disintegration), but not the permeability of the studied drugs. When tablets are crushed the effect of the thickener on drug dissolution is avoided. Consequently, crushing the tablets would be a recommendation for these drugs if the use of a thickener is necessary in patients with dysphagia.

1. Introduction

Elderly people are the most rapidly growing patient group worldwide with an expected proportion of 30% of the population of subjects above 80 years of age by 2050 in developed countries [1]. Aging comes with many diseases and disabilities such as dysphagia, the difficulty in the swallowing process, which impairs eating, drinking and oral medication administration [2] (see Table 1).

The prevalence of dysphagia depends on multiple factors and the prevalence in different settings is not clear. The general estimates suggest that at least 15% of the elderly population suffers from dysphagia. [3]. In addition, dysphagia increases the risk of malnutrition and pneumonia [2].

Elderly patients are usually poly-medicated and most of the frequently used drugs in this age group are administered as immediate-release oral tablets. Due to the dysphagia condition, caregivers of the geriatric units use several strategies to facilitate medication intake [4]. Administration with semisolid food instead of water, crushing the tablets or the use of thickeners are frequently employed procedures to maintain patient adherence to treatment [5].

It is generally accepted that the presence of thickeners helps to control the speed, direction, duration and clearance of the bolus. Although there is no scientific evidence to support the use of thickeners, this is the strategy of first choice in patients with dysphagia in most health institutions [6].

The amount of thickener depends on the fluid volume ingested and the required consistency. There are 3 consistency levels; 'Nectar Thick, Honey Thick or Pudding Thick'. Although the majority affirmed that the thickeners generally were an effective intervention strategy, the effectiveness of the consistency in the form of 'nectar' was preferred over higher viscous presentations [7].

The efficacy of thickeners in patients with dysphagia to ease swallowing is highly proven [8,9]. There are also several indications that the thickeners may affect disintegration and dissolution processes of solid dosage forms, finally affecting therapeutic efficacy [10]. For instance, Tomita et al. [11,12] observed that for Vogiblose, a BCS class 3 compound [13] therapeutically indicated for lowering glucose levels the immersion of the tablets in a commonly used thickener resulted in

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Table 1
Excipient composition of immediate release tablets of the selected drugs.

Aspirin 500 mg Ratiopharm	Atenolol 100 mg ALIUD PHARMA
Corn starch	Microcrystalline cellulose
Cellulose powder	Crospovidone
Sintrom 4 mg MERUS LABS	Dimethicone
Lactose monohydrate	Hypromellose
Corn starch	Macrogol 6000
Pregelatinized starch	Magnesium stearate (Ph. Eur.)
Anhydrous colloidal silicon dioxide	Corn starch
Magnesium stearate	α-Hydro-ω-octadecyloxypoly (oxyethylene) − 5
Ramipril 10 mg AbZ Pharma	Poly (ethyl acrylate-co-methyl methacrylate)
Sodium bicarbonate	Fumed silica
Lactose monohydrate	Sorbic acid (Ph. Eur.)
Croscarmellose sodium	Talc
Pregelatinised starch (from maize starch)	Titanium dioxide (E 171)
Sodium stearyl fumarate (Ph.Eur.)	Iron (III) oxide (E 172)
Candesartan 32 mg 1ª Pharma	**Valsartan (Valsartan 320 mg PUREN)**
Sodium docusate	Lactose monohydrate
Sodium lauryl sulfate	Microcrystalline cellulose
Calcium carmellose	Croscarmellose sodium
Pregelatinized corn starch	Povidone K29-K32
Hydroxypropyl cellulose	Talc
	Magnesium stearate
Lactose monohydrate	Water-free silica colloidal anhydrous.
	Polyvinyl alcohol
Magnesium stearate	Macrogol 3350
	Talk
Red iron oxide (E172)	Lecithin (contains soy oil) (E322)
	Titanium dioxide (E171)
Purified water	Black iron oxide (E172)
	Sunset yellow (E110)

less glucose levels reduction attributed to a slower tablet disintegration and dissolution A similar effect was reported for Mitiglinide, a BCS class 2 compound [14]. When the tablets were immersed in xanthan gum solutions the measured glucose levels in humans were higher than the ones measured in subjects taking the non-immersed tablets [15]. Those studies suggest that thickeners could influence drug pharmacodynamics by their effects on disintegration and dissolution and thus their use needs to be monitored in some clinical situations and their effects carefully characterized.

In this study, the effects of a commonly used thickener on disintegration, dissolution and subsequent absorption of 6 drugs frequently used in elderly patients in two different administration conditions is reported aiming at exploration of the most convenient way to circumvent difficulties in drug release in the presence of the thickener.

2. Material and methods

2.1. Compounds

Six compounds were selected; Aspirin (Aspirin 500 mg Ratiopharm, BCS class I [16]), Atenolol (Atenolol 100 mg ALIUD PHARMA, BCS class III [17]), Candesartan (Candesartan 32 mg 1ª Pharma, BCS class II [18]), Ramipril (Ramipril 10 mg AbZ Pharma, BCS class I [19]), Acenocumarol (Sintrom 4 mg MERUS LABS, BSC class II [20]) and Valsartan (Valsartan 320 mg PUREN, BCS class II [21]). These compounds are frequently used in geriatric patients; their tablets are very often crushed before administration.

The thickener used was Resource ThickenUp Clear ® (Nestlé Health Science, Germany, GmbH, D-60523, Frankfurt), which is mainly composed of; Maltodextrin (corn, potato), thickener (xanthan gum), fiber and mineral salt (potassium chloride).

A high-fat and high-calorie (approximately 800–1000 kcal) meal is recommended as a test meal for food-effect studies [22]. The amount of thickener used does not provide a significant amount of kcal. For this reason, we considered that our experimental conditions reflected a fasted state. The studied media were prepared in absence and in the presence of thickener:

- For the disintegration test: water, water at pH 1.2 (2.92 g NaCl and 7.1 mL of HCl 97% were added to 1 L of water and adjusted to pH1.2 with HCl 97% or NaOH 10 M.) and FaSSIF-v2 [23].
- For the dissolution test: BCS-based aqueous media buffered at pH1.2 (2.92 g NaCl and 7.1 mL of HCl 97% were added to 1L of water and adjusted to pH1.2 with HCl 97% or NaOH 10 M), pH 4.5 buffer (2.99 g of sodium acetate and 14 mL of acetic acid were added to 1L of water and adjusted to pH 4.5 with acetic acid or NaOH 10 M), pH 6.8 buffer (6.81 g of monopotassium phosphate and 2.2 mL of NaOH 10 M were added to 1L of water and adjusted to pH 6.8 with orthophosphoric acid or NaOH 10 M)[24] and FaSSIF-v2.

To prepare the media with thickener, 1.2 g (one tablespoon)/ 250 mL was added and the mixture was stirred overnight at room temperature. A nectar consistency was reached with this thickener concentration. This procedure of media with thickener preparation was chosen to obtain a homogeneous medium and to reduce variability even though it does not reflect the actual administration conditions. Stirring the thickener in the media for 20 min, resulted in a heterogeneous mixture.

2.2. Disintegration test

The disintegration time was measured using the modified disintegration test device developed at Johannes Gutenberg University. This device is a modification of the disintegration apparatus of the PhEur / USP described previously by Kindgen et al. [25]

The movement of the container is carried out by means of a numerical computerized control. This allows to adjust the speed and direction of the movement. With these variations, different velocity profiles can be generated in the 3 dimensions (Fig. 1c).

For this study, circular movements were designed in the three dimensions of the space (Fig. 1d) at different speeds. The speed remains linear and constant during the experiment.

The modified disintegration test device was used to determine the disintegration times of the different formulations. The volume used was 1000 mL of test medium and the temperature was maintained at 37 ± 1 °C, throughout the experiment.

By using the modified device, disintegration times under varying hydrodynamic conditions were investigated. The speeds established in these experiments varied between 20 and 120 mm / s. Disintegration time was checked visually when no solid residue was left inside the chamber. Disintegration times were measured for 3 tablets and they were reported as means ± standard deviation (SD) [25].

2.3. Dissolution test

USP apparatus 2 was used for the dissolution tests of the three compounds for which a high effect of the thickener on the disintegration was observed (Atenolol, Candesartan and Valsartan). The formulations were studied as intact and crushed tablets, respectively, at pH 1.2, pH 4.5, pH 6.8 and in FaSSIF-v2 (with and without thickener). The volume of media used was 500 mL per vessel and the temperature was maintained at 37 °C ± 0.5 °C. Due to the volume used, atenolol dissolution took place in sink conditions while for candesartan and valsartan non-sink conditions prevailed. The stirring speed was set at 50 rpm. The sampling times in all media were 5, 10, 15, 20, 30, 45, 60, 90 and 120 min, respectively. Sampling was performed manually using 1 mL glass syringes connected with stainless steel sampling devices with incorporated filters (10 μm Cannula Filters UHMW). Samples were

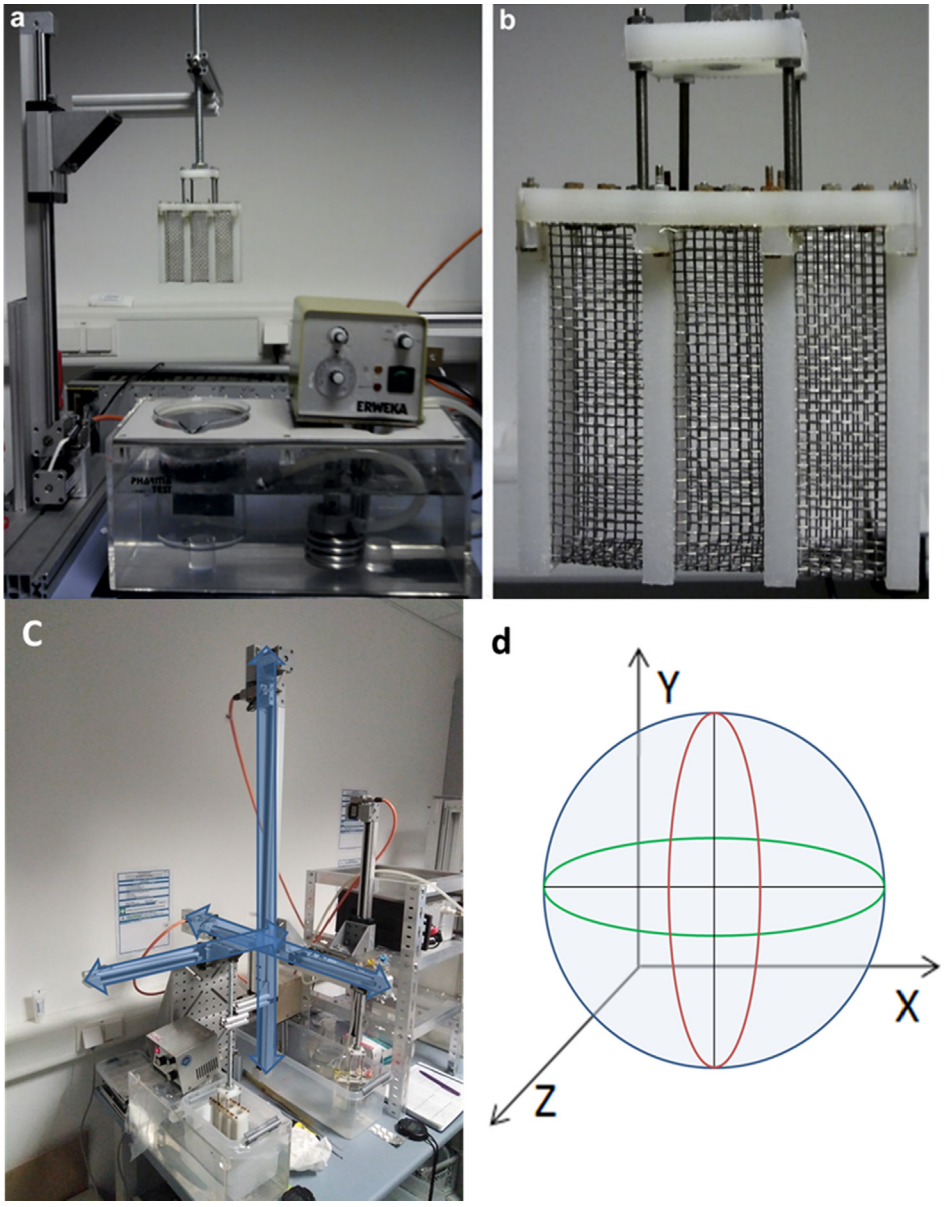

Fig. 1. Modified disintegration tester: Basket (a and b). Reproduced with permission from Elsevier [25]. Modified disintegration tester 3D (c) and three-dimensional movement (d).

immediately analyzed for drug concentration. In order to maintain constant volumes during the experiment, the sample volume was replaced with preheated fresh medium. All dissolution experiments were performed in triplicate.

For the administration of the crushed tablet, the tablet is crushed using a commercial crusher, Fig. 2.

To compare the dissolution profiles, the similarity factor f2 was calculated. This factor was calculated with the FDA method, where the sampling points are included in the calculation until both profiles exceed 85% [26].

The samples of Atenolol (273.9 nm) and Valsartan (225.7 nm) were analyzed by UV-spectrometry (PerkinElmer Lambda 35 UV/VIS Spectrometer). Candesartan samples were analyzed by HPLC. Details of the method are described in table 2 with the validation parameters of linearity, accuracy, precision and quantification limit.

2.4. Rat permeability studies

The Scientific Committee of the Faculty of Pharmacy, Miguel Hernández University approved these studies as they comply with the guidelines described in Directive 86/609 of the EC, the Convention of the Council of Europe ETS 123 and the Spanish national laws that regulate the use of animals in research.

The “closed loop” in situ perfusion method based on the Doluisio technique was used to calculate the absorption rate coefficients and the permeability values of the drugs studied. These parameters were determined in the whole small intestine ($n = 6–7$) of Wistar Rats weight approximately 300 g (3 months old). They were anesthetized using pentobarbital (40 mg / kg). An isolated compartment was created in the small intestine (≈ 100 cm) by the aid of two syringes. The technique was described previously in detail by Ruiz-Picazo et al. [27–29].

The samples were collected every 5 min up to a period of 30 min and they were centrifuged for 5 min at 5000 r.p.m. to separate the solid components. All samples were analyzed by high performance liquid chromatography (HPLC) as described in Table 3. The methods were validated with adequate linearity, precision, accuracy ($R > 0.99$ and coefficient of variation $< 5\%$).

A brief summary of the procedures described by Ruiz-Picazo et al.

Fig. 2. Pill Crusher.

Table 2
Thickener composition (Resource ThickenUp Clear®).

Composition of a tablespoon		
Energetic Value	3.7	Kcal
Fat	0	g
_total fatty acids	0	g
saccharides	0.74	g
_sugar	0.02	g
Fiber	0.32	g
Protein	0	g
Salt	0.032	g
Sodium	13	mg
Potassium	4.8	mg

[27–29] is quoted below:

To accurately calculate the absorption rate constants, a correction of the experimental concentrations is necessary to account for the water reabsorption process which produces a reduction in the volume of the perfused solutions. Water absorption was considered as an apparent zero order process using the next Eq. (1):

$$k_o = (V_0 - V_{end})/t_{end} \quad (1)$$

where, V_{end} is the remaining volume at the end of the experiment (t_{end}) in the rat intestine, k_o is the aqueous reabsorption constant and V_o the initial perfusion volume. The perfused volumes at each time point (V_t) were estimated from V_o and k_o. Finally, the experimental concentrations (C_e) were corrected to obtain the real concentrations (C_t) by means of the following equation:

$$C_t = C_e(V_t/V_0) \quad (2)$$

where C_t represents the corrected drug gut concentration in the absence of any water reabsorption at time t, and C_e represents the actual experimental value. The C_t values (corrected concentrations) were used to calculate the actual absorption rate coefficients [30].

The absorption rate coefficient (k_a) was determined by nonlinear regression analysis of the remaining concentrations in lumen (C_t) versus time.

$$C_t = C_0 e^{-k_a t} \quad (3)$$

This k_a value was transformed into permeability value with the following relationship:

$$P_{eff} = k_a R/2 \quad (4)$$

where R is the effective radius of the intestinal segment. R was calculated considering the intestinal segment as a cylinder with the relationship:

$$Volume = \pi R^2 L \quad (5)$$

The estimate was made taking into account the volume of perfusion of the experiment (10 mL) as well as the length of the intestine of the Wistar rat (100 cm) represented as (L) in Eq. (5)."

2.5. Rheological characterization

The rheological properties of the different fluids were characterized in a rotational rheometer RV 12 (HAAKE, Germany). This method is based on the plate-plate system.

600 µL of each sample were placed on the bottom plate previously set at 37 °C. The upper plate (P35 Ti L), was set to a height of 0.5 mm. Shear stress values (resistance to rotation in Pa) were recorded every 0.3 s in the range of shear rates from 3 to 600 s^{-1}.

3. Results and discussion

Fig. 3 summarizes the disintegration times for the six drug products in the six media. As can be seen in Fig. 3, by adding thickener to the

Table 3
HPLC methods of atenolol, candesartan and valsartan and validation parameters.

Compound	UV nm	Mobile phase	Flow	Retention Time (min)	Sample Volume	Linearity	Range (mg/mL)	Accuracy (% error)	Precision (cv %)	LoQ (mg/mL)
Atenolol	231	5:90:5 (v/v) Methanol:Acidic Water:Acetonitrile	1 mL/min	3.5	40 µL	r^2 = 0.999	0.0008–0.027	1.07	< 2	0.0013
Candesartan	260	80:2:18 (v/v) Metanol:Acidic Water:Acetonitrile	1 mL/min	1.2	90 µL	r^2 = 0.999	0.0015–0.15	1.23	< 2	0.0084
Valsartan	250	55:45 (v/v) Acidic Water:Acetonitrile	1 mL/min	1.83	µL	r^2 = 0.999	0.013–1.134	0.97	< 2	0.0477

Colum used Nova Pak® Waters (C18 3.9 × 150 mm; 4.0 µm)

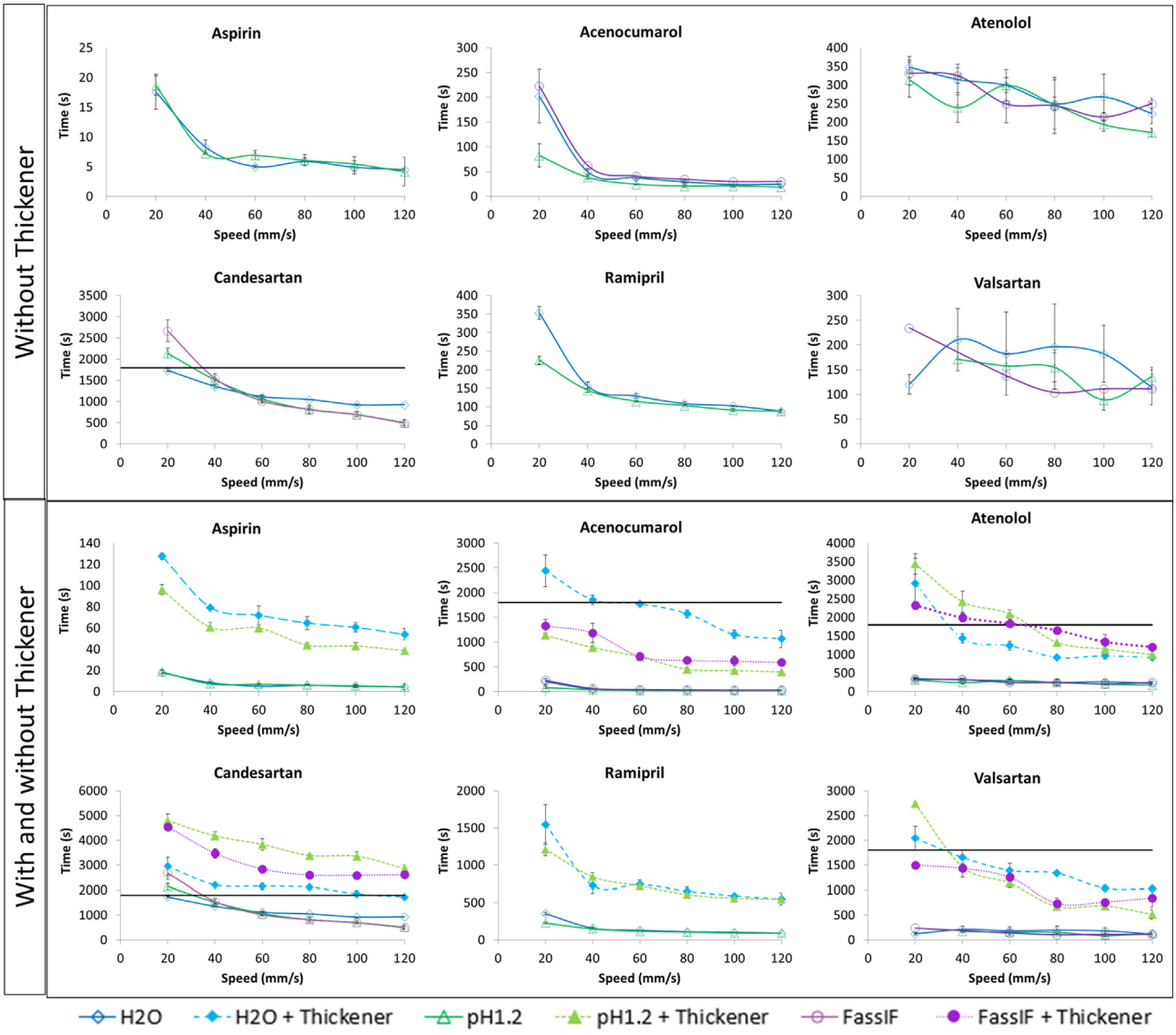

Fig. 3. Disintegration times of Aspirin, Acenocumarol, Atenolol, Candesartan, Ramipril and Valsartan tablets vs speed, in different media. Horizontal line = 1800 s (30 min).

different media, the disintegration time increases significantly in all cases, even reaching more than 30 min (1800 s horizontal line in the figures) at low speeds, in the case of Atenolol, Candesartan and Valsartan products.

These three pharmaceutical products present magnesium stearate in their composition. The Acenocumarol formulation (Sintrom) also presents this excipient and showed longer disintegration time than Aspirin and Ramipril, but its disintegration time did not reach 30 min in any of the studied media.

Magnesium stearate is commonly used as a lubricant for solid pharmaceutical formulations. Ariyasu et al. studied the mechanism by which this lubricant can cause a delay in Metformin tablet dissolution (BCS class III). They proposed that the low solubility and slow dissolution and diffusion of magnesium stearate could limit tablet dissolution [31].

On the other hand, Yang et al. showed that magnesium stearate hampers tablet swelling that could retard tablet disintegration [32].

Uzunovic et al. evaluated the effect of two level amounts of magnesium stearate on ranitidine (BCS III) tablet dissolution. They found that the higher amount of lubricant produced slower dissolution rate [33].

Our hypothesis is that the negative effect of magnesium stearate in the disintegration process is promoted by the increased viscosity due to the thickener.

Disintegration of immediate-release tablets in vivo takes place in the proximal part of the gastrointestinal tract. The factors that govern this process were identified in vivo: they include the viscosity of the media, the precipitation of food components on the tablet surface and the changes in hydrodynamics in the surrounding media of the solid dosage form [34].

The new disintegration apparatus is able to simulate in vivo hydrodynamic conditions better than the USP disintegration model [25,35]. Although there is only limited information about fluid velocities and forces on tablets in vivo, these different scenarios can be simulated using the modified disintegration test device. However, to date, the validation of the device is limited by the lack of experimental in vivo disintegration times [25,36]. Viscosity, water diffusivity and media flow velocity are shown to be important factors affecting dosage form disintegration [34,37]. As viscosity is one of the relevant factors, the effect of the thickener on media viscosity was measured and the results are presented on Fig. 4.

The presence of thickener in the media leads to a pseudoplastic flow

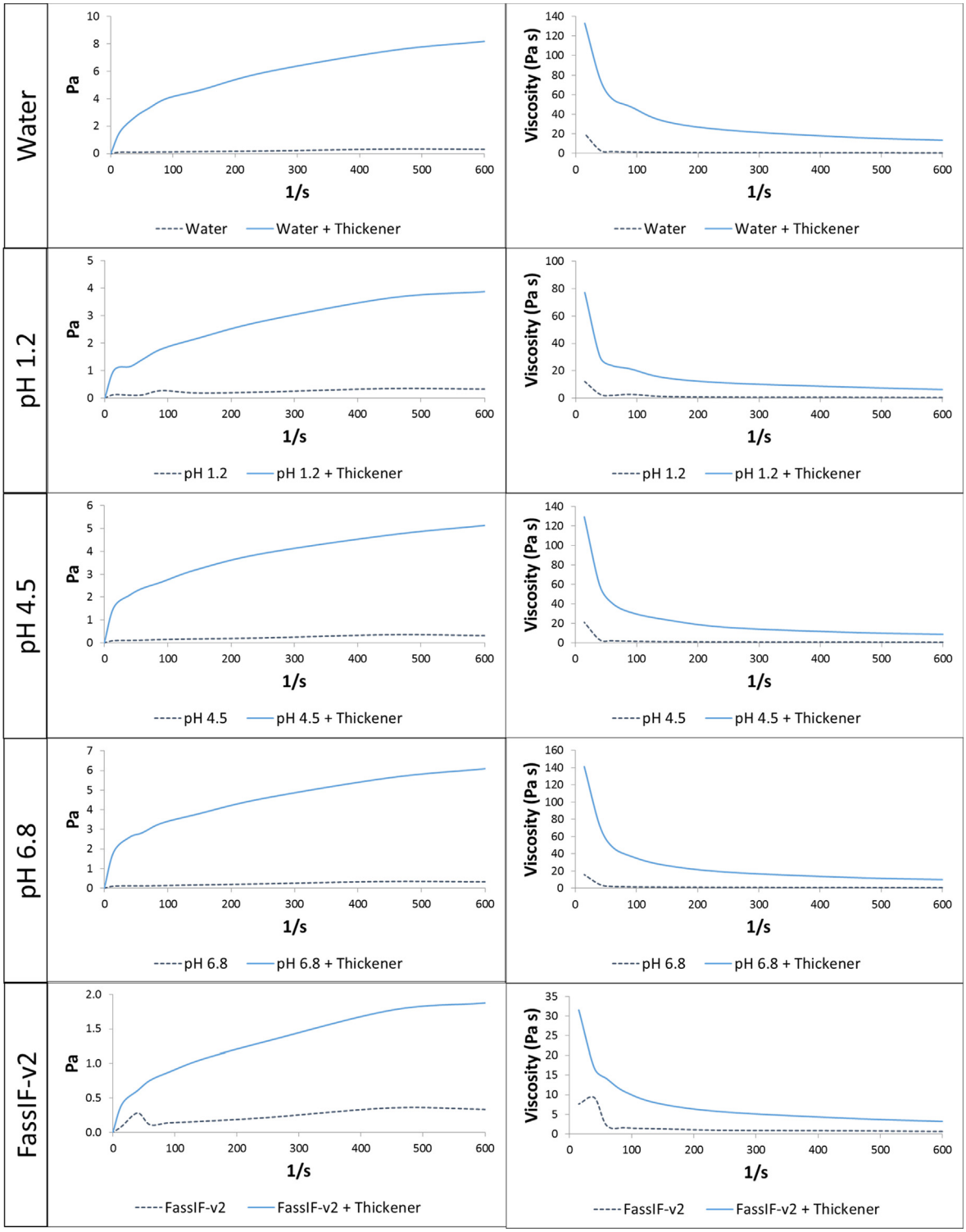

Fig. 4. Rheological profiles of the media studied with and without thickener. (Left) Shear stress values (or resistance) in Pa are represented on the Y axis versus shear rates (1/s). (Right) Viscosity values in Pa*s are represented on the Y axe versus shear rates (1/s).

behavior with viscosity values clearly higher in the presence of the thickener [38,39].

Other authors have seen that food-induced viscosity can delay the breakdown and subsequent release of API from the solid dosage form, which can lead to a severe reduction in bioavailability [40–42]. This negative effect of viscosity could eventually be diminished by the adequate selection of excipients. Some attempts to minimize food effects on formulation disintegration and dissolution have been recently published [43,44].

Food induced viscosity can delay disintegration and in consequence release of the drug for low permeability compounds which may lead to a reduction in absorbed fraction [44]. Cvijic et al. simulated *in silico* the absorption process of trospium chloride in fasted and fed state. They demonstrated that the decreased dissolution in viscous medium, was one of the predominant mechanisms for the negative food effect on trospium absorption [45].

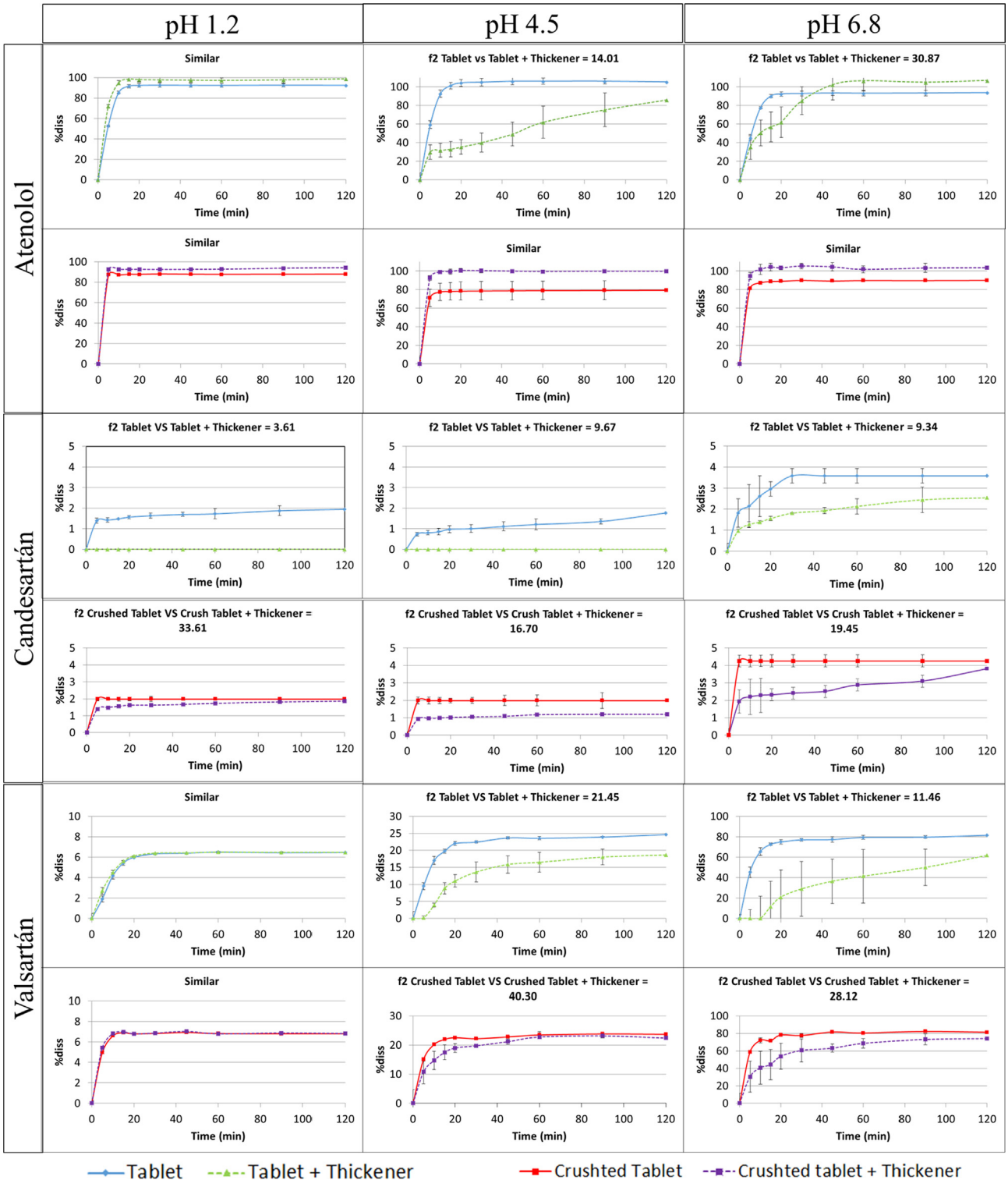

Fig. 5. Dissolution profiles of Atenolol, Candesartan and Valsartan in pH 1.2. 4.5 and 6.8 media, assayed in the form of intact and crushed tablets, respectively, in the presence and in the absence of thickener.

The disintegration process is mainly based on two mechanisms, the shear forces that are applied to the tablet during its transit through the gastrointestinal tract and, the most relevant, the swelling of the tablet itself when the liquid penetrates into the pores [46]. Viscosity can affect both mechanisms; thus, higher viscosities corresponding to higher shear forces could promote tablet disintegration. However, experimental data indicate that the predominant effect seems to be the reduction of water diffusivity and water penetration into tablet pores. Thereby, higher viscosities of disintegration fluids generally can result in longer disintegration times [47,48].

Even if for the present formulations only results from in vitro disintegration experiments are available, the in vivo published results with other BCS class 3 and 2 drugs suggest that the presence of the thickener may affect product performance. The clinical relevance will depend on each drug pharmacodynamics but it deserves further research [11,12,15].

Subsequently, the effect on the dissolution rate was evaluated for those three drug products for which a marked effect of the thickener on their disintegration times was observed. Fig. 5 represents the dissolution profiles of Atenolol, Candesartan and Valsartan formulations.

As can be seen in Fig. 5, for the Atenolol product (BCS class III), no differences were observed in presence or in absence of thickener when the tablets were crushed. This fact could be expected due to the high solubility of the drug and the fact that the tablet has been pre-disintegrated. With Atenolol intact tablets no effect of the thickener was observed at acidic pH, but a marked effect was present at pH 4.5 and 6.8 resulting in non-similar profiles. Assuming that in vivo dissolution in the stomach is reflected in our in vitro test at pH 1.2, then either in presence or in absence of the thickener, Atenolol tablet disintegration and dissolution would be similar. Thus no effect of rate and extent of absorption would be expected as Atenolol in solution would be emptying from the stomach. In the previously mentioned paper from Tomita et al. [11] about another class III drug Voglibose, no information about disintegration in acidic conditions that might have caused the differences in absorption in presence of thickener was given. Tomita *et. al.* studied the effect of food thickeners on the breakdown of Levofloxacin tablets (BCS I) in vitro and in vivo in humans. Even if food thickener delayed in vitro disintegration there was no effect observed in vivo. [49].

In case of Candesartan (acid BCS class II), due to its low solubility, the dissolved percentage did not reach 5% at any pH. For the intact tablets, the effect of the thickener is very evident at all pH's showing a clear delay of dissolution. With Candesartan crushed tablets only some effect is observed at pH 6.8 indicating slower disintegration and dissolution with the thickener. For this drug, the recommendation to avoid any interference of the thickener with absorption would be always to crush the tablets before intake.

Similar results to those of Candesartan were observed for the Valsartan (acid BCS Class II) formulation, with the exception of intact tablets at pH 1.2. The thickener affected disintegration and dissolution of Valsartan intact tablets at pH 4.5 and 6.8 and only a minor effect of the thickener was observed when crushing the tablets. Consequently, the same recommendation should be made for this drug product, i.e. of crushing the tablet for administration together with thickener.

Crushing tablets for administration is standard practice when treating patients with dysphagia. Crushing tablets, if their pharmaceutical form allows it, not only helps with their correct administration but can also improve the pharmacokinetic profile. Cattaneo et al. found that HIV patients who chewed Raltegravir (BCS II) tablets presented significantly higher plasma concentrations. The plasma profiles of these patients also presented less variability compared to patients who swallowed the intact tablet [50].

Manrique et al. studied the effect of thickeners on Acetaminophen dissolution in different dosage forms. The release of acetaminophen was delayed (between 12 and 50% in 30 min) on immediate release tablets which would have not met the specifications of the pharmacopoeias for this type of pharmaceutical form [9].

In summary, the results showed that the thickener negatively affects the dissolution process. The clinical relevance of this fact will depend on the characteristics of the drug. On the other hand, crushing the tablet can help to avoid the effect of the thickener.

Nevertheless, for class II and IV drug products in the absence of an IVIVC, the results in the BCS-based media might not be predictive of the in vivo outcome. We do not know if these observed differences in the presence of thickener for the intact tablets are biopredictive.

Fig. 6 shows the permeability values obtained by the Doluisio technique for the different compounds selected in the presence and absence of thickener.

The differences are not statistically significant but the presence of thickener shows a slight trend to increase the permeability of the drug in the case of Candesartan and Valsartan. The in situ perfusion tests were performed at drug concentrations equivalent to the dose/250 mL.

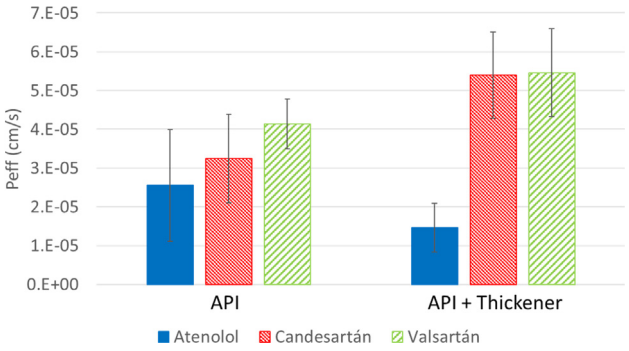

Fig. 6. Permeabilities of Atenolol, Candesartan, and Valsartan in the presence and absence of thickener obtained by the in situ Doluisio method in Wistar rat (n = 4–6).

For Atenolol and Valsartan consequently a drug solution was tested as it was possible to dissolve the whole dose in the perfusion buffer. For Candesartan, however, a suspension was obtained. This is a limitation of the study in the sense that the apparent permeability obtained is a combination of dissolution and drug permeation which makes the interpretation of results more difficult. These experiments were done with the API to avoid the influence of the excipients and characterize the effect of the thickener on the permeation process. Apparently the thickener did not interfere with membrane permeability but from the dissolution test it seems to affect dissolution and disintegration.

The increased viscosity hinders intestinal absorption [41]. Lower permeabilities in the presence of thickener were expected due to the increased diffusional resistance in the aqueous media. Atenolol data is consistent with this. On the other hand, the apparent increase in permeability of valsartan and candesartan can be explained by the methodological characteristics of Doluisio's method in which the absorption rate is measured from drug luminal disappearance. The hypothesis for those two drugs is that part of the thickener is adsorbed to the intestinal membrane (slowing down its absorption) but capturing the free drug whose apparent concentration in the samples is then underestimated, and the apparent absorption rate coefficient overestimated. Another experimental design is necessary to elucidate this mechanism.

In order to confirm the potential in vivo effects, it would be interesting to perform an in vivo oral administration test in Wistar rats with and without thickener and to characterize systemic drug levels.

In clinical practice, crushing tablets is a commonly used strategy in patients with dysphagia [51]. How this procedure influences the treatment depends mainly on the pharmaceutical form. For sustained-release formulation or enteric-coated tablets this measure is not recommended, since the release of the drug would be drastically altered [52–54].

4. Conclusion

The thickener commonly used in patients with dysphagia was shown to significantly affect the release processes (dissolution and disintegration), but not the permeability of the studied drugs. In all the assayed drug products, the disintegration time increases for all disintegrator speeds and media studied when thickener is present. In the dissolution tests in USP II Apparatus, it was demonstrated that the thickener delayed the dissolution of Atenolol, Candesartan and Valsartan drug products. When the tablets are crushed the effect of the thickener can be avoided.

Consequently, crushing the tablets would be a recommendation for these drugs if the use of a thickener is necessary in patients with dysphagia.

Declaration of Competing Interest

The authors declare no conflict of interest.

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