

## Crushed Tablets: Does the Administration of Food Vehicles and Thickened Fluids to Aid Medication Swallowing Alter Drug Release?

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**ABSTRACT - Purpose.** To evaluate the influence of co-administered vehicles on *in vitro* dissolution in simulated gastric fluid of crushed immediate release tablets as an indicator for potential drug bioavailability compromise. **Methods.** Release and dissolution of crushed amlodipine, atenolol, carbamazepine and warfarin tablets were tested with six foods and drinks that are frequently used in the clinical setting as mixers for crushed medications (water, orange juice, honey, yoghurt, strawberry jam and water thickened with Easythick powder) in comparison to whole tablets. Five commercial thickening agents (Easythick Advanced, Janbak F, Karicare, Nutilis, Viscaid) at three thickness levels were tested for their effect on the dissolution of crushed atenolol tablets. **Results.** Atenolol dissolution was unaffected by mixing crushed tablets with thin fluids or food mixers in comparison to whole tablets or crushed tablets in water, but amlodipine was delayed by mixing with jam. Mixing crushed warfarin and carbamazepine tablets with honey, jam or yoghurt caused them to resemble the slow dissolution of whole tablets rather than the faster dissolution of crushed tablets in water or orange juice. Crushing and mixing any of the four medications with thickened water caused a significant delay in dissolution. When tested with atenolol, all types of thickening agents at the greatest thickness significantly restricted dissolution, and products that are primarily based on xanthan gum also delayed dissolution at the intermediate thickness level. **Conclusions.** Dissolution testing, while simplistic, is a widely used and accepted method for comparing drug release from different formulations as an indicator for *in vivo* bioavailability. Thickened fluids have the potential to retard drug dissolution when used at the thickest levels. These findings highlight potential clinical implications of the addition of these agents to medications for the purpose of dose delivery and indicate that further investigation of thickened fluids and their potential to influence therapeutic outcomes is warranted.

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### INTRODUCTION

The oral route is the most convenient for medication administration. Solid dose forms such as tablets, pills or capsules are preferred for the oral delivery of active pharmaceutical ingredients, providing accuracy in the dose, maximal storage stability, low cost, as well as patient adherence and compliance with the dosage regime. However, medications often cannot be safely administered to a patient if the oral route is compromised.

Anatomical and physiological complications associated with the oral, pharyngeal and esophageal phases of swallowing are known as dysphagia (1). A consequence of dysphagia can be aspiration of food, drink or medication leading to risk of airway obstruction or pneumonia. Dysphagia is generally associated with other

disease-related conditions such as Parkinson's disease, multiple sclerosis, stroke, cancer and dementia and consequently is most prevalent in the older population (2). Individuals who do not have a problem with swallowing food and drink can still manifest a psychological aversion to swallowing solid dosage forms (3). Factors such as the type of formulation, size, shape and surface characteristics of medications as well as a patient's body position are crucial for the delivery of medications (3, 4).

There have been some attempts to quantify the extent to which difficulties swallowing solid medications affect the population.

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In a study of 792 customers (69-89 yrs) of community pharmacies in England who pharmacists suspected may have difficulties swallowing tablets, 60% acknowledged having problems (5). Difficulties swallowing tablets and capsules accounted for an average of 22% of nursing home residents in the UK, based on a survey of 540 nurses (6). In the USA, up to 40% of 64 residents in an aged care facility reported having difficulties swallowing tablets and capsules while 20% of a control group with an average age of 30 had the same problem (7).

Difficulty swallowing solid dose medication is ideally addressed by the prescriber finding an alternative dosage form, which may require the prescribed medicine to be compounded into a liquid preparation or a change to a different medicine (8). However, in the absence of an alternative, solid dosage forms are invariably modified by patients and carers into a form that can be swallowed. For example, in the UK, 61% of staff in nursing homes crushed or opened medications for patients (6), and 25% of oral doses were altered in a mental institution (9). In Australia, medications were altered before being given to the patient in 34% of 408 observations, in aged care facilities (10) and nurses at 79% of 97 health facilities altered medicines to ease administration (11). This commonly involves crushing tablets or opening capsules and mixing the contents into food or fluids such as apple sauce, jam, custard, yoghurt, honey or juice (11-17). Patients suffering from dysphagia often have their fluid and dietary intake managed by the use of thickening agents in order to ensure safe swallowing and avoid aspiration into the airway (18). Medications for these patients may also be delivered by crushing and mixing with 'thickened fluids' (11), which are liquids such as water or juice thickened to the required viscosity. There are generally three thickness levels used, with the viscosity prescribed often increasing with severity of dysphagia (18).

While it is generally recognised by health professionals that tablets or capsules that are designed to have modified release properties should not be crushed due to the potential for toxicity, other medications are not often associated with any potential for negative outcome (19). Immediate release solid medications are designed to disintegrate and dissolve quickly in the gastrointestinal tract, so crushing may be expected to result simply in a slightly faster absorption. However, while this is the case for some medications (20, 21) crushing could result in higher bioavailability (22, 23) due

to enhanced dissolution and mass transfer, but it may also lead to sub-therapeutic drug levels due to loss of the dose during crushing and transfer (10, 24). Additionally, it is recognised that delivering medications with food or drink may impact drug bioavailability, with fruit juices such as grapefruit, orange or apple juice affecting absorption of numerous medicines (25-27) and foods potentially affecting physiologic conditions such as gastric emptying (17, 28). Generally, crushing tablets or opening capsules and mixing with a small quantity (e.g. two tablespoons) of food such as pudding, yoghurt or apple sauce does not significantly alter bioavailability (12-15). However, mixing crushed phenytoin tablets with pudding resulted in impaired absorption in comparison to the use of apple sauce (16) and mixing enteric-coated beads of didanosine with yoghurt or apple sauce delayed absorption (17). The effect of mixing crushed tablets into thickened fluids on drug absorption has not previously been addressed, but there is evidence that absorption of whole digoxin, penicillin and metformin tablets may be reduced when consumed with guar gum as a source of dietary fibre (29, 30) and dissolution rate of benzoic acid tablets is reduced when tested in dissolution media thickened using xanthan gum or guar gum (31). Alterations in bioavailability such as this are of particular concern for drugs that have a narrow therapeutic index because the concentration absorbed into the blood stream may not reach that required to elicit the therapeutic effect.

This study aimed to evaluate the influence of thickened fluids and other commonly used food and liquid vehicles (jam, yoghurt, juice and honey) on drug dissolution from crushed tablets. The *in vitro* dissolution test performed under specific conditions can be used as a prognostic tool for evaluating the bioavailability of certain drugs (32). While it cannot entirely replace *in vivo* testing, *in vitro* dissolution testing can provide insights on the physicochemical process involved and provide an indication of whether *in vivo* tests are warranted (33).

## METHODS

### Materials

Four generic immediate release formulations (IR) were used. Amlodipine besylate 10 mg tablets (Sandoz) and atenolol 50 mg tablets (Sandoz) represent some of the most common medicines modified in hospitals (11). Carbamazepine 200 mg tablets (Sandoz) and warfarin 5 mg tablets (Marevan) represent medications with a narrow

therapeutic index. These drugs were also chosen to provide a range of solubilities in water and for the presence of a chromophore within the chemical structure to enable analysis using UV spectroscopy. There were three liquids used for drug delivery in this study (water, orange juice and honey), two semi-solid food vehicles (jam, yoghurt), and six commercial food thickening agents (Easythick, Easythick Advanced, Janbak F, Karicare, Nutilis, Viscaid) (Tables 1 and 2). Thickened fluids were prepared as directed by the manufacturer at three thickness levels indicated for dysphagic patients (18); mildly thick (level 150), moderately thick (level 400) and extremely thick (level 900). Spoon measurements of the powder were converted to weight (Table 2) and added into water to reach the desired percentage (% w/v). Mixtures were stirred using a stick blender for 3 minutes until the powder was dispersed. Samples were maintained at 4°C overnight to ensure consistency and microbiological stability, and then equilibrated at room temperature before testing.

#### Vehicle characterisation

Vehicles were agitated by spoon for 5 seconds. pH was measured using a S220 SevenCompact pH meter (Mettler-Toledo, Port Melbourne, Vic) and a pre-calibrated pycnometer was used for

density measurements. Rheology of food fluids and thickening agents was measured using two rheometers, chosen as appropriate to the vehicle: AR 1500ex (TA Instruments) with a large vane or concentric cylinder at 37°C, or HAAKE MARS III (Thermo Fisher Scientific, Scoresby, Vic) with cone and plate fixture, 35 mm diameter, 2° angle at 37°C. The effect of the thickened fluids on dissolution media viscosity was measured using an AR-G2 (TA Instruments) with cone and plate fixture, 40 mm diameter, 2° angle at 37°C for a sample of media taken at 15 minutes and 3 hours into a dissolution test of each thickener at level 900. The viscosity of dissolution media containing thickener at level 900 that was completely dispersed within the media was measured using an AR 1500ex with concentric cylinder at 37°C; complete dispersion was achieved by adding the quantity of thickener powder that would be used to prepare 15 g thickened fluid at level 900 into 900 ml dissolution media. The majority of test vehicles were non-Newtonian with a viscosity that is highly dependent on shear rate. However, while the rheological curves for each sample was measured, for brevity and simplicity, the value for viscosity reported herein is  $\eta_{50}$ , i.e. the measurement at 50 s<sup>-1</sup>.

**Table 1.** Physicochemical characteristics and rheological attributes of the food and drink vehicles used in this study.

Vehicle	Brand	Type	Composition <sup>a</sup>	pH	Density	Viscosity (cP) <sup>b</sup>	Type of flow
Water	-	purified	water	6.7	1.00	0.8	Newtonian <sup>c</sup>
Orange juice	Just Juice	pulp free	orange juice, water, sugars, preservatives	3.2	1.04	2.76	Newtonian <sup>c</sup>
Honey	Capillano	Australian	honey	3.8	1.42	3750	Newtonian <sup>c</sup>
Jam	Golden Circle	strawberry	strawberries, pectin, food acids, natural colour, sugar	3.0	1.32	3120	Non-Newtonian <sup>c</sup>
Yoghurt	Yoplait	vanilla flavour	milk, solid, sugar, cream, fructose, thickeners (corn starch, halal gelatine), preservatives, acidity regulator, vanilla bean seed, natural colours, live yoghurt cultures: <i>Streptococcus thermophilus</i> , <i>Acidophilus</i> , <i>Bifidobacterium</i>	4.5	1.08	723	Non-Newtonian <sup>c</sup>

<sup>a</sup> taken from the product label; <sup>b</sup> measured at 50 s<sup>-1</sup> and 37°C; <sup>c</sup> AR 1500ex

### Drug release and dissolution

One (amlodipine, carbamazepine) or two (atenolol, warfarin) tablets were crushed using a mortar and pestle; tablet quantities were chosen to produce adequate drug concentrations for spectrophotometric detection. The powder obtained was then transferred into a 30 mL plastic cup filled with 15 g of the vehicles, as an estimation of the quantity typically used for medication delivery. Powder medications were incorporated by hand with a metallic spatula and agitated for one minute to disperse the solid. For comparison, whole tablets delivered with 15 mL water were tested. USP dissolution test apparatus II (VK7000, Varian, Mulgrave, Vic) was used with 900 mL of pH 1.2 simulated gastric fluid (SGF) without enzymes (34) at 37°C and a paddle rotation speed of 50 rpm (34, 35). Dissolution media recommended for each drug varied between the USP and BP; in this study a single standard environment was chosen to allow direct comparison of multiple drugs and multiple vehicles. Dispersions of the drug and the vehicle were placed into the dissolution vessel and 5 mL samples were collected at 1, 3, 5, 10, 15, 20, 30, 45, 90, 150 and 180 minutes through a stainless steel cannula assembled with full flow filter (10 µm, Varian) into 5 mL plastic syringes. 5 mL of fresh SGF was replaced immediately into dissolution vessels at every sampling point. Dissolution tests were also performed for the vehicles without drugs as the control. Samples were filtered through 0.45 µm nylon membranes (Millipore). Samples containing yoghurt were additionally centrifuged for 10 min at 4000 rpm prior to filtration. Calibration curves of each drug in SGF were prepared using stock solutions containing one (amlodipine, carbamazepine) or two (atenolol, warfarin) tablets dissolved in 1 L SGF and absorbance measured at 240 nm (amlodipine), 274 nm (atenolol), 280 nm (warfarin) and 285 nm (carbamazepine) using a Spectrophotometer Hitachi U-1900, (Scientific Instrument & Optical Sales, Brisbane, Qld). To account for background absorbance associated with the vehicles, results for the controls were subtracted from the absorbance of the vehicle containing drug. Cumulative percentage of the drug being dissolved was obtained and plotted against sample time. All tests and calibration curves were repeated in triplicate.

In the first experiment, crushed tablets of all four medications (amlodipine, atenolol, carbamazepine, warfarin) were tested for their release from three liquids (water, orange juice, honey), two semi-solid food vehicles (jam,

yoghurt) and one thickened fluid (Easythick, level 900). Whole tablets with water were also tested for comparison. Additionally, crushed warfarin mixed with Easythick (level 900) was compared with crushed warfarin mixed with water using a medium of SGF containing 3.2 g/L pepsin (800-2500 units/mg pepsin from porcine gastric mucosa, Sigma-Aldrich) to check whether this version of the dissolution media prescribed by the BP could improve drug release from the thickened fluid (34). In the second experiment, dissolution from five other thickening agents (Easythick Advanced, Janbak F, Karicare, Nutilus, Viscaid) were investigated at three thickness levels (150, 400, 900) using crushed atenolol tablets. Whole and crushed atenolol tablets in water were re-tested at the same time for comparison.

The results were analysed for differences in drug dissolution from food vehicles and thickening agents with one way ANOVA ( $p < 0.005$ ) and a Bonferroni post hoc test using GraphPad Prism version 5 (GraphPad software, San Diego, CA, USA).

### RESULTS

Amlodipine and atenolol whole tablets exhibited very rapid dissolution in SGF, with more than 85% of the drug dissolved in the first 10 minutes and complete dissolution achieved by 30 minutes (Figure 1 a,c). Dissolution of carbamazepine and warfarin tablets was slower, taking 2 and 2.5 hours respectively to reach 85% (Figure 1 e,g). As a general guide, the amount of drug measured in a dissolution test for immediate release tablets should be not less than 85% of the labeled amount within 30 minutes according to the FDA (36). Whole tablets of amlodipine and atenolol met these criteria but carbamazepine and warfarin did not (Table 3). However, it should be noted that the dissolution of carbamazepine tablets should be in a media that includes a surfactant and at 75 rpm according to the USP, and dissolution of warfarin should be assessed in water at 50 rpm (USP) or at pH 6.8 and 100 rpm (BP); these environments would be expected to be more conducive to dissolution of these particular drugs. Crushing the tablets and delivering with water resulted in faster dissolution, with carbamazepine and warfarin tablets reaching 85% dissolution within 60 and 20 minutes respectively (Figure 1 e,g).

Mixing the crushed tablets with orange juice, as an alternative Newtonian thin fluid that was similar in viscosity to water (Table 1), resulted in similar dissolution profiles to crushed tablets in water for all of the medications (Figure 1 b,d,f,h).

Honey, also a Newtonian fluid but considerably higher in viscosity (Table 1), caused only a small delay in dissolution for amlodipine and atenolol and this had no influence on % dissolved at 30 minutes (Table 2). Carbamazepine dissolution appeared to be slower in honey than water (Figure 1 f), with only 40% dissolved at 30 minutes instead of 77%, but this was not statistically significant (Table 3). However, honey significantly slowed dissolution of warfarin when compared with crushed tablets in water (Figure 1 h), reducing the proportion dissolved at 30 minutes to 44% instead of 90% (Table 3). In fact the dissolution profiles for carbamazepine and warfarin in honey more closely resembled the dissolution of the whole tablets than crushed tablets in water.

The use of jam or yoghurt as a vehicle, both thick fluids with non-Newtonian properties (Table

1), produced variable results. For atenolol, yoghurt was no different to orange juice or water, but it slowed dissolution in a similar way to honey for amlodipine and warfarin (Figure 1; Table 3). Jam generally reduced dissolution rate to a greater extent than yoghurt (Figure 1); the slight delay in dissolution for atenolol had no influence on the measurement at 30 minutes, but the slowed dissolution for amlodipine and warfarin had an impact (Table 3). The effect of yoghurt and jam on carbamazepine dissolution was large, reducing the 30 minute measurement to 51% and 37% respectively, which were more similar to dissolution of the whole tablet (57%) than crushed tablet in water (77%) but, due to variation between replicates within the carbamazepine experiment (particularly with yoghurt), these changes were not statistically significant (Table 3).

**Table 2.** Physicochemical characteristics and rheological attributes of the commercial thickeners used in this study. Spoon measurements indicated for each product were converted to weight and added to water to give the concentration (% w/v) for each thickness level.

Vehicle	Brand	Composition <sup>a</sup>	Thickness	Conc. (%w/v)	pH	Density	Viscosity (cP) <sup>b</sup>	Type of flow
Easythick	Flavour Creations	maltodextrin, xanthan gum	Level 900	7.3	5.6	1.01	767	Non-Newtonian <sup>d</sup>
Easythick Advanced	Flavour Creations	maltodextrin, xanthan gum, vitamin C, calcium chloride	Level 900	4.32	4.4	1.01	1250	Non-Newtonian <sup>c</sup>
			Level 400	1.70	4.8	1.00	414	
			Level 150	0.87	4.8	1.00	176	
Janbak F	Janbak Industries	xanthan gum	Level 900	2.2	6.0	0.99	1252	Non-Newtonian <sup>c</sup>
			Level 400	1.15	6.2	1.00	465	
			Level 150	0.76	6.2	1.00	260	
Karicare	Nutricia	maltodextrin, maize starch, carob bean gum	Level 900	40	5.1	1.03	1711	Non-Newtonian <sup>c</sup>
			Level 400	20	5.3	1.03	483	
			Level 150	8	5.4	1.00	15	
Nutilus	Nutricia	maltodextrin, modified maize starch, tara gum, xanthan gum, guar gum	Level 900	16	5.6	1.02	4090	Non-Newtonian <sup>c</sup>
			Level 400	12	5.7	1.02	3380	
			Level 150	8	5.7	1.02	1860	
Viscaid	Janbak Industries	guar gum	Level 900	1.4	6.3	0.99	1681	Non-Newtonian <sup>c</sup>
			Level 400	0.67	6.2	0.99	465	
			Level 150	0.33	6.5	0.99	47	

<sup>a</sup> taken from the product label; <sup>b</sup> measured at 50 s<sup>-1</sup> and 37 °C; <sup>c</sup> AR 1500ex; <sup>d</sup> HAAKE MARS III

Easythick at level 900 caused the greatest restriction in drug release for all four medications tested. Atenolol, which was largely unaffected by any of the other vehicles, exhibited only 50% release by 30 minutes (Table 3) and took 3 h to reach 85% (Figure 1 d). Amlodipine also released only 50% by 30 minutes, a significant reduction (Table 3), but carbamazepine and warfarin reached only 14% by 30 min and 40 - 50% after 3 h (Figure 1). There was no additional release of warfarin from thickened fluid when tested using SGF containing pepsin as the dissolution medium (Figure 2), which is an alternative simulation of the gastric environment (34, 35).

The delayed release of four crushed medications by Easythick at level 900 led to the subsequent investigation of drug release from a further five commonly used thickening agents, with consideration of the preparation thickness (Figure 3). Using atenolol tablets as the model drug, at thickness level 150 there was a minor and non-significant delay in dissolution; at least 85% of the medication was released and dissolved within 30 minutes with all of the products except Janbak F which allowed dissolution of only 76% (Table 4). It was observed that when added to the dissolution vessel, thickened fluids containing the crushed tablets initially became dispersed and mixed with SGF but later formed a single lump, and that lump only broke into smaller pieces for Nutilis.

At level 400, Easythick Advanced and Janbak F significantly slowed the dissolution of atenolol (Figure 3), allowing only 46 and 68% dissolution

respectively at 30 minutes in comparison to 87 – 98% for the other thickened fluids at the same thickness and the whole tablet or crushed tablet with water (Table 4). Observations of the samples loaded into the vessel indicated that either they remained as a single mass for the whole experiment (Easythick Advanced, Janbak F and Karicare) or broke into small pieces (Nutilis, Viscaid) and later formed a single clump (Nutilis).

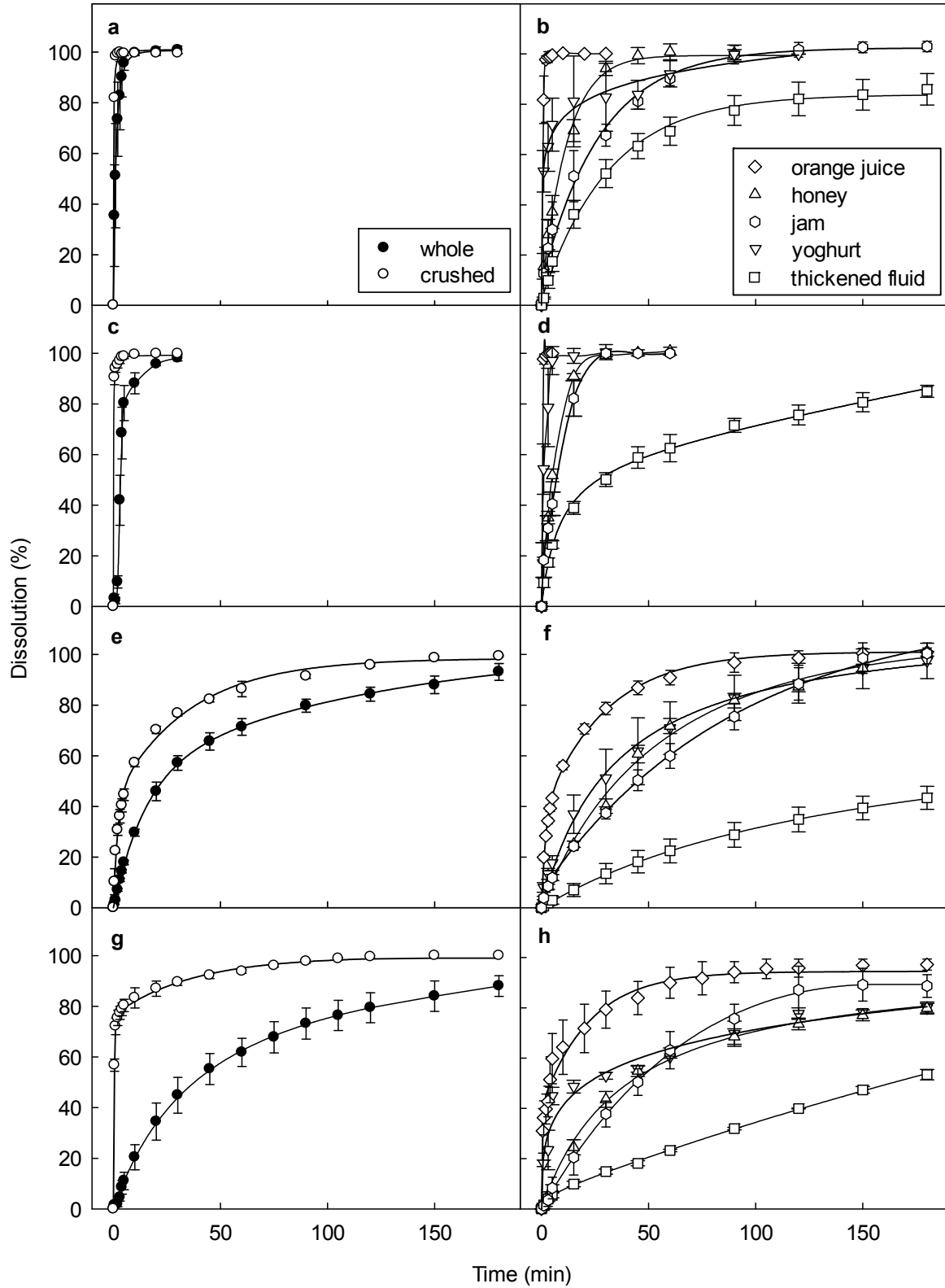
When used at level 900, all of the thickened fluids retarded dissolution when compared with whole tablets or crushed tablets in water, with 36 – 62% release in 30 minutes (Table 4) and a great deal of variation between replicate tests (Figure 3). The samples were all observed to remain in a single lump for the whole experiment, avoiding complete mixing with the dissolution media. Lack of mixing was confirmed for level 900 thickeners by testing dissolution media viscosity at 15 minutes and 3 hours into the dissolution test, with all values being lower than measured when the thickener was completely dispersed in the dissolution media (Table 5).

## DISCUSSION

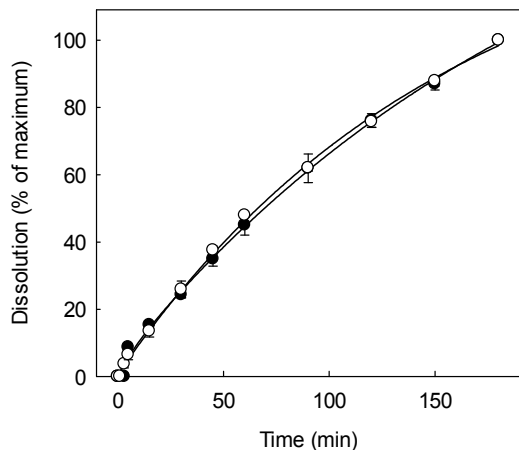
The most notable outcome from this study was that thickened fluids, prepared using commercial powder thickeners that are designed to produce a thickness that improves the likelihood of dysphagic patients to be able to safely swallow liquids, can significantly delay dissolution of drugs mixed into them.

**Table 3.** The percentage dissolution (mean  $\pm$  standard error; n = 3) in simulated gastric fluid at 30 minutes for amlodipine, atenolol, carbamazepine and warfarin whole tablets delivered with 15 g water and crushed tablets mixed into 15 g of various vehicles. Within each column, measurements with the same superscript letter are not significantly different (P<0.05).

	Percentage of drug dissolved at 30 minutes			
	Amlodipine	Atenolol	Carbamazepine	Warfarin
Whole tablets	100.7 $\pm$ 1.5 <sup>a</sup>	98.1 $\pm$ 1.1 <sup>a</sup>	57.0 $\pm$ 2.8 <sup>ac</sup>	44.9 $\pm$ 7.1 <sup>a</sup>
Crushed tablets:				
Water	99.5 $\pm$ 0.4 <sup>a</sup>	99.8 $\pm$ 0.2 <sup>a</sup>	76.7 $\pm$ 1.0 <sup>a</sup>	89.5 $\pm$ 1.3 <sup>b</sup>
Orange juice	100.2 $\pm$ 0.3 <sup>a</sup>	100.0 $\pm$ 0.0 <sup>a</sup>	78.7 $\pm$ 2.4 <sup>a</sup>	79.3 $\pm$ 7.4 <sup>b</sup>
Honey	94.3 $\pm$ 2.8 <sup>ac</sup>	99.2 $\pm$ 0.5 <sup>a</sup>	40.1 $\pm$ 2.9 <sup>ac</sup>	43.6 $\pm$ 3.2 <sup>a</sup>
Strawberry jam	67.7 $\pm$ 4.4 <sup>bc</sup>	100.0 $\pm$ 0.0 <sup>a</sup>	37.4 $\pm$ 2.4 <sup>ac</sup>	37.8 $\pm$ 5.1 <sup>ad</sup>
Yoghurt	82.8 $\pm$ 13.5 <sup>acd</sup>	100.5 $\pm$ 3.0 <sup>a</sup>	51.2 $\pm$ 11.4 <sup>ac</sup>	53.0 $\pm$ 1.3 <sup>a</sup>
Easythick (level 900)	52.4 $\pm$ 5.6 <sup>bd</sup>	50.1 $\pm$ 2.7 <sup>b</sup>	13.4 $\pm$ 4.0 <sup>bc</sup>	14.9 $\pm$ 1.0 <sup>cd</sup>



**Figure 1.** Dissolution of amlodipine (a,b), atenolol (c,d), carbamazepine (e,f) and warfarin (g,h) in simulated gastric fluid using whole tablets and crushed tablets mixed with water (a,c,e,g) and crushed tablets mixed with orange juice, honey, jam, yoghurt and thickened fluid (Easythick at thickness level 900) (b,d,f,h). The data shows mean  $\pm$  standard error for 3 replicates.



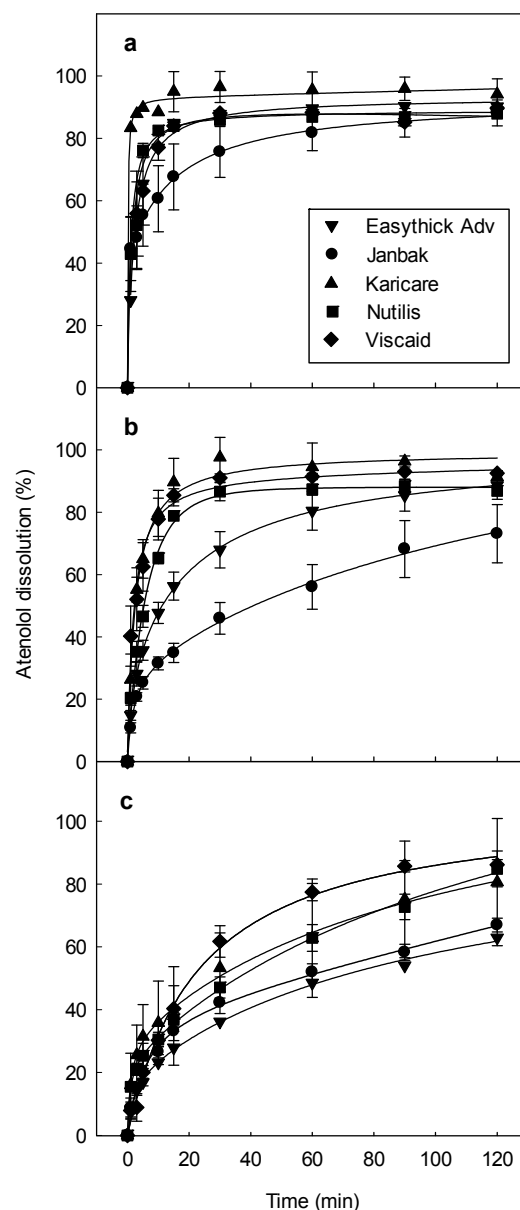
**Figure 2.** Dissolution in simulated gastric fluid with and without pepsin for crushed warfarin tablets mixed with Easythick at thickness level 900. The data shows mean  $\pm$  standard error for 3 replicates.

At level 900, which is the thickest consistency in Australia prescribed for individuals with dysphagia, Easythick significantly delayed dissolution of all four medicines tested. Because of this, we further investigated the product range, choosing a similar product that is also based primarily on xanthan gum (Janbak F) and products that are comprised of other gum and starch thickeners. All five tested retarded release of atenolol, which was unaffected by any of the food and drink products tested, when used at level 900. Furthermore, the thickeners based on xanthan gum also affected dissolution when used at the intermediate thickness, level 400. Other countries may use even thicker consistencies, for example in the USA the thickest level is 'spoon thick' which is  $\eta_{50} > 1750$  cP (18), which may be expected to retard drug release to an even greater extent than that observed here.

Thick food products such as honey, jam and yoghurt, which are also used to aid delivery of crushed medications for people who cannot or do not like to swallow whole tablets and capsules, had a relatively small and drug-dependent impact on dissolution. In particular, we found that jam delayed the dissolution of amlodipine in comparison to whole and crushed tablets, and yoghurt was associated with large variation in dissolution between replicate tests for amlodipine and carbamazepine. While jam, yoghurt and honey slowed dissolution for crushed carbamazepine and warfarin, this actually served to create a release profile that was more like that

of the whole tablet than the crushed tablet, which reinforces the fact that each dosage form has the potential to respond differently to crushing and mixing with vehicles such as these.

The Biopharmaceutical Classification Scheme (BCS) classifies drugs according to two major physicochemical properties, solubility and permeability, that contribute to bioavailability upon oral administration (32).



**Figure 3.** Dissolution profiles in simulated gastric fluid for crushed atenolol tablets mixed with the thickened fluids Easythick Advanced, Janbak F, Karicare, Nutilis and Viscaid at three viscosity levels: a) level 150, b) level 400 and c) level 900. The data shows mean  $\pm$  standard error for 3 replicates.



**Table 4.** The percentage dissolution (mean  $\pm$  standard error; n = 3) in simulated gastric fluid at 30 minutes for atenolol mixed in water or a thickened fluid prepared at three thickness levels. Measurements with the same superscript letter are not significantly different (P<0.05).

	Percentage of drug dissolved at 30 minutes		
	Level 150	Level 400	Level 900
Whole tablets with water	97.0 $\pm$ 2.7 <sup>a</sup>		
Crushed tablets in water	96.0 $\pm$ 0.9 <sup>a</sup>		
Crushed tablets in thickener at:			
Easythick Advanced	87.0 $\pm$ 2.3 <sup>acf</sup>	68.0 $\pm$ 5.8 <sup>bcg</sup>	36.2 $\pm$ 1.4 <sup>d</sup>
Janbak F	75.6 $\pm$ 8.2 <sup>ace</sup>	46.0 $\pm$ 5.1 <sup>bd</sup>	42.2 $\pm$ 6.0 <sup>dg</sup>
Karicare	96.5 $\pm$ 5.0 <sup>a</sup>	97.6 $\pm$ 6.4 <sup>a</sup>	53.3 $\pm$ 11.1 <sup>deg</sup>
Nutilus	85.9 $\pm$ 0.4 <sup>acf</sup>	86.6 $\pm$ 2.9 <sup>acf</sup>	47.1 $\pm$ 3.4 <sup>dg</sup>
Viscaid	88.1 $\pm$ 0.8 <sup>acf</sup>	91.0 $\pm$ 1.3 <sup>ac</sup>	61.5 $\pm$ 8.7 <sup>defg</sup>

**Table 5.** Viscosity (measured at a shear rate of 50 s<sup>-1</sup>) of the dissolution media at 15 minutes and 3 hours of the dissolution test following addition of 15 g of thickened fluid at prepared at level 900 thickness. Also shown is the concentration and viscosity of the dissolution media if dispersion of the vehicle was complete, achieved by thoroughly mixing the quantity of thickener powder that would be used to prepare 15 g thickened fluid at level 900 into 900 ml SGF. For comparison, the viscosity of water and SGF at 50 s<sup>-1</sup> is 0.8 cP.

Vehicle	Dissolution media viscosity (cP) <sup>a</sup>		Complete dispersion	
	15 minutes	3 hours	concentration (%w/v)	viscosity (cP) <sup>b</sup>
Easythick Advanced	0.81	1.10	0.07	5.24
Janbak F	0.80	1.56	0.04	5.92
Karicare	0.80	1.30	0.67	1.66
Nutilus	0.81	0.93	0.27	2.19
Viscaid	0.82	0.82	0.02	1.09

<sup>a</sup>AR-G2 cone and plate fixture, <sup>b</sup>AR 1500ex concentric cylinder

Active ingredients with high solubility and high permeability profile are BCS class I substances, and amlodipine is an example (37). For these drugs it is the dosage form that is likely to be the rate limiting step for absorption and so we may expect the delay in dissolution exhibited particularly by the thickened fluid could translate into a clinically significant effect. BCS class II compounds exhibit low solubility with high permeability, so the dosage form can potentially further hinder dissolution and therefore absorption. Carbamazepine is within this class (38, 39), as exhibited by the slow dissolution of the whole tablet which was improved by crushing. Warfarin has been classified as BCS class I when used as the sodium salt and tested in water (37, 38) and BCS II when used as the free acid (39) slow dissolution from the whole warfarin sodium tablet tested in simulated gastric fluid (causing the warfarin to become unionized and therefore less soluble) suggests that BCS II classification is most appropriate for the conditions in our study. Both carbamazepine and warfarin have a narrow therapeutic index and are associated with serious

side effects if bioavailability is inconsistent, so the significant delay in dissolution caused by thickened fluids is a concern. Drugs with high solubility but low permeability are grouped into BCS class III, and in this study atenolol is the example (39). While alterations to dissolution rate caused by the dosage form may be of relatively low importance for BCS III medications, for which absorption is mostly limited by permeability, the extent of the delay in drug release caused by thickened fluids at level 900 may have the potential to have a clinically significant effect.

There is the potential for interactions between food components, drugs, dosage form excipients and gastrointestinal contents (40). Food vehicles can form a physical barrier that prevents mixing with gastrointestinal fluids, making drug release difficult and reducing exposure of the active ingredient at the site of absorption (41-43). For example, jam contains pectin, which forms a gel network that is strengthened by the presence of fruit pieces (44), and this is likely to be responsible for retarding amlodipine dissolution

in this study. However, it is clear that at certain concentrations the thickening agents, particularly those based primarily on xanthan gum, produced much more of a barrier to drug release. Viscosity at a single shear rate of  $50 \text{ s}^{-1}$  is not a good indicator for likelihood of impeding drug dissolution.

The thickening agents are all comprised of natural gums and starches which hydrate and form highly shear thinning viscoelastic solutions, some of which were gel-like, when added to water. Polymer solution rheology depends on the concentration, conformation in the solvent (e.g. water) and interaction between polymer chains (45). The conformation of xanthan gum chains is rigid rod type (46). In contrast, polymer chains of galactomannans (guar gum) are flexible random coil type whose shape continually fluctuates (47), while starch is highly branched polymer that forms swollen granules (48). Xanthan gum is the only polymer that carries a charge; while there could be the potential for direct interaction with charged drugs, the nutritional information for all of the thickeners indicate that they contain sodium (e.g. Easythick Advanced 1.5 g/100g, Janbak F 1g/100g) and this would be expected to form ionic interactions with the acidic groups of the xanthan gum. Consequently it is most likely that the highly ordered xanthan gum network simply traps drug molecules within it, and at the higher concentrations of xanthan gum (level 400 and level 900) this significantly impaired drug dissolution and diffusion into the surrounding simulated gastric fluid. At the greatest thickness (level 900), the networks formed by the other products were entangled enough to affect drug dissolution. The fact that thickening agents containing natural gums are associated with a propensity to impair drug dissolution is unsurprising, since they are able to impart sustained-release properties to solid dose formulations. Notably, xanthan gum is better able than guar gum to retard drug release (49-51).

These structured fluids have shear thinning and solid-like behaviour. At low shear stresses, the solutions exhibit higher viscosity. Once the shear stress applied is above a critical value, the solutions yield, flow or fracture and viscosity drops (45). In the dissolution vessel, which represents the physiological conditions within the stomach, the shear rates within the media are expected to distribute from 0.2 to  $92 \text{ s}^{-1}$  at 50 rpm (52). Clearly there are limitations to the conclusions that can be drawn when a simple dissolution environment is used. Further research is required to consider other issues, particularly

the effect of swallowing on bolus structure and integrity as this would be expected to alter drug release profile. It is possible that forces acting during swallowing may break up the single lump of gel into multiple smaller lumps before it gets to the stomach. Alternatively, with impaired swallowing some of the thickened fluid may remain in the pharynx and be delayed in reaching the stomach. Shear rates within the oral cavity, pharynx and oesophagus vary as a function of both physiological and bolus variables. Tongue pressure and coordination, in addition to saliva lubrication characteristics will affect speed of movement and potential deformation of the bolus. The viscosity, density, yield stress and elastic properties of the bolus interact with these physiological variables. Combined, these factors will have most impact for individuals with dysphagia where tongue strength and control is often impaired and there can be severe deficits in over- or under-production of saliva (53, 54). Although the shear rate of  $50 \text{ s}^{-1}$  is most often reported to express the shear rate associated with swallowing, there is little evidence to support this and it is likely that there are a broad range of shear rates operating within the deglutitive system (45, 55-57).

## CONCLUSION

Coadministration of immediate release crushed tablets with food based vehicles or thickening agents provides a functional approach to medicine administration as it reduces the discomfort caused by solid dosage forms for patients with swallowing difficulties, but with it comes the potential for unexpected drug release and dissolution profiles. *In vitro* release and dissolution of medications when crushed and mixed with common food vehicles or thickening agents may be influenced by the properties (e.g. viscosity) and structure of the carrier. This may be critical for certain medications with a narrow therapeutic index or when immediate release is required for fast therapeutic action. These findings bring into question the potential clinical implications of the addition of these agents to medications for the purpose of dose delivery and indicate that further investigation of thickened fluids and their potential to influence therapeutic outcomes is warranted.

Where the addition of a vehicle is considered clinically necessary to aid medication delivery, yoghurt is the most appropriate of the products tested in this study because it can produce the mechanical profile required for oral

processing in dysphagic patients without severely limiting drug dissolution. However, variability in composition and textural attributes between brands needs to be considered. Honey and jam also have an appropriately high viscosity for oral processing without a major delay in dissolution, but they have an adhesive quality that makes them sticky in the mouth, there are large variations between brands and product type, and their high sugar content makes them generally unsuitable for regular use due to issues with dental care. Where possible, dose alteration (e.g. crushing medicines) should be avoided and alternate dose forms or routes of administration should be found.

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## REFERENCES

- Matsuo K, Palmer JB. Anatomy and physiology of feeding and swallowing: Normal and abnormal. *Phys Med Rehabil Clin N Am*. 2008; 19(4):691-707.
- Cook IJ, Weltman MD, Wallace K, Shaw DW, McKay E, Smart RC, et al. Influence of aging on oral-pharyngeal bolus transit and clearance during swallowing: scintigraphic study. *Am J Physiol Gastr L*. 1994; 266(6):G972-G977.
- Hansen DL, Tulinius D, Hansen EH. Adolescents' struggles with swallowing tablets: barriers, strategies and learning. *Pharm World Sci*. 2008; 30:65-69.
- Chisaka H, Matsushima Y, Wada F, Saeki S. Dynamics of capsule swallowing by healthy young men and capsule transit time from the mouth to the stomach. *Dysphagia*. 2006; 21:275-279.
- Strachan I, Greener M. Medication-related swallowing difficulties may be more common than we realise. *Pharm Pract*. 2005; 15(10):411-414.
- Wright D. Medication administration in nursing homes. *Nurs Stand*. 2002; 16(42):33-38.
- Kottke MK, Stetsko G, Rosenbaum SE, Rhodes CT. Problems encountered by the elderly in the use of conventional dosage forms. *J Geriatr Drug Ther*. 1990; 5(2):77-89.
- Burridge N, Deidun D. Australian don't rush to crush handbook. Therapeutic options for people unable to swallow solid oral medicines. The Society of Hospital Pharmacists of Australia, Collingwood, Australia, 2011.
- Stubbs J, Haw C, Dickens G. Dose form modification – a common but potentially hazardous practice. A literature review and study of medication administration to older psychiatric inpatients. *Int Psychogeriatr*. 2008; 20(03):616-627.
- Paradiso LM, Roughead L, Gilbert AL. Crushing or altering medications: what's happening in residential aged-care facilities? *Australas J Ageing*. 2002; 21(3):123-127.
- Nissen LM, Haywood A, Steadman KJ. Solid medication dosage form modification at the bedside and in the pharmacy of Queensland hospitals. *J Pharm Pract Res*. 2009; 39(2):129-134.
- Lee ID, Hunt TL, Bradley CR, Copp C, Griffiths L, Brobst-Kromer J. Effects on the pharmacokinetics and pharmacodynamics in the elderly of coadministering ramipril with water, apple juice, and applesauce. *Pharm Res*. 1996; 13(4):639-642.
- Gidal BE, Maly MM, Kowalski J, Rutecki PA, Pitterle ME, Cook DE. Gabapentin absorption: effect of mixing with foods of varying macronutrient composition. *Ann Pharmacother*. 1998; 32(4):405-409.
- McLean A, Browne S, Zhang Y, Slaughter E, Halstenson C, Couch R. The influence of food on the bioavailability of a twice-daily controlled release carbamazepine formulation. *J Clin Pharmacol*. 2001; 41(2):183-186.
- Fay MA, Sheth RD, Gidal BE. Oral absorption kinetics of levetiracetam: The effect of mixing with food or enteral nutrition formulas. *Clin Ther*. 2005; 27(5):594-598.
- Jann MW, Bean J, Fidone GS. Interaction of dietary pudding with phenytoin. *Pediatrics*. 1986; 78(5):952-953.
- Damle BD, Yan JH, Behr D, O'Mara E, Nichola P, Kaul S, et al. Effect of food on the oral bioavailability of didanosine from encapsulated enteric-coated beads. *J Clin Pharmacol*. 2002; 42(4):419-427.
- Jukes S, Cichero JAY, Haines T, Wilson C, Paul K, O'Rourke M. Evaluation of the uptake of the Australian standardized terminology and definitions for texture modified foods and fluids. *Int J Speech Lang Pathol*. 2012; 14(3):214-225.
- Nguyen T-M-U, Lau ETL, Steadman KJ, Cichero JAY, Dingle K, Nissen LM. Pharmacist, general practitioner and nurse perceptions, experiences and knowledge of medication dosage form modification. *Integrated Pharmacy Research and Practice* 2013; 3:1-9.
- Lippert C, Gbenado S, Qiu CF, Lavin B, Kovacs SJ. The bioequivalence of telithromycin administered orally as crushed tablets versus tablets swallowed whole. *J Clin Pharmacol*. 2005; 45(9):1025-1031.
- Doods Ashely ES, Zaas AK, Fang AF, Darnle B, Perfect JR. Comparative pharmacokinetics of voriconazole administered orally as either crushed

- or whole tablets. *Antimicrob Agents Chemother.* 2007; 51(3):877-880.
22. Zafar MU, Farkouh ME, Fuster V, Chesebro JH. Crushed clopidogrel administered via nasogastric tube has faster and greater absorption than oral whole tablets. *J Interv Cardiol.* 2009; 22(4):385-389.
  23. Henney HR 3rd, Fitzpatrick A, Stewart J, Runyan JD. Relative bioavailability of tizanidine hydrochloride capsule formulation compared with capsule contents administered in applesauce: a single-dose, open-label, randomized, two-way, crossover study in fasted healthy adult subjects. *Clin Ther.* 2008; 30(12):2263-2271.
  24. Manessis A, Lascher S, Bukberg P, Darmody T, Yen V, Sadek S, et al. Quantifying amount of adsorption of levothyroxine by percutaneous endoscopic gastrostomy tubes. *J Parenter Enteral Nutr.* 2008; 32(2):197-200.
  25. Lilja JJ, Raaska K, Neuvonen PJ. Effects of orange juice on the pharmacokinetics of atenolol. *Eur J Clin Pharmacol.* 2005; 61(5-6):337-340.
  26. Bailey DG. Fruit juice inhibition of uptake transport: a new type of food-drug interaction. *Br J Clin Pharmacol.* 2010; 70(5):645-655.
  27. Jeon H, Jang IJ, Lee S, Ohashi K, Kotegawa T, Ieiri I, et al. Apple juice greatly reduces systemic exposure to atenolol. *Br J Clin Pharmacol.* 2013; 75(1):172-179.
  28. Fleisher D, Sweet BV, Parekh A, Boullata JI. Drug absorption with food, in Boullata JI, Armenti VT (eds). *Handbook of Drug-Nutrient Interactions.* Humana Press, New York, NY, pp. 209-241, 2010.
  29. Huupponen R, Seppälä P, Iisalo E. Effect of guar gum, a fibre preparation, on digoxin and penicillin absorption in man. *Eur J Clin Pharmacol.* 1984; 26(2):279-281.
  30. Gin H, Orgerie MB, Aubertin J. The influence of guar gum on absorption of metformin from the gut in healthy volunteers. *Horm Metab Res.* 1989; 21(2):81-83.
  31. Sarisuta N, Parrott EL. Relationship of dissolution rate to viscosity of polymeric solutions. *J Pharm Sci.* 1982; 71(12):1375-1380.
  32. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutical drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm Res.* 1995; 12(3):413-420.
  33. Dressman JB, Amidon GL, Reppas C, Shah VP. Dissolution testing as a prognostic tool for oral drug absorption: Immediate release dosage forms. *Pharm Res.* 1998; 15(1):11-22.
  34. British Pharmacopoeia 2013. The Stationery Office, London, UK, 2013.
  35. The United States Pharmacopeia 34: The National Formulary 29. United States Pharmacopeial Convention, Rockville, MD, 2011.
  36. Guidance for Industry. Dissolution testing of immediate release solid oral dosage forms. United States Food and Drug Administration, Rockville, MD, 1997.
  37. Lindenberg M, Kopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. *Eur J Pharm Biopharm.* 2004; 58(2):265-278.
  38. Kasim NA, Whitehouse M, Ramachandran C, Bermejo M, Lennernas H, Hussain AS, et al. Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. *Mol Pharm.* 2004; 1(1):85-96.
  39. Wu CY, Benet LZ. Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. *Pharm Res.* 2005; 22(1):11-23.
  40. Persson E, Gustafsson A-S, Carlsson A, Nilsson R, Knutson L, Forsell P, et al. The effects of food on the dissolution of poorly soluble drugs in human and in model small intestinal fluids. *Pharm Res.* 2005; 22(12):2141-2151.
  41. Shono Y, Jantratid E, Janssen N, Kesisoglou F, Mao Y, Vertzoni M, et al. Prediction of food effects on the absorption of celecoxib based on biorelevant dissolution testing coupled with physiologically based pharmacokinetic modeling. *Eur J Pharm Biopharm.* 2009; 73(1):107-114.
  42. Abrahamsson B, Albery T, Eriksson A, Gustafsson I, Sjöberg M. Food effects on tablet disintegration. *Eur J Pharm Sci.* 2004; 22(2-3):165-172.
  43. Parojcic J, Vasiljevic D, Ibric S, Djuric Z. Tablet disintegration and drug dissolution in viscous media: Paracetamol IR tablets. *Int J Pharm.* 2008; 355(1-2):93-99.
  44. Carbonell E, Costell E, Duran L. Rheological behaviour of sheared jams. Relation with fruit content. *J Texture Stud.* 1991; 22(1):33-43.
  45. Stokes JR. 'Oral' rheology, in Chen J, Engelen L (eds), *Food Oral Processing: Fundamentals of Eating and Sensory Perception.* Wiley-Blackwell, Oxford, UK, pp 225-263, 2012.
  46. Lapasin R, Prici S. *Rheology of Industrial Polysaccharides: Theories and Applications.* Springer, Glasgow, UK, 1995.
  47. Robinson G, Ross-Murphy SB, Morris ER. Viscosity-molecular weight relationships, intrinsic chain flexibility, and dynamic solution properties of guar galactomannan. *Carbohydr Res.* 1982; 107(1):17-32.
  48. Morris VJ. Starch gelation and retrogradation. *Trends Food Sci Tech.* 1990;1:2-6.
  49. Mughal MA, Iqbal Z, Neau SH. Guar gum, xanthan gum, and HPMC can define release mechanisms and sustain release of propranolol hydrochloride. *AAPS PharmSciTech.* 2011; 12(1):77-87.
  50. Varshosaz J, Tavakoli N, Eram SA. Use of natural gums and cellulose derivatives in production of

- sustained release metoprolol tablets. *Drug Deliv.* 2006; 13(2):113-119.
51. Varshosaz J, Tavakoli N, Kheirolah F. Use of hydrophilic natural gums in formulation of sustained-release matrix tablets of tramadol hydrochloride. *AAPS PharmSciTech.* 2006; 7(1):E24.
52. Kukura J, Baxter JL, Muzzio FJ. Shear distribution and variability in the USP Apparatus 2 under turbulent conditions. *Int J Pharm.* 2004; 279(1-2):9-17.
53. Cassolato SF, Turnbull RS. Xerostomia: clinical aspects and treatment. *Gerodontology.* 2003; 20(2):64-77.
54. Senner JE, Logemann J, Zecker S, Gaebler-Spira D. Drooling, saliva production, and swallowing in cerebral palsy. *Dev Med Child Neurol.* 2004; 46(12):801-806.
55. Nicosia MA. Theoretical estimation of shear rate during the oral phase of swallowing: effect of partial slip. *J Texture Stud.* 2013; 44(2):132-139.
56. Stokes JR, Boehm MW, Baier SK. Oral processing, texture and mouthfeel: From rheology to tribology and beyond. *Curr Opin Colloid Interface Sci.* 2013; 18(4):349-359.
57. Cutler AN, Morris ER, Taylor LJ. Oral perception of viscosity in fluid foods and model systems. *J Texture Stud.* 1983; 14(4):377-395.