Drug Development and Industrial Pharmacy

ISSN: 0363-9045 (Print) 1520-5762 (Online) Journal homepage: https://www.tandfonline.com/loi/iddi20

Oral medication delivery in impaired swallowing: thickening liquid medications for safe swallowing alters dissolution characteristics

Yady J. Manrique, Arron M. Sparkes, Julie A.Y. Cichero, Jason R. Stokes, Lisa M. Nissen & Kathryn J. Steadman

To cite this article: Yady J. Manrique, Arron M. Sparkes, Julie A.Y. Cichero, Jason R. Stokes, Lisa M. Nissen & Kathryn J. Steadman (2016) Oral medication delivery in impaired swallowing: thickening liquid medications for safe swallowing alters dissolution characteristics, Drug Development and Industrial Pharmacy, 42:9, 1537-1544, DOI: 10.3109/03639045.2016.1151033

To link to this article: https://doi.org/10.3109/03639045.2016.1151033

Published online: 02 Mar 2016.

Submit your article to this journal

Article views: 945

View related articles

View Crossmark data

Citing articles: 10 View citing articles

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=iddi20

KINDERFARMS Ex. 1013
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 2016
VOL. 42, NO. 9, 1537–1544
http://dx.doi.org/10.3109/03639045.2016.1151033

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

Oral medication delivery in impaired swallowing: thickening liquid medications for safe swallowing alters dissolution characteristics

Yady J. Manrique[a], Arron M. Sparkes[a], Julie A.Y. Cichero[a], Jason R. Stokes[b], Lisa M. Nissen[c] and Kathryn J. Steadman[a]

[a]School of Pharmacy, The University of Queensland, Brisbane, Australia; [b]School of Chemical Engineering, The University of Queensland, Brisbane, Australia; [c]School of Clinical Sciences, Queensland University of Technology, Brisbane, Australia

ABSTRACT

Acetaminophen (paracetamol) is available in a wide range of oral formulations designed to meet the needs of the population across the age-spectrum, but for people with impaired swallowing, i.e. dysphagia, both solid and liquid medications can be difficult to swallow without modification. The effect of a commercial polysaccharide thickener, designed to be added to fluids to promote safe swallowing by dysphagic patients, on rheology and acetaminophen dissolution was tested using crushed immediate-release tablets in water, effervescent tablets in water, elixir and suspension. The inclusion of the thickener, comprised of xanthan gum and maltodextrin, had a considerable impact on dissolution; acetaminophen release from modified medications reached 12–50% in 30 min, which did not reflect the pharmacopeia specification for immediate release preparations. Flow curves reflect the high zero-shear viscosity and the apparent yield stress of the thickened products. The weak gel nature, in combination with high G' values compared to G'' (viscoelasticity) and high apparent yield stress, impact drug release. The restriction on drug release from these formulations is not influenced by the theoretical state of the drug (dissolved or dispersed), and the approach typically used in clinical practice (mixing crushed tablets into pre-prepared thickened fluid) cannot be improved by altering the order of incorporation or mixing method.

ARTICLE HISTORY
Received 10 October 2015
Revised 20 January 2016
Accepted 25 January 2016
Published online 1 March 2016

KEYWORDS
Acetaminophen; dissolution; dysphagia; rheology; viscosity

Introduction

The range of oral dosage forms available, from solids such as tablets and capsules to liquids such as elixirs and suspensions, are designed to address the therapeutic needs of the majority of the population including infants, adults and the elderly. However, patients with impaired ability to swallow (i.e. dysphagia) vary in their ability to swallow food and fluids without aspiration into the airways[1]. Whole tablets and capsules should be avoided for people with swallowing impairments due to the risk of aspiration and penetration into the airway[2]. Oral liquid dose forms represent an alternative to the use of solid dose forms for people with swallowing issues, but thin fluids leave dysphagic patients at risk of aspiration as a consequence of the poor control of liquids. In the absence of alternatives, the most common solution to the medication delivery dilemma for dysphagic patients is to crush tablets and open capsules, and mix the powder with food[3,4], thickened fluid or naturally thick food vehicles, such as yoghurt, jam or pudding[5–7]. The use of thickeners to facilitate safe swallowing of fluids is a result of the rheological properties of these agents[8] as the increased viscosity of the fluid leads to better control over the timing of opening of the valves involved in swallowing, reducing the chance of transit straight into the airway[9].

Previous research has demonstrated that water thickened with commercial polysaccharide thickeners, has the potential to negatively impact the release of conventional crushed tablets when they are used in replacement of water. The effects were thickener and viscosity-dependent, with products containing xanthan gum and higher thicknesses causing the greatest restriction in drug release[10].

The aim of this research is to determine whether the state of drug aggregation within the thickened water (i.e. dissolved or dispersed) is an important determinant of drug release. Acetaminophen (paracetamol) is a good example of an active ingredient available in several solid and liquid oral formulations. Acetaminophen tablets are the most commonly modified medicine for adults and children in Australian hospitals[5] and most commonly cited as being difficult to swallow[11]. It is available in dosage forms that provide paracetamol in solution (syrup and dissolved effervescent tablets) and dispersed state (suspension, crushed immediate release tablets in water). The hypothesis to be tested is that the limitation on drug release is reduced when the acetaminophen is dissolved rather than dispersed within the thickened water. Two approaches can be applied to test this hypothesis, firstly to vary the order of adding the components to allow acetaminophen to dissolve in water and then mix into thickened water, as opposed to the standard clinical practice of dispersing crushed tablet powder into pre-thickened water. The second approach is to compare the effect on drug release of thickening commercial products that have acetaminophen dissolved (effervescent tablet, elixir) or dispersed (suspension). Additionally, detailed rheological characterization of the thickened products was carried out to consider the contribution of viscoelasticity and yield stress to restriction on drug release.

Material and methods

Materials

The dosage forms studied were available in Australia in 2012 when this work was conducted: Panadol immediate release tablets 500 mg, round and film coated (marketed in Australia with statements declaring these forms do not have any ingredient that improves absorption), Panadol rapid soluble effervescent tablets

CONTACT Kathryn J. Steadman k.steadman@uq.edu.au School of Pharmacy, The University of Queensland, Brisbane, Qld 4072, Australia
© 2016 Informa UK Limited, trading as Taylor & Francis Group

KINDERFARMS Ex. 1013
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

500 mg, Panadol children's 5–12 years raspberry flavor elixir (48 mg/mL), and Panadol children's 5–12 years color-free orange flavor suspension (48 mg/mL). Deionized water or deionized water thickened with Easythick (Flavour Creations, Brisbane, Australia) was used as the drug delivery vehicle. Easythick (contents: maltodextrin, xanthan gum, sodium chloride) was prepared using the quantity indicated by the manufacturer to produce the thickest level described by the Australian National Standards for dysphagic patients[12,13], level 900, which indicates that the apparent viscosity at a shear rate of 50^{-1} should be greater than 900 mPas. Spoon measurements of the thickener were converted to weight to provide the desired percentage (%w/v). To produce thickened water at level 900, each 185 mL of water required 5 teaspoons of the thickener, equivalent to 13.5 g (7.3% w/v), so for 15 mL of water 1.1 g of thickener was added.

Experimental design

The role in drug release of the method used to incorporate crushed tablets into the thickened water was investigated by varying both the order of addition of the three components, crushed tablet, water and thickener powder, and the technique used to add the medication (manually with a spatula versus mechanical high speed stirrer). The variations in the order of addition were:

- Variant 1: thickener + water, then crushed tablet (i.e. the water was thickened before the crushed tablet was mixed in)
- Variant 2: crushed tablet + water, then thickener (i.e. the crushed acetaminophen tablet was suspended in the water before the water was thickened)
- Variant 3: crushed tablet + thickener, then water (i.e. the crushed tablet was mixed with the thickener powder before the water was thickened)

Additionally, the potential to thicken commercially available liquid dosage forms was investigated using acetaminophen in solution (i.e. effervescent tablet, elixir) and suspension. The entire experiment was replicated three times.

Sample preparation

Preparation of solid formulations by manual incorporation

For variant 1, which represents standard clinical practice[5–7], one immediate release acetaminophen tablet was crushed in a mortar and pestle and the contents transferred to a 30 mL disposable plastic cup. Thickened water was prepared by adding 3.6 g of thickener powder to 50 mL water and mixed with a hand stick blender (Tiffany 200W) with stainless steel shaft at stirring level 2 for 1 min until a uniform mass was formed, then 15 g of this thickened water was added to the cup containing one crushed tablet and manually mixed with a metallic spatula for 3 min.

For variant 2, one acetaminophen tablet was crushed and transferred to weighing paper, then to a 30 mL disposable cup. The mortar and pestle and weighing paper were rinsed with 10 and 5 mL (15 mL total) of deionized water and added into the cup. 1.1 g thickener powder was gradually incorporated and stirred until homogeneous.

For variant 3, one acetaminophen tablet was crushed and transferred to weighing paper, then to a 30 mL disposable cup. 1.1 g of thickener powder was added to the cup containing the crushed tablet and stirred. Then the mortar and pestle and weighing paper were rinsed with 10 and 5 mL (15 mL total) of deionized water and added into the cup and mixed.

All samples were manually mixed with a stainless steel spatula for 5 min until the mixture was visually homogeneous. To allow full hydration and swelling, after the thickener and water were mixed, samples were covered with a double layer of Parafilm® M (Sigma-Aldrich, Pty. Ltd., Sydney, Australia) and kept at 4 °C overnight prior to dissolution testing; once swelling is complete, gum-based thickeners do not change viscosity[14]. For variant 3, the thickened water prepared overnight was manually mixed with the crushed tablet 15 min before dissolution testing.

Weights of the intact tablet, mortar and pestle with and without residuals, empty disposable cup and disposable cup with crushed contents were noted.

Preparation of solid formulations by mechanical incorporation

In order to use an overhead stirrer for mechanical incorporation, the quantity prepared was up-scaled to produce an appropriate volume. Three and half acetaminophen tablets were crushed in a mortar and pestle and the solid transferred into a 100 mL glass beaker.

For variant 1, thickened water was prepared by adding 3.6 g of thickener powder to 50 mL of deionized water in a measuring cylinder and mixed.

For variant 2, 50 mL water was added to the beaker containing crushed tablets, and then 3.6 g thickener powder was added and mixed.

For variant 3, 3.6 g thickener powder was added to the beaker containing crushed tablets, and then a volume of 50 mL of water was added and mixed.

All the samples were mixed using an IKA® RW20 digital overhead stirrer, with a crossed blade impellor (Thermo Fisher Scientific Australia Pty Ltd, Scoresby, Australia) at 400 rpm for 5 min. For the purpose of de-aeration, 30 g of mechanically mixed samples and thickened water used in variant 1 were transferred to 50 mL centrifuge tubes and centrifuged (Eppendorf Centrifuge 5804 R, VWR International, Pty Ltd, Brisbane, Australia) at 2000 rpm for 2 min at 20 °C. These were then covered with a double layer of Parafilm® M kept at 4 °C overnight prior to dissolution testing to allow full hydration and swelling. For variant 1, the thickened water was recombined in a glass beaker after removal from refrigerated storage and mixed with the crushed tablets. 15 g of samples (equivalent to 1 crushed tablet) were weighed into a 30 mL disposable plastic cup 15 min before dissolution testing.

Weights of the intact tablet, mortar and pestle with and without residuals, empty disposable cup and disposable cup with crushed contents were noted.

Preparation of liquid formulations

The quantity of thickener added to liquid formulations was the quantity required to thicken water to level 900. A dose of 15 mL of elixir or suspension formulations were measured, placed into a 30 mL disposable plastic cup, and 1.1 g of thickener powder was added and mixed with a stainless steel spatula for 5 min to ensure the thickener was well dispersed. One effervescent tablet was dissolved in 100 mL water, and 7.3 g of thickener powder was added and mixed until a thick solution free of powder was formed. Thickened samples were covered with a double layer of Parafilm® M and kept at 4 °C overnight.

Methods

Drug release and dissolution

For the dissolution studies, prepared samples were removed from refrigeration and allowed to sit at room temperature for 15 min

KINDERFARMS Ex. 1013
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

prior to starting dissolution testing. The samples were tested using USP dissolution apparatus II (VK7000, Varian, Mulgrave, Victoria, Australia) with 900 mL of simulated gastric fluid (SGF) pH 1.2 without enzymes[15] at 37 °C and paddle speed of 50 rpm. 3 mL samples were collected at 1, 3, 5, 10, 25, 30, 60, 90, 120, 150, 180 min through stainless steel cannula assembled with flow filter (10 μm, Varian) into 3 mL plastic syringes and 3 mL of fresh SGF was added at every sampling point[16]. In this study, we used one dissolution environment to allow direct comparison of multiple dosage forms.

Samples were filtered through 0.45 μm nylon membranes (Grace Davison Discovery Sciences, Alltech Associates Pty Ltd, Victoria, Australia) and diluted to obtain the desired concentrations to enable readings using UV spectroscopy. A calibration curve was constructed and the absorbance of acetaminophen samples was measured at 244 nm Hitachi U-1900 Spectrophotometer (Hitachi Australia Pty, Ltd, Sydney, Australia). Whole tablet in 15 mL water, crushed tablet in 15 mL water (dispersed by agitation with a metallic spatula), the elixir, suspension and dissolved effervescent medications without thickener were performed for comparison. Thickened water without medication was measured as control. To account for background absorbance associated with the thickener, absorbance readings for the control (always < 0.015) were subtracted from the absorbance of the samples containing drug. Cumulative dissolution of acetaminophen was plotted against time and analyzed for differences in dissolution at 30 min with one-way ANOVA ($p < 0.05$) and a Bonferroni post-hoc test using GraphPad Prism version 6 (GraphPad software, San Diego, CA); all data tested complied with the assumptions of ANOVA for normality and equality of variance.

The Korsmeyer–Peppas model was fitted to the cumulative release versus time plots using SigmaPlot 12.0 (Systat Software, Inc. San Jose, CA). The Korsmeyer–Peppas is an empirical equation that correlates the amount of the drug released (M_t) and the exponential function of the release profile:

$$M_t/M_\infty = kt^n \quad (1)$$

where M_t is the amount of drug release at time t, M_∞ is the total drug released over the duration of the experiment, k is the kinetic constant, and n is the release exponent[17]. Cumulative release profiles were compared using the similarity factor, f_2[18].

Rheological measurements

Samples were prepared following the same conditions and at the same time as for dissolution testing. Rheological attributes of the elixir and dissolved effervescent tablet without thickener were measured in a stress controlled rheometer G2 (TA instruments C/O Waters Australia, Pty, Ltd, Sydney, Australia) using cone and plate titanium 40 mm, 2 deg, 63 μm truncation attachment at 37 °C. Samples were equilibrated for 2 min prior to measuring. The cone and plate was used to give constant shear rate throughout the sample, so the viscosity does not vary within the geometry. Thickened samples were also measured in the cone and plate, but for several measurements artefacts arose including slip, and confinement of undissolved particulates from the comminuted tablets; such phenomena are described in detail by Davies and Stokes[19]. To overcome these particular issues, a vane-in-cup geometry was used, which is appropriate to characterize the rheology of structured fluids with characteristics of a weak gel that contains yield stress, as described by Stokes and Telford[20]. Thickened water, suspension, thickened liquid dosage forms and one crushed tablet manually mixed into thickened water (variant 1) were prepared, equilibrated at 37 °C for 30 min and the measurements taken in a AR 1500ex stress controlled rheometer (TA instruments C/O Waters Australia, Pty, Ltd, Sydney, Australia) with a large aluminium vane at 37 °C. The linear viscoelasticity of the samples were characterized using small amplitude oscillatory testing: the viscous (loss modulus, G'') and elastic properties (storage modulus, G') were obtained as a function of frequency. Small oscillatory measurements were carried out on the prepared samples. Stress sweep tests were first performed from 0.1 to 100 Pa, with 1 Hz frequency value at 37 °C, to determine the linear viscoelastic region. The stress was linear with strain across a brand frequency range at 1 Pa and therefore frequency sweep tests were performed from 10.0 to 0.1 Hz, with 1 Pa constant stress at 37 °C.

Results

Based on the weight of powder contained in the cups prior to mixing with thickened water and assuming that 100% corresponded to 500 mg of the content declared in one tablet, between 3% to 4% of drug was lost during the crushing, weighing and transfer into the cups with no difference between method variants. This loss has not been accounted for in the results, but indicates that the total % dissolution that could be obtained from the crushed tablets could reach a maximum of 96 to 97%.

Dissolution experiments

Acetaminophen is classified in the Biopharmaceutical Scheme as BCS class III, but possesses some attributes of the BCS class I substances[21]. Its solubility is not pH dependent within physiological range, having a pKa value of 9.5, so adjusting the dissolution media pH used in this study would not be expected to affect dissolution. Acetaminophen whole and crushed tablets delivered with water exhibited rapid and complete dissolution in SGF with over 96% of the drug released and measured in the first 30 min (Figure 1A, Table 1). Similarly, acetaminophen was immediately released from the elixir and the effervescent tablet (Figure 2A and B, Table 2). In contrast, the suspension exhibited moderate release under the conditions of this dissolution test, with only 30% released in 30 min (Figure 2C, Table 2).

Modified solid dosage forms

Using crushed tablets, the effect of the state of drug aggregation (dissolved or dispersed), the order of adding components, and mixing method were investigated. The standard clinical method of preparation, in which crushed tablets were mixed into 15 g of prethickened water (variant 1), resulted in only 36% acetaminophen being dissolved in the first 30 min (Table 1). Thickener slowed dissolution for all formulations involving crushed tablets, irrespective of whether manual or mechanical mixing was used or the order of incorporation of the components (Figure 1B and C, Table 1). The manual mixing method produced formulations with faster release of acetaminophen than mechanical mixing ($p < 0.001$) with differences of 9.5, 15.2 and 13.7% at 30 min for variants 1, 2 and 3, respectively (Table 1).

The dissolution profiles for the crushed tablets in thickened fluid were compared to the intact dosage form by the similarity factor f_2[18]. All medications delivered with thickened water invariably resulted in f_2 of less than 50 (Table 1), which confirms that the dissolution profiles were dissimilar and predicts that differences are likely to occur *in vivo*. The Korsmeyer–Peppas model fitted the dissolution profiles well ($r^2 = 0.98$–0.99; Table 1). The release exponent n was 0.41 to 0.49, indicating primarily Fickian diffusion-controlled release.

KINDERFARMS Ex. 1013
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

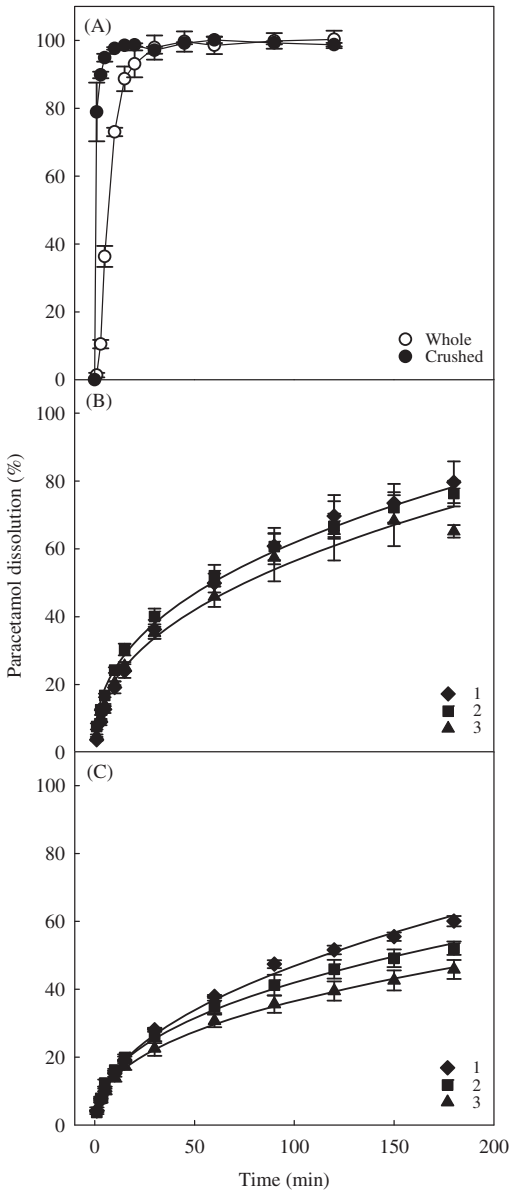

Figure 1. Dissolution of whole and crushed acetaminophen tablets delivered with 15 mL water (A), and crushed tablets delivered in 15 g thickened water (B, C). The crushed tablet was incorporated into the thickened water by manual (B) and mechanical mixing (C) with three different variants 1, 2 and 3. The data shows mean ± se for three replicates for dissolution tests performed in SGF at 37 °C and 50 rpm. The lines in (B) and (C) are fits to the Korsmeyer–Peppas model.

Modified liquid dosage forms

The quantity of thickener required to thicken water to level 900 was added to acetaminophen elixir, dissolved effervescent tablet and suspension, resulting in a significant change in dissolution profile in comparison to the unthickened products. The quantity of acetaminophen dissolved at 30 min was reduced for all three formulations, with differences caused by addition of thickener of 52, 86 and 22% for the effervescent tablet, elixir and suspension, respectively (Figure 2). The similarity factor f_2 was estimated for each modified medication with respect to its intact dosage form, and in all cases f_2 was lower than 50, which confirmed the lack of similarity.

Table 1. The percentage dissolution (mean ± standard error, $n = 3$) in simulated gastric fluid at 30 min for acetaminophen immediate release whole and crushed tablets delivered with 15 mL of water and crushed tablets with 15 g of thickened water using two mixing methods (manual, mechanical) and three order of addition variants (1, 2, 3).

Formulation	% Dissolved at 30 min	Similarity factor f_2	Korsmeyer–Peppas n (SE)	Korsmeyer–Peppas r^2 (SE)
Whole tablet	96.7 ± 1.3%[b]			
Crushed tablet in:				
Water	98.3 ± 0.2%[b]			
Thickened water				
Manual				
Variant 1[a]	36.3 ± 2.8%[cd]	19.1	0.49 (0.018)	0.99 (2.18)
Variant 2	40.1 ± 2.3%[c]	20.5	0.41 (0.013)	0.99 (1.80)
Variant 3	35.3 ± 1.7%[cd]	18.6	0.43 (0.028)	0.98 (3.44)
Mechanical				
Variant 1	26.8 ± 1.8%[ec]	15.4	0.47 (0.018)	0.99 (1.60)
Variant 2	24.9 ± 1.1%[ec]	14.3	0.42 (0.014)	0.99 (1.33)
Variant 3	21.6 ± 3.2%[e]	13.0	0.42 (0.009)	0.99 (0.74)

Values of % dissolution with different superscript alphabalic symbols are significantly different ($p < 0.05$). Similarity factor (f_2) with respect to the whole tablet and Kosmeyer–Peppas release exponent n (±SE) and r^2 (±SE) were calculated.
[a]Standard method used in clinical practice.

The Korsmeyer–Peppas model was fitted to the dissolution profiles (r^2= 0.97-0.99; Table 2) except the unthickened effervescent tablet and unthickened elixir because the acetaminophen was already in solution in these formulations before the dissolution test started. The release exponent n was close to 0.5, indicating primarily Fickian diffusion-controlled release, though it varied to a greater extent for the thickened liquid formulations (0.34 to 0.58) than the thickened crushed tablet formulations (0.41 to 0.49).

Rheology of the thickened medications

All samples containing thickener exhibited non-Newtonian shear-thinning behavior with viscosity values dependent on the shear stress applied to the sample (Figure 3). Unthickened acetaminophen suspension also exhibited non-Newtonian behavior, reflecting the structured vehicle contained in the suspension. The viscosity of the elixir and dissolved effervescent tablet was very low and similar to water and remained invariable with stress (data not shown), typical of Newtonian behavior.

A shear rate of 50 s^{-1} was chosen for comparison as it is commonly used in evaluation of fluid foods as an indicator of the dominant shear rate operating in the oral cavity[22] and is the shear rate used for the number category system for texture-modified fluids in the US and Australia[23]. The elixir and effervescent tablet with no thickener exhibited low viscosity of 15 and 8 mPas (Table 3). Water thickened to level 900 was indeed characteristic of its texture-modified fluid category with a viscosity of 917 mPas, while addition of a crushed tablet to the thickened water reduced viscosity to 625 mPas but addition of thickener to the effervescent tablet in water increased viscosity to 1540 mPas, presumably associated with different excipients contained in the immediate release and effervescent tablets. With a viscosity of 403 mPas, the suspension may be categorized as level 400, but addition of thickener resulted in a very thick liquid (4380 mPas); the thickened elixir was also very thick (3650 mPas) despite the primary formulation having very low viscosity and Newtonian behavior.

Relative differences between formulations (Table 3) in zero-shear viscosity (i.e. at very low shear rate, <1 Pa) and infinite-shear viscosity values (i.e. at high shear stress >100 Pa) largely echoed the relationships observed in viscosity at 50 s^{-1}, except that the crushed immediate release tablet in thickened water was more similar to the effervescent tablet in thickened water at low and

KINDERFARMS Ex. 1013
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

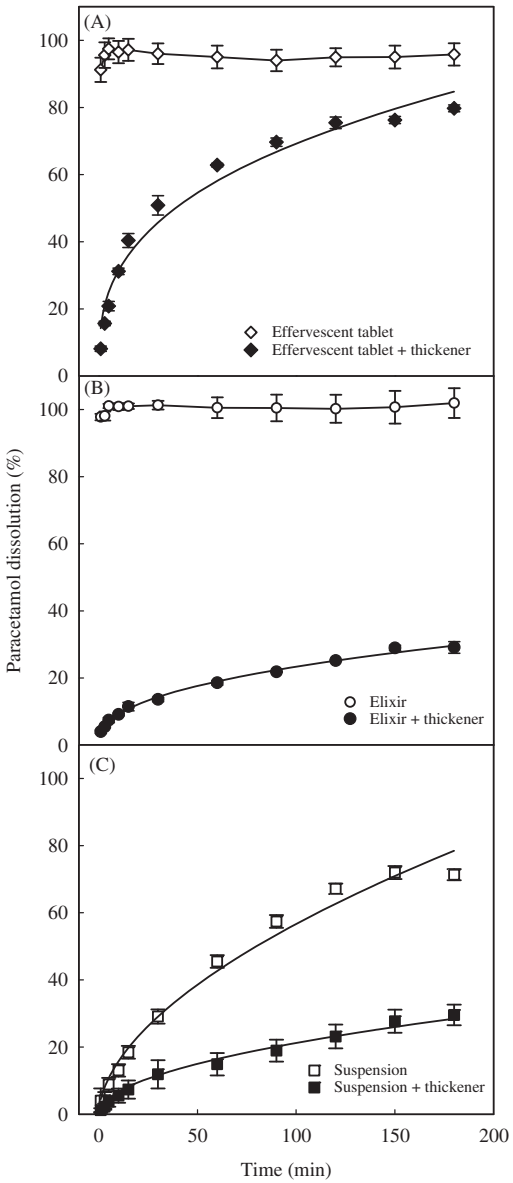

Figure 2. Dissolution of acetaminophen from (A) effervescent tablet, (B) elixir, (C) suspension. 15 mL of medications were delivered straight from the bottle (B, C) or dissolved in water (A) (open symbols) or mixed with the quantity of thickener required to produce thickened water at level 900 (filled symbols). The data shows mean ± se for three replicates for dissolution tests performed in SGF at 37 °C and 50 rpm. The curves are fits to the Korsmeyer–Peppas model except for unthickened formulations in (A) and (B).

high shear stresses. The apparent yield stress, which is the stress value at which viscosity decreases by several orders of magnitude so flow occurs[24], also highlighted the greater resistance to flow of the thickened suspension (39 Pa) in comparison to the other thickened formulations (17-26 Pa) and the unthickened suspension (2.7 Pa) (Table 3).

The thickened formulations were semi-solid in appearance. The mechanical spectra were obtained and the results expressed in terms of an elastic storage modulus (G') and viscous loss modulus (G'') (Figure 4). The thickened samples and the unthickened suspension all behaved as viscoelastic solids with G' dominating over G'' across a substantial frequency (v) range (cycles/s). Thickened effervescent tablet and crushed tablet in thickener were very

Table 2. The percentage dissolution (mean ± standard error: $n = 3$) in simulated gastric fluid at 30 min for acetaminophen intact liquid dosage forms and with thickener added.

Formulation	% Dissolved at 30 min	Similarity factor f_2	Korsmeyer–Peppas n (SE)	Korsmeyer–Peppas r^2 (SE)
Effervescent tablet	96.0 ± 2.1%			
Elixir	101.0 ± 3.1%			
Suspension	30.0 ± 1.3%		0.55 (0.040)	0.98 (4.81)
Effervescent tablet + thickener	50.8 ± 2.9%	11.7	0.34 (0.026)	0.97 (4.63)
Elixir + thickener	13.6 ± 0.7%	2.8	0.40 (0.013)	0.99 (0.68)
Suspension + thickener	12.0 ± 4.2%	31.6	0.58 (0.021)	0.99 (0.74)

Similarity factor (f_2) of the thickened liquids with respect to the intact liquids and Kosmeyer–Peppas release exponent n (±SE) and r^2 (±SE) were calculated.

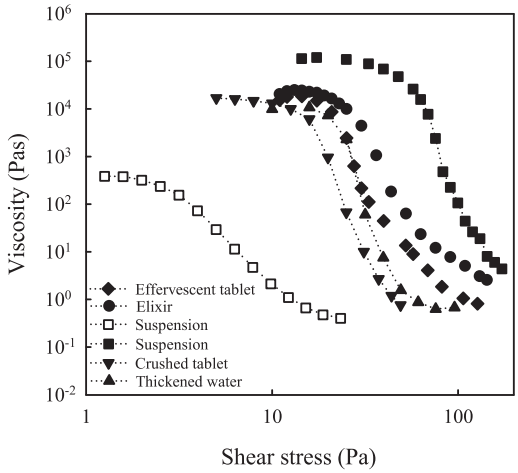

Figure 3. Flow curves for dosage forms with (filled symbols) and without (open symbols) thickener at 37 °C using a vane tool. One representative flow curve from three replicates is shown. The unthickened effervescent tablet and elixir are not shown due to low viscosity (Table 3) that did not change with shear stress.

similar in response to the thickened water alone. As defined by Stokes, a weak gel is a substantially diluted system that displays a solid-like behavior but is also able to exhibit steady state flow[24]. As these fluids flow above an apparent yield stress, they are referred to here as weak gels.

Discussion

The presence of thickened fluid, irrespective of the dosage form or the method of preparation, had a substantial impact on *in vitro* drug dissolution. The extent of the effect depended upon the aggregation state of the drug contained in the dosage form and on other components of the dosage form. It is well known that increasing dissolution media viscosity retards release by increasing disintegration and dissolution time[25,26] but that was not the reason for the delayed dissolution in this case because 15 g of thickened fluid does not appreciably increase the viscosity of 900 mL of SGF[10].

Method variant 1 with manual mixing was designed to be most similar to typical clinical practice, in which thickened fluid is prepared and then a crushed tablet is added into it and mixed with a spatula or spoon. This standard method resulted in acetaminophen dissolution being only 36% by 30 min, with a dissimilar release profile (f_2<50) to that of the whole tablet. The amount of drug measured in a dissolution test for immediate release tablets should not be less than 85% of the labeled amount within 30 min according to FDA guidance information for immediate release solid forms[27]; however, acetaminophen dissolution did not reach this level even

KINDERFARMS Ex. 1013
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

Table 3. Rheology of acetaminophen effervescent tablet, elixir and suspension with and without thickener added, measured at 37 °C.

Formulation	Viscosity 50 s^{-1} (Pas)	Zero-shear viscosity n_0 (Pas)	Infinite-shear viscosity n_∞ (Pas)	Yield stress σ_y (Pa)
Water	0.0009 (0.000)			
Effervescent tablet	0.008 (0.001)			
Elixir	0.015 (0.000)			
Suspension	0.403 (0.010)	357	0.403	2.7
Effervescent tablet + thickener	1.540 (0.110)	17 010	0.812	19
Elixir + thickener	3.650 (0.450)	22 923	2.542	26
Suspension + thickener	4.380 (0.152)	114 389	4.424	39
Crushed tablet + thickener	0.625 (0.029)	16 056	0.761	17
Water + thickener	0.917 (0.095)	10 982	0.626	14

Viscosity at 50 s^{-1} was interpolated from viscosity-shear rate data with standard error in brackets calculated from three replicate flow curves. Zero-shear viscosity, infinite-shear viscosity and apparent yield stress values were extrapolated from one of the three replicate flow curves.

at 3 h. Importantly, since only 3-4% was lost during crushing and transfer, some acetaminophen was still entrapped within the thickened fluid.

No improvement in acetaminophen release and dissolution were gained by altering the method of preparation. For instance, mixing the tablet powder with water first, to suspend and partially dissolve the acetaminophen prior to adding the thickener powder (variant 2) did not affect acetaminophen dissolution. The only alteration in dissolution was caused by using mechanical instead of manual mixing, causing a significant reduction in dissolution. The treatment of the samples after preparation using the mechanical mixer (i.e. air elimination by centrifugation, required to stop the thickened fluid chunks from floating in the dissolution chamber) may have been associated with the increased entrapment of the drug.

The use of commercial liquid dosage forms was investigated as a potential alternative to crushed tablets for delivery of a thickened oral medication dose. Acetaminophen effervescent tablets dissolved in water and acetaminophen elixir were low-viscosity products ($\eta 50 < 15$ mPas) in which acetaminophen was present in solution. These reached 100% dissolution immediately on addition to the test vessel. Adding thickener to these formulations increased their viscosity, which negatively impacted the rate and extent of drug release into the media. The viscosity of these thickened formulations was higher than thickened water ($\eta 50 = 917$ mPas), and the elixir ($\eta 50 = 3650$ mPas) was more strongly affected than the effervescent tablet in water ($\eta 50 = 1570$ mPas), indicating that the excipients within the different formulations interacted with the thickener to influence viscosity.

In the acetaminophen suspension, the drug is expected to be dispersed and partially dissolved in the structured vehicle ($\eta 50 = 403$ mPas), so not surprisingly, dissolution was slower than for acetaminophen in solution with only 30% dissolving within 30 min. In fact, the suspension only reached 85% dissolution after 2 h of the test, with a profile that was more similar to the crushed tablet in thickened fluid ($f_2 = 60$) than the whole tablet ($f_2 < 50$). Slow release of acetaminophen from a commercial suspension has also been measured using a flow through cell with and without a dialysis adapter, with 40-60% being released in 30 min[28]. Addition of thickener reduced release further, producing a dissolution curve that was very similar to that of the thickened elixir even though the viscosity of the thickened suspension was much higher ($\eta 50 = 4380$ mPas). Adding the thickener increased the complexity of the microstructure, increasing the zero-shear and infinite-shear viscosity as well as apparent yield stress to the highest values of all of the thickened formulations.

The results suggest that the weak gel nature of the formulations and rheological variables have a substantial effect on drug dissolution and release into SGF. The products with the highest elastic modulus (G'), i.e. greater solid-like behavior, were associated with the greatest restriction on acetaminophen release. Similarly, formulations with higher apparent yield stress values, i.e. requirement for a higher shear stress to break the structure and cause it to flow, exhibited slowest dissolution profiles. Rheological parameters, such as apparent yield stress, control breakup of the swallowed bolus and its flow behavior along the gastrointestinal tract. The high yield stress values for the thickened elixir (26 Pa) and thickened suspension (39 Pa) are both values that exceed the maximum range indicated for the thickest fluids (14-21 Pa) according to the Australian Fluid Level Standards[13]. With such high yield stress values it is possible that shear forces in the stomach are sufficient to only partially shear the samples, as computer simulations indicate that shear forces are only 10-30 Pa in the antrum and <1 Pa in the fundus[29,30]. This is expected to impact on drug release and therefore availability for absorption.

There are multiple factors not tested in this study that could alter drug release from the thickened fluids and cause release *in vivo* to be faster and/or greater than that obtained here, for example the fasted or fed state determines enzyme activity in the mouth and gastrointestinal tract and may cause preliminary breakdown of the bolus[31], and peristaltic mixing, gastric emptying and gastrointestinal transit time are expected to be important determinants of bolus integrity[32]. The thickening agent itself is also an important consideration. Previous studies have demonstrated that increased viscosity, regardless of the thickening agent used, impedes drug release in *in vitro* studies[10]. However, certain attributes may predispose some thickening agents to be better suited for drug delivery than others. For example, starch-based thickening agents will be heavily dependent on amylase in the oral cavity and small intestine[33], whereas xanthan gum breaks down as a result of interactions with gut bacteria in the lower intestinal tract[34].

It is not clear from the results whether the delay in dissolution is due to restriction on dissolution within the thickener and/or diffusion out of the thickener. On the one hand, improvement in release occurred when the acetaminophen was in solution within the thickener, as for the dissolved effervescent tablet (50% at 30 min) in comparison to being dispersed in the thickener as for the crushed tablet (36% at 30 min). This may be taken to indicate that release was slower if the drug powder had to dissolve prior to diffusing. On the other hand, the thickened elixir and thickened suspension exhibited the same dissolution profile but the acetaminophen was presumed to be in solution in the elixir but dispersed in the suspension. However, these comparisons are complicated by the different dosage forms and associated excipients involved. For example, guar gum viscosity is increased by polyols[35], such as those present in the elixir (sorbitol) and suspension (maltitol and sorbitol), so similar effects are anticipated with xanthan gum. Furthermore, the quantity of thickener added to each formulation was calculated for use in water, so reducing the quantity added to account for the composition of the dispersing

KINDERFARMS Ex. 1013
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

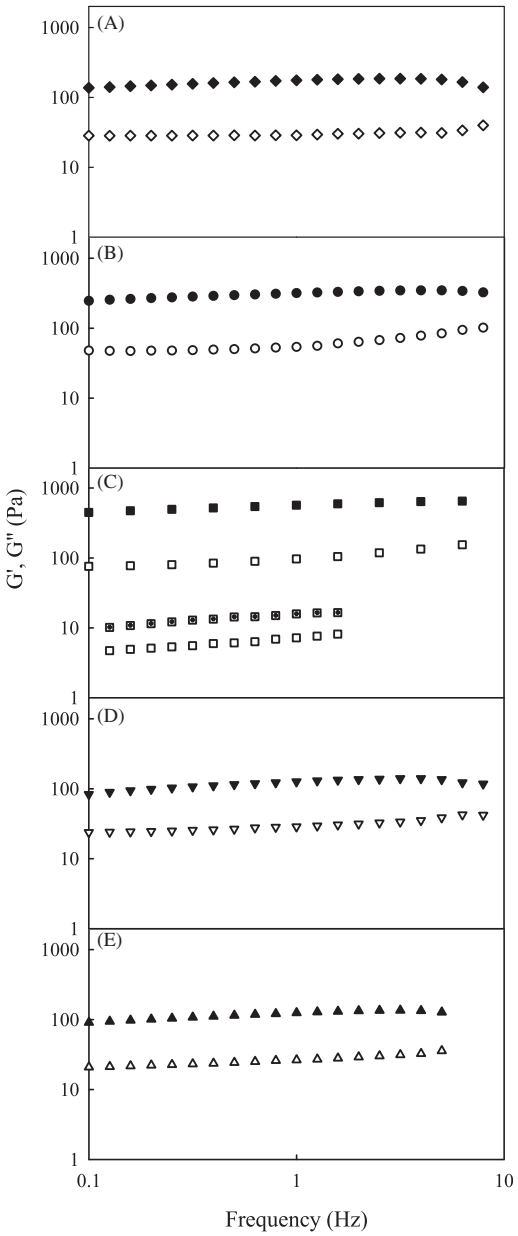

Figure 4. Mechanical spectrum of acetaminophen dosage forms thickened samples. Shown here are the elastic or storage modulus G' (Pa) (filled symbols) and viscous or loss modulus, G'' (Pa) (open symbols) as a function of frequency (v) expressed in Hertz (cycles/s) at 37 °C, with a vane tool attachment for the (A) effervescent tablet, (B) elixir, (C) suspension, (D) crushed tablet and (E) thickened water. The modulus with and without thickener are shown for the suspension; elixir and dissolved effervescent tablet exhibit constant viscosity. One representative sample from three replicates is presented.

media would be required for complex formulations such as this[8,36,37].

Conclusions

This study demonstrated that dissolution is affected by the presence of thickeners added to facilitate oral ingestion of medicines. Drug release from thickened medications was unaffected by the state of aggregation of the drug, e.g. dissolved in the thickened elixir and effervescent tablet and dispersed in the thickened suspension. Each dosage form has the potential to respond in a different manner to the addition of thickening agents due to the presence of excipients. This has implications for the therapeutic effect of the drug when given in this manner. The typical clinical practice approach of preparing the thickening agent and then adding the crushed medication with manual stirring was not improved by altering the order of addition or mixing method. The rheology of the thickened products indicated that the weak gel structures of the formulations considerably impacted drug dissolution and release into SGF, so the greatest viscoelasticity and apparent yield stress values exhibited the slowest and most restricted dissolution. The results of the current study indicate that *in vivo* trials are warranted.

Disclosure statement

The authors report no declarations of interest.

Funding information

The authors would like to thank The University of Queensland for providing scholarship funding to YJM.

References

1. Marik PE, Kaplan D. Aspiration pneumonia and dysphagia in the elderly. Chest 2003;124:328–36.
2. Carnaby-Mann G, Crary M. Pill swallowing by adults with dysphagia. Arch Otolaryngol Head Neck Surg 2005;131:970–5.
3. Wright D. Medication administration in nursing homes. Nurs Stand 2002;16:33–8.
4. Schiele J, Quinzler R, Klimm H-D, et al. Difficulties swallowing solid oral dosage forms in a general practice population: prevalence, causes, and relationship to dosage forms. Eur J Clin Pharmacol 2013;69:937–48.
5. Nissen LM, Haywood A, Steadman KJ. Solid medication dosage form modification at the bedside and in the pharmacy of Queensland hospitals. J Pharm Prac Res Sci 2009;39:129–34.
6. 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;20:616–27.
7. Haw C, Stubbs J. Administration of medicines in food and drink: a study of older inpatients with severe mental illness. Int Psychogeriatr 2010;22:409–16.
8. Sopade PA, Halley PJ, Cichero JAY, Ward LC. Rheological characterisation of food thickeners marketed in Australia in various media for the management of dysphagia. I: water and cordial. J Food Eng 2007;79:69–82.
9. Steele C, Alsanei W, Ayanikalath S, et al. The influence of food texture and liquid consistency modification on swallowing physiology and function: a systematic review. Dysphagia 2015;30:2–26.
10. Manrique-Torres YJ, Lee DJ, et al. Crushed tablets: does the administration of food vehicles and thickened fluids to aid medication swallowing alter drug release? J Pharm Pharm Sci 2014;17:207–19.
11. Marquis J, Schneider MP, Payot V, et al. Swallowing difficulties with oral drugs among polypharmacy patients attending community pharmacies. Int J Clin Pharm 2013;35:1130–6.

KINDERFARMS Ex. 1013
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

12. Jukes S, Cichero JAY, Haines T, et al. Evaluation of the uptake of the Australian standardized terminology and definitions for texture modified foods and fluids. Int J Speech Lang Pathol 2012;14:214–25.
13. Hadde EK, Cichero JAY, Nicholson TM. Viscosity of thickened fluids that relate to the Australian National Standards. Int J Speech Lang Pathol 2016. [Epub ahead of print]. doi: 10.3109/17549507.2015.1081289.
14. Garcia J, Chambers E, Matta Z, Clark M. Viscosity measurements of Nectar- and Honey-thick liquids: product, liquid, and time comparisons. Dysphagia 2005;20:325–35.
15. British Pharmacopoeia Commision. The British Pharmacopoeia 2012. 2012 ed. London (UK): TSO; 2012. A323 p.
16. United States Pharmacopoeia. The United States Pharmacopoeia USP 34. The National Formulary NF 29. [711] Dissolution 1. 2011 ed. Rockville (MD): The United States Pharmacopoeial Convention; 2011:278–85.
17. Korsmeyer RW, Gurny R, Doelker E, et al. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm 1983;15:25–35.
18. Shah VP, Tsong Y, Sathe P, Liu J-P. In vitro dissolution profile comparison – statistics and analysis of the similarity factor, f2. Pharm Res 1998;15:889–96.
19. Davies GA, Stokes JR. Thin film and high shear rheology of multiphase complex fluids. J Non Newt Fluid Mech 2008;148:73–87.
20. Stokes J, Telford J. Measuring the yield behaviour of structured fluids. J Non Newt Fluid Mech 2004;124:137–46.
21. Kalantzi L, Reppas C, Dressman JB, et al. Biowaiver monographs for immediate release solid oral dosage forms: acetaminophen (paracetamol). J Pharm Sci 2006;95:4–14.
22. Stokes JR, Boehm MW, Baier SK. Oral processing, texture and mouthfeel: from rheology to tribology and beyond. Curr Opin Colloid Interface Sci 2013;18:349–59.
23. Dietitians Association and Speech Pathology Association of Australia L. Texture-modified foods and thickened fluids as used for individuals with dysphagia: Australian standardised labels and definitions. Nutr Dietetics 2007;64:S53–76.
24. Stokes JR. Food biopolymer gels, microgel and nanogel structures, formation and rheology. In: Bhandari B, Roos YH, eds. Food materials science and engineering. Oxford, UK: Wiley-Blackwell; 2012:151–76.
25. Parojcic J, Vasiljevic D, Ibric S, Djuric Z. Tablet disintegration and drug dissolution in viscous media: paracetamol IR tablets. Int J Pharm 2008;355:93–9.
26. Radwan A, Wagner M, Amidon GL, Langguth P. Bio-predictive tablet disintegration: effect of water diffusivity, fluid flow, food composition and test conditions. Eur J Pharm Sci 2014;57:273–9.
27. Food and Drug Administration. Guidance for industry: dissolution testing of Immediate Release Solid Oral Dosage Forms. Rockville, MD: US Department of Health and Human Services, FDA, Center for Drug Evaluation and Research; August 1997. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070237.pdf [last accessed 22 Feb 2016].
28. Gao Z, Westenberger B. Dissolution testing of acetaminophen suspension using dialysis adapter in flow-through apparatus: a technical note. AAPS Pharm Sci Tech 2012;13:944–8.
29. Marciani L, Gowland PA, Fillery-Travis A, et al. Assessment of antral grinding of a model solid meal with echo-planar imaging. Am J Physiol Gastrointest Liver Physiol 2001;280:G844–9.
30. Pal A, Abrahamsson B, Schwizer W, et al. Application of a virtual stomach to evaluate gastric mixing and breakdown of solid food. Gastroenterology 2003;124:A673–4.
31. Robyt JF, French D. The action pattern of porcine pancreatic α-Amylase in relationship to the substrate binding site of the enzyme. J Biol Chem 1970;245:3917–27.
32. Kostewicz ES, Abrahamsson B, Brewster M, et al. In vitro models for the prediction of in vivo performance of oral dosage forms. Eur J Pharm Sci 2014;57:342–66.
33. Butterworth PJ, Warren FJ, Ellis PR. Human α-amylase and starch digestion: an interesting marriage. Starch Stärke 2011;63:395–405.
34. Daly J, Tomlin J, Read NW. The effect of feeding xanthan gum on colonic function in man: correlation with in vitro determinants of bacterial breakdown. Br J Nutr 1993;69:897–902.
35. Moser P, Cornelio ML, Nicoletti Telis VR. Influence of the concentration of polyols on the rheological and spectral characteristics of guar gum. LWT - Food Sci Tech 2013;53:29–36.
36. Sopade PA, Halley PJ, Cichero JAY, et al. Rheological characterisation of food thickeners marketed in Australia in various media for the management of dysphagia. II. Milk as a dispersing medium. J Food Eng 2008;84:553–62.
37. Sopade PA, Halley PJ, Cichero JAY, et al. Rheological characterisation of food thickeners marketed in Australia in various media for the management of dysphagia. III. Fruit juice as a dispersing medium. J Food Eng 2008;86:604–15.

KINDERFARMS Ex. 1013
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051