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Do Thickening Agents Used in Dysphagia Diet Affect Drug Bioavailability?

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ABSTRACT

Swallowing oral solid dosage forms is challenging in patients with dysphagia who are at risk of aspiration or choking. The most common method to facilitate drug administration in dysphagia patients is to mix the powdered drug with a small amount of thickened water, however little is known about the effects of this method on in vivo bioavailability of drugs. This study aimed to evaluate the impact of thickened liquids on dissolution rate and bioavailability of levetiracetam as a model drug. Powdered commercial tablets of levetiracetam, carbamazepine, atenolol and cefixime were mixed with water thickened with two commercial thickeners, modified maize starch (MS) and xanthan gam (XG), at three thickness levels: nectar, honey and pudding in test groups, and mixed with only water in the control group. At the first stage, the effects of thickened water on in vitro drug release of 4 drugs (levetiracetam, carbamazepine, atenolol and cefixime) were tested by using dialysis membrane method. Addition of both thickeners significantly reduced the release of three drugs compared to the control group, except carbamazepine. Levetiracetam which had the highest solubility was chosen as the model drug for in vivo experiments. In the second stage, New Zealand albino female rabbits (n=24) were divided into two groups as: control group (water+drug, n=6) and test group (thickened water+drug, n=18). Powdered levetiracetam tablets were mixed with water thickened with XG (n=9, 1.2%, 2.4%, 3.6%) and MS (n=9, 4%, 6%, 8%) at three thickness levels and administered to the rabbits by intragastric gavage. Blood samples were collected at 9 time points following administration. After two-weeks of wash-out, test groups were crossed over and sample collection was repeated. Blood samples were analysed using liquid chromatography with tandem mass spectrometry (LC-MS/MS). An in vitro-in vivo correlation (IVIVC) model was developed using in vitro drug dissolution (%) and in vivo plasma concentrations of levetiracetam for control group and test groups. The peak plasma concentration (C_{max}) was lower and time to reach C_{max} (t_{max}) was relatively higher in test groups compared to control group. The lowest C_{max} was detected at the highest thickness level, however, the differences between groups were not statistically significant (p=0.117 and p=0.495 for C_{max} and t_{max}, respectively). No significant difference in total amount of levetiracetam absorbed (AUC) was found between groups (p=0.215 and p=0.183 for $AUC_{infinity}$ and AUC_{last}, respectively). The comparisons according to the type of thickener also revealed that pharmacokinetic parameters did not significantly differ between groups, except for a significantly lower C_{max} when drug was mixed with MS-thickened water at nectar consistency (1.2%) compared to drug mixed with XG (4%) at the same thickness level (p=0.038). A good correlation was observed between in vitro and in vivo data, which was characterized by higher r^2 values as the concentration of the thickening agents was increased, but not for all thickness levels studied, indicating an inability of this in vitro model to fully predict the in vivo response. These results suggest that regardless of the thickness level, the administration of levetiracetam with two commercial thickening agents commonly used in dysphagia for safe swallowing, do not affect the pharmacokinetic efficiency and thus, the bioavailability of the drug.

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1. Introduction

Dysphagia is generally described as a symptom or disorder characterized by difficulty or inability to form and transfer bolus safely from mouth to oesophagus (Clavé and Shaker, 2015). Dysphagia may affect all individuals across the lifespan however, its prevalence is significantly higher in geriatric populations and in specific conditions, e.g., stroke, neurodegenerative disorders and malignancies of head and neck (Baijens et al., 2016; Ihara et al., 2018; Kalf et al., 2012; Park et al., 2013; Rofes et al., 2018; Serra-Prat et al., 2012). If not treated, dysphagia may lead to serious complications including dehydration, malnutrition and life-threatening aspiration pneumonias (Carrión et al., 2019). Treatment strategies such as swallowing exercises, compensatory techniques or dietary modifications aim to reduce the risk of aspiration, increase the safety of swallowing and hence to provide adequate nutrition and hydration (Clavé et al., 2006; Steele, 2012; Steele et al., 2015).

Dysphagia patients usually have trouble in swallowing certain consistencies, particularly solid foods, and thin liquids (Leonard et al., 2014; Saitoh et al., 2007). In addition, dysphagia may adversely affect the ability to swallow solid oral medications such as tablets and capsules in both paediatric and geriatric populations (Hansen et al., 2008; Liu et al., 2016; Marquis et al., 2013; Schiele et al., 2013; Stegemann et al., 2012). This is more challenging in the elderly because of age-related impairment in swallowing function and a high rate of polypharmacy due to presence of multiple chronic diseases (Lau et al., 2018; Maher et al., 2014; Marengoni et al., 2011). Studies conducted in different settings (e.g. ambulatory patients attending to general practice, independent-living community residents, hospitals or residents in aged-care facilities) have shown that between 15% to 45% of older people experience difficulty in swallowing solid oral medications, with approximately a 3.5-fold higher prevalence in the presence of dysphagia (Liu et al., 2016; Mc Gillicuddy et al., 2016; Mehuys et al., 2012; Roy et al., 2007; Schiele et al., 2013; Tordoff et al., 2010; Wright, 2002).

Theoretically, alternative administration routes (e.g. parenteral or topical) or alternate dosage forms such as liquids (e.g. syrup, effervescent, elixir etc.), orodispersable tablets or mini-tablets may be considered for patients with difficulty in swallowing solid oral dosage forms (Lau et al., 2018; Stegemann et al., 2012). However, an alternative route or dosage form may not always be available or suitable in clinical practice.

Aspiration of thin liquids is very common in patients diagnosed with dysphagia (Leonard et al., 2014; Newman et al., 2016; Serra-Prat et al., 2012; Speyer et al., 2019). These patients require all fluids to be thickened to a safe and an appropriate consistency before consumption by adding thickening agents such as starch or gum-based thickeners (Steele et al., 2015). The need for the use of thickened fluids also applies to orally administered drugs or liquids used to swallow solid oral medications. For example, any alternative liquid dosage form which does not have an appropriate consistency needs to be avoided due to risk of aspiration. Additionally, patients who are unable to drink thin fluids safely without aspiration should avoid taking medicines with thin water.

For patients who have difficulty in swallowing tablets or capsules and require thickened fluids to prevent aspiration, the most commonly used strategy to take solid oral dosage forms is crushing tablets or opening capsules, and take the powdered medicine with a mouthful of food vehicle or thickened liquids (Barnes et al., 2006; Haw and Stubbs, 2010; Nissen et al., 2009; Paradiso et al., 2002; Schiele et al., 2013; Stubbs et al., 2008; Wright, 2002). In some cases, thickening of a liquid alternative dose can also be considered. However, there have been some concerns about a possible interaction of thickened liquids when administered with drugs, particularly for Class I and III medications according to Biopharmaceutics Classification System (BCS) (Cichero, 2013). Data from in vitro studies showed that mixing crushed tablets with thickened water significantly reduced drug dissolution and release (Manrique et al., 2014, 2016). The impact was reported to be more apparent with the highest therapeutic thickness level used to prevent aspiration, and with xanthan-gum based products (Manrique et al., 2014). However, little is known about the effect of co-administration of drugs with thickened liquids on in vivo bioavailability of drugs, as in the case of patients with dysphagia. This study was designed to investigate whether; *1)* the dissolution rate of a model drug is affected by mixing it within thickened water prepared with two commercial thickening agents at three therapeutic thickness levels used in dysphagia management, and *2)* any alterations arising from co-administration of drug with thickened water have any impact on its in vivo bioavailability.

2. Materials and methods

This experimental study was carried out in two stages. In the first stage, the effect of co-administration of thickened liquids on in vitro release of four drugs with different solubility characteristics were investigated by using dialysis membrane method. The main objective of these experiments was to determine a model drug to continue in vivo experiments. Of the four drugs tested, levetiracetam which belongs to BCS I class and had the highest dissolution rate was selected as the model drug to eliminate the impact of physicochemical properties on pharmacokinetic parameters.

Ethical approval for this study was obtained from Kobay Laboratory (Ankara, Turkey) Animal Experiments Local Ethics Committee (Approval Date: 31st May 2018; Approval Number/ID: 282).

2.1. Materials

In vitro release of crushed levetiracetam (Keppra 500 mg film-coated tablet; BCS Class I), carbamazepine (Tegretol 200 mg tablet; BCS Class II), atenolol (Nortan 50 mg film-coated tablet; BCS Class III) and cefixime (Zimaks 400 mg film-coated tablet; BCS Class IV) were tested after mixing with thickened liquids at three thickness levels in comparison to crushed tablets with water. These drugs were selected as they were widely used to treat chronic diseases in both pediatric and adult populations in our centre. Several other factors including their diverse solubility characteristics in water, as well as the size and shape of tablets (e.g., difficult to swallow by patients) were also considered during selection.

Only two commercial thickening agents were available in Turkey during the study period: Nestle Resource Thicken Up Clear (xanthan gum, maltodextrin, potassium chloride) and Abbott Multithick (modified maize starch). It has been well-established that the extent of drug release can be affected by the type of thickening agent (Cichero, 2013; Manrique et al., 2014). Hence, both thickeners were used in this study to evaluate the effects of co-administration of thickened liquids on in vitro drug release.

2.2. Sample preparation

50 mL of thickened water samples were prepared at three viscosity levels recommended by 'American National Dysphagia Diet' to prevent aspiration of liquids in dysphagia patients: nectar (51-350 cPa), honey (351-1750 cPa), and pudding (>1750 cPa) consistency (American Dietetic Association, 2002). These consistencies are equivalent to 'Level 2', 'Level 3' and 'Level 4' according to the latest terminology developed by International Dysphagia Diet Standardisation Initiative (IDDSI) framework to describe the level of fluid thickness (Cichero et al., 2017).

Manufacturer's instructions were followed during sample preparation. Spoon measurements of thickeners for each viscosity level were converted to weight, transferred into plastic containers and mixed with deionized water to provide the desired percentage of weight per volume (w/v%). Samples were initially stirred by using a stick to disperse the thickener in water, and with a magnetic stirrer (FinePCR 4S; South Korea) to ensure homogeneity. All samples were prepared at room temperature and held for 5 minutes to stabilize the viscosity before addition of powdered tablets.

Tablets were crushed in a mortar and pestle, and weighed with a microbalance (Shimadzu AX 200, Japan) on a weighing paper to ensure the predetermined concentration of the drug for dissolution studies. In test groups, powdered tablets were added into 50 mL of thickened water prepared for each consistency level, and tablet powder was suspended in deionized water were used as control. All samples were mixed using a magnetic stirrer (FinePCR 4S; South Korea) for three minutes.

The pH of thickened samples was measured using a pH-meter (Sartorius PP-20; Germany). The viscosity measurements were made by a cone plate viscometer (Brookfield Viscometer DV2T; Brookfield Engineering Labs.; Inc.; USA) using CP-40 spindle (40 mm diameter, 2° angle) at 37°. Viscosity versus shear rate curves were created for each thickened sample, and the measurements at 50 s^{-1} were presented since this value is accepted as a reasonable shear rate representing the bolus

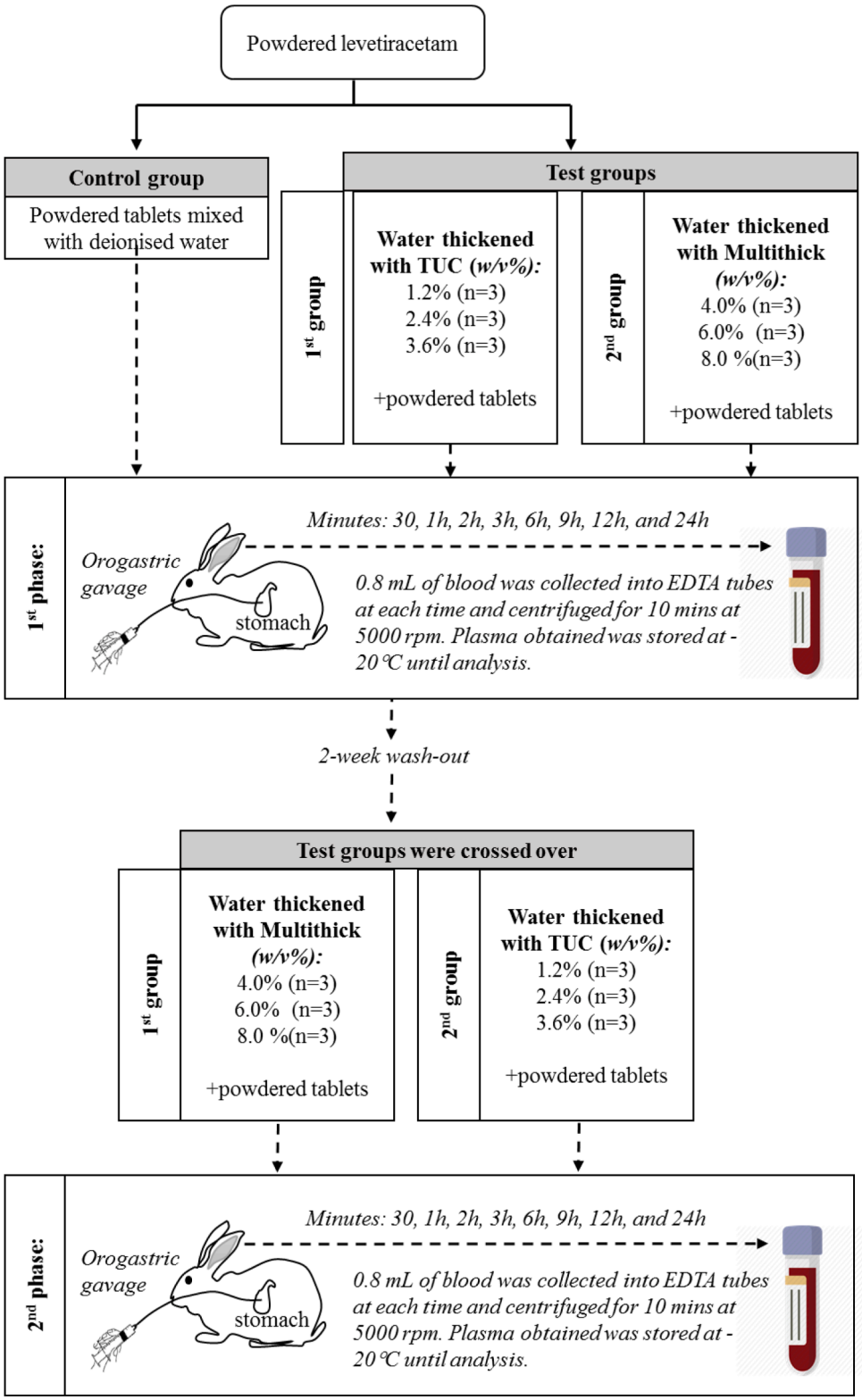

Fig. 1. Summary of in vivo experimental design. Abbreviations: TUC, Thicken Up Clear; w/v%, percentage of weight/volume.

flow during swallowing (Newman et al., 2016).

2.3. In vitro drug release

In vitro drug release of four drugs from thickened samples (test groups) and water (control group) was assessed by membrane dialysis method during 24 h (37°C, 100 rpm, pH 7.4 phosphate buffer). 5 mL samples of crushed tablets, weighed to ensure the predetermined concentration of the active ingredient and mixed with thickening agents, were placed in dialysis bags and 50 mL of pH 7.4 phosphate buffer was used as dissolution media. 2 mL samples were taken from the dissolution media at 5 min, 15 min, 30 min, 1 h, 2 h, 3h, 6 h and 24 h. The volume of dissolution media was maintained during the experiments by adding the same amount of fresh media. The percentage of active ingredients dissolved in dissolution media were analysed using high performance liquid chromatography (HPLC) methods described in the United States Pharmacopoeia (USP) 38 monographs. All experiments were performed in triplicate. Dissolution profiles were compared by using $f2$ similarity factor (Shah et al., 1998).

2.4. In vivo experimental design

In vivo experimental design was summarised in Fig. 1. Female New Zealand rabbits (n=24) weighing around 3.0-3.5 kg were used. Animals were not allowed to access food and water in the last 16 h pre-administration. After samples were administered by gavage, water and food was reintroduced in 3 h and 6 h, respectively.

Levetiracetam was used as the model drug in in vivo experiments. A dose of 54 mg/kg was selected by taking into consideration of the dose used in previous studies to evaluate the pharmacokinetics of the same drug in different species including rabbits (Strolin Benedetti et al., 2004). Samples of test groups (i.e., thickened liquids prepared with two thickening agents at three viscosity levels) were prepared following the same instructions as described in in vitro tests. Crushed levetiracetam was then added into thickened samples (test groups) at a concentration of 25 mg/mL and stirred manually for 20 seconds and administered by intragastric gavage (2 mL/kg).

Animals were placed into individual metabolic cages and divided into two groups as control and test group. The animals in the control group (n=6) received crushed levetiracetam tablet mixed with water alone. The animals in the test group (n=18) were randomly allocated to take crushed levetiracetam tablet either mixed with water and xanthan gum-based thickener at nectar, honey and pudding consistencies (n=3 for each consistency: w/v% was 1.2%, 2.4% and 3.6%, respectively) or with water thickened at the same three consistencies with modified maize starch (n=3 for each consistency: w/v% was 4%, 6% and 8%, respectively).

Rabbits were restrained during blood collection. Blood was taken from central ear artery at nine time points following gavage administration: at 0.5, 1, 1.5, 2, 3, 6, 9, 12 and 24 h. Approximately 0.8 mL of blood was collected into EDTA tubes at each time and centrifuged for 10 minutes at 5000 rpm. Plasma obtained was stored at -20°C until analysis.

Considering the time required for complete elimination of levetiracetam from circulation (i.e. at least 7 times the half-life of levetiracetam) and full recovery of ear arteries (approximately between 10 to 15 days), animals underwent a two-week washout period. At the end of this period, test groups were crossed over and blood samples were collected after intragastric gavage administration. Levetiracetam was determined in plasma samples using liquid chromatography–mass spectrometry (LC-MS/MS) method.

2.5. Determination of pharmacokinetic parameters

The levetiracetam concentration was measured in plasma samples using liquid chromatography tandem mass spectrometry (LC-MS/MS, Shimadzu LCMS-8030, Japan). The validated method was adapted from Yeap et al. (Yeap et al., 2014) using slight modifications described below. Briefly, a reversed phase column (4.6 × 100 mm; 3.5 µm) was used with the mobile phase mixture of 0.1% formic acid and acetonitrile including 0.1% formic acid (1:1, v/v) at a flow rate of 0.4 mL/min. The column temperature was set at 30°C and the analysis time was 6.5 minutes. All data were processed by the LabSolutions software (version 5.72, Shimadzu). A plasma sample of 200 µL was transferred into an Eppendorf tube and 200 µL of acetonitrile containing 1 µg/mL of procainamide (internal standard) was added. The samples were vortexed at 10 seconds and centrifuged at 10 000 rpm for 10 min. The supernatants were transferred into a vial with an insert and injected into the LC-MS/MS system. Calibration curves were created by plotting the concentration against the peak area values of the standard solutions prepared by spiking of blank plasma in the range of 0.5-40 µg/mL from the 1000 µg/mL stock solution of levetiracetam. The regression equation was y=0.0182x + 0.2261 with a high regression coefficient (0.9991). The limit of detection (LOD) and limit of quantification (LOQ) were 0.01 µg/mL and 0.05 µg/mL, respectively. There were not any peaks from blank plasma samples indicating the selectivity of the method.

The pharmacokinetic parameters were estimated using plasma drug concentration-time profile by non-compartmental analysis (Phoenix WinNonlin, USA). The area under the plasma drug concentration–time profile (AUC), the plasma peak drug concentration (C_{max}) and the time to reach C_{max} (t_{max}) were calculated by the linear trapezoidal rule.

2.6. Assessment of in vitro – in vivo correlation (IVIVC)

The main objective of in vitro-in vivo correlation is to estimate the in vivo reflections of the in vitro formulation parameters by using a mathematical model. In this part of the study, correlation analysis was performed between in vitro dissolution results (percent of drug dissolved in vitro) and in vivo plasma concentrations of levetiracetam for control group (crushed tablet mixed with thin water) and test groups (crushed tablet mixed with thickened water samples). Since the number of sampling time points did not exactly match each other, the time points for each case (in vitro and in vivo) have been analyzed by a mathematical model to increase the number of time points for a stronger correlation equation.

For this purpose, interpolation of the data for unknown time instants for every 5 minutes were predicted by piecewise cubic Hermite interpolating polynomials (PCHIP) by using MATLAB software (Karakucuk et al., 2019). A Hermite interpolation polynomial is represented as follows Eq. (1) (Fritsch and Carlson, 1980); let $\{t_1, t_2, \ldots, t_N\}$ denote the time instants at which the in vitro or in vivo measurements are made and let $\{y_1, y_2, \ldots, y_N\}$ denote the corresponding measured values. Then, let the interpolated value of the data at time t be $f(t) = p_i(s)$ on each subinterval of time, i.e, for $t_i \le t \le t_{i+1}$, $i = 1\ldots, N-1$, where $s = \frac{t-t_i}{t_{i+1}-t_i}$ and

$$p_i(s) = \begin{bmatrix} s^3 & s^2 & s & 1 \end{bmatrix} \begin{bmatrix} 2 & -2 & 1 & 1 \\ -3 & 3 & -2 & -1 \\ 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} y_i \\ y_{i+1} \\ d_i \\ d_{i+1} \end{bmatrix}. \quad (1)$$

In Eq. (1), d_i and d_{i+1} are the first derivatives at t_i and t_{i+1}, which are chosen such that $f(t)$ is piecewise monotonic between every measurement instant.

As a result, the above equation predicted the values both for in vitro dissolution and in vivo plasma concentrations of levetiracetam using the consecutive four time points by the equation. Finally, many equations were realized for the prediction of the values at missing time points for every 5-minute time intervals that exactly fits the complete polynomial curve. At the end, a common time point data were estimated until the maximum plasma concentration was reached, which reflects the point where drug absorption is equal to drug elimination. After this point,

elimination process starts to govern the plasma profile pattern and absorption is completed.

The in vitro in vivo correlation was investigated by using the same time points for in vitro dissolution and in vivo plasma concentration data and the results were evaluated through the r^2 values of the regression line.

2.7. Statistical analysis

All statistical analysis was performed using the statistical software package program SPSS for Windows, version 25.0 (SPSS, Inc. Chicago, IL). One-way ANOVA was used to compare the difference in pharmacokinetic parameters between control and test groups. Homogeneity of variances was assessed by Levene's test. Dunnett method was used in post-hoc analysis by considering the control group as the reference category. A p value of <0.05 was considered as statistically significant.

3. Results

3.1. In vitro drug release

Viscosity of thickening agents was measured at body temperature (37°C) and at a constant shear rate ($50s^{-1}$) representative of bolus flow during swallowing (Table 1). To determine the impact of thickeners on drug release, dissolution rate of four drugs from thickened samples were compared with the dissolution of the crushed tablets mixed with thin water as a control group. The addition of both thickeners significantly reduced the dissolution rate of crushed levetiracetam, cefixime and atenolol tablets compared to control groups ($f2<50$). In the absence of thickening agents, the solubility ranged between 63% to 75% at 1 h, 90% to 98.8% at 6 h, and more than 97% at 24 h was observed in the control groups. The extent of reduction was dependent on the thickness level as higher concentrations of both thickening agents caused the slowest drug release into the dissolution media. At the highest thickness levels, the maximum amount drug dissolved (%) in the media at 1 h only reached to 32-44% for levetiracetam, 10-40% for cefixime, and 35-38% for atenolol, respectively. The solubility also remained lower in the test groups compared to the control group at 6 h and 24 h (Fig. 2a–c, Suppl. Tables 1-3). However, the dissolution of carbamazepine was not affected from addition of thickeners which has the lowest solubility even in the control group (Fig. 2a–d and Suppl. Tables 1-4). In the first 1h, a solubility of 15.6±2.0% was achieved for carbamazepine mixed with thin water, while the mean solubility was approximately 14% for the same drug mixed with thickened water (Fig. 2d, Suppl. Table 4). At the end of 24 h, the amount of carbamazepine dissolved in the media (%) was still lower than 75% in the control group, and <70% in the test groups.

Since the dissolution profiles of the crushed tablets mixed with thickened water were similar among the three drugs, only levetiracetam (BCS Class I) was selected to continue in vivo experiments by considering its high dissolution rate, so the potential hindering effect of the dosage form on drug solubility could be minimized. The sensitivity of the analytical method was also considered to ensure that plasma concentration of the medication would not be below the limit of detection (LOD) and limit of quantitation (LOQ).

3.2. In vivo experiments

The effects of type and concentration of thickening agents on pharmacokinetics of levetiracetam are presented in Tables 2-3 and Figs. 3-4. Following administration, the maximum plasma concentration (C_{max}) of levetiracetam and time taken to achieve C_{max} (t_{max}) in the control group were detected as 52.9±8.9 μg/mL and 1.6 hours, respectively. C_{max} was lower in the experiment groups (ranged between 33.0-50.6 μg/mL) and this level was reached within 1.3 to 2.2 hours, which was slightly longer than in the control group. The lowest C_{max} was obtained when crushed tablets were administered by mixing crushed tablets in water thickened with modified starch in comparison to control group and samples prepared with xanthan gum. However, the difference in C_{max} and t_{max} between control and experiment groups were statistically insignificant ($p=0.117$ and $p=0.495$ for C_{max} and t_{max}, respectively). Also, there was no statistically significant difference in total exposure to levetiracetam (AUC) between control and experiment groups ($p=0.215$ and $p=0.183$ for AUC_{all} and AUC_{∞}, respectively).

Paired comparisons showed that the differences in pharmacokinetic parameters between groups were not significant except a lower C_{max} found in modified starch group compared to xanthan gum at nectar consistency ($p=0.038$). Overall, these results indicate that irrespective of the type of thickening agent and the viscosity (thickness) of the fluid, co-administration of levetiracetam with thickening agents does not alter the pharmacokinetic efficacy and bioavailability of the drug.

3.3. In vitro - in vivo correlation (IVIVC)

Basically, in vitro-in vivo correlation concept has been applied to extended-release dosage forms for granting biowaiver from bioequivalence studies (FDA; 1997). Although a full in vitro-in vivo correlation model was not designed as described in the guideline, the possible relationships between in vitro dissolution and in vivo plasma concentrations of levetiracetam were evaluated. As seen from the Fig. 5, a better correlation was obtained between in vitro and in vivo data when crushed tablets were mixed with thickened water at the highest consistencies (i.e. honey and pudding consistencies), as indicated from the r^2 values ranged between 0.92 – 0.99. However, a lower level of IVIVC was observed between in vitro dissolution and in vivo response when crushed tablets mixed with thickened water at the lowest therapeutic thickness level (i.e. nectar consistency). This is in accordance with the spirit of the IVIVC as mentioned in the FDA guideline. Levetiracetam can be classified as a BCS Class I drug with high solubility and high permeability. The results show that increased concentration of the

Table 1
Composition, pH and viscosity measurements of thickeners.

Type of commercial thickener [a]	Composition	Thickness level	Concentration (w/v%)	pH	Viscosity (cP)[b]
Thicken Up Clear (Nestle)	Maltodextrin, xanthan gum, potassium chloride	Nectar	1.2	5.7	156.3
		Honey	2.4	5.7	219.7
		Pudding	3.6	5.6	1019.6
Multithick (Abbott)	Modified maize starch	Nectar	4.0	5.3	235.5
		Honey	6.0	5.5	698.2
		Pudding	8.0	5.6	1452.3

Abbreviations: w/v%: weight per volume (%).
[a] Information was obtained from product label.
[b] Viscosity was measured with 50 s^{-1} shear rate at 37°C (Brookfield Viscometer DV2T, Brookfield Engineering Labs., Inc., USA). Thickened samples were prepared following the instructions of the manufacturer for thickener to be added in 100 mL water for each thickness level. Spoon measurements of thickeners for each viscosity level were converted to weight.

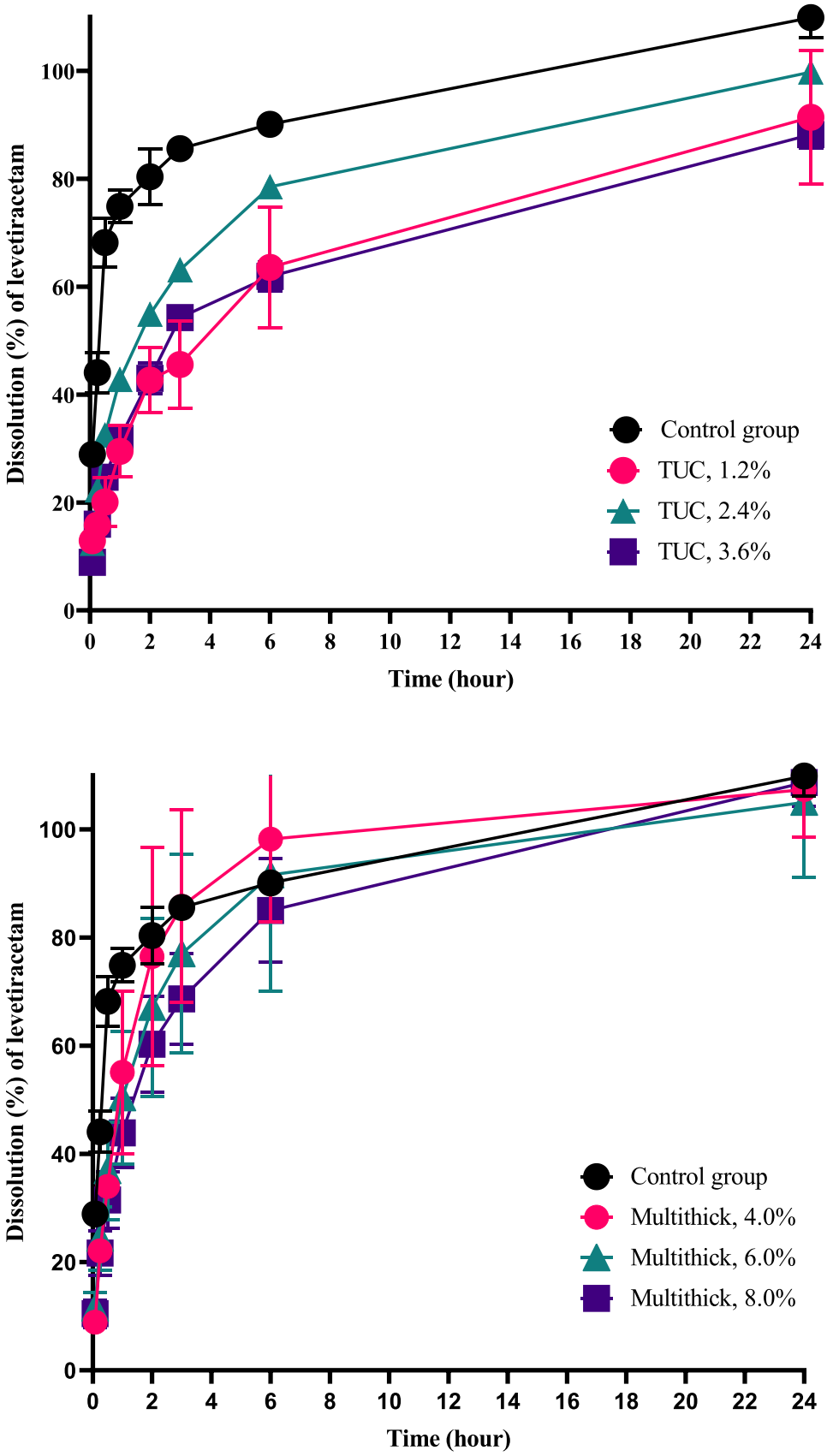

Fig. 2a. In vitro release profile of powdered levetiracetam mixed with thin water (control group) and water thickened with xanthan gum-based (top figure; Thicken Up Clear mixed with water at 1.2%, 2.4% and 3.6% concentrations) and modified starch-based products (bottom figure; Multithick mixed with water at 4%, 6% and 8% concentrations). Abbreviations: TUC, Thicken Up Clear.

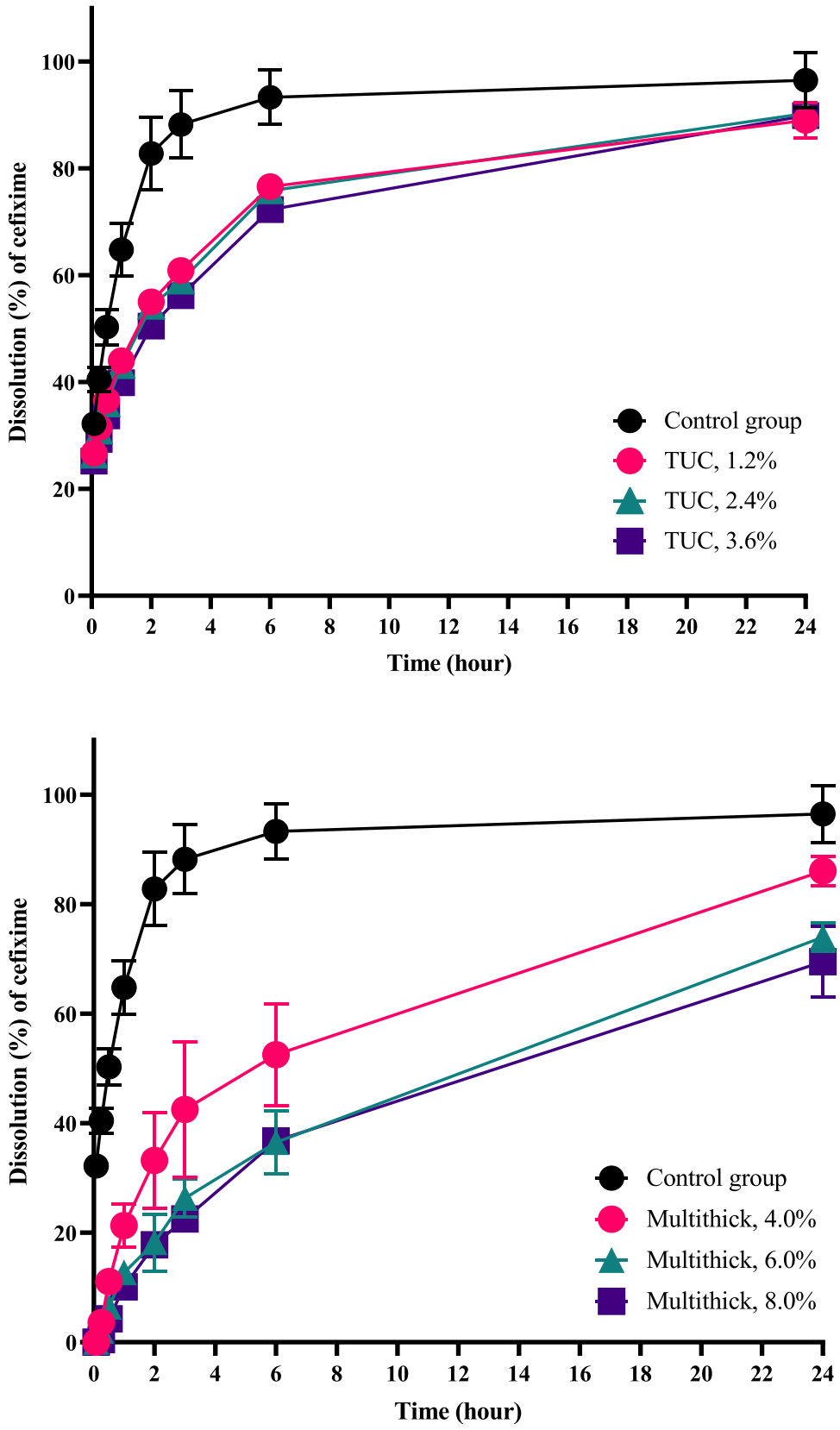

Fig. 2b. In vitro release profile of powdered cefixime mixed with thin water (control group) and water thickened with xanthan gum-based (top figure; Thicken Up Clear mixed with water at 1.2%, 2.4% and 3.6% concentrations) and modified starch-based products (bottom figure; Multithick mixed with water at 4%, 6% and 8% concentrations). Abbreviations: TUC, Thicken Up Clear.

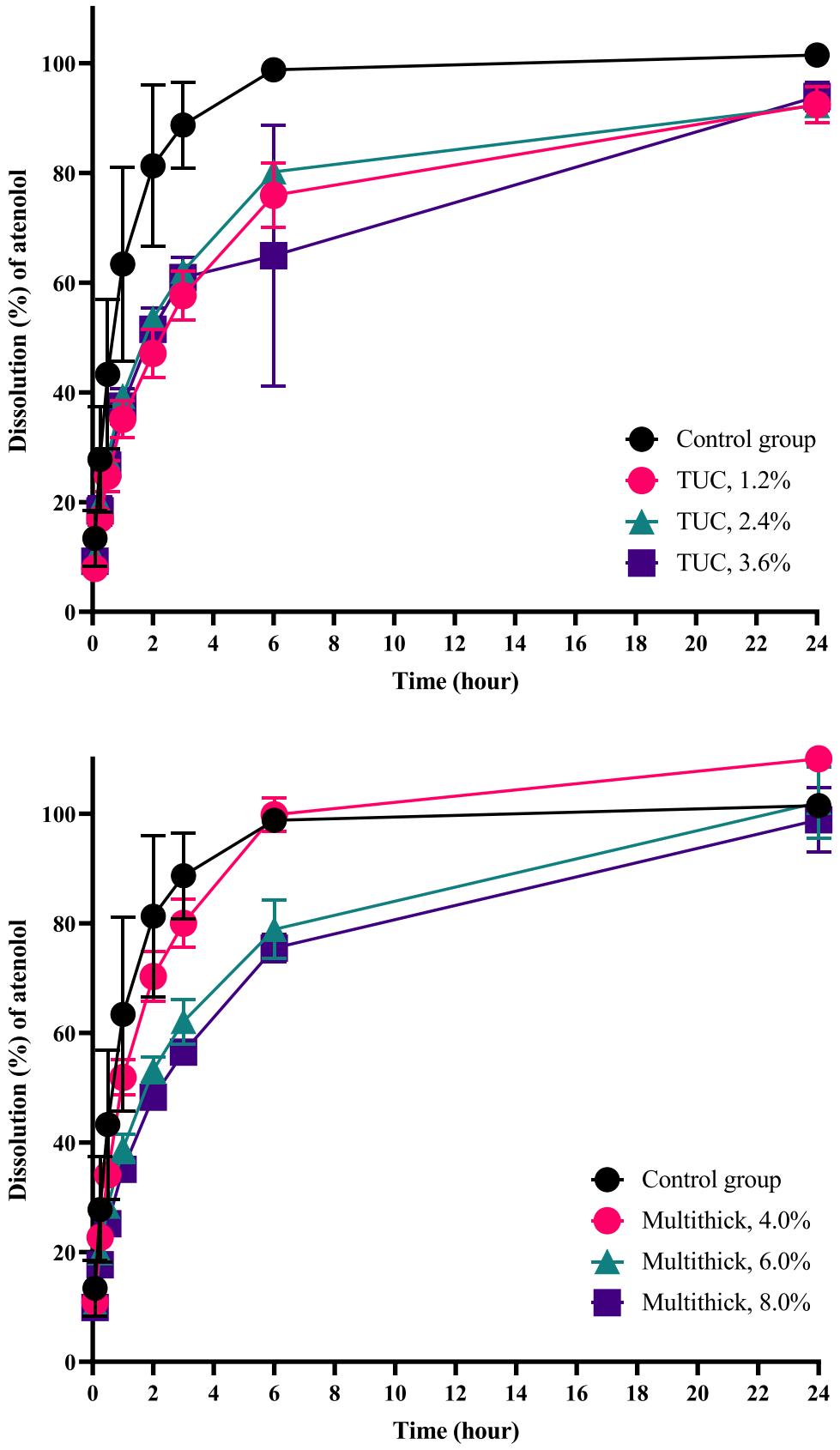

Fig. 2c. In vitro release profile of powdered atenolol mixed with thin water (control group) and water thickened with xanthan gum-based (top figure; Thicken Up Clear mixed with water at 1.2%, 2.4% and 3.6% concentrations) and modified starch-based products (bottom figure; Multithick mixed with water at 4%, 6% and 8% concentrations). Abbreviations: TUC, Thicken Up Clear.

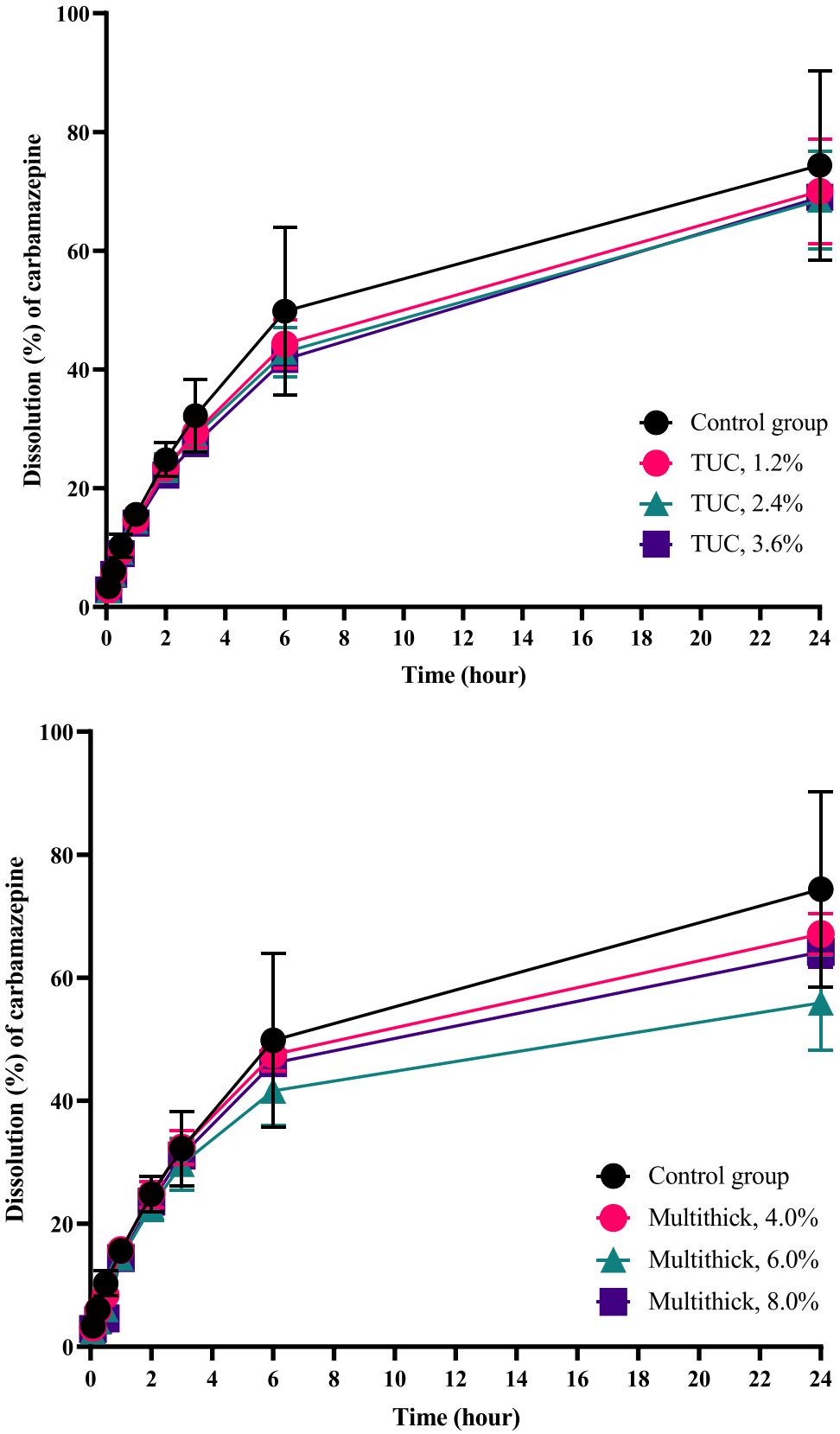

Fig. 2d. In vitro release profile of powdered carbamazepine mixed with thin water (control group) and water thickened with xanthan gum-based (top figure; Thicken Up Clear mixed with water at 1.2%, 2.4% and 3.6% concentrations) and modified starch-based products (bottom figure; Multithick mixed with water at 4%, 6% and 8% concentrations). Abbreviations: TUC, Thicken Up Clear.

Table 2
Plasma pharmacokinetic parameters (mean±SD) of a single dose powdered levetiracetam mixed with water (control group) and thickened water (test samples) before administration.

Formulations[a]	C_{max} (μg/mL)	t_{max} (hour)	AUC_{all}	AUC_{last}
Control	52.9 ± 8.90	1.6 ± 0.95	306.2 ± 56.87	313.4 ± 53.36
TUC, 1.2%	50.4 ± 8.41	1.5 ± 0.35	327.2 ± 77.11	327.2 ± 77.11
TUC, 2.4%	50.6 ± 9.67	2.2 ± 1.89	335.5 ± 124.76	335.5 ± 124.76
TUC, 3.6%	44.6 ± 13.03	1.0 ± 0.55	263.9 ± 81.63	260.5 ± 85.53
Multithick, 4.0%	36.2 ± 10.61	1.3 ± 0.61	254.9 ± 76.09	254.9 ± 76.09
Multithick, 6.0%	35.1 ± 15.98	1.6 ± 0.80	223.2 ± 104.22	223.2 ± 104.22
Multithick, 8.0%	33.0 ± 24.32	1.5 ± 0.50	205.34 ± 121.92	199.9 ± 113.02
P[b]	0.117	0.495	0.215	0.183

Abbreviations: TUC, Thicken Up Clear; SD, standard deviation; C_{max}, maximum plasma concentration; t_{max}, time to maximum plasma concentration; AUC_{all}, the area under the curve from the time of dosing to the time of the last observation; AUC_{last}, the area under the curve from the time of dosing to the last measurable concentration.

[a] In test groups, powdered commercial tablets of levetiracetam was mixed with water thickened with two commercial thickeners (xantan gum based thickener, TUC and starch-based thickener, Multithick) at three thickness levels (w/v%): concentrations of 1.2%, 2.4% and 3.6% for TUC samples and 4.0%, 6.0% and 8.0% for Multithick samples, respectively. Tablet powder was suspended in deionized water were used as control.

[b] ANOVA test was used for comparison between control and test groups.

thickening agents responded as a simulator of the extended-release microenvironment for the in vivo dissolution of the levetiracetam.

4. Discussion

This experimental study was designed to investigate whether a significant delay in drug dissolution caused by mixing crushed tablets with thickened water, a common method which is used for drug administration in patients with dysphagia, has a clinically meaningful impact on its pharmacokinetic efficacy. Similar to the findings of previous studies (Manrique et al., 2014, 2016), the current in vitro experiments showed a slower drug release by adding crushed tablets into thickened water prepared at three thickness levels with two commercial thickeners which are both widely used to prevent aspiration in dysphagia patients. However, the results of our in vivo experiments revealed that this alteration does not seem to have a negative impact on bioavailability of the same drug.

According to the biopharmaceutical classification system, oral dosage forms are classified into four categories based on two important physicochemical properties, 'solubility' and 'intestinal permeability', both affecting bioavailability of the orally administered drug (Amidon et al., 1995). Class I and III medications have been reported to have a poor bioavailability when administered with thickened liquids (Huupponen et al., 1984; Watanabi et al., 1992). In the first step of this study, in vitro dissolution rate of four drugs with widespread clinical use and have different solubility was evaluated by dialysis membrane method. Among these four drugs, only carbamazepine within BCS Class II showed a similar drug release profile to the control group after mixing with thickened samples. The low solubility of this drug even in the control group (i.e., dispersed in water alone) is thought to be responsible for this finding, as only 15.6% of carbamazepine was released into the media after 60 minutes compared to dissolution rates ranged between 63.4 – 74.9% for three other drugs tested.

Similar findings were obtained in previous in vitro studies comparing the drug dissolution and release of crushed atenolol, amlodipine, carbamazepine, warfarin (Manrique et al., 2014) and acetaminophen tablets (Manrique et al., 2016) when mixed with thin or thickened water with xanthan gum and modified starch based thickening agents at different viscosity levels. Studies showed that drug dissolution tested using SGF at 30 minutes in thickened water was significantly delayed compared to dissolution in thin water, particularly at "moderate-to extremely" thick levels (honey and pudding consistencies) (Manrique et al., 2014). The most apparent delay in dissolution was observed for BCS class II drugs including carbamazepine and warfarin where only 13.4% and 14.9% of the drugs were dissolved in SGF at 30 minutes, respectively. These findings have raised the question whether this change in drug dissolution with thickened liquids would result in a clinically relevant impact on drug bioavailability, which was the main topic of our research. Data obtained from this current in vitro experiment did not only reflect the retarding effect of thickened drinks when mixed with crushed tablets but was also used as a basis for selection of levetiracetam as model drug to continue to in vivo experiments.

Although several hypotheses have been suggested to explain the adverse effects of thickened liquids on drug release, increased viscosity of the dissolution media (i.e., simulated gastric fluid) by adding thickening agents was proposed as the leading factor. Previous studies have consistently shown that an increase in viscosity in gastric fluids or in dissolution media may cause the formation of a physical barrier that prevents the drug molecules from mixing with gastrointestinal fluids (i.e., by interfering wetting of tablets), prolonged gastric emptying or intestinal transit time and slower diffusion of drug molecules from intestinal membrane to the viscous lumen (Abrahamsson et al., 2004; Cvijić et al., 2014; Huupponen et al., 1984; Jaffe et al., 1971; Parojčić et al., 2008; Radwan et al., 2014, 2013, 2012; Reppas et al., 1998; Sarisuta and Parrott, 1982). However, most of these effects were observed when the viscosity of media was markedly increased (e.g., 500 cP) such as high fibre consumption with meals or thickening of dissolution media by adding thickening agents directly into the media (Radwan et al., 2013, 2012). In contrast, data is limited on the effects of administering drugs

Table 3
Comparison of plasma pharmacokinetic parameters (mean±SD) of levetiracetam according to the type of thickening agent.

	Nectar consistency (w/v%)			Honey consistency (w/v%)			Pudding consistency (w/v%)		
	TUC (1.2%)	Multithick (4.0%)	*P*[a]	TUC (2.4%)	Multithick (6.0%)	*P*[a]	TUC (3.6%)	Multithick (8.0%)	*P*[a]
C_{max} (μg/mL)	50.4±8.41	36.2±10.61	**0.038**	50.6±9.67	35.1±15.98	0.076	44.6±13.03	33.0±24.32	0.136
t_{max} (hour)	1.5±0.35	1.3±0.61	0.602	2.2±1.89	1.6±0.80	0.835	1.0±0.55	1.5±0.50	0.415
AUC_{all}	327.2±77.11	254.9±76.09	0.153	335.5±124.76	223.2±104.22	0.098	263.9±81.63	205.3±121.92	0.116
AUC_{last}	327.2±77.11	254.9±76.09	0.153	335.5±124.76	223.2±104.22	0.098	260.5±85.53	199.9±113.02	0.094

Abbreviations: TUC, Thicken Up Clear; SD, standard deviation; C_{max}, maximum plasma concentration; t_{max}, time to maximum plasma concentration; AUC_{all}, the area under the curve from the time of dosing to the time of the last observation; AUC_{last}, the area under the curve from the time of dosing to the last measurable concentration.

Samples were prepared by mixing powdered commercial tablets of levetiracetam with water thickened with two commercial thickeners (xanthan gum based thickener, TUC and starch-based thickener, Multithick) at three thickness levels (w/v%): concentrations of 1.2%, 2.4% and 3.6% for TUC samples and 4.0%, 6.0% and 8.0% for Multithick samples, respectively.

[a] Dunnett test was used for comparison.

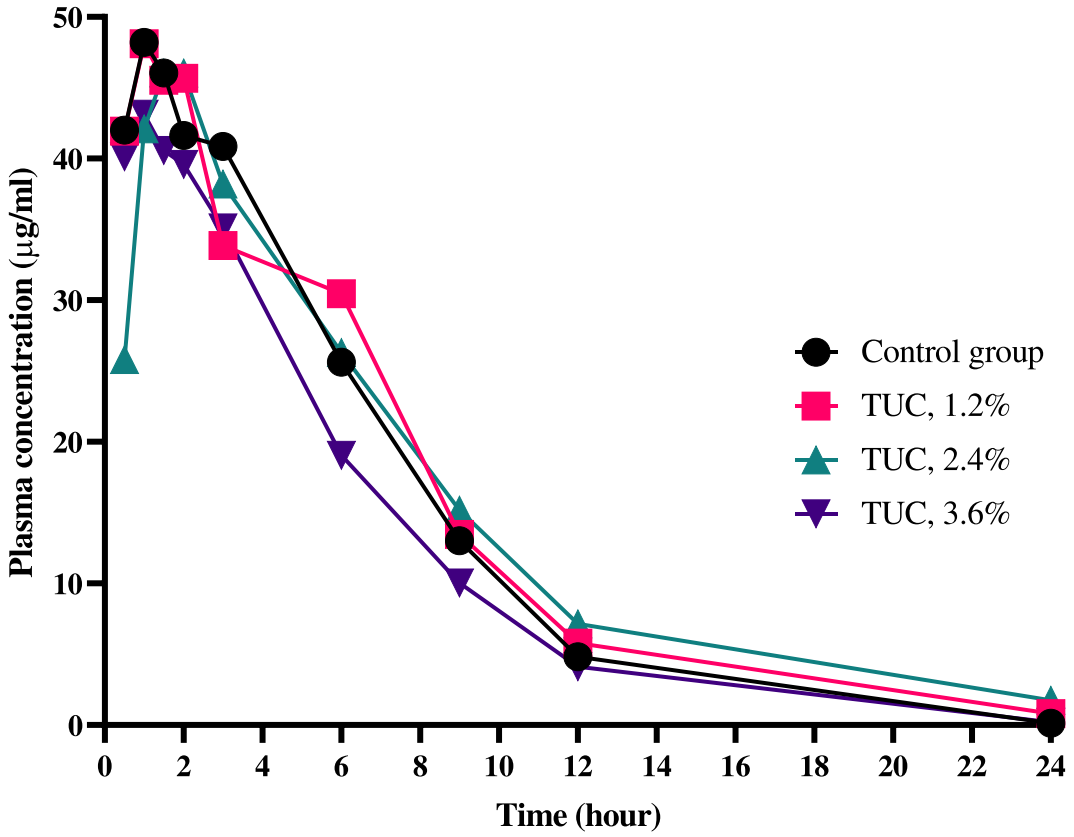

Fig. 3. Plasma concentration of levetiracetam versus time after administration of a single dose in rabbits; powdered tablets were mixed with water (control group) and water thickened with xanthan gum-based product (test groups; Thicken Up Clear mixed with water at 1.2%, 2.4% and 3.6% concentrations). Abbreviations: TUC, Thicken Up Clear.

with a small amount of thickened liquid (e.g., 15 grams bolus) on drug release or bioavailability, as in the case for drug administration in dysphagia patients (Manrique et al., 2014, 2016; Radhakrishnan et al., 2014; Tomita et al., 2016).

In an in vitro study, Manrique et al. (Manrique et al., 2014) found that mixing crushed atenolol tablets with thickened water prepared with all types of thickening agents at the highest consistency level significantly restricted dissolution of the drug. At lower consistencies (e.g., nectar and honey), only products based on xanthan gum delayed dissolution. The authors confirmed these results in another study where the effects of preparation method or dosage form (e.g., tablet, effervescent, elixir, suspension etc.) on acetominofen dissolution were also evaluated (Manrique et al., 2016). Irrespective of the mixing method, dispersion of acetominofen within thickened water at the highest thickness level (i.e., pudding consistency) considerably slowed drug release in all dosage forms tested. During the dissolution test, samples were also taken from 900 mL of simulated gastric fluid (SGF) to measure the contribution of 15 grams thickened water on media viscosity (Manrique et al., 2014). At the end of 3 hours, the greatest dissolution media viscosity was only 1.56 cP (range = 0.82 to 1.56 for all five thickening agents) which was close to the gastric fluid viscosity at fasting state in humans (range = 1.73 to 9.3 cP) (Pedersen et al., 2013). Although these findings indicate a possible role for thickening agents to slow dissolution rate, depending on the type and dose of thickener, it was clear that these effects were not mainly associated with increased dissolution media viscosity. Instead, delayed dissolution was mostly attributed to the ability of thickening agents to form a network barrier around the powdered drug, trapping drug molecules within this gel-like structure that resulted with an impairment in drug diffusion into the dissolution media. Hydrocolloids, such as modified starch and xanthan gum-based thickeners, are a group of long chain polymers that forms viscous dispersions and/or gels when added into water. Their thickening effect arises from physical entanglement of conformationally disordered polymer chains (i.e., random coils) in concentrated dispersions. These biopolymers also have a gel formation characteristic which involves the cross-linking of the polymer chains to form a three-dimensional network that traps the water within and forms a rigid viscoelastic structure that is resistant to flow (Saha and Bhattacharya, 2010). Hence, it is not surprising that drug molecules can also be trapped within this gel structure as water molecules, avoiding them to release into the dissolution media. Although the authors observed that drug molecules tend to remain in a single lump in all thickened samples at the greatest viscosity level and did not completely disperse in the dissolution media, this was more apparent for samples prepared with xanthan gum-based thickeners (Manrique et al., 2014). It is known that the thickening and/or gel-forming effects highly depends on the type (i.e., conformation of polymer chains, chain rigidity, electrostatic charge, etc.) and concentration of the polymer used (Saha and Bhattacharya, 2010). Thus, thickeners with more rigid type chains such as xanthan gum, and an increase in the concentration of thickener in the sample are expected to lead a more significant decrease in drug dissolution rate by forming a more complex network around drug molecules.

This is the first study published to investigate the retarding effects of two types of thickening agents, which are widely used to prevent aspiration in dysphagia patients, and three therapeutic thickness levels on drug bioavailability in a living organism rather than an experimental dissolution environment. In our study, the results revealed that C_{max} and AUC were lower particularly for those prepared with modified starch or at higher viscosity levels, and t_{max} was relatively higher in the experiment groups than in the control group, though the differences were not statistically significant. There is limited evidence from a few in vivo studies on the effects of thickeners on pharmacokinetic parameters of

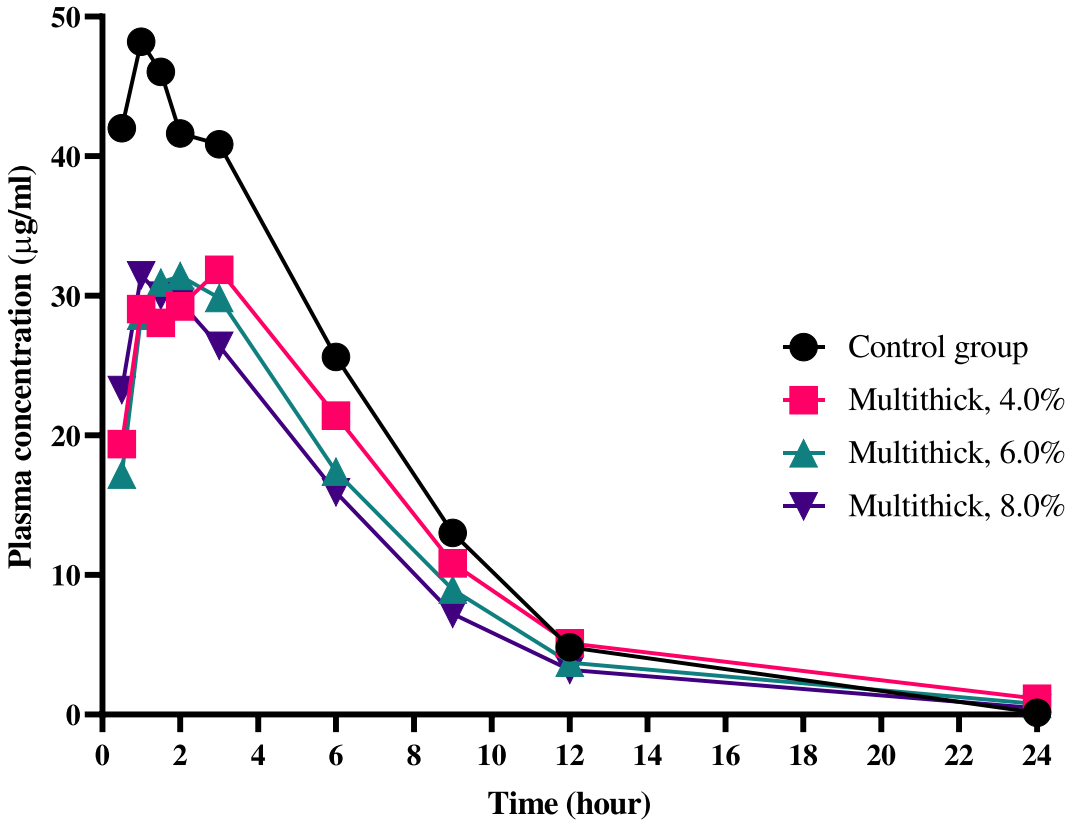

Fig. 4. Plasma concentration of levetiracetam versus time after administration of a single dose in rabbits; powdered tablets were mixed with water (control group) and water thickened with xanthan gum-based product (test groups; Multithick mixed with water at 4.0%, 6.0% and 8.0% concentrations).

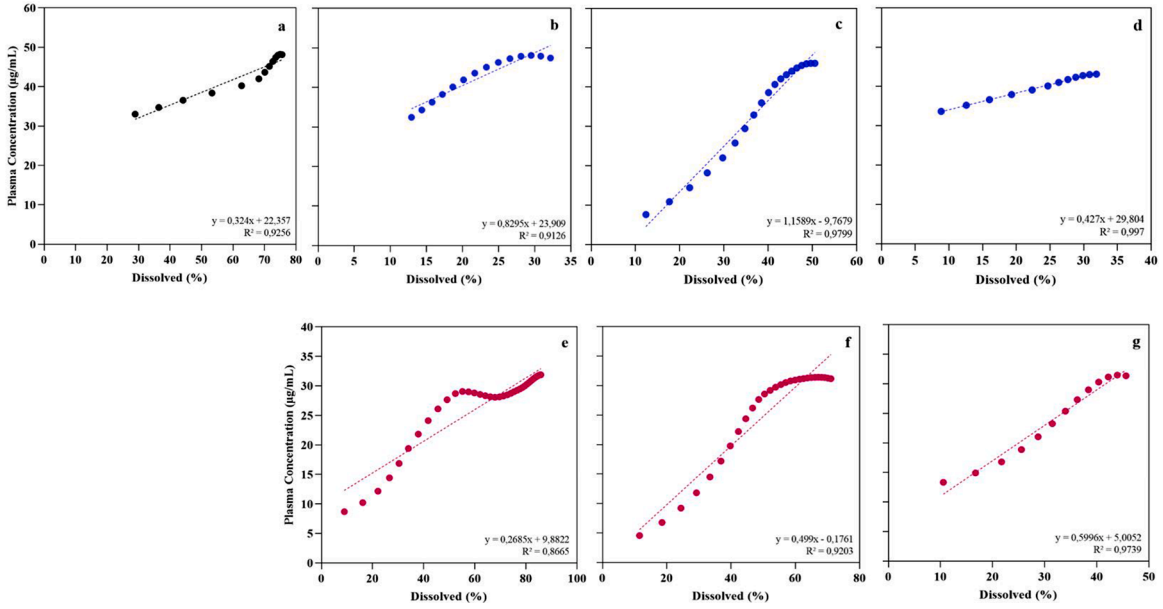

Fig. 5. In vitro–in vivo correlation (IVIVC) plots of "% dissolved" versus "plasma concentration" for **(a)** crushed LEV tablet mixed with thin water; **(b-d)** crushed LEV tablet + water thickened with TUC (w/v%) 1.2%, 2.4%, and 3.6% concentrations; and **(e-g)** crushed LEV tablet + water thickened with Multithick (w/v%) 4%, 6% and 8% concentrations, respectively. Abbreviations: LEV, Levetiracetam; TUC, Thicken Up Clear; w/v%, percentage of weight/volume.

drugs and the results were conflicting (Radhakrishnan et al., 2014; Tomita et al., 2016). In these studies, only a single viscosity level or thickening agent was used. In another study by Radhaskrinan et al. (Radhakrishnan et al., 2014), crushed paracetamol tablets were administered to healthy subjects with thickened water using xanthan gum at the thickest level for dysphagia patients in Australia. Results were compared to whole tablets taken with water as a reference formulation and pharmacokinetic profile was measured using saliva samples. Delivering crushed tablets with thickened water had a lower C_{max}, although t_{max} and total exposure to paracetamol ($AUC_{0\text{-}8h}$) were

similar between groups. The authors concluded that these small alterations in pharmacokinetic parameters was unlikely to cause a meaningful effect on clinical efficacy of paracetamol which contrasts with previous in vitro studies using the same drug, thickener and thickness level and showed a large effect that might adversely affect drug absorption. The authors also evaluated the correlation between in vitro-in vivo methods and found that IVIVC model failed to predict pharmacokinetic parameters accurately. In another study by Tomita et al. (Tomita et al., 2016) in vitro dissolution tests and animal experiments revealed that agar gum-based thickeners did not affect magnesium oxide release from a mixture of tablets dispersed in thickened water or its laxative activity after oral administration to mice, but some xanthan gum thickeners led to a slower dissolution rate and decreased laxative activity of the drug. The authors also concluded that the results of dissolution testing and in vivo investigation of laxative activity were not always consistent. Our findings also supported these results, as we failed to show a good correlation between in vitro dissolution and in vivo response at all thickness levels that have been investigated.

Some hypotheses have been suggested to explain the contrasting results between in vitro dissolution tests and in vivo experiments. First, a standard dissolution test serves as a simple environment that simulates the gastric fluids and physiology. Thus, it is not able to measure the effects of whole swallowing process on bolus structure including oral, pharyngeal and oesophageal phases. Additionally, thickened liquids are non-Newtonian fluids which shows shear-thinning properties as the shear rate increases (Irgens, 2014). The shear rate during a standard dissolution test is usually lower than the shear rate of a bolus during swallowing due to tongue pressure or peristalsis of the muscles (Steele et al., 2015). As a result, viscosity and integrity of a thickened bolus during swallowing are not expected to remain constant or stable. Instead, the gel structure, which is thought to be responsible for delayed drug dissolution by simply trapping drug molecules, is likely to break and degrade, allowing facilitation of drug release when the bolus enters the stomach. In our study, oral, pharyngeal and oesophageal phases of swallowing were all by-passed since, thickened samples were administered directly into the stomach by intragastric gavage. Hence, the aforementioned effect of swallowing physiology on bolus degradation and drug release from thickened samples is unlikely. However, gastric peristalsis and mixing, rate of gastric emptying and intestinal transit time also play a significant role in bolus integrity and structure, and it is not possible to create a full identical in vitro environment to simulate all these physiological processes in a living organism (Alqahtani et al., 2013). Accordingly, the dissolution of levetiracetam was found to be decreased after mixing with thickened samples in our in vitro experiments, but we still did not observe any difference in total absorption of levetiracetam despite the use of intragastric administration method.

This study also aimed to investigate the effect of type of thickener on drug bioavailability. Although non-significant, C_{max} and AUC were both lower when crushed levetiracetam was delivered with water thickened with modified starch-based thickener compared to xanthan gum-based thickener in all viscosity levels. According to the data from in vitro research comparing starch and xanthan-gum based thickeners, the effect of thickener addition on drug dissolution was more pronounced for samples thickened with products that were primarily based on xanthan gum such that all thickening agents led to a significant delay in drug dissolution only in the greatest thickness level where xanthan gum-based thickeners were also found to retard dissolution at the intermediate thickness level (Manrique et al., 2014). However, it is not reasonable to make a comparison between these findings, as ingredients (e.g., additives, excipients, type and number of thickening agents included) and dissolving properties as well as the amount of thickener (i.e., w/v%) needed to achieve the same apparent viscosity may vary between different brands or manufacturers, and also between countries. The xanthan gum-based product that was used in this study (Resource Thicken Up Clear, Nestle) is a new generic, patented thickener manufactured by innovative technology enabling rapid thickening and stabilization, as well as easy and complete mixing without leaving any lumps. It ensures to reach the desired apparent viscosity when used in lower concentrations (e.g., w/v% needed for nectar, honey and pudding consistencies is 1.2%, 2.4% and 3.6% for Resource Thicken Up Clear versus 4%, 6% and 8% for Multithick, respectively). As previously mentioned, polymer concentration is one of the factors influencing the viscosity by forming a more complex network barrier as the amount of thickener increases in the dispersion (Saha and Bhattacharya, 2010). In this study, the thickener concentrations added into water to reach the same level of thickness level used in previous studies was lower for xanthan gum-based thickener, and higher for modified starch-based product which may explain the difference between the results. Furthermore, we observed that Resource Thicken Up Clear allowed better mixing with powdered drug, resulting in a clear solution as compared to samples thickened with Multithick which had lumps after addition and mixing with powdered tablets.

Our work had several limitations. First, thickened samples were delivered by intragastric gavage to animals. Thus, alterations in bolus viscosity, structure, and integrity due to shear rate or yield stress during swallowing were not taken into consideration. Secondly, compared to in vitro experiments, in vivo models have an advantage to mimic the complex interactions and dynamics of many factors affecting drug release, absorption and metabolism in the digestive tract. However, digestion and absorption physiology may differ between rodents and humans. According to the type of thickening agent, the extent of hydrolysis of gel structure (or fermentation by colonic bacteria as in the case of xanthan gum) and the release of water and drug molecules in rodent gastrointestinal tract can be different than in those in humans. Finally, levetiracetam was used as a model drug in this study due to several reasons mentioned in the methods, but levetiracetam has a wide therapeutic index. It is rapidly and almost completely absorbed after oral ingestion (Ulloa et al., 2009). This study provided evidence that administration of levetiracetam with thickeners at therapeutic levels to prevent aspiration in dysphagia patients do not have a significant impact on its pharmacokinetic efficacy. However, it should be noted that this may depend on the therapeutic index of drugs, and any alterations in pharmacokinetic parameters caused by delivering medications with thickened liquids can significantly affect clinical efficacy, particularly for drugs with a narrow therapeutic index.

5. Conclusions

Solid oral dosage forms are widely prescribed in adult and elderly populations, but swallowing whole tablets and capsules is challenging in patients with dysphagia who are at great risk of aspiration or choking. Mixing crushed tablets or powdered drugs with thickened liquids which are safe to swallow is a common method in practice to cope with this problem. In vitro studies suggested a significant impact of this method on dissolution rate of drugs, particularly when thickened samples were prepared with xanthan-gum based thickeners or at greatest thickness level, but evidence from a limited number of in vivo studies has revealed inconsistent results. This study investigated whether dissolution and bioavailability are affected when crushed tablets are taken with water thickened with two commercial thickening agents at therapeutic thickness levels used to eliminate aspiration in clinical practice. In vitro experiments supported previous data of which dissolution profile is altered after mixing crushed tablets with thickened water regardless of the type of thickener or viscosity level. However, total exposure of drug was not affected by delivering crushed tablets with thickened water even at the greatest therapeutic viscosity level. Although non-significant, the influence of a new generic xanthan-gum based product on pharmacokinetic efficacy was lower than of a traditional modified starch-based thickener. Since the impact on dissolution or bioavailability decreases with an increase in viscosity level, the thickness level recommended to a patient to establish swallowing safety should be considered before any attempts to use thickened liquids as a drug vehicle.

This study provided evidence effects of co-administration of a model drug with thickened liquids on pharmacokinetic parameters, however this interaction, hence the extent of its clinical effects may change according to the physiochemical properties and therapeutic index of the drug or to the type of thickener used. In addition, dose modifications such as crushing tablets or opening capsules may have other negative consequences. Clinicians, pharmacists, dietitians, and nurses should work together for optimal management of dysphagia patients. Further research is needed to maximize patient's safety by developing clinical practice guidelines particularly for health professionals who prescribe or administer drugs to dysphagia patients.

Declarations of interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2022.106197.

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