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The relative importance of internal and external physical resistances to mass transfer for caffeine release from apple pectin tablets

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ABSTRACT

The relative importance of the physical resistances to mass transfer have been explored by using halved 13 mm diameter apple-pectin tablets containing caffeine, in different external stirring environments within a beaker containing simulated gastric fluid. The effects of different external (outside of the tablets) mass-transfer resistances to the tablets created through two different stirrer types and stirrer speeds, and different internal (inside of the tablets) mass-transfer resistances created through different tablet concentrations and thicknesses, have been studied. These studies enable internal diffusion coefficients of caffeine through the apple pectin matrix to be estimated, as well as estimating the external mass-transfer coefficients from benzoic acid dissolution, which are in the range of 6.5×10^{-6} m/s – 2.4×10^{-5} m/s for the 0.6 mm thick tablets and 4.0×10^{-6} m/s – 1.6×10^{-5} m/s for the 7 mm thick tablets. The diffusion coefficients for different caffeine concentrations in the apple pectin half-tablets have also been calculated in this study. The diffusivity of caffeine in the 7 mm half-tablets with 1% caffeine through 99% pectin was around $(1.8 \pm 0.5) \times 10^{-10}$ m^2/s. This study points towards the development of multifilm mass-transfer theory for food digestion to create a more fundamentally based understanding of in-vitro digestion systems as an addition to the use of realistic in-vitro food digestion apparatus and give a better correlation between in-vitro and in-vivo digestion tests.

1. Introduction

Mass transfer plays an important role in human digestion, with Cussler (1997) suggesting that mass-transfer theory should be used more extensively in this context. When the overall mass-transfer coefficient (K_1) is based on phase 1 (for example, the food), there is a well-known equation (Cussler, 1997) for the overall mass-transfer rate (N_A) for solute A between the solid (food) and liquid (gastric solution):

$$N_A = K_1 A (C_1 - H C_2) \quad (1)$$

Where A is the interfacial area (between the two phases) for mass transfer, C_1 is the concentration of the solute in phase 1, H is the equilibrium or partition coefficient between the two phases at the interface, and C_2 is the concentration of the solute in the free stream (bulk) of phase 2. The mass-transfer rate is therefore split into three parts, (a) the mass-transfer coefficient, (b) the interfacial area between the phases, mainly a geometrical parameter, and (c) the concentration driving force, mainly a chemical parameter. Mass-transfer coefficients represent the physical resistance to mass transfer. In the digestion of food (a solid phase) into a solution (a liquid phase), there is a phase boundary at the surface of the food material (Fig. 1), as would be expected in two-film mass-transfer theory (Cussler, 1997). Inside the material, there is an internal boundary layer, where mass transfer of the solute occurs from the internal bulk of the food material to the surface of the food. Outside the food material, there is an external boundary layer, where mass transfer of the solute occurs from the surface of the food into the bulk of the solutions (the freestream) inside the gastrointestinal tract. The thickness of each boundary layer is related to the mass-transfer coefficient and to the resistance to mass transfer in each boundary layer; a high mass-transfer coefficient corresponds to a low mass-transfer resistance and to a thin boundary layer, and vice versa.

It is a common misconception that two-film mass transfer is only applicable to steady-state mass transfer. However, the only requirement for steady state in this theory (Cussler, 1997) is that the interface region should be thin, so the flux across it must achieve steady state quickly relative to the rates of change for the bulk concentrations. In two-film mass-transfer theory, Cussler (1997) has shown that the equation for the overall mass-transfer coefficient between the inside of the food (solid

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material) and the bulk of the solution (the free stream) is given by:

$$\frac{1}{K_1}=\frac{1}{k_1}+\frac{H}{k_2} \quad (2)$$

The mass transfer coefficient for the internal (phase 1) boundary layer is k_1, and k_2 is the mass transfer coefficient for the external (phase 2) boundary layer. Equation (2) shows that the overall resistance to mass transfer (left-hand side) is the sum of the internal resistance to mass transfer ($1/k_1$) and the external resistance (H/k_2).

Mass-transfer coefficients have been infrequently studied and reported in digestion studies, with the work of Tao et al. (1974) and Tharakan et al. (2010) being rare examples. However, in the closely related field of tablet dissolution in pharmacological studies, mass transfer has been more commonly mentioned (Cussler, 1997; Dannenfelser and Yalkowsky, 1996; Raslan and Maswadeh, 2006) although the measurement of quantitative mass-transfer coefficients has been very rare, for the active pharmaceutical ingredient (API), as the solute, into the dissolution medium, as the solvent. Nevertheless, studying mass transfer from tablets is still a subject of active study (D'Arcy et al., 2010, 2006, 2005).

Many in-vitro food digestion systems have been reviewed by Zhong and Langrish (2020) and Li et al. (2020). These systems range from simple beaker and stirrer systems (SHIME) (Molly et al., 1994) to. The beaker and stirrer systems introduced by Molly et al. (1994) are still used, in slightly modified ways, for recent studies (Dhital et al., 2016; Li et al., 2019), possibly because of their simplicity and affordability, despite the development of very sophisticated and realistic human models (Keppler et al., 2020). Studying the mass transfer processes involved in digestion using beaker and stirrer systems is therefore still relevant and significant.

In the literature, the solid matrices for dissolution studies have included potato (Abdel-Kader, 1992; Garrote et al., 1984; Garrote et al., 1988; Kozempel et al., 1982), peas (Abdel-Kader, 1991), carrots (Oliveira and Silva, 1992) and pickle (Pflug, 1967). For these studies, the solutes have included niacin (Kozempel et al., 1982), ascorbic acid (Abdel-Kader, 1991; Garrote et al., 1988), glucose (Abdel-Kader, 1992; Garrote et al., 1984), thiamine (Kozempel et al., 1982), sodium chloride (Kozempel et al., 1982), and reducing sugars (Oliveira and Silva, 1992). There is always a challenge in achieving a suitably low amount of biological variability in natural food materials to allow the process variability to be unambiguously assessed. In the sample preparation process, a fixed diameter cylinder template has been generally used (Oliveira and Silva, 1992) or the material has been cut into slices with a set thickness (Abdel-Kader, 1992). Previous workers have used leaching (Oliveira and Silva, 1992), blanching (Kozempel et al., 1982) or soaking-blanching (Garrote et al., 1984) methods to allow the solute to diffuse out of the food matrix into the solution. The diffusivity of different solutes under different temperature conditions has also been tested, and the range of diffusivities will be discussed in the context of the results from this work later in this paper.

In this work, we report on the use of caffeine, as a model solute, through a solid apple pectin matrix (a half-tablet, an internal environment), as a model food, into simulated gastric solution (an external environment) and estimate internal mass-transfer resistances and diffusion coefficients, comparing the internal and external mass-transfer resistances. The application of this theory to estimate the balance between internal and external mass-transfer resistances does not appear to have been carried out in the literature before, and this work addresses this gap.

2. Materials and methods

2.1. Materials

In this study, the following items of equipment have been used. A Buchi-B290 Mini Spray Dryer (Flavil, Switzerland) was used to make the powders, with the rationale being to create powders with specific ratios of caffeine to pectin. A 15T Hydraulic Press Machine for Powder Pellet Pressing (Tmax, Fujian, China) has been used to make the tablets.

For the dissolution experiments, a hot plate stirrer HSD 330 (İzmir, Turkey), a 150 ml beaker (internal diameter is 49.65 mm, height is 69.62 mm), a large round stirrer (diameter is 34.82 mm, thickness is 11.22 mm), and a small bar stirrer (length is 20.56 mm, thickness is 5.61 mm) have also been used in the dissolution experiments. A 3D-printed tablet holder (Jaycar Electronics, Sydney, Australia) has been used, as described by Langrish et al. (2021) and shown in Fig. 2, to ensure that the shear stresses and shear strain rates are the same for all the tablets. The rationale for the dissolution arrangement has been to create an external dissolution environment that is similar to those reported and used in Dhital et al. (2016) and Li et al. (2019). The benefit of the platform is to ensure that the shear stresses around the tablets are reproducible from tablet to tablet and from experiment to experiment. A locally manufactured temperature-controlled box has been used to maintain the temperatures of the equipment at 37°C using light bulbs and an on-off temperature controller. A Cary 60 UV–Vis Spectrophotometer (Santa Clara, California) has been used to measure the absorbances of solutions and their concentrations.

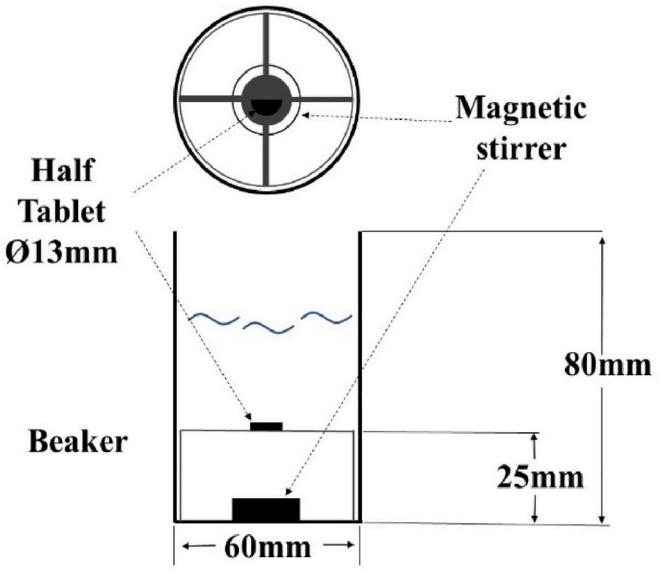

Fig. 2. 3D printed bracket for caffeine release from apple pectin half-tablets into SGF. solutions.

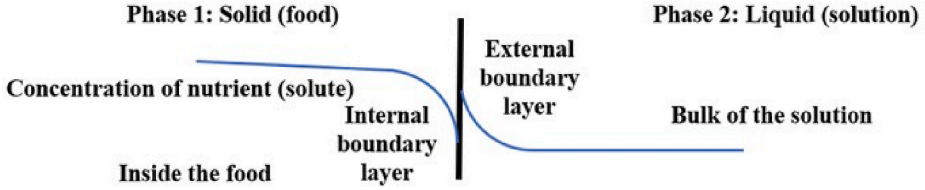

Fig. 1. Two-film mass transfer theory applied to food digestion.

Other items have included, 10 ml and 1 ml pipettes, a test tube (15 mL), and an electronic balance (±0.01g) (Mettler P2000, Küsnacht, Switzerland), analytical balances (±0.0001g) (Mettler A240, Küsnacht, Switzerland), and a laboratory drying oven (LabTec, Melbourne, Australia).

Concentrated hydrochloric acid (32%) (HCl) and caffeine powder (1,3,7- Trimethylxanthine) (Laboratory grade) were purchased from Sigma-Aldrich, Australia. Pectin (apple) powder was purchased from Morlife Pty Ltd. Pepsin (1:2500), D-glucose anhydrous and sodium chloride (NaCl) (Laboratory grade) were purchased from Chem-Supply Australia. Benzoic acid ($C_7H_6O_2$) (Laboratory grade) was purchased from Fluka. The rationale for the use of caffeine/pectin tablets has been explained at the end of the introduction.

2.2. Methods

2.2.1. Spray drying technique

Spray drying has been used to make an effective blend of caffeine and apple pectin. Specific amounts of caffeine and apple pectin have been weighed out in the required ratio. These materials have been dissolved in water and have been stirred well. A Buchi-B290 Mini Spray Dryer has been used to spray dry the solution, with the following operating conditions. The liquid flow rate was 7.5 ml/min, and the main air flow rate was 35 m^3/h. The inlet air temperature has been 190°C. These spray-dried powders have then been used to make caffeine/pectin tablets.

2.2.2. Tableting

For caffeine/pectin tablets, the thickness of the fast-release tablets has been about 0.6 mm. About 0.1 g of the dried powder from spray drying has been weighed and has been placed into the tablet-making mold, which has been put into the tablet-making machine. A force of 0.5 tonnes has been used for tablet making, and this force has been applied for 30s. Then this 0.6 mm tablet has been cut in half with a tablet cutter, giving two equal half disks, as with the majority of normal tablet cutters.

For the slow-release tablets, the thickness of the slow-release tablets has been about 7 mm. About 1.2 g of the dried powder from spray drying has been weighed and placed into the tablet-making mold, which has been put into the tablet-making machine. A force of 8 tonnes has been used for tablet making and applied for 30 s. Then this 7 mm tablet has been cut in half with the same tablet cutter. After making and cutting the tablets, this project has used half-tablets to do the dissolution tests in these controlled-release experiments in SGF. Half-tablets have been used to reduce any variations in the internal composition of the two half-tablets in each experimental pair, where the experimental pair consisted of a fast release (low internal resistance to mass transfer relative to external mass-transfer resistance) and slow release (high internal resistance) half-tablet. Pure caffeine tablets were not used because they broke up too rapidly.

The benzoic acid tablets were much simpler than the caffeine/pectin tablets, because they are made from pure benzoic acid powder. The method for producing benzoic acid tablets is very commonly described in the literature, with examples being Bai and Armenante (2009) and Bai et al. (2007).

2.2.3. Design of the beaker experimental setup

A beaker system model has been used in these experiments as the simulated gastric environment, with the controlled-release matrix represented by tablets that have been made from spray-dried powders. A 3D-printed tablet holder (Fig. 2) has been used to separate the tablet and the stirrer, in order to avoid direct contact between the stirrer and the tablet, which might break the tablet, changing the length scales for both internal and external mass transfer during the experiment. Avoiding this breakage has then improved the repeatability of the entire system. The 3D bracket has also ensured that the flow field and the environment of the fluid shear stresses have been reproducible from experiment to experiment. A 150 ml glass beaker has been used for the experiments.

In order to simulate the human environment, simulated gastric fluid (SGF) has been prepared and used in the dissolution process. SGF consists of 2 g NaCl per liter of water and 3.2 g pepsin (Hibbins et al., 2017). Finally, 7 ml HCl has been added to adjust the pH to the typical pH in the stomach of around 1.7 (Wickham et al., 2012). To prevent the SGF solution from overflowing in the beaker while using the maximum amount of solution to minimize the effect of sampling on the concentrations, 130 ml of SGF solution has been used in these experiments. The rotation of the stirrer has been used to simulate the peristalsis of the gastric system. In order to ensure similarity with body temperatures, the whole process has been carried out in a 37°C temperature-controlled box.

2.2.4. Design of the operating conditions for the SGF study

In order to study the relative importance of internal and external mass-transfer resistances quantitatively, the controlled release experiment has been divided into four parts, as shown in Table 1.

For the inside of the materials, the low concentration of caffeine has been intended to give a low diffusion coefficient for caffeine through the apple pectin tablet, and conversely the high concentration one has been intended to give a high diffusion coefficient. The thin tablet has been intended to give a low internal mass-transfer resistance by giving a short length scale (L_e) for the diffusion process, while the thick tablet has been intended to give a high internal mass-transfer resistance for the converse reason. For the outside of the materials, the small stirrer and low stirrer speed have been intended to give a low external mass-transfer coefficient, which corresponds to a high external mass-transfer resistance, and vice versa.

To study the external mass-transfer resistance independently, benzoic acid tablets have been used to compare the external mass-transfer coefficients for benzoic acid and caffeine. Benzoic acid has been recommended for external mass-transfer studies by Cussler (1997), because of its simplicity and due to its uncomplicated dissolution process compared with many other solutes. The benzoic acid powder has been pressed into 0.6 mm, and 7 mm thick tablets through the same procedure as the caffeine-pectin mixture. The tablets have been cut in half, and each half-tablet has been placed into the same in-vitro beaker system. Samples have been taken at 2 min, 4 min, 6 min, 8 min, 10 min, and 15 min from the start of the experiment.

Basic mass-transfer theory can be used to estimate the mass-transfer coefficient (K) from the slope of the solute concentration-time curve (dC/dt), the saturation concentration of the solute in the solution, the volume of the solution (V) and the interfacial area for the solute and the solvent (A), as follows:

$$K = \frac{V}{A}\frac{dC}{dt}\frac{1}{C_{sat}} \tag{3}$$

The solubility of caffeine in water is 21.6 g/l at room temperature (Dannenfelser and Yalkowsky, 1996), and this value has been checked for SGF. The tablet has been put into the beaker system and kept at 37°C. Then the filtered solution has been placed in a temperature-controlled box.

Table 1
Experimental design for controlled release experiments.

	Stirrer	Concentration of Caffeine	Thickness	Stirrer speed
Fast release	Small (12 mm)	High (90 wt%)	Thin (0.6 mm)	100 rpm
	Large (35 mm)	High (90 wt%)	Thin (0.6 mm)	200 rpm
Slow release	Small	Low (1 wt%)	Thick (7 mm)	100 rpm
	Large	Low (1 wt%)	Thick (7 mm)	200 rpm

2.2.5. UV analysis method

The UV spectrum test of the obtained filtrate has been used to calculate the concentration of the caffeine and benzoic acid in the solution. The calibration curve of benzoic acid and caffeine has been measured using UV visible spectrophotometry (at 225 nm for benzoic acid, and at 274 nm for caffeine) and used to assess the benzoic acid and caffeine concentrations after simulated digestion as a function of time.

3. Results and discussion

3.1. The release curves for the apple-pectin tablets

For the apple-pectin tablets, the raw data for the concentrations as functions of time are shown in Figs. 3 and 4. In Figs. 3 and 4, (b) includes repeated experiments at the same conditions as (a). Reviewing Figs. 3 and 4, Fig. 3 shows the raw data for the fast release experiments, and Fig. 4 shows the raw data for the slow-release experiments. For Fig. 3, the initial slopes of the concentration-time data have been used to estimate the external mass-transfer coefficients, because the caffeine is lost from the outside of the tablets in the initial stages of digestion, and the initial internal resistance to mass transfer is negligible in this period. The lack of quantitative similarity between the different conditions suggests the significance of the impact of the external mass-transfer coefficients on the entire caffeine-release process. The external mass-transfer resistance is very significant, not negligible, for the entire caffeine release process for these half-tablets, even when the external conditions favor high external mass-transfer coefficients and correspondingly low external mass-transfer resistances, so it is very difficult to eliminate the effects of external conditions for these half-tablets.

In Fig. 3, there is a small induction time in the development of the fluid flow pattern after inserting the half-tablet and the tablet holder in the solution. This induction time is greater with the smaller stirrer and results in a poorer fit at small times. In Figs. 3 and 4, the actual concentrations were obtained from the release experiments, while the fitting concentrations were achieved from the calculation by using Eq. (4) (Langrish et al., 2021). C_{max} (the saturation concentration of the solute) and τ (a time constant for mass transfer) were calculated via excel solver by minimizing the squared difference between actual and fitting concentrations, and then the fitting points were linked to obtaining the fitting lines.

$$\boldsymbol{C} = \boldsymbol{C}_{max}\left[1 - \boldsymbol{e}^{\left(\frac{-t}{\tau}\right)}\right] \tag{4}$$

For Fig. 4 (high internal mass-transfer resistance), a clear feature of all the curves is the presence of an almost linear, quasi steady-state, relationship between the concentration and the time for all the curves. Furthermore, all the curves are almost identical, despite the differences in external digestion conditions (different stirrers and rotational speeds). The almost linear, quasi steady-state, relationship, and the similarity of all the concentration-time curves, justifies the use of an overall mass-transfer coefficient, which can be separated (through the use of an overall mass-transfer resistance) into internal and external resistances. The internal resistances then enable the diffusivities to be estimated. The quasi steady-state rate of mass transfer partially justifies the assumptions in two-film mass-transfer theory.

3.2. Caffeine-pectin tablets with low internal mass-transfer resistance (90 wt% caffeine, thin tablet)

Here, high caffeine concentrations and low thickness (0.6 mm) tablets were selected to ensure that the internal resistance to mass transfer of caffeine through pectin was low. The initial dissolution rate was expected to be closely related to the external mass-transfer coefficients obtained from the benzoic acid tablets, because of the low internal mass-transfer resistances in both tablets (90% caffeine, pure benzoic acid). The concentrations have been measured as functions of time, and typical results are shown in Fig. 3.

For these fast-release experiments, the initial values ($t = 0$) of the overall mass-transfer coefficients (K_1) have been $(2.92 \pm 0.08) \times 10^{-6}$ m/s for the small stirrer at 100 rpm and $(8.5 \pm 0.1) \times 10^{-6}$ m/s for the large stirrer at 200 rpm (experiments in triplicate). These initial overall mass-transfer coefficients (at $t = 0$ s) may be compared with the benzoic acid measurements for the same size of half-tablets, $(6.5 \pm 1.1) \times 10^{-6}$ m/s for the small stirrer at 100 rpm and $(2.4 \pm 0.1) \times 10^{-5}$ m/s for the large stirrer at 200 rpm, as shown in Table 2. The results in Table 2 are physically reasonable, because if the Sherwood numbers are similar for the small and large tablets with a given stirrer and rotational speed, then the larger the tablet, the smaller is the external mass-transfer coefficient (see Table 3).

At first sight, it may appear that the benzoic acid coefficients are different from those for the caffeine-pectin system, but the difference is systematic (a factor of approximately 2.5) and may be explained. The formula for the Sherwood number is $Sh = k\,L/D$, where k is the external mass-transfer coefficient, L is the length scale and D is the (liquid-phase) diffusivity, and the Sherwood number is probably similar for the caffeine and benzoic acid tablets. The diffusion coefficient (diffusivity) of caffeine through the water at 25°C is 6.8×10^{-10} m^2/s (Spiro and Selwood, 1984), and that for benzoic acid through the water at the same conditions is 10×10^{-10} m^2/s (Cussler, 1997). With the viscosity of SGF being greater than that for water, the diffusivity of caffeine through SGF is less than that for caffeine through the water. These considerations mean that the liquid-phase diffusivity for caffeine (in the SGF solution at 37°C) is less than that for benzoic acid (in DI water at 25°C). The length scale may be larger for the caffeine tablet due to swelling than for the benzoic acid tablet. These differences in length scales and diffusivities mean that the external mass-transfer coefficients for caffeine should be lower than those for benzoic acid, as is observed here. We, therefore, suggest that the external mass-transfer coefficients for caffeine into SGF

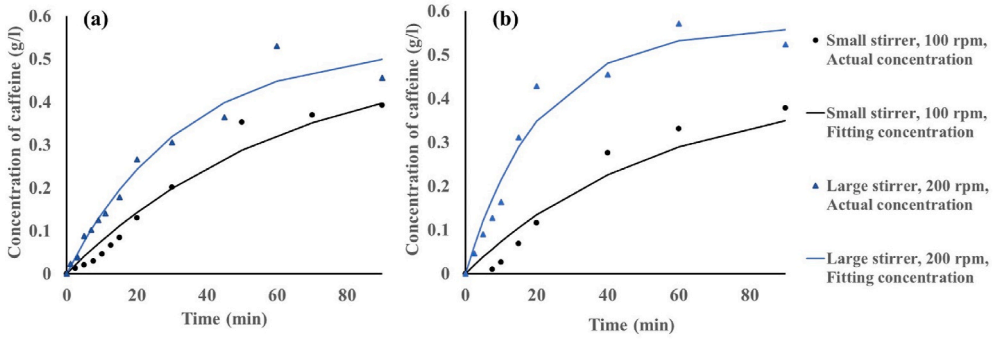

Fig. 3. Concentration-time curves for caffeine from apple pectin half-tablets ((a) and (b), repeat experiments) for different fast-release experiments. Solid phase: apple-pectin tablet (0.6 mm) with 90 wt% caffeine; Liquid phase: SGF.

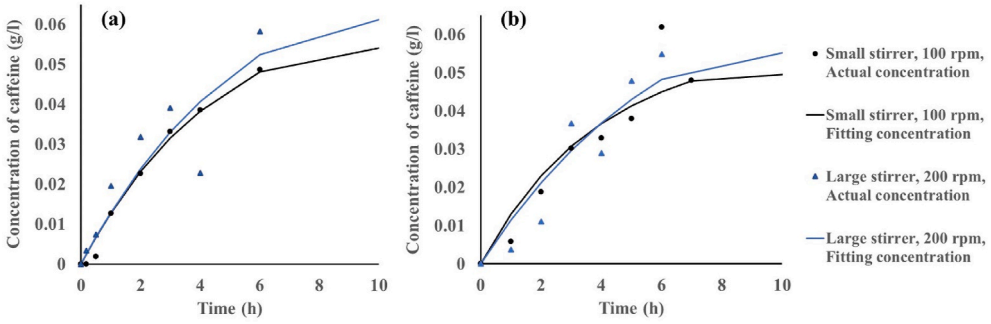

Fig. 4. Concentration-time curves for caffeine from apple pectin half-tablets ((a) and (b), repeat experiments) for different slow-release experiments. Solid phase: apple-pectin tablet (7 mm) with 1 wt% caffeine; Liquid phase: SGF.

Table 2
Summary of external mass-transfer coefficients (m/s) from benzoic acid tablets and apple pectin caffeine tablets experiments (numbers of replicates in brackets).

Materials	Thickness	Small stirrer (100 rpm)	Large stirrer (200 rpm)
Benzoic acid	Thin tablets (0.6 mm thick)	$(6.5 \pm 1.1) \times 10^{-6}$ (6)	$(2.4 \pm 0.4) \times 10^{-5}$ (6)
	Thick tablets (7 mm thick)	$(4.0 \pm 0.2) \times 10^{-6}$ (4)	$(1.6 \pm 0.2) \times 10^{-5}$ (4)
Apple pectin and caffeine	Thin tablets (0.6 mm thick)	$(2.9 \pm 0.1) \times 10^{-6}$ (3)	$(8.5 \pm 0.1) \times 10^{-6}$ (3)
	Thick tablets (7 mm thick)	$(1.8 \pm 0.1) \times 10^{-8}$ (3)	$(1.9 \pm 0.03) \times 10^{-8}$ (3)

Table 3
The particle size of the spray-dried pectin and caffeine powders (in units of μm).

	D_v (50)
Pure pectin	8.0 ± 0.4
1% caffeine	7.4 ± 0.4
10% caffeine	10.4 ± 0.2
90% caffeine	5.3 ± 0.04
Pure caffeine	4.3 ± 0.02

were close to the overall mass-transfer coefficients. These external coefficients were the same as the initial mass-transfer coefficients measured here, $(2.92 \pm 0.08) \times 10^{-6}$ m/s for the small stirrer at 100 rpm and $(8.5 \pm 0.1) \times 10^{-6}$ m/s for the large stirrer at 200 rpm.

3.3. Caffeine-pectin tablets with high internal mass-transfer resistance (1 wt% caffeine, thick tablet)

These tablets are expected to have much higher internal mass-transfer resistances due to the lower caffeine concentrations and the greater tablet thicknesses. These higher internal resistances mean that the overall release rates show a significant period of quasi steady state release where the release rates are almost linear and are independent of the external mass-transfer resistances. This expectation is met with the experimental results, as shown in Fig. 4 for the first 4 h, with divergence after this time due to the differing break-up behavior of the tablets.

Furthermore, since the overall release rate under quasi steady-state conditions is independent of the external conditions, the overall mass-transfer resistance is almost the same as the internal mass-transfer resistance, which is much greater than the external mass-transfer resistance, as demonstrated by the independence of the overall release rate and the external conditions. This consideration means that the internal solid-phase diffusion coefficient of 1 wt% caffeine through apple pectin can be obtained from the overall release rate, as discussed in the following section, given the absence of external mass-transfer resistance.

3.4. Analysis of diffusion coefficients for caffeine in apple pectin matrix, comparison with the literature for solute diffusion in foods

Foods, as biological materials, are very variable in their properties, including the diffusion coefficients. , creating A model system, as used here (apple pectin matrix with caffeine as a solute), moderates the biological variability, and we can assess the variability by reviewing Fig. 4 Most of the papers on assessing diffusion coefficients in the literature do not consider the effects of the external mass-transfer resistances or coefficients (Abdel-Kader, 1992; Garrote et al., 1984; Garrote et al., 1988; Kozempel et al., 1982; Oliveira and Silva, 1992; Pflug, 1967; Selman et al., 1983). The work of Kozempel et al. (1982) is an example of a paper where the researchers have implicitly assumed that the external mass-transfer resistance is negligible, because they do not include an analysis of the mass-transfer coefficients or resistances in their work, in the way that we have done in this paper. Another work of Abdel-Kader (1992) used an agitated water bath to reduce the external mass-transfer resistance in the blanching treatment of potato slabs to measure glucose losses. However, the external mass-transfer resistance was ignored in the calculation of the diffusion coefficients. Our work here has considered these coefficients and resistances, which are very important for the different operating conditions shown in Fig. 3.

Likewise, previous analyses of diffusion coefficients from experimental data using mathematical modelling, as summarized by Varzakas et al. (2005) in their Table 2, have all used solutions to Fick's second law of diffusion (similar to those originally developed by Crank (1975)), ignoring the external mass-transfer resistance (Binkley and Wiley, 1981; Bressan et al., 1981; Kincal and Kaymak, 1987; Leach et al., 1994; Rodger et al., 1984; Tomasula and Kozempel, 1989). In this work, we have carefully considered the possibility of external mass-transfer resistance by comparing the release profiles under different external conditions. The situation in Fig. 4, for the fast-release half-tablets, shows the effects of external conditions and external mass-transfer coefficients and resistances cannot be automatically neglected. Fig. 5 shows that it is necessary to review the results of several experiments to assess whether external mass-transfer resistances are negligible or not. Our work identifies the need to inspect several release curves (or do some other analysis) to assess the importance of external mass-transfer resistances in calculating internal diffusion coefficients. This consideration means that works that automatically ignore the external mass-transfer resistances may give diffusion coefficients that are unclear and uncertain.

In the situation shown in Fig. 4, with negligible external mass-transfer resistance, conventional diffusion theory (ignoring external mass transfer effects) may be used to assess the internal diffusion coefficients. A typical solution to Fick's second law of diffusion for an infinite slab is given by the following equation (Rodger et al., 1984):

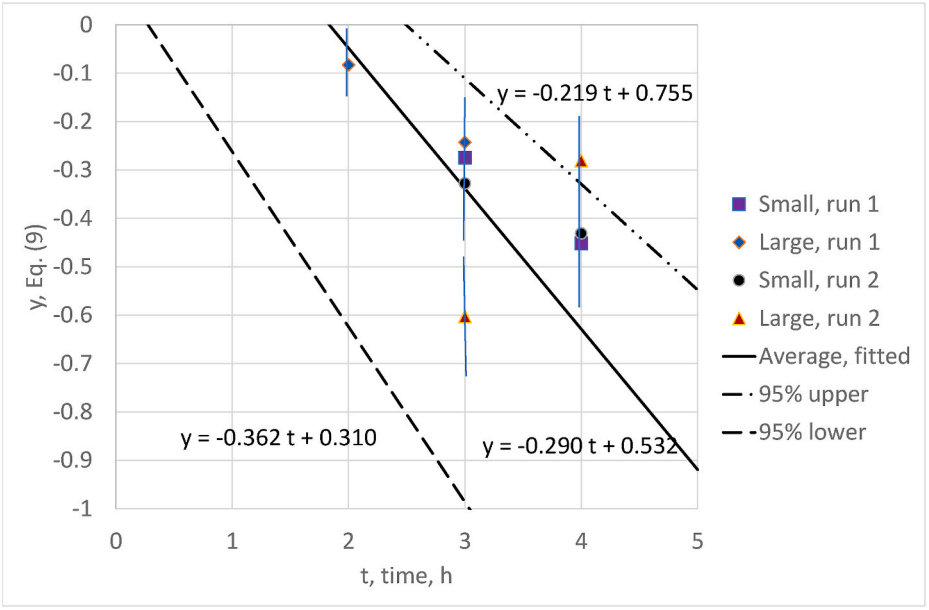

Fig. 5. Fitted diffusion curves for caffeine from apple pectin half-tablets, all slow-release experiments, including upper and lower 95% confidence limits. The error bars are shown *for the y values*; those for the times are negligible.

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp\left[\frac{-D\,(2n+1)^2 \pi^2\, t}{l_1^2}\right] \tag{5}$$

Here M_t is the mass of solute released or absorbed after time t, and M_∞ is the maximum, long term mass. After a relatively short time after the beginning of the diffusion, only the first term in Eq. (5) become significant, and Eq. (5) reduces to the equation:

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2} \exp\left[\frac{-D\,\pi^2\, t}{l_1^2}\right] \tag{6}$$

Eq. (6) suggests that a plot of

$$y = \ln\left[\frac{\pi^2}{8}\left(1 - \frac{M_t}{M_\infty}\right)\right] = \ln\left[\frac{\pi^2}{8}\left(\frac{C_{max} - C}{C_{max}}\right)\right] \tag{7}$$

as a function of time should give a slope of $-D\,\pi^2/{l_1}^2$.

If the half-tablet (7 mm thick (l_1), 6.5 mm wide at the maximum width, l_2) is regarded as a two-dimensional slab, equations (6) and (7) are replaced with the equations (Kaymak-Ertekin, 2002):

$$\frac{M_t}{M_\infty} = 1 - \frac{64}{\pi^4} \exp\left[-\left(\frac{\pi^2}{l_1^2} + \frac{\pi^2}{l_2^2}\right) D\, t\right] \tag{8}$$

Eq. (8) suggests that a plot of

$$y = \ln\left[\frac{\pi^4}{64}\left(1 - \frac{M_t}{M_\infty}\right)\right] = \ln\left[\frac{\pi^4}{64}\left(\frac{C_{max} - C}{C_{max}}\right)\right] \tag{9}$$

as a function of time should give a slope of $-D\,(\pi^2/(4\,{l_1}^2) + \pi^2/(4\,{l_2}^2))$, with $l_1 = 7$ mm and $l_2 = 6.5$ mm. Then, the diffusion coefficient for 1% caffeine through apple pectin may be estimated from the slopes in Fig. 5 ($(-0.29 \pm 0.07)\ h^{-1} = (-8 \pm 2) \times 10^{-5}\ s^{-1}$) as being $(1.8 \pm 0.5) \times 10^{-10}\ m^2 s^{-1}$ at 37°C.

This value may be compared with the liquid-phase diffusion coefficient (D) of caffeine through water of $6.8 \times 10^{-10}\ m^2 s^{-1}$ at 25°C (Spiro and Selwood, 1984). On one hand, it would be expected that the diffusion coefficient should be lower for caffeine diffusion through a solid (here, apple pectin). On the other hand, the temperature in our experiment (37°C) was intended to resemble that in the human body, and being greater than 25°C, the diffusion coefficient would be expected to increase as well. Hence the similarity in diffusion coefficients ($1.8 \pm 0.5 \times 10^{-10}\ m^2 s^{-1}$ at 37°C here, compared with $6.8 \times 10^{-10}\ m^2 s^{-1}$ at 25°C in Spiro and Selwood (1984), seems reasonable. Reviewing the diffusion coefficients from the wider literature, the range in the review of Varzakas et al. (2005) is from $3.07 \times 10^{-10}\ m^2 s^{-1}$ for soluble solids through carrots at 60°C (Selman et al., 1983) to $793 \times 10^{-10}\ m^2 s^{-1}$ for niacin through potato at 77°C (Kozempel et al., 1982). Again, in the literature, previous workers have often used blanching methods to estimate the diffusion coefficient of the diffusing substance (solute), and the temperature is generally above 60°C.

3.5. The importance of two-film mass-transfer theory for the analysis of solute diffusion in foods

Returning to the concepts behind two-film mass-transfer theory as expressed in Eq. (2), the first term in Eq. (2) refers to the external mass-transfer resistance ($1/k_1$), while the second refers to the internal mass-transfer resistance (H/k_2). The ratio of these resistances (internal to external) is the mass-transfer Biot number, discussed in Pordage and Langrish (1999):

$$Bi_m = \frac{H/k_2}{1/k_1} = \frac{H\,k_1}{k_2} \tag{10}$$

If the Biot number is low (less than 0.05), the concentration is effectively constant throughout the material, and external mass-transfer resistance is dominant, and vice-versa.

In order to assess the approximate value of the partition or equilibrium constant (H), specifically if the swollen pectin tablets adsorb caffeine significantly, the following experiment was designed. The pectin powders (1.2 g) without any caffeine were pressed into 7 mm tablets with a force of 8 tons. The tablet was placed into the same beaker system. The SGF solution was adjusted to contain a concentration of 1% caffeine concentration. Aliquots (1 mL) of the solution were sampled at different time intervals and tested for their caffeine concentrations by UV–visible spectroscopy. It has been found that the concentration of caffeine in the SGF solution remained constant at around 0.95 g/L after 24 h. There was no significant change in the concentration of caffeine. Therefore, it appears that there is little adsorption of caffeine on pectin and that the partition coefficient for caffeine between solid phase (apple pectin) and liquid phase (SGF with 1% caffeine) is close to unity ($H = 1$).

For the 7 mm thick tablets (1% caffeine) with an equivalent length

scale of 4.65 mm, the external mass-transfer coefficients were 4.0×10^{-6} m s^{-1} (small stirrer) and 1.6×10^{-5} m s^{-1} (large stirrer) (Table 2). An estimate of the internal mass-transfer resistance is the length scale (4.65×10^{-3} m) divided by the diffusion coefficient (1.8×10^{-10} m^2 s^{-1}, from section 3.4), giving an estimate of the internal mass-transfer coefficient of 3.9×10^{-8} m s^{-1}. All these values give mass-transfer Biot numbers from 50 to 413, confirming the dominance of internal mass-transfer resistance in Fig. 4.

The situation for the 0.6 mm thick tablets (90% caffeine) is that the external mass-transfer coefficients were 6.5×10^{-6} m s^{-1} (small stirrer) and 2.4×10^{-5} m s^{-1} (large stirrer) (Table 2). With 90% caffeine, the internal mass-transfer resistance to caffeine movement is likely to be very small, making the internal mass-transfer coefficient very large and leading to low mass-transfer Biot numbers (likely to be less than 0.1), consistent with the strong effect of the external dissolution conditions shown in Fig. 3.

These measurements and calculations demonstrate the ability of the two-film mass-transfer theory to extract useful information about the effective internal solid-phase diffusion coefficient of food solutes through food solids in simulated in-vitro digestion systems. These assessments also point towards the development of multifilm mass-transfer theory for food digestion to create a more fundamentally based understanding of in-vitro digestion systems as an addition to the use of realistic in-vitro food digestion apparatus and give a better correlation between in-vitro and in-vivo digestion tests.

4. Conclusions

By using beaker and stirrer systems, the halved 13 mm diameter tablets with benzoic acid or caffeine/apple pectin have been used to study the internal and external mass transfer coefficients. The different stirrer types and stirrer speeds as well as different concentrations and thicknesses of the tablets have been varied to change the external environment. The external mass-transfer coefficients from the benzoic acid measurements for the 0.6 mm thick half-tablets were $(6.5 \pm 1.1) \times 10^{-6}$ m/s for the small stirrer with the experiments at 100 rpm and $(2.4 \pm 0.1) \times 10^{-5}$ m/s for the large stirrer at 200 rpm. For 90% caffeine in apple pectin, the initial values of the overall mass-transfer coefficients (K_1) have been $(2.92 \pm 0.08) \times 10^{-6}$ m/s for the small stirrer at 100 rpm and $(8.5 \pm 0.1) \times 10^{-6}$ m/s for the large stirrer at 200 rpm. These two sets of measurements are consistent when the differences in length scales (due to pectin tablet swelling) and diffusivities of benzoic acid and caffeine are considered. The effective internal solid-phase diffusion coefficient (D) of 1% caffeine through apple pectin has been estimated to be $(1.8 \pm 0.5) \times 10^{-10}$ m^2/s, demonstrating the ability of these measurements, interpreted using two-film mass-transfer theory, to extract useful information about the effective internal solid-phase diffusion coefficient of food solutes through food solids in simulated *in-vitro* digestion systems.

CRediT authorship contribution statement

Shu Cheng: Formal analysis, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Chao Zhong:** Formal analysis, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Timothy A.G. Langrish:** Conceptualization, Methodology, Writing – original draft, Supervision, Writing – review & editing. **Yongmei Sun:** Formal analysis, Methodology. **Zelin Zhou:** Formal analysis, Methodology. **Zexin Lei:** Formal analysis, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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