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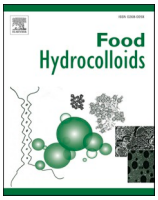

Glass transition effects on the molecular transport of caffeine from condensed k-carrageenan/polydextrose systems

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ABSTRACT

We investigate the effect of added KCl on the glass transition of potassium-κ-carrageenan/polydextrose and molecular transport of caffeine. Samples were prepared with 2% (w/w) κ-carrageenan, 82% (w/w) polydextrose and 1% (w/w) caffeine to a total solids level of 85% (w/w). KCl was added at 0, 50, 100 and 200 mM to induce a dependence of structural properties on the potassium ion concentration. High-resolution spectral data over a wide spectral range for the tertiary system were collected using Fourier transform infrared spectroscopy (FTIR), which were complemented by tangible evidence of its morphology with scanning electron microscopy (SEM). Work then focused on the estimation of the mechanical (T_{gm}) and calorimetric (T_{gc}) glass transition temperature using in-shear dynamic oscillation and modulated differential scanning calorimetry (MDSC). Molecular transport of caffeine in the condensed polysaccharide/co-solute system was followed with UV–*vis* spectroscopy over a wide temperature range (−20 to 30 °C) and modelled with extended diffusion theory. Time-dependent mass transport of the diffusant was correlated to the structural relaxation of the polymeric matrix seen in increasing values of the mechanical glass transition temperature with higher additions of potassium counterions to κ-carrageenan. It was concluded that the mechanical glass transition temperature has a prominent effect on the release kinetics of caffeine in these materials, as compared to the calorimetric glass transition temperature.

Authorship contribution statement

Diah Ikasari: Methodology, Data modeling, Writing - original draft. **Vilia Darma Paramita:** Supervision, Data modeling, Writing - review & editing. **Stefan Kasapis:** Funding acquisition, Conceptualization, Supervision, Writing - review & editing.

1. Introduction

Caffeine is a popular bioactive compound naturally found in many plant crops, including coffee, tea and chocolate. It is known to have advantages as a pain reliever and psychotherapeutic by producing vasoconstricting, anti-inflammatory and stimulating effects (Temple et al., 2017). As a hydrophilic bioactive compound, it has been investigated in drug delivery systems in several forms, including tablet/powders, chewing gum, topical gel, solid lipid nanoparticles, nano-emulsion and hydrogel beads (Shakeel, 2017). The use of excipients to entrap/encapsulate caffeine is essential to control its release and preserve its bioavailability in the human GI tract. Hydrocolloids have been proposed as good carriers (e.g. tablets of spray-dried casein powder) for the bioactive compound especially *via* chemical or physical crosslinking that can slow down its release in the surrounding media over several hours/days according to the requirements of the therapeutic dose (Tan, Ebrahimi, & Langrish, 2019).

κ-Carrageenan is a sulphated linear polysaccharide made from D-galactose as well as 3,6-anhydro D-galactose units (Evageliou, Ryan, & Morris, 2019). As an ionic polysaccharide is highly affected by the presence of cations in solution that can induce a disorder-to-order transition. It is sensitive, in particular, to potassium ions that form bridges with the D-galactose sulfate group supporting the formation of double helices upon cooling, which at high enough concentrations of the polysaccharide create aggregated gels with extensive thermal hysteresis (Viebke, Piculell, & Nilson, 1994; Stenner, Matubayasi, & Shimizu, 2016). The effect of potassium and other cations (sodium and calcium) on the thermal stability and aggregation of κ-carrageenan has been studied by differential scanning calorimetry (Evageliou et al., 2019) and compressive elastic modulus analysis (Wang, Yuan, Cui, & Liu, 2018).

It has further been shown that the degree of aggregation is also

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determined by the concentration of the prevalent cations (potassium, sodium and calcium) found in most preparations of the polysaccharide with industrial interest (Morris, Rees, & Robinson, 1980; Nickerson, Paulson, & Hallet, 2004). The effect of temperature is to partially disturb the fine network structure leading to the formation of ordered super-strands that align in parallel or compactly pack together upon cooling (Núñez-Santiago, Tecante, Garnier, & Doublier, 2012; Rochas & Rinaudo, 1984). Such reorientations in the ordered conformation control the mechanism of bioactive compound release in advanced delivery vehicles. In this respect, the rubber-to-glass transformation of condensed materials becomes of importance in the optimisation of drug release (Jiang & Kasapis, 2011; Slade & Franks, 2002).

Polydextrose is a massively branched low-molecular weight polymer of glucose comprising random glycosidic bonds, which are α and β (1–2), (1–3), (1–4) and (1–6) arrangements (Stowell, 2009). The polymer has an average degree of polymerisation (DP) of 10 with the molecular weight ranging from 162 to 20,000 Da (Ribeiro, Zimeri, Yildiz, & Kokini, 2003). Polydextrose is available in the form of a viscous solution or amorphous powder due to the high degree of polydispersity, and it is relatively stable in acidic conditions and high temperature. Its glass transition temperature is mainly influenced by the increase in moisture content of the material, which reflects the plasticizing effect of water molecules. Polydextrose is highly soluble in water, but insoluble in glycerol, propylene glycol, and ethanol which was confirmed experimentally in this work (Craig, Anderson, Holden, & Murray, 2008).

Vitrification of the amorphous component of high solid biomaterials brings into play the concept of glass transition temperature (T_g), which is considered as an index of convenience in the control of the rate of physicochemical, enzymatic and biological processes (Roudaut, Simatos, Champion, Contreras-Lopez, & Le Meste, 2004; Gray, Bowen, Farhat, & Hill, 2008; Chaudhary, Panyoyai, Small, Shanks, & Kasapis, 2017). Within the glassy state, i.e. at temperatures below T_g, molecular motion is drastically restricted due to diminishing local hole free volume in the polymeric matrix (Hoare & Kohane, 2008; Panyoyai, Bannikova, Small, & Kasapis, 2015). Formulation of the framework of free volume in the theory of diffusion for concentrated polymer/solvent and polymer/plasticizer systems allows quantification of the molecular transport of the bioactive compound in targeted delivery systems *via* the estimation of the apparent diffusion coefficient (Jadhav, Gaikwad, Nair, & Kadam, 2009; Paramita, Bannikova, & Kasapis, 2015).

A recent investigation on the molecular transport of nicotinic acid from bovine and fish gelatin networks, demonstrated the effect of the glass transition temperature, i.e. at conditions of minimum fluctuations in local hole free volume, on the diffusion coefficient of the bioactive compound and the decoupling of its rapid diffusion from the structural relaxation (α-transition) of the polymeric network (Ikasari, Paramita, & Kasapis, 2020). In the present study, we induce distinct three-dimensional structures in the κ-carrageenan/polydextrose system with variable additions of potassium ions to record a range of glass transition temperatures. The measured diffusion coefficients of caffeine are examined in relation to the temperature band of the mechanical and calorimetric glass transition temperatures, which measure distinct distance scales (from micro to macromolecular) in vitrification processes. Thus, the overall objective of this work is to follow the release mechanism of caffeine, as affected by changes in the structural relaxation of κ-carrageenan/polydextrose systems with potassium ion addition and ascertain the role of the thermomechanical glass transition temperature on the picture of molecular motion of the bioactive compound.

2. Materials and methods

2.1. Materials

κ-Carrageenan, extracted from *Euchema cottonii* type III, was purchased from Sigma–Aldrich Co. (Sydney, Australia). As a co-solute, Sta-Lite III polydextrose powder (95% purity with 4% moisture) was supplied by Wilmar BioEthanol Pty. Ltd. (Victoria, Australia). Caffeine [$C_8H_{10}N_4O_2$] used as the bioactive compound was purchased from Sigma–Aldrich Co. in the form of white powder at a ReagentPlus grade. Ethanol (100%) was the release medium in diffusion experimentation and was purchased as an anhydrous colorless liquid from Sigma-Aldrich Co. Potassium chloride was supplied by Sigma–Aldrich a Co. and Milli-Q Type II water was used for ingredient hydration.

2.2. Sample preparation

κ-Carrageenan was changed into the potassium form by eluting Amberlite IR-120 resin with 0.1 M HCl until pH reached 1.0. The resin was then submerged in 2 M KCl solution to convert H^+ to K^+ form and the remaining of the potassium ions were removed by rinsing with water. This is indicated by a clear solution when titrated with $AgNO_3$. The resin was heated to 90 °C and mixed at that temperature with 0.5% (w/w) aqueous κ-carrageenan for 30 min to achieve ion exchange to the potassium form. The resulted solution was then poured into 43 mm diameter when full cellulose-based semi-permeable tubes and dialysed overnight by submerging in Mili-Q water at ambient temperature. This was followed by freeze-drying of the polysaccharide solution. Ionic composition of both commercial and purified κ-carrageenan samples was analysed by us using atomic absorption spectrometry (Varian Inc., Palo Alto, USA). Commercial κ-carrageenan contained 2.32% potassium, 0.07% magnesium, 0.78% sodium and 0.52% calcium, whereas the purified κ-carrageenan exhibited high levels of potassium (7.31%), and low levels of magnesium (0.02%), sodium (0.19%) and calcium (0.21%). Experimental materials were prepared by mixing 2% (w/w) potassium κ-carrageenan, 82% (w/w) polydextrose and 1% (w/w) caffeine. In doing so, κ-carrageenan in the potassium form was dispersed in Milli-Q water, containing 0, 50, 100 or 200 mM KCl, with constant stirring at 90 °C for 10 min followed by addition of caffeine and polydextrose. Thus, four different solutions were prepared to pursue the goals of this study. Finally, solutions were poured in a beaker and placed in a vacuum oven to remove gently excess water. They formed cylindrical gels of 15% (w/w) moisture content with dimensions of 4 cm diameter and 0.5 cm thickness.

2.2. Experimental analysis

2.2.1. Fourier transform infrared spectroscopy (FTIR)

Measurements were conducted on a Spectrum Two GladiATR-Fourier transform infrared spectroscopy instrument (Perkin Elmer, Pike Technologies, Norwalk, US) using a protocol by Panyoyai et al. (2015) with some modifications. Samples of κ-carrageenan, polydextrose, caffeine and their mixtures without and with the addition of 50, 100 and 200 mM KCl were scanned at 600-4000 cm^{-1} with a resolution of 4 cm^{-1} and averaged over 64 scans. Each preparation was recorded three times to yield overlapping interferograms.

2.2.2. Scanning electron microscopy (SEM)

Freeze-dried samples of κ-carrageenan, polydextrose and their mixtures with and without caffeine, 50, 100 and 200 mM KCl were sputtered with iridium coating. They were then analysed using FEI Quanta 200 SEM (Hillsboro, Oregon, USA) under an intense electron beam and high vacuum conditions of 0.6 Torr with a working distance of 10–12 mm following a method by Paramita et al. (2015) with some modifications. Multiple micrograph images of the specimens were taken using an accelerated medium voltage of 30 kV and a spot size of 5. The experimental protocol resulted in high-quality images at a magnification of 3000 ×.

2.2.3. Modulated differential scanning calorimetry (MDSC)

The thermal transitions of single polydextrose and κ-carrageenan/polydextrose matrices with and without the addition of caffeine, 50, 100 and 200 mM KCl were recorded using Q2000 (TA Instruments, New

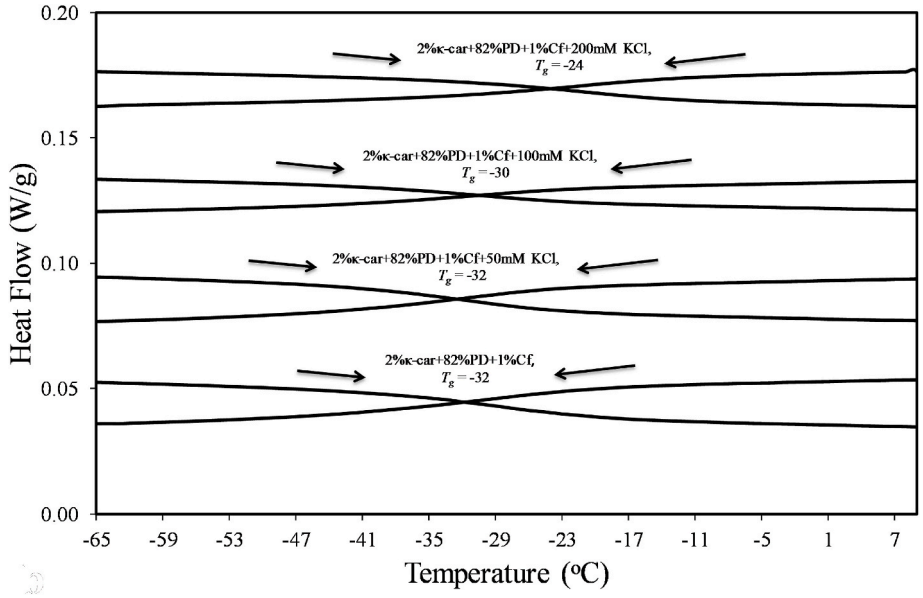

Fig. 3. Modulated DSC thermograms of heating and cooling for 2% κ-car/82% PD/1% Cf, 2% κ-car/82% PD/1% Cf/50 mM KCl, 2% κ-car/82% PD/1% Cf/100 mM KCl, 2% κ-car/82% PD/1% Cf/200 mM KCl arranged successively upwards (scanned at a rate of 1 °C/min).

Table 1
Glass transition parameters and caffeine transport characteristics in κ-carrageenan/polydextrose systems.

System	T_{gc} (°C)	T_{gm}(°C)	T_o (°C)	C_1°	C_2° (deg)	f_g	$E_{a\ matrix}$ (kJ/mol)	$E_{a\ caffeine}$ (kJ/mol)	D_{eff} (m^2/s)	Diffusion exponent, n	Transport mechanism
85% PD	−32	−13	−11	11.1	49	0.039	248.5	–	–	–	–
2% κ-car + 83% PD	−34	−20	−18	10.4	52	0.041	235.4	–	–	–	–
2% κ-car + 83% PD +50 mM KCl	−33	−19	−18	10.6	51	0.040	275.1	–	–	–	–
2% κ-car + 83% PD +100 mM KCl	−31	−17	−14	10.2	53	0.042	276.7	–	–	–	–
2% κ-car + 83% PD +200 mM KCl	−27	−16	−14	10.4	52	0.041	278.0	–	–	–	–
2% κ-car + 82% PD + 1% Cf	−32	−4	−3	10.6	51	0.044	271.2	9.1	4.64×10^{-6}	0.85 ± 0.04	Anomalous
2% κ-car + 82% PD + 1% Cf + 50 mM KCl	−32	0	1	10.6	51	0.042	318.2	14.5	1.34×10^{-6}	0.82 ± 0.02	Anomalous
2% κ-car + 82% PD + 1% Cf + 100 mM KCl	−30	5	6	10.6	51	0.042	319.9	23.0	1.78×10^{-8}	1.03 ± 0.04	Case II
2% κ-car + 82% PD + 1% Cf + 200 mM KCl	−24	10	11	10.6	51	0.041	333.7	24.7	4.05×10^{-9}	0.99 ± 0.03	Case II

Average values with a standard deviation are reported for the diffusion exponent, n, throughout the experimental temperature range (−20 to 30 °C).
Values of the effective diffusion coefficient, D_{eff}, are at 5 °C.

quantified using UV–*vis* spectrophotometry at λ_{max} = 273 nm and the Beer-Lambert Law *via* a standard absorbance-concentration fit with a high linear regression coefficient (r^2 = 0.992; data are not shown). Fig. 6a represents a typical profile of caffeine release in the κ-carrageenan/polydextrose matrix at various additions of KCl over 120 min at 30 °C. Increasing times of observation yield higher amounts of caffeine diffusion out of the device, as does the absence of the counterion. Thus, after 120 min of observation, the concentration of released caffeine is 0.54 and 0.18 mg/ml at 0 and 200 mM KCl, respectively.

Fig. 6b illustrates the outcomes of caffeine diffusion as a function of KCl addition within the experimental temperature range of this investigation at 120 min. It appears that the levels of potassium ions underline a rate-limiting step of the entire diffusion sequence achieving high kinetics of release at 30 °C, which is above the mechanical glass transition temperature of the system, i.e. within the glass transition region (Table 1). On the other hand, relatively limited release is observed at −20 °C, which is below T_{gm}, i.e. within the glassy stage of the matrix. The validity of these experimental observations was confirmed using a two-way ANOVA test followed by Tukey's post hoc test, which indicated that the release of caffeine was significantly affected by the KCl additions and the time/temperature settings of this investigation (cutoff for significance is $p < 0.05$).

Next, the caffeine release was followed by an easy-to-apply model (Ritger & Peppas, 1987):

$$\frac{M_t}{M_\infty} = kt^n \tag{4}$$

where, M_t and M_∞ are the caffeine concentrations during experimentation and at completion, k is a characteristic constant of the bioactive compound-polymer system, t is time in seconds, and n is the kinetic diffusion exponent. For the cylindrical disks of this investigation, n values between 0.45 and 0.89 denote an anomalous transport, which becomes a non-Fickian or Case II transport at higher estimates (Siepmann & Siepmann, 2008). Using the gradient in the plot of ln M_t/M_∞ *versus* ln t from equation (4), we obtain for the κ-carrageenan/polydextrose/caffeine matrices at four KCl additions n values within the range of 0.82–1.03 (Table 1). These estimates are at the interface of anomalous and Case II transport, an outcome that

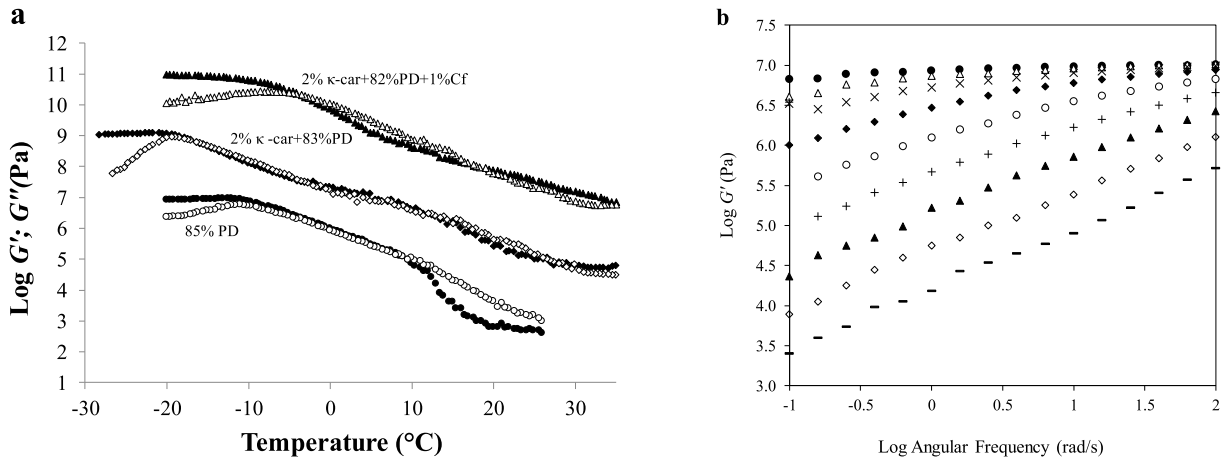

Fig. 4. **(a)** Cooling profiles of G' (closed symbol) and G'' (open symbol) for 85% PD (circle), 2% κ-car/83% PD (square) and 2% κ-car/82% PD/1% Cf (triangle) scanned at a rate of 1 °C/min, angular frequency of 1 rad/s and strain of 0.01%, and **(b)** Mechanical spectra of 2% κ-car/82% PD/1% Cf as a function of angular frequency for G' at 17(−), 13(◊), 9(▲), 5(+), 1(○), −3(◆), −7(x), −11(Δ), −15(●) arranged successively upwards.

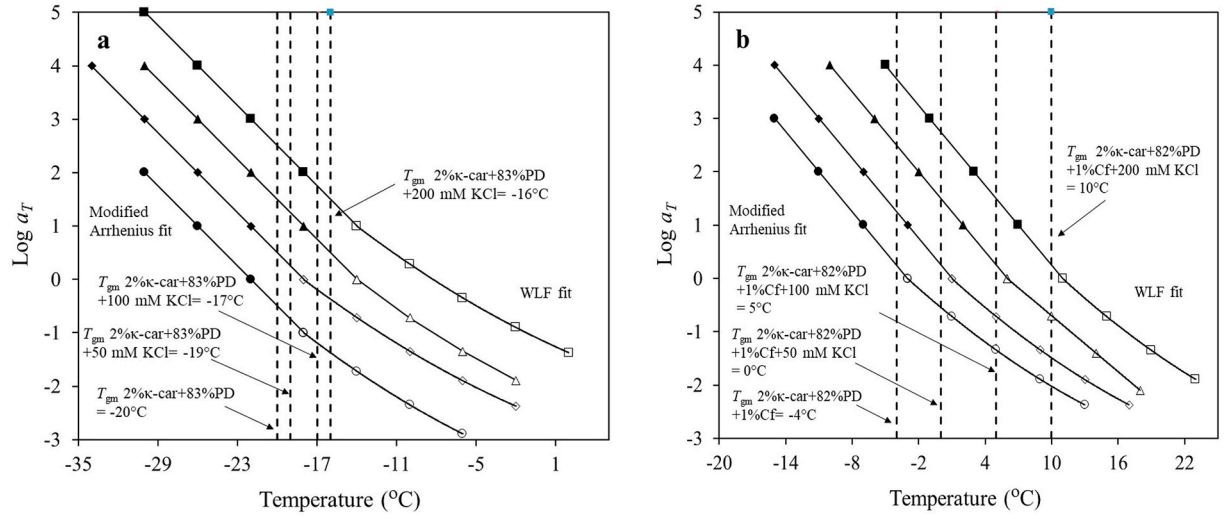

Fig. 5. WLF and modified Arrhenius fits of the shift factors (a_T) within the glass transition region (open symbols) and glassy state (closed symbols) for **(a)** 2% κ-car/83% PD (circle), 2% κ-car/83% PD/50 mM KCl (diamond), 2% κ-car/83% PD/100 mM KCl (triangle), 2% κ-car/83% PD/200 mM KCl (square), and **(b)** 2% κ-car/82% PD/1% Cf (circle), 2% κ-car/82% PD/1% Cf/50 mM KCl (diamond), 2% κ-car/82% PD/1% Cf/100 mM KCl (triangle), 2% κ-car/82% PD/1% Cf/200 mM KCl (square), with the dash line showing the predictions of the mechanical glass transition temperature.

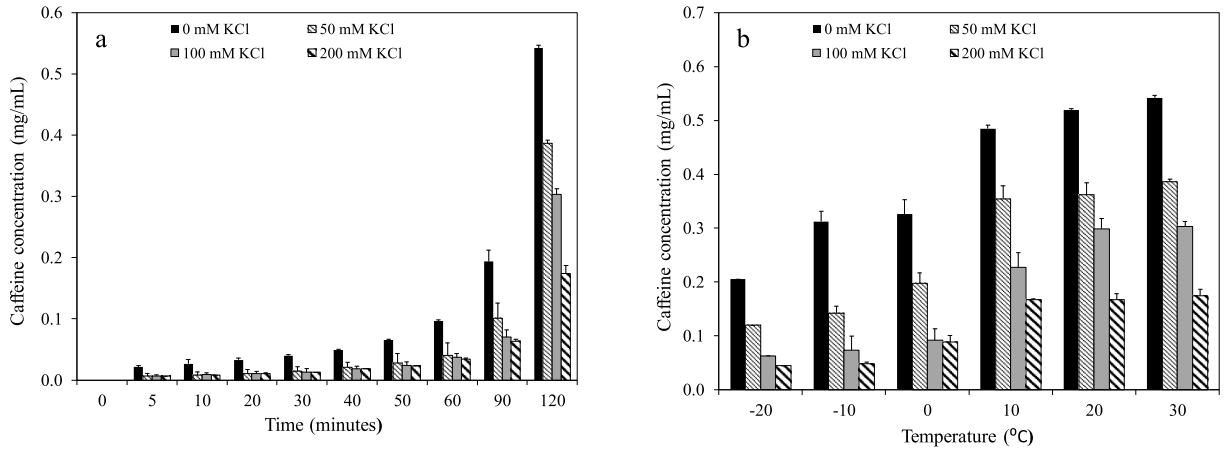

Fig. 6. Caffeine release for 2% κ-car/82% PD as function of **(a)** time at 30 °C and **(b)** temperature after 120 min.

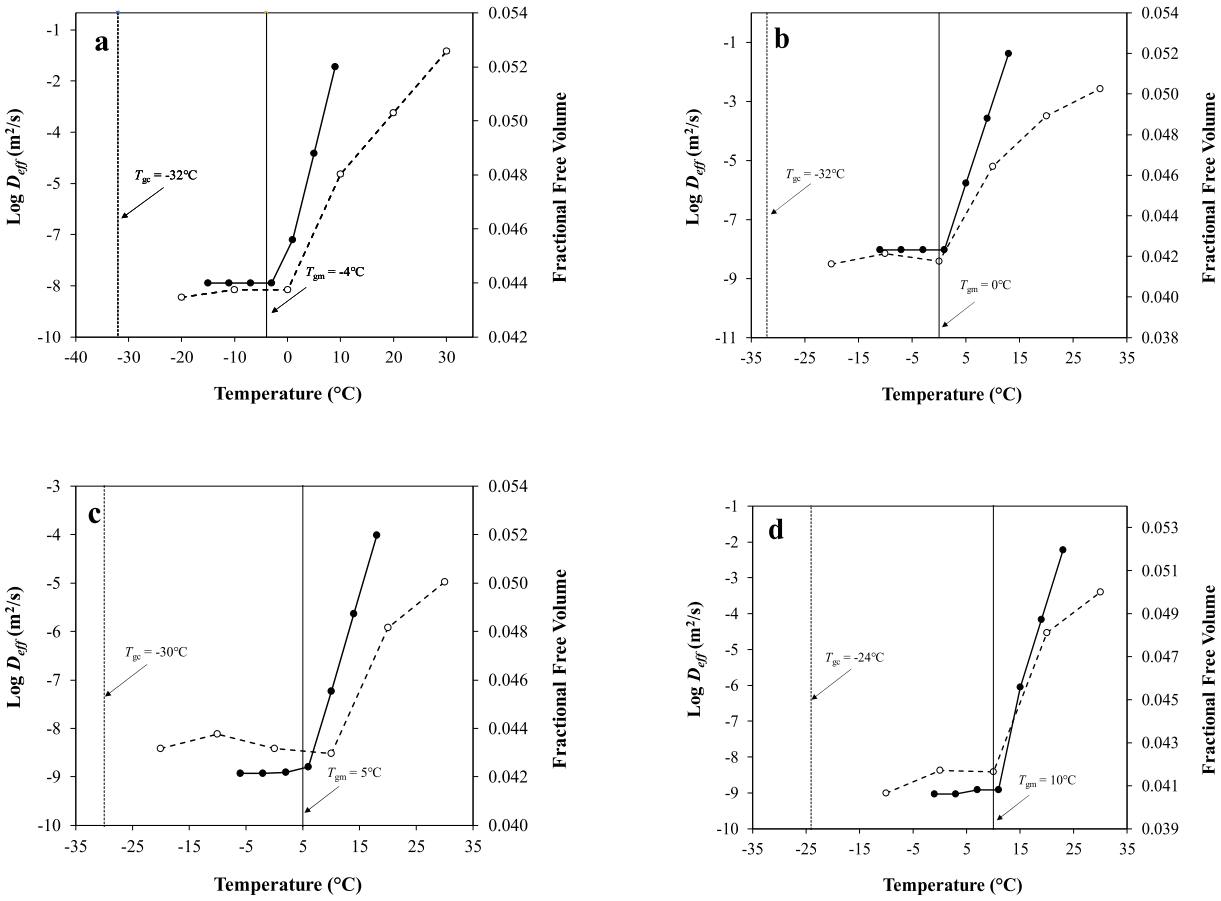

Fig. 8. Effective diffusion coefficient of caffeine (◯, left y-axis) and fractional free volume of 2% κ-car/82% PD/1% Cf (●, right y-axis) at **(a)** 0 **(b)** 50, **c)** 100 and **(d)** 200 mM KCl, with indications of the mechanical and calorimetric glass transition temperatures.

Therefore, the fundamental principle in the driving force of diffusion coefficient and fractional free volume in relation to the mechanical glass transition temperature, as developed from equation (6) for increasing temperature, should be also applicable to solvent infusion, leading in both cases to increasing fluctuations in local hole free volume. This approach can serve as the basis for further explorations in the design of model systems closer to industrial application.

[†]Footnote: We have utilised the relationship between caffeine concentration and time (e.g. Fig. 6a) to argue for a zero-order reaction rate, with the gradient being the rate constant, $k = dx/dt$. This allows calculation of the so-called "spectroscopic shift factor": $\log a_T = \log (k_o/k)$, where k_o is the rate constant at the reference temperature, T_o. Thus, $E_{a\ caffeine}$ can be estimated using the modified Arrhenius equation and outcomes are shown in Table 1; further discussion on the spectroscopic shift factor can be found in Paramita and Kasapis (2018).

4. Conclusions

We have designed high-solid biomaterials with vitrification properties over a wide range of temperatures by incorporating a natural polymer, κ-carrageenan, a non-caloric co-solute, polydextrose, and judicious additions of potassium counterions. The aim was to achieve controlled drug release *via* the effective entrapment of caffeine in these materials. Utilisation of the concept of normalized temperature difference variables demonstrated that the diffusion coefficients of caffeine for all systems can be reduced to a common pattern regardless of their physicochemical characteristics. Within the glass transition region of the polysaccharide/co-solute matrices at various levels of added potassium ions, a newly proposed equation for the caffeine diffusion coefficient in relation to the fractional free volume at the glass transition temperature yields the so-called coupling parameter. It was observed that potassium counterion stabilisation of the κ-carrageenan helices increases the decoupling effect between matrix motion and caffeine diffusion. It has been noted earlier in the literature that in this type of systems the mechanical glass transition temperature is distinct from its calorimetric counterpart, with the former being an accurate measure of structural relaxation within the region of α-dispersion. It appears that T_{gm} controls the mass transport of caffeine in the polysaccharide based matrix, an outcome which is congruent with data on the diffusion of nicotinic acid from protein (gelatin) matrices with distinct molecular weight distributions (Ikasari et al., 2020), and bodes well for the design of delivery vehicles with advanced bio-functionality.

Declaration of interests

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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References

Al-Ruqaie, I. M., Kasapis, S., Richardson, R. K., & Gordon, M. (1997). The glass transition zone in high solids pectin and gellan preparations. *Polymer, 38*, 5685–5694.
Arridge, R. G. C. (1975). The glass transition. In R. G. C. Arridge (Ed.), *Mechanics of polymers* (pp. 24–50). Oxford: Clarendon Press.

Bourbon, A. I., Cerqueira, M. A., & Vicente, A. A. (2016). Encapsulation and controlled release of bioactive compounds in lactoferrin-glycomacropeptide nanohydrogels: Curcumin and caffeine as model compounds. *Journal of Food Engineering, 180*, 110–119.

Chaudhary, V., Panyoyai, N., Small, D. M., Shanks, R. A., & Kasapis, S. (2017). Effect of the glass transition temperature on alpha-amylase activity in a starch matrix. *Carbohydrate Polymers, 157*, 1531–1537.

Craig, S. A. S., Anderson, J. M., Holden, J. F., & Murray, P. R. (2008). Bulking agents: Polydextrose. In H. van Bekku, H. Röper, & A. G. J. Voragen (Eds.), *Carbohydrates as organic raw materials III* (p. 222). John Wiley & Sons.

Ehlich, D., & Sillescu, H. (1990). Tracer diffusion at the glass transition. *Macromolecules, 23*, 1600e1610.

Evageliou, V. I., Ryan, P. M., & Morris, E. R. (2019). Effect of monovalent cations on calcium-induced assemblies of kappa carrageenan. *Food Hydrocolloids, 86*, 141–145.

Ferry, J. D. (1980). *Viscoelastic properties of polymers*. New York: John Wiley & Sons.

Ganapathy, S., O'Brien, J. A., & Randolph, T. W. (1996). Do solute-solute interactions affect activation-limited reactions? A brownian dynamics study. *The Journal of Supercritical Fluids, 9*(1), 51–55.

Gray, D. A., Bowen, S. E., Farhat, I., & Hill, S. E. (2008). Lipid oxidation in glassy and rubbery-state starch extrudates. *Food Chemistry, 106*, 227–234.

Hoare, T. R., & Kohane, D. S. (2008). Hydrogels in drug delivery: Progress and challenges. *Polymer, 49*, 1993–2007.

Ikasari, D., Paramita, V. D., & Kasapis, K. (2020). Mechanical *versus* calorimetric glass transition temperature in the diffusion of nicotinic acid from a condensed gelatin/glucose syrup system. *Food Hydrocolloids, 109*, 106046.

Jadhav, N. R., Gaikwad, V. L., Nair, K. J., & Kadam, H. M. (2009). Glass transition temperature: Basics and application in pharmaceutical sector. *Asian Journal of Pharmaceutics, 3*(2). https://doi.org/10.4103/0973-8398.55043

Jiang, B., & Kasapis, S. (2011). Kinetics of a bioactive compound (Caffeine) mobility at the vicinity of the mechanical glass transition temperature induced by gelling polysaccharide. *Journal of Agricultural and Food Chemistry, 59*, 11825–11832.

Kasapis, S. (2008). Recent advances and future challenges in the explanation and exploitation of the network glass transition of high sugar/biopolymer mixtures. *Critical Reviews in Food Science and Nutrition, 48*, 185–203.

Kasapis, S., & Al-Marhoobi, I. M. (2005). Bridging the divide between the high- and low-solid analyses in the gelatin/κ-carrageenan mixture. *Biomacromolecules, 6*, 14–23.

Kasapis, S., & Sablani, S. S. (2005). A fundamental approach for the estimation of the mechanical glass transition temperature in gelatin. *International Journal of Biological Macromolecules, 36*(1–2), 71–78.

Mangione, M. R., Giacomazza, D., Bulone, D., Martorana, V., Cavallaro, G., & San Biagio, P. L. (2005). K+ and Na+ effects on the gelation properties of κ-carrageenan. *Biophysical Chemistry, 113*, 129–135.

Morris, E. R., Rees, D. A., & Robinson, G. (1980). Cation-specific aggregation of carrageenan helices: Domain models of polymer gel structure. *Journal of Molecular Biology, 138*, 349–362.

Ngai, K. L., & Plazek, D. J. (1995). Identification of different modes of molecular motion in polymers that cause thermorheological complexity. *Rubber Chemistry and Technology, 68*, 376–434.

Nickerson, M. T., Paulson, A. T., & Hallet, F. R. (2004). Dilute solution properties of k-carrageenan polysaccharides: Effect of potassium and calcium ions on chain conformation. *Carbohydrate Polymers, 58*, 25–33.

Núñez-Santiago, M. C., Tecante, A., Garnier, C., & Doublier, J. L. (2012). Rheology and microstructure of κ-carrageenan under different conformations induced by several concentrations of potassium ion. *Food Hydrocolloids, 25*, 32–41.

Panyoyai, N., Bannikova, A., Small, D. M., & Kasapis, S. (2015). Controlled release of thiamin in a glassy κ-carrageenan/glucose syrup matrix. *Carbohydrate Polymers, 115*, 723–731.

Panyoyai, N., & Kasapis, S. (2016). A free-volume interpretation of the decoupling parameter in bioactive-compound diffusion from a glassy polymer. *Food Hydrocolloids, 54*, 338–341.

Paramita, V. D., Bannikova, A., & Kasapis, S. (2015). Release mechanism of omega-3 fatty acid in κ-carrageenan/polydextrose undergoing glass transition. *Carbohydrate Polymers, 126*, 141–149.

Paramita, V. D., & Kasapis, S. (2018). The role of structural relaxation in governing the mobility of linoleic acid in condensed whey protein matrices. *Food Hydrocolloids, 76*, 184–193.

Paramita, V. D., & Kasapis, S. (2019). Molecular dynamics of the diffusion of natural bioactive compounds from high-solid biopolymer matrices for the design of functional foods. *Food Hydrocolloids, 88*, 301–319.

Ribeiro, C., Zimeri, J. E., Yildiz, E., & Kokini, J. L. (2003). Estimation of effective diffusivities and glass transition temperature of polydextrose as a function of moisture content. *Carbohydrate Polymers, 51*, 273–280.

Ritger, P. L., & Peppas, N. A. (1987). A simple equation for description of solute release_ II. Fickian and anomalous release from swellable devices. *Journal of Controlled Release, 5*, 37–42.

Rochas, C., & Rinaudo, M. (1984). Mechanism of gel formation in κ-carrageenan. *Biopolymers, 23*, 735–745.

Roudaut, G., Simatos, D., Champion, D., Contreras-Lopez, E., & Le Meste, M. (2004). Molecular mobility around the glass transition temperature: A mini review. *Innovative Food Science & Emerging Technologies, 5*(2), 127–134. https://doi.org/10.1016/j.ifset.2003.12.003

Shakeel, F. (2017). Rheological behavior and physical stability of caffeine loaded water-in-oil nanoemulsions. *Chiang Mai Journal of Science, 44*(3), 1049–1055.

Siepmann, J., & Siepmann, F. (2008). Mathematical modeling of drug delivery. *International Journal of Pharmaceutics, 364*, 328–343.

Siepmann, J., & Siepmann, F. (2012). Modeling of diffusion controlled drug delivery. *Journal of Controlled Release, 161*(2), 351–362.

Slade, L., & Franks, F. (2002). Appendix I: Summary report of the discussion symposium on chemistry and application technology of amorphous carbohydrates. In H. Levine (Ed.), *Amorphous food and pharmaceutical systems* (p. xexxvi). Cambridge: The Royal Society of Chemistry.

Stenner, R., Matubayasi, N., & Shimizu, S. (2016). Gelation of carrageenan: Effects of sugars and polyols. *Food Hydrocolloids, 54*, 284–292.

Stowell, J. D. (2009). Polydextrose. In S. S. Cho, & P. Samuel (Eds.), *Fiber ingredients: Food applications and health benefits* (pp. 137–196). Boca Raton: CRC Press.

Tan, S., Ebrahimi, A., & Langrish, T. (2019). Controlled release of caffeine from tablets of spray-dried casein gels. *Food Hydrocolloids, 88*, 13–20.

Temple, J. L., Bernard, C., Lipshultz, S. E., Czachor, J. D., Westphal, J. A., & Mestre, M. A. (2017). The safety of ingested caffeine: A comprehensive review. *Frontiers in Psychiatry, 8*(80).

Viebke, C., Piculell, L., & Nilsson, S. (1994). On the mechanism of gelation of helix forming biopolymers. *Macromolecules, 27*, 4160–4166.

Wang, Y., Yuan, C., Cui, B., & Liu, Y. (2018). Influence of cations on texture, compressive elastic modulus, sol-gel transition and freeze-thaw properties of kappa-carrageenan gel. *Carbohydrate Polymers, 202*, 530–535.