Mechanical *versus* calorimetric glass transition temperature in the diffusion of nicotinic acid from a condensed gelatin/glucose syrup system

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ABSTRACT

Condensed systems of 25% (w/w) bovine gelatin (Mw = 173 kDa) or 25% (w/w) fish gelatin (Mw = 60 kDa) with 59% (w/w) glucose syrup and 1% (w/w) nicotinic acid to a total solids level of 85% (w/w) were prepared in this study. Analysis was carried out using Fourier transform infrared spectroscopy (FTIR), wide angle X-ray diffraction (WAXD), scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and small deformation dynamic oscillation in-shear. Work allowed elucidation of the micromolecular and macromolecular properties focusing on the estimation of the mechanical (T_{gm}) and calorimetric (T_{gc}) glass transition temperature of these systems. A combined protocol of free volume and reaction rate theories was considered to rationalise results in the vicinity of the glass transition region. Following this, a diffusion procedure of nicotinic acid was set up over a wide temperature range (from 5 to −40 °C) using UV–*vis* spectroscopy and an appropriate chromogenic reaction to detect the presence of the bioactive compound. Time dependence of the mass transfer of nicotinic acid throughout the delivery vehicle of gelatin/co-solute was followed using diffusion theory. The treatise unveiled the correlation between structural relaxation of the vitrified matrix and release kinetics of the diffusant.

1. Introduction

Often, processed food is regarded as amorphous, making the transformation from the rubbery to glassy consistency a key factor affecting the stability and quality of the end product (Le Meste, Champion, Roudaut, Blond, & Simatos, 2002; Slade & Levine, 1991). Rapid cooling encourages vitrification around the so-called glass transition temperature (T_g), which results in limited physicochemical, enzymatic and biological activity in materials (Gray, Bowen, Farhat, & Hill, 2008; Roudaut, Simatos, Champion, Contreras-Lopez, & Le Meste, 2004). Characterisation of the molecular mechanisms during vitrification is carried out by several experimental tecnhiques that can lead to a variation in the obtained estimates of the glass transiton temperatrure (Chaudhary, Panyonyai, Small, Shanks, & Kasapis, 2017; Zhong, Tan, & Langrish, 2019). To provide a bird's eye view of all the molecular mechanims contributing to this type of physical behaviour, parallel application of mechanical and calorimetric techniques is desirable (Abiad, Carvajal, & Campanella, 2009).

Adoption of a mechanical approach requires monitoring the viscoelastic response of a polymer arising from motions of distinct molecular moieties. These can encompass long length scales due to the entire molecular chain and its association with neighbouring molecules to form a three-dimensional structure (Kasapis, Al-Marhoobi, & Mitchell, 2003a; Paramita, Bannikova, & Kasapis, 2016). A polymer with a high molecular weight will have a low specific volume and thus results in a high glass transition temperature (Abiad et al., 2009). Differential scanning calorimetry, on the other hand, monitors the heat flow of a material at a given heating rate, which can be used to estimate its heat capacity. This is then sensitive to the total concentration of solids the sample is made of, which determines the amount of heat needed to raise its temperature one degree centigrade (Kasapis & Sablani, 2005). The functionality of a material to form active "structural ties" or inactive "dead ends", according to the cascade formalism in the context of gelation, is a secondary consideration in the derivation of the calorimetric glass transition temperature.

Amongst the hydrocolloids used in the food and pharmaceutical industries, gelatin maintains its popularity due to biocompatibility, unique melt-in-the-mouth property and formation of a rubbery/glassy network with vivid clarity (Deszczynski, Kasapis, MacNaughton, & Mitchell, 2002; Kasapis, Al-Marhoobi, Deszczynski, Mitchell, & Abeysekera, 2003b). Besides the mammalian gelatin, fish gelatin produced by the partial hydrolysis of collagen-rich fish skin or scale, has been utilised in

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product development to address dietary (vegetarian/vegan) or religious (in particular, Muslim and Hindu) habits/concerns, and allow utilisation of some of the by-products of the fishing industry. It contains a high content of imino acids and is commonly produced at a relatively low molecular weight yielding distinct physical properties from the mammalian counterpart (Avena-Bustillos et al., 2006; Pang, Deeth, Yang, Prakash, & Bansal, 2017; Sila, Martinez-Alvarez, Krichen, Gómez-Guillén, & Bougatef, 2017; Zhou, Mulvaney, & Regenstein, 2006).

In addition to the structural characteristics of amorphous polymers, there is an increasing interest in the rubber-to-glass dispersion with emphasis on the release of bioactive compounds. These are delivery systems in the shape of slabs, cylinders and spheres used in the controlled release of drugs, nutrients, antioxidants, fragrances, etc. (Hoare & Kohane, 2008). They have been researched in terms of the time and temperature of transport, and the chemistry, size, morphology and swellability/solubility of the material (Paramita & Kasapis, 2019; Zarzycki, Modrzejewska, & Nawrotek, 2010). Thus, the effect of molecular weight on the retardation of caffeine release has been reported for protein-polysaccharide matrices under acid, bile and yogurt storage conditions (Hernández-Marín, Lobato-Calleros, Román-Guerrero, Alvarez-Ramirez, & Vernon-Carter, 2016).

Nicotinic acid (also known as vitamin B3) is an essential vitamin, which plays a significant role in regulating metabolism, including the digestive system, human skin and mental health (Gehring, 2004). Lack of nicotinic acid in daily intake leads to severe photosensitive dermatitis, called pellagra (Bui, Small, & Coad, 2013; Gehring, 2004). Nicotinic acid can be found in both animal and plant products, such as milk, fish, beef, eggs, cereals and fruits (Lešková et al., 2006; Panyonyai, Bannikova, Small, Shanks, & Kasapis, 2016). However, a proportion of nicotinic acid is lost during boiling, pressure cooking, microwaving and stir-frying. Upon food preparation, retention of the vitamin is reported to be from 45 to 60% (Lešková et al., 2006) and is one of the most commonly added "fortification vitamins" found in foods.

The present work researches two types of gelatin with distinct molecular weight and physicochemical fingerprints impacting structural properties. They are utilised in a high-solid preparation in the presence of glucose syrup to function as entrapping and then delivery vehicles of nicotinic acid. The working protocol allows elucidation of the fundamental relationship between kinetics of the bioactive compound release and physicochemical characteristics of the polymeric system. This is achieved in terms of the concepts of glass transition temperature, apparent diffusion coefficient and coupling parameter between supporting matrix and diffusant.

2. Materials and methods

2.1. Materials

Type B bovine gelatin (SKU G9382), bloom = 225, $M_w \approx 173$ kDa, and fish gelatin from cold-water fish skin (SKU G7041), bloom = 85, $M_w \approx 60$ kDa, were purchased from Sigma-Aldrich Co. (Sydney, Australia). Glucose syrup, as the co-solute, was supplied by Edlyn Foods Pty. Ltd. (Victoria, Australia). The product has a total solids level of 81% (w/w), with the dextrose equivalent (DE) being ≈ 42. Nicotinic acid ($C_6H_5NO_2$, $M_w = 123.11$ Da, purity $\geq 99.5\%$) and ethanol ($\geq 99.5\%$) were both obtained from Sigma-Aldrich (Sydney, Australia) and used as the diffusant and release medium, respectively.

2.2. Sample preparation

Gelatin solutions were prepared by hydrating 10% (w/w) bovine or fish gelatin in Milli-Q water type II overnight at 4 °C. The protein mixture was heated to 55 °C with constant stirring for 30 min until a clear solution was obtained. Meanwhile, the glucose syrup was tempered at 55 °C before adding to the gelatin solution. The gelatin/

glucose syrup mixture was continuously stirred at 55 °C for another 10 min to obtain a homogenous mixture with the desired level of solid being 25% (w/w) gelatin plus 60% (w/w) glucose syrup. Similarly, samples were made with 1% (w/w) nicotinic acid, 25% (w/w) gelatin plus 59% (w/w) glucose syrup to reach a total level of solids of 85% (w/w). Single preparations of 25% (w/w) bovine or fish gelatin and 85% (w/w) glucose syrup were also prepared to serve as the reference systems.

2.3. Experimental analysis

Fourier transform infrared spectroscopy (FTIR): Measurements were performed by using Spectrum Two GladiATR-Fourier transform infrared spectroscopy (Perkin Elmer, Pike Technologies, Norwalk, US). A single preparation of bovine or fish gelatin, glucose syrup and their mixtures with nicotinic acid were scanned at 600-4000 cm^{-1} with resolution of 4 cm^{-1} averaged over 64 scans. Each experiment was repeated three times resulting in overlapping interferograms.

Wide angle X-ray diffraction (WAXD): Measurements were performed with a Bruker D4 Endeavour (Karlsruhe, Germany). Samples of gelatin, glucose syrup and their mixtures with nicotinic acid were freeze-dried prior to analysis. They were then loaded onto the observation chamber and exposed to an accelerated voltage of 40 kV and current at 40 mA. Data obtained were in the 2θ range of 5–90° with measuring intervals of 0.1° and were processed using DIFFRACplus Evaluation (Eva), version 10.0, revision 1. Each test was repeated three times yielding identical diffractograms.

Differential scanning calorimetry (DSC): Measurements were performed on the gelatin/glucose syrup/nicotinic acid systems using Q2000 (TA instruments, New Castle, DE) with a refrigerated cooling system (RCS90). About ten mg of the sample was loaded onto the T_{zero} aluminium pans and sealed hermetically with an empty pan serving as the reference. Samples were equilibrated at 60 °C for 20 min followed by cooling from 60 to −90 °C and heating to 60 °C. The scan rate was 1 °C/min with a modulation rate of 0.53 °C for every 40s. During experimentation, nitrogen gas was purged into the cell chamber at a rate of 50 mL/min. Each run was repeated three times yielding consistent thermograms.

Dynamic oscillatory measurements: These were conducted on AR-G2 rheometer (TA Instruments, New Castle, DE). Single preparations and mixtures of gelatin with glucose syrup were loaded onto the preheated Peltier plate at 60 °C using a 10 mm parallel-plate measuring geometry. Silicone oil (BDH, 50 cS) was applied at the edges of the measuring geometry to minimize moisture loss. Samples were cooled to −50 °C at a constant rate of 1 °C/min, angular frequency of 1 rad/s and 0.01% of strain, which is within the polymer's linear viscoelastic region (LVR). Once the cooling run was complete, they were heated at the same rate and frequency sweeps were taken at 0.1–100 rad/s every 3 °C. Mechanical spectra were subjected to a time-temperature superposition (TTS) to construct the master curve of viscoelasticity for these systems. Isochronal and isothermal routines were carried out in triplicate returning consistent results.

Scanning electron microscopy (SEM): Single systems of gelatin and their mixtures with glucose syrup and nicotinic acid were freeze-dried prior to experimentation. They were coated with iridium and analyzed under the intense electron beam of FEI Quanta 200 SEM (Hillsboro, Oregon, USA). Analysis was carried out under high vacuum conditions of 0.6 Torr with a working distance of 10 mm at 1500 times magnification. Topography images were taken using accelerated medium voltage of 15 kV and spot size of 3.5. Multiple microscopy images were attempted and typical outcomes are shown here.

Diffusion studies: Two grams of samples containing gelatin, glucose syrup and nicotinic acid were prepared in beakers with 4 cm diameter and 0.5 cm thickness. These, and 4 ml of ethanol in a separate test tube, were equilibrated overnight at the temperatures of −40, −30, −20, −10, 0, and 5 °C; internal sample temperatures were confirmed using a digital
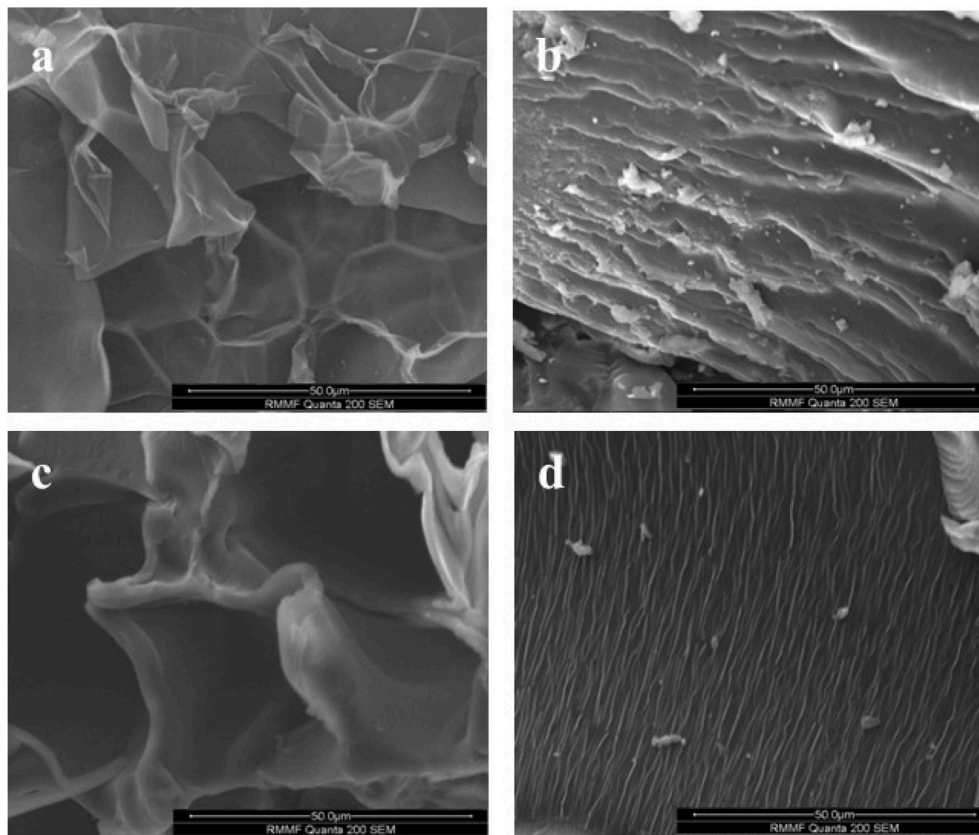
Fig. 4. SEM micrographs of **(a)** 25% bovine gelatin, **(b)** 25% bovine gelatin with 59% glucose syrup and 1% nicotinic acid, **(c)** 25% fish gelatin and **(d)** 25% fish gelatin with 59% glucose syrup and 1% nicotinic acid.

a_T, as follows (Kasapis & Shrinivas, 2010):

$$\log a_T = \log \frac{k_0}{k} \tag{4}$$

where, k_0 represents the rate constant at the reference temperature of $-13\,°C$ and $-33\,°C$ for bovine and fish gelatin, respectively. The series of spectroscopic shift factors were plotted against temperature to allow estimation, *via* the modified Arrhenius equation, of activation energies for the diffusion of nicotinic acid in bovine (25.2 kJ/mol) and fish (19.7 kJ/mol) gelatin in Table 1. These are about an order of magnitude below the tabulated E_a values of structural relaxation of the two polymeric matrices hence reflecting the high freedom of nicotinic acid mobility that underpins diffusion.

To advance further the direct comparison of molecular dynamics between polymeric matrices with glassy consistency and bioactive compound transport, we made a start with the power-law equation of Ritger and Peppas (1987):

$$\frac{M_t}{M_\infty} = kt^n \tag{5}$$

where, M_t and M_∞ denote the absolute amounts of the diffusant during experimentation and its completion, k is a constant characteristic of the bioactive compound-polymer system, t is given in seconds, and n is the kinetic diffusion exponent. For the cylindrical disk of the present investigation, n values of 0.45 and 0.89 describe Fickian and Case II diffusion kinetics, with those below, above and in-between being known as Less Fickian, Super Case II and anomalous transport (Ozdemir & Floros, 2001; Siepmann & Siepmann, 2008).

Application of equation (5) to our data, in a double logarithmic form, allows estimation of the kinetic diffusion exponent in Table 2. High n values at the low temperature end, e.g. 1.31 at $-30\,°C$, indicate a Super

Case II mechanism in the glassy state of the bovine gelatin mixture, where release kinetics are controlled by the rate-limiting polymeric relaxation. On the other hand, at 5 °C, which lies well above the bovine gelatin T_{gm} ($-14\,°C$), an n estimate of 0.44 is obtained arguing for a Fickian diffusion as the rate-controlling process. Between the two bounds, an anomalous transport is recorded, where both mechanisms contribute equally to the release kinetics ($n = 0.66$ at $-10\,°C$). Qualitatively, a similar profile is obtained for the fish gelatin/glucose syrup mixture, but with the anomalous transport that includes a Fickian diffusion contribution, making inroads into temperatures as low as -20 °C due to the lower T_{gm} ($-34\,°C$). As before, within the glassy state, structural relaxation of the matrix, as opposed to Fickian diffusion, is the predominant mechanism of nicotinic acid (Super Case II) transport.

To estimate the apparent diffusion coefficient, D, absorbance readings were converted to diffused nicotinic-acid concentrations and Fick's second law was employed for $M_t/M_\infty \leq 0.4$ (Busk & Labuza, 1979; Siepmann & Siepmann, 2012):

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi R^2}\right)^{1/2} - \frac{Dt}{R^2} \tag{6}$$

where, R represents the radius of the cylindrical disk. We were then able to utilise the apparent diffusion coefficient of the bioactive compound in a recently derived mathematical expression that argues for a linear relationship with a function of the fractional free volume of the polymeric matrix, as follows (Panyoyai & Kasapis, 2016):

$$\log D_T = \log D_{Tg} + \frac{\xi}{2.303}\left[\frac{1}{f_g} - \frac{1}{f}\right] \tag{7}$$

where, D_T, f and D_{Tg}, f_g are the apparent diffusion coefficient and fractional free volume at T and T_g, respectively, and ξ represents the critical
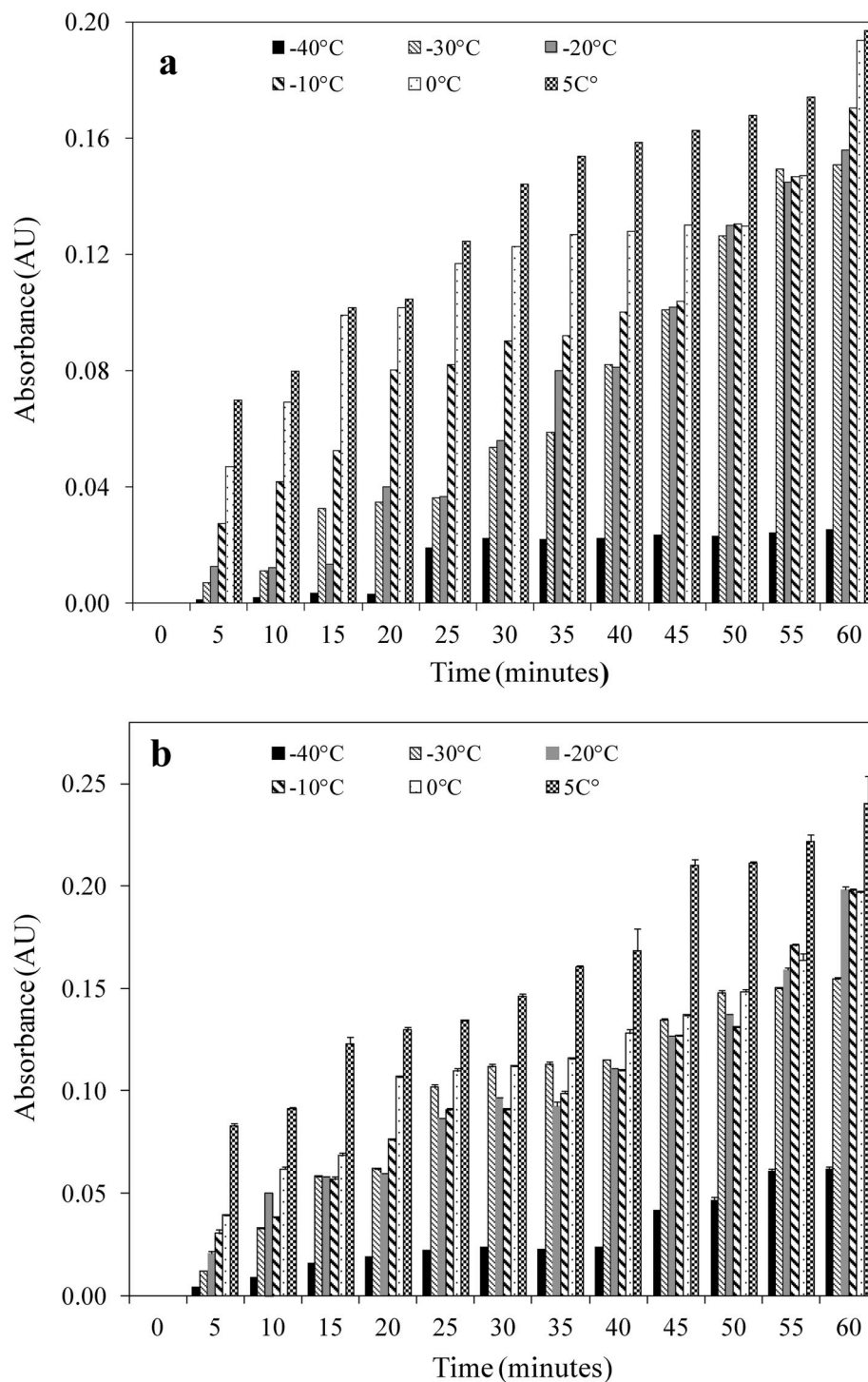
Fig. 5. Absorbance of 1% nicotinic acid following diffusion from **(a)** 25% bovine gelatin with 59% glucose syrup and **(b)** 25% fish gelatin with 59% glucose syrup as function of time at the experimental temperatures of −40 (■), −30 (⊠), −20 (■), −10 (◪), 0 (□) and 5(▨) °C obtained at 262 nm.

molecular volume of the jumping unit of a bioactive compound to that of the polymeric matrix. This relationship was found to be valid within the glass transition region of spray dried whey protein used as an encapsulant and delivery vehicle of nicotinic acid.

Utilisation of the combined protocol of equations (6) and (7) allows derivation of the apparent diffusion coefficients of nicotinic acid, which are then plotted in logarithmic form against a reciprocal function of free volume for the bovine/and fish gelatin/glucose syrup matrices (Fig. 6). Good linear relationships are obtained ($r^2 = 0.980$), which allow estimation of gradients being 0.346 and 0.137 for bovine and fish gelatin,

respectively. These values reflect effectively a coupling parameter, ξ, that increases with nontrivial interactions between polymeric network and bioactive compound. They argue for a fundamental relationship between free volume, which diminishes in the connective bovine-gelatin network and high estimates of its coupling parameter. The corresponding term, 1- ξ, denotes a decoupling parameter, its values for the high-solid bovine and fish gelatin systems are 0.654 and 0.863, encompassing an estimate of 0.70 for molecularly interacting hybrid polyurethanes in biodegradable stent coating (Guo, Knight, & Mather, 2009).

a higher mechanical T_g, as compared to the fish gelatin counterpart. In both types of gelatin, estimates of the mechanical glass transition temperature are well above those of the calorimetric glass transition temperature for the chosen level of total solids in the mixture and experimental settings. The mechanical manifestation of vitrification relates to the ability of gelatin to form a network that governs the patten of nicotinic acid transport. This increasingly departs from concentration gradient (i.e. Fickian) considerations in the glassy state of the polymer and, instead, exhibits anomalous to Super Case II kinetics. Structural cooperativity between vitamin and polymer was quantified *via* the recently introduced concept of coupling parameter arguing for a strong interaction between the two constituents in the high-solid system. Rheology is well qualified to monitor network connectivity, which appears to govern molecular dynamics in the diffusion of nicotinic acid, as opposed to the calorimetric T_g.

Declaration of competing interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodhyd.2020.106046.

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