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Molecular dynamics of the diffusion of natural bioactive compounds from high-solid biopolymer matrices for the design of functional foods

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ABSTRACT

Delivery of techno- and bio-functionality in all-natural processed foods is an area of steadily increasing fundamental and technological interest. One of the main aspects in this field is based on the diffusion of natural bioactive compounds that have been incorporated in high-solid biopolymers matrices. Organoleptic considerations dictate that the delivery vehicles are characterised by a highly amorphous fraction in the biopolymer network. Molecular diffusion in the amorphous state is a complex process associated with the effect of the glass transition temperature (T_g) on the mobility of low molecular-weight bioactives. This work will review the molecular dynamics of high-solid biopolymer systems, and model food preparations in the presence of co-solute, in relation to the diffusion kinetics of natural bioactive compounds. Literature indicates that the metastable properties of condensed biopolymer networks traversing the rubber-to-glass transition region affect significantly the diffusion kinetics of bioactive compounds. These have been modelled using concepts from the classical and improved diffusion theory to unveil a relationship between apparent diffusion coefficient of bioactives and free volume characteristics of the condensed biopolymer network. Further work is required in added value foods, sourcing inspiration from the "sophisticated pharmaceutical research", to develop food systems that control transport phenomena for targeted release from a specific dosage form.

1. Introduction

Food is a complex system undergoing many physical and chemical transformations during processing and subsequent storage. These transformations are governed by molecular movements within the end product and reflect its overall stability and quality perception (Capuano, Oliviero, & van Boekel, 2017; Le Meste, Champion, Roudaut, Blond, & Simatos, 2002). Broadly speaking, a food matrix can be classified as a low-solid system (< 40% w/w), intermediate-solid system, (40–70% w/w), and high-solid system (typically 70–95% w/w), where the presence of co-solute like glucose syrup assists in the binding of water molecules to prevent crystallisation, hence facilitating sample vitrification upon cooling to subzero temperatures (Kasapis, Al-Marhoobi, Deszczynski, Mitchell, & Abeysekera, 2003a).

Structural elements of the food matrix control thermodynamic and kinetic aspects of techno-functionality and, as is increasingly understood, bio-functionality (Champion, Le Meste, & Simatos, 2000; Fundo, Quintas, & Silva, 2015). Regarding the latter, a major issue in the food industry is the preservation of bioavailability in commercial formulations. For example, essential fatty acids, vitamins, polyphenols, enzymes and various antioxidants are known to be sensitive to environmental conditions of temperature, moisture content and pH (Zhang, Wang, Shi, & Pan, 2017). They require an entrapping matrix to protect them from harsh environmental conditions, with biopolymers from plants, animals or microorganisms being frequently utilised as such. Biopolymers are partially amorphous materials sensitive to structural transformations from liquid to solid-like glassy consistency upon thermal treatment (Angell, 1995a; Debenedetti & Stillinger, 2001; Slade & Levine, 1991a). The molecular phenomenon associated with this step change in heat capacity and coefficient of expansion is referred to as the glass transition temperature (T_g) (Abiad, Carvajal, & Campanella, 2009; Roos, 2010).

The effect of T_g on maintaining desirable performance in the designed formulation can be observed, for instance, in an oil microcapsule composed of methyl linoleate, lactose and gelatin. The rates of lipid oxidation and oil diffusion are considerably affected by the collapse of the matrix and subsequent crystallisation of lactose when the mixture is subjected to temperatures above its glass transition temperature (Shimada, Roos, & Karel, 1991). It is desirable, therefore, to understand the phenomenology of biomaterial vitrification in order to predict

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Table 4 (*continued*)

Biopolymer	Crosslinker	Bioactive compound	Geometry of the system	Summary of findings	References
Guar gum succinate – sodium alginate (GGS-SA)	Barium ions	Ibuprofen	Beads	Bead swelling and Ibuprofen release profiles were higher at pH 7.4 than pH 1.2 due to the pH-dependent expansion of the GGS-SA network	Seeli et al. (2016)
Xanthan gum	Sodium trimetaphosphate (STMP)	Bovine serum albumin (BSA)	Hydrogel cylindrical disk	(1) An increase in cross-linking density led to a lower swelling ratio of hydrogels (2) Xanthan gum/STMP hydrogels with a porous and interconnected structure display good release-controlled properties for BSA (3) A burst release was observed for the first 10 h with a less Fickian diffusion ($n < 0.45$) followed by a step change in subsequent experimentation up to 50 h with an anomalous transport behaviour ($n > 0.45$)	Tao et al. (2016)
Casein	Genipin	Bovine serum albumin (BSA)	Slab hydrogel	(1) At pH 1.2, the swelling ratio of the hydrogel and the release amount of the entrapped BSA were relatively low, as opposed to rapid diffusion at pH 7.4 (2) Transport behaviour of BSA followed Fickian and pseudo-Fickian release profiles, with the latter being observed at high amounts of genipin (10 mmol/L) that correspond to a dense casein network limiting the diffusion of the protein	Song et al. (2009)
Sodium caseinate	Glyoxal, calcium chloride and transglutaminase	Lysozyme	Film	(1) Immersing the film at pH near the isoelectric point of sodium caseinate causes the protein to become insoluble and therefore significantly accelerates the release of lysozyme, but a slower release profile is recorded when a crosslinking agent is added (2) Diffusivity of lysozyme as a result of the addition of crosslinkers followed the relationship: glyoxal > transglutaminase > calcium chloride	De Souza, Fernández, López-Carballo, Gavara, and Hernández-Muñoz (2010)
Casein	Genipin	Alfuzosin hydrocloride	Spray-dried nanoparticles	(1) Increasing amount of crosslinking agent results in significant reduction of drug release (about 27%) after 24-h release at concentration of drug to polymer of 1:5 (2) Decrease in release profile of drug by 20% was recorded when the crosslinking period was extended from 1 to 5 h (3) Anomalous release profile was calculated based on the Korsmeyer–Peppas model indicating the effect of drug coupling with polymer relaxation	Elzoghby et al. (2013)
Gelatin	Genipin	Morphogenetic protein 2 (rhBMP-2)	Spherical microparticles	(1) The release rate of rhBMP-2 was dependent on the degree of crosslinking of the gelatin/genipin system (2) Controlled release of rhBMP-2 was governed by: (a) Hydrogen binding potential of the gelatin/genipin network enhanced the ability of the matrix to bind rhBMP-2 through its glycosylated molecule (b) The intermolecular binding caused by genipin crosslinking increased the tortuosity of the matrix, thereby increasing the retention of rhBMP-2	Solorio, Zwolinski, Lund, Farrell, and Stegemann (2010)
Gelatin	Genipin	Lysozyme	Film	(1) Rapid release of lysozyme from gelatin/genipin films at acidic pH (pH 3.8), as compared to neutral pH (pH 7.0), which was due to the degradation of the film at acidic conditions (2) Release behaviour of lysozyme from the delivery system followed a two-step biphasic process, namely: burst effect and a constant slow release (3) At the first step (burst effect), the release of lysozyme linearly increased over time, as observed in the microbial inhibition activity of this bioactive agent (4) Diffusion of lysozyme in the films decreased gradually as genipin concentration increased	Ma et al. (2013)

behaviour in the matrix, with interactions being mainly physical through opposite charges (Pal, Paulson, & Rousseau, 2013). Bonferoni et al. (2004) described the release behaviour from λ-carrageenan of timolol maleate, an alkaline drug used by mouth to treat high blood pressure and chest pain due to insufficient blood flow to the heart. Release is controlled according to therapeutic requirements due to drug crosslinking with an anionic λ-carrageenan-rich environment, as compared to the rapid release non-interaction profile of the drug with gelatin.

Ionic profile of the release medium can promote diffusion of bioactive compounds by facilitating disentanglement of the crosslinking knots of the biopolymer network or erosion of the matrix (Kono, Otaka, & Ozaki, 2014; Mondal, Li, & Wang, 2015; Seeli, Dhivya, Selvamurugan, & Prabaharan, 2016; Song et al., 2009). The release of β-carotene from genipin-crosslinked κ-carrageenan/carboxymethyl cellulose beads to buffer solutions at acidic conditions (pH 1.2) was 2.5 times less compared to the near neutral system (pH 7.4) (Muhamad, Fen, Hui, & Mustapha, 2011). At pH 7.4, beads swelled due to the electrostatic repulsion of ionised carboxyl groups of carboxymethyl cellulose, which forms hydrogen bonds at acidic conditions. Opposite trend was observed on lysozyme release from gelatin/genipin films (Ma, Tang, Yin, Yang, & Qi, 2013). Rapid release of lysozyme occurred when the system is subjected to acidic conditions (pH 3.8) in contrast to neutral pH (pH 7.0). Burst release of lysozyme from this composite system was related to the degradation of the film, which was triggered by acid hydrolysis of gelatin networks and the breakdown of genipin-gelatin crosslinks at low pH conditions.

6.4. Effect of penetrants

Besides considerations of the matrix density/crosslinking and molecular interactions between polymeric network and bioactive agent that have been discussed in earlier sections, morphological characteristics of penetrant molecules, i.e. size, shape, conformational chemistry and electrolyte nature, influence the behaviour of delivery vehicles. Thus, the ability of penetrant to infuse in the polymeric matrix depends on interactions and space availability, and often becomes the rate limiting process in drug release (Langer & Peppas, 1981; Pal et al., 2013). When the "particle size" of the solute is larger than the mesh size of the network, the former is unable to infuse and this is often called 'screening effect' of the polymer (Hoare & Kohane, 2008; Langer & Peppas, 2003). Evidence of such phenomenon was reported in genipin-crosslinked casein systems during "drug" preparation requiring infusion of a BSA solution to the casein xerogel (Song et al., 2009). Movement of large penetrant molecules can be controlled by chain disentanglement, structural relaxation or swelling of the matrix, which increases its utility *via* the creation of a "large hole size" (Zhang & Schweizer, 2015).

In the case of a small size penetrant, self-diffusion, i.e. when the chemical potential gradient of the species equals zero, is generally governed by the free volume of the matrix. In a high-solid system, penetrant could randomly transport throughout the matrix by hopping from one available space to another (Zhao, Wang, & Zhang, 2007). This is accomplished by infusing molecules that possess enough energy to overcome the intermolecular attractive forces between penetrants and/or with the neighbouring polymer chains (Barrer, 1957; Danner, 2014). This theory of molecular 'jump' is often associated with a thermal process and activation energy that flows through the system following a series of random walk motions (Mehrer, 2007, pp. 55–67). The relationship between molecular size and activation energy of infusion was discussed by Xu, Chen, Wang, and Yang (2015), suggesting that small molecules normally have a lower activation energy and their kinetic rate increases about 2 or 3 times every 10 °C depending on the critical penetrant dimension in relation to the mesh size of the polymeric network.

The shape of penetrant molecule also has a remarkable effect on transport phenomena (George & Thomas, 2001). Atomic arrangement of molecules leading to a well-defined morphology affects their binding capacity to adjacent penetrant molecules and/or polymeric network chains (Leahy-Dios & Firoozabadi, 2007). Douglass and McCall (1958) suggested that the mechanism of infusion for long-chained hydrocarbon molecules should consist of multiple displacements of chain segments rather than of molecules as a whole. In addition, compounds made of linear molecules branching out exhibit diffusion that is in general up to 30% slower than the spherical counterparts (Hayduk & Buckley, 1972).

6.5. Effect of temperature

It is well understood that temperature fluctuation affects considerably molecular movement. The process of diffusion occurs rapidly with heating due to structural relaxation creating vacant spaces in the matrix that allows rapid movement of penetrants through these channels (Panyoyai & Kasapis, 2016; Vrentas & Duda, 1977a). A variety of small biomolecules has been studied, in relation to their diffusion with increasing temperature, including water molecules, vitamins and phenolic compounds (Panyoyai et al., 2016a; Paramita, Bannikova, & Kasapis, 2016b; Mulet, Sanjuan, Bon, and Simal, 1999). Early studies on breakfast cereals have demonstrated an exponential relationship between water infusion and temperature increment that followed the Arrhenius law (Bakshi & Singh, 1980; Nicolin, Neto, Paraíso, Jorge, & Jorge, 2015). An extensive moisture content was employed, ranging from 0 to 1.4 g H_2O per g of cereal solids, to yield a reduction in the activation energy of infusion with water addition. For a given level of solids, the rate of transport was temperature dependent, and relatively sensitive to temperature in cereal formulations with a very low moisture content (Hsu, 1983; Le Meste, Voilley, & Colas, 1991, pp. 123–138).

More recently, it has been reported that at experimental temperatures in the vicinity of the glass transition region the molecular process of free volume governs diffusion of small penetrants. This concept addresses the increasing level of interactions with denser polymeric matrices at low temperatures that restrict the movement of small penetrants (Vrentas & Duda, 1977b). The glass transition temperature constitutes an index of convenience for monitoring diffusion, with the effect of higher temperatures traversing the glass transition region being an increase in the vacant spaces that accelerate the movement of diffusing species (Panyoyai & Kasapis, 2016; Paramita & Kasapis, 2018a). Recent work has also built on the idea by Barrer (1957) that increasing temperature provides thermal energy to overcome the attractive forces between polymer segments, or small molecules and polymer chains thus enhancing transport phenomena. Compliant results have been reported for a range of bioactive compounds, e.g. essential fatty acids from carbohydrate or protein slabs, vitamins from high-solid microcapsules, caffeine from high energy preparations, etc. (Panyoyai, Bannikova, Small, Shanks, & Kasapis, 2016b; Paramita & Kasapis, 2018b).

6.6. Effect of water and other plasticisers

Plasticisers like water and small molecule co-solute lead to an increase in intermolecular space or free volume, in a way analogous to temperature, and these "mobility enhancers" eventually decrease T_g (Ferry, 1980; Slade & Levine, 1991b). In milk powder, for instance, a ten-decade reduction in calorimetric T_g was found as a result of water plasticising from about 0 to 0.44 a_w (Silalai & Roos, 2010). Lourdin et al. (1997) showed that low molecular-weight glycerol caused a significant reduction in T_g compared to other plasticisers following the order glycerol > lactic acid sodium > sorbitol, with the molecular weights being 92, 112 and 182 g/mol, respectively (Lourdin et al., 1997).

Glycerol and sorbitol reduce intermolecular forces between adjacent chain segments, spacing them out, to allow infusion of water molecules in increasingly hydrated solid-like matrices, or diffusion of small

bioactive molecules to the release media (Delgado, Peltzer, Wagner, & Salvay, 2018; Gomi, Fukuoka, Takeuchi, Mihori, & Watanabe, 1996). Mixtures of iota-carrageenan with fluorescein demonstrated the effectiveness of water in altering the diffusion coefficient of fluorescein compared to glycerol (Karbowiak et al., 2006). Effect of lipids in assisting diffusion of solute in biopolymer based matrices was shown by Yoshida, Bastos, and Franco (2010). Thus, potassium sorbate transport from chitosan films increased fourfold in the presence of palmitic acid. The diffusion process was facilitated by the formation of voids or distances within the films due to the multilayer structure of lipid-chitosan emulsion. Potassium sorbate was allowed to move freely between chitosan chains as a result of considerable matrix swelling, about 40% of the thickness of a single chitosan film (Yoshida et al., 2010).

Non-Fickian diffusion mechanism was observed for potassium sorbate transport from edible whey protein films in the presence of plasticiser. Diffusivity ranged from 5.38–9.76 $\times 10^{-11}$ m^2/s at ambient temperature depending on the type of plasticiser. Thus, the presence of low molecular weight sorbitol in the whey protein matrix allowed rapid transport of potassium sorbate (9.76 $\times 10^{-11}$ m^2/s) compared to a sorbitol-beewax composite plasticiser (8.34 $\times 10^{-11}$ m^2/s), whereas inclusion of a liquid sugar fraction yielded a diffusion coefficient of 4.44 $\times 10^{-10}$ m^2/s (Ozdemir & Floros, 2001). In the case of whey protein/glucose syrup blends, increase in the transport volume of linoleic acid was recorded due to free spaces within the high-solid and vitrified matrix facilitated by protein substitution with plasticiser (glucose syrup) (Paramita et al., 2017).

7. Quantification of the relationship between free volume and molecular diffusion

Free space between adjacent chains can be manipulated to dictate transport phenomena of entrapped bioactive compounds through the unoccupied voids in the polymeric matrix. The "hole" free volume should be large enough for molecules to reptate or "jump into" and is continuously redistributed by thermal fluctuations determining transport patterns (Tonge & Gilbert, 2001; Vrentas & Vrentas, 2003). Diffusion is governed by the formation of sufficient size holes and energy thresholds, which are affected by the physicochemical nature of the matrix, its molecular weight and crosslinking, temperature, penetrant, and the presence of water or other plasticisers discusses thus far (Danner, 2014; Duda, 1985; George & Thomas, 2001; Holowka & Bhatia, 2014, pp. 7–58; Langer & Peppas, 1981; Pal et al., 2013; Zielinski & Duda, 1992).

The earlier model of free volume developed to explain the mechanism of molecular diffusion was by Cohen and Turnbull (1959). A ternary system of polymer, solvent and penetrating molecule (plasticiser) was used by assuming a low concentration for the third party. In this system, the probability, $P(v^*)$, of finding a hole free volume exceeding the critical volume (v^*) of the penetrant was:

$$P(v^*) = A\ exp\left(-\frac{bv^*}{f_v}\right) \tag{32}$$

where, A is a constant, b is a numerical factor of the order of unity and f_v is the free volume per molecule, i.e. the total free volume divided by the number of molecules. The Cohen and Turnbull theory emphasised the importance of molecular size by assuming that diffusion only occurs when the size of penetrating molecules is smaller than the solvent, hence following the solvent movement.

Next, Fujita (1961) considered that the process of diffusion in the above system is assisted by the redistribution of free volume, which does not require energy change, the hole free volume is large enough to accommodate the jumping molecule, and $P(v^*)$ is equal to diffusant mobility (m_d). Since the molecule was assumed to be self-diffusing, the following equation could be developed:

$$D = A\ R\ T\ exp\left(-\frac{B}{f_v}\right) \tag{33}$$

where, D is the self-diffusion coefficient, A is a proportionality factor, R is the gas constant, T is the absolute temperature (K), and B is equal to bv^* denoting the minimum hole size to permit molecular displacement. The latter parameter does not consider the variation of temperature or polymer concentration making the theory only applicable to small molecules and dilute or semi-dilute polymeric solutions with organic solvent (Masaro & Zhu, 1999).

To overcome the aforementioned shortcomings, Vrentas and Duda (1977b) were able to develop a model that follows solute diffusion in a wide range of temperatures and polymer concentrations. In doing so, the free volume of diffusing agent and polymer was added to the formula in addition to their activation energy and molecular weight. Assumptions underlying the Vrentas-Duda diffusion model include the volume of diffusant and polymer that makes the overall volume of the system, the thermal expansion coefficient averages over a range of experimental temperatures, the hole free volume is specific to diffusing agent and polymer, and the activation energy of the jumping component is determined by the polymer concentration and surrounding attractive forces, which yield the following equation (Rossi, Perale, & Masi, 2016, pp. 9–33; Zielinski & Duda, 1992):

$$D_1 = D_0\ exp\left(\frac{-E}{RT}\right) exp\left[\frac{-(\omega_1 \widehat{V_1^*} + \omega_2 \xi \widehat{V_2^*})}{\omega_1\left(\frac{K_{11}}{\gamma_1}\right)(K_{21} - T_{g1} + T) + \omega_2\left(\frac{K_{12}}{\gamma_2}\right)(K_{22} - T_{g2} + T)}\right] \tag{34}$$

$$D = D_1(1 - \phi_1)^2(1 - 2\chi\phi_1) \tag{35}$$

where, D_1 is the self-diffusion coefficient, D is the polymer/diffusing agent mutual diffusion coefficient, D_0 is a pre-exponential factor, $\widehat{V_1^*}$ and $\widehat{V_2^*}$ are the minimum hole free volume of diffusing agent and polymer, ω_1 and ω_2 are the mass fractions of the components, γ_1 and γ_2 are the the overlap factors for the free volume for the components, T_g is the glass transition temperature of the system, ϕ_1 is the penetrant volume fraction, K_{11} and K_{12} are the free volume parameters of the penetrant, K_{21} and K_{22} are the free volume parameters of the polymer, and ξ is the ratio of the critical molecular volume of the penetrant "jumping unit" to that of the polymeric matrix "jumping unit" (Rossi et al., 2016, pp. 9–33).

Recently, the above discussion has been simplified by considering that the unoccupied volume of the solid-like matrix is small (about three percent of the total free volume of the polymer in the rubbery state) and does not change significantly below its glass transition temperature (Vrentas & Duda, 1978). Above T_g, however, molecular transport is affected by the increasing free volume in tandem with polymer relaxation. Segmental mobility with increasing temperature causes a constant progression in the viscoelastic properties of the polymeric matrix, which promotes penetrant diffusion. The mathematical relationship describing this behaviour follows a WLF type solution, as discussed earlier for the free volume theory in Section 4.3 (Champion, Hervet, Blond, Le Meste, & Simatos, 1997):

$$-\log a_T = \log\left[\frac{D(T)}{D(T_g)}\right] = \frac{C'_{1g}(T - T_g)}{C'_{2g} + (T - T_g)} \tag{36}$$

where, $D(T)$ and $D(T_g)$ are the apparent diffusion coefficients at experimental and glass transition temperatures, respectively. In the context of diffusion studies, the WLF parameters take the following form:

$$C'_{1g} = \xi\ C_{1g} \tag{37}$$

$$C'_{2g} = C_{2g} \tag{38}$$

hence bringing together the diffusion school of thought (parameter ξ) with the fractional free volume at the glass transition temperature (f_g).

For $T \geq T_g$, the assumption of a rapid and linear development of the fractional free volume within the glass transition region can be considered in terms of the thermal expansion coefficient (α_f) to produce the equivalent of equation (9) for the glass transition temperature:

$$f = f_g + \alpha_f (T - T_g) \tag{39}$$

From equations (36)–(39), a simplified mathematical expression was developed between diffusion coefficient and fractional free volume (Panyoyai & Kasapis, 2016):

$$\log D(T) = \log D(T_g) + \frac{\xi}{2.303}\left[\frac{1}{f_g} - \frac{1}{f}\right] \tag{40}$$

It argues for a linear relationship between log [D (T)] and ($1/f_g$-$1/f$) that makes ξ a coupling parameter between small-molecule diffusion and matrix structural relaxation. Furthermore, it emphasizes the viscoelastic properties of the polymeric matrix within the glass transition region that govern the diffusion of penetrants with increasing free volume due to the relaxation of polymeric segments. This quantification of the cooperativity between biopolymer and organic compound interactions allows the informed manipulation of bio-functionality release in several functional materials, as it will be discussed next.

8. Application of the combined free volume/molecular diffusion theory

This is essentially a physical approach that has been carried out extensively to monitor the sustainable release of small chemical compounds or large macromolecules from single to quaternary polymer/co-solute systems (Danner, 2014; Masaro & Zhu, 1999; Rossi et al., 2016, pp. 9–33; Siebel, Schabel, & Scharfer, 2017; Vrentas & Duda, 1977a,b). For oxygen and helium atoms in amorphous polyisobutylene, diffusion proceeded by quick hopping of the chemical elements from one cavity to another following anomalous transport behaviour. Due to the small size of the penetrating chemicals, movement occurred rapidly and their molecular order was maintained (Müller-Plathe, Rogers, & van Gunsteren, 1992). For large molecules, diffusion of plasticisers, e.g. di-*n*-alkyl phthalates, in PVC involves cooperative movements encompassing the displacement of molecular fractions with dimensions up to the entire molecular length, which is governed by temperature, concentration and activation energy. The temperature dependence of plasticiser diffusion increased from 5.0 to 6.1×10^{-8} cm^{-2}/s at 82 and 91 °C, respectively. The opposite was true for the variation in chain length of *n*-alkyl groups, where longer branched chains were more difficult to diffuse compared to the shorter counterparts due to the screening effect of the polymer matrix (Coughlin, Mauritz, & Storey, 1990; Mauritz & Storey, 1990; Mauritz, Storey, & George, 1990).

The approach found application mainly in the pharmaceutical industry for the development of drugs used as different types of medicine and medications. For example, the apparent diffusion coefficient of 5% paclitaxel from polyhedral oligosilsesquioxane thermoplastic polyurethanes (POSS TPUs) showed a three orders of magnitude change from 1.2×10^{-15} m^2/s to 8.0×10^{-19} m^2/s with increasing glass transition temperature (Guo, Knight, & Mather, 2009). Similar results were found for the diffusion of ethanol in a polydimethylsiloxane (PDMS) membrane (Mafi, Raisi, Hatam, & Aroujalian, 2014), with the increase in total free volume from the plasticising action of the penetrating liquid resulting in a cascading effect of greater permeation in the hydrophobic membrane (Guo et al., 2009).

Despite being well discussed in the synthetic polymer and drug research, literature is relatively scant on the application of the combined concept of molecular diffusion and free volume to natural polymers and food systems. A study on porous broccoli florets and stalks suggests the importance of micro/macroscopic pores or channels for moisture diffusion in vegetable matrices (Table 5). Combination of the Fickian and Vrentas-Duda models allowed quantification of transport phenomena with increasing temperature in terms of apparent diffusion coefficients, equilibrium moisture content and kinetics of diffusion that were found to be higher in broccoli florets due to their porous structure (Jin, van der Sman, & van Boxtel, 2011). Work on well controlled preparations of biopolymer systems (e.g. κ-carrageenan or high methoxy pectin) also argued that the molecular movement of entrapped bioactive compounds is governed by the physical state and void creation within the solid-like matrix (Panyoyai et al., 2015; Panyoyai et al., 2017).

This correlation between physical explanation of transport phenomena and monitoring the apparent diffusion coefficient has been used at length for studies of natural bioactive compounds, as shown in Table 5. It encompasses whey protein, waxy maize starch and polysaccharide/glucose syrup matrices as slabs or microspheres entrapping/encapsulating ascorbic acid, thiamine hydrochloride, nicotinic acid, tocopheryl acetate, α-linolenic, oleic and linolenic acids. Furthermore, an example of the temperature variation in the apparent diffusion coefficient of vitamin (ascorbic acid) from a high-solid biopolymer matrix (2% w/w high-methoxy pectin +77.6% w/w polydextrose) in relation to the fractional free volume of the matrix is reproduced in Fig. 6a (Panyoyai et al., 2016a). It clearly demonstrates the relationship between D_{eff} and f_v within the glass transition region of the polymer/co-solute system. Molecular movement effectively seizes at temperatures below T_g characterised by an f_g value of about 0.040, whereas it accelerates monotonically with increasing temperature reaching D_{eff} estimates of about 10^{-7} m^2/s at a fractional free volume (f_o) of about 0.061 (Paramita et al., 2017). Diffusion mode varies from Less Fickian to Anomalous transport depending on molecular weight and hydrophilic to hydrophobic nature of vitamins and fatty acids employed in these studies.

Equation (40) was applied successfully to natural polymer/bioactive compound systems to generate *via* linear fits of log [D (T)] and ($1/f_g$-$1/f$) values of ξ, i.e. the coupling parameter between the two constituents. This is depicted in Fig. 6b for linoleic acid release from whey protein/glucose syrup matrices as a function of co-solute concentration (Paramita & Kasapis, 2018b). They constitute evidence of the extent of interaction between fatty acid and proteinaceous network increasing in an exponential fashion, which was attributed to the reduction in the critical molecular volume of the jumping unit of the polymer with the introduction of the low molecular weight co-solute (glucose syrup). Calculated ξ values were $6.0–12.0 \times 10^{-3}$ for vitamins and $4.3–7.5 \times 10^{-3}$ for fatty acids, whereas these were found to be around 0.70 for strongly interacting hybrid polyurethanes in biodegradable stent coating (Guo et al., 2009). Hall and Torkelson (1998) suggested that the value of the coupling parameter increases on increasing the probe size/diffusant in relation to the polymer mesh size.

9. Conclusions

This review addresses issues of bioactive compound delivery for specific applications following incorporation in functional systems made of natural polymers with or without co-solute. In particular it focuses on the effect of vitrification in polymer matrices, used as carriers of bioactivity, which determines the transport rates of diffusant molecules. There is still limited information in the literature, but it appears that the free volume theory combined with the concept of apparent diffusion coefficient provides a physical explanation of transport phenomena in bioglassess with interest in functional foods and nutraceuticals. These can serve as adaptable delivery vehicles of various morphologies and geometries in relation to external physicochemical and biological stimuli. Relatively simple mathematical expressions can be constructed to quantitatively follow bioactive compound release thus describing a diffusion theory that encompasses the concept of dynamic coupling between polymeric matrix and diffusant motion. This fundamental relationship between diffusion coefficient, fractional free volume and coupling parameter has been shown to work for the controlled release of vitamins and essential fatty acids from

Table 5
Diffusion coefficient of water molecules and bioactive compounds from biopolymers and food systems using combined theory of diffusion and free volume.

Biopolymer matrix or food system	Diffusing agent	Diffusion Coefficient, D, m^2/s	Notes	References
Sucrose 30–65.3% (w/w)	Fluorescein	2×10^{-21} to 8×10^{-24}	Combined Arrhenius and modified WLF diffusion theory	Champion et al. (1997)
Broccoli stalks dried at 90 °C	Water	1.56×10^{-9} to 3.20×10^{-9}	Combined Fickian diffusion and free volume theory	Simal, Rossello, Berna, and Mulet (1998)
Broccoli florets at 35–70 °C	Water	0.86×10^{-8} to 1.67×10^{-8}	Combined Fickian diffusion and free volume theory	Mulet et al. (1999)
Chitosan films crosslinked with genipin (0–14% crosslink density)	Vitamin B12	3.44×10^{-7} to 2.39×10^{-8}	Combined Fickian diffusion and free volume theory for a crosslinked polymer	Jin and Song (2006)
Scleroglucan–borax gel system	Theophylline Vitamin B12 Myoglobin	$(8.07 \pm 0.85) \times 10^{-6}$ $(3.67 \pm 0.22) \times 10^{-6}$ $(1.21 \pm 0.21) \times 10^{-6}$	Peppas diffusion equation combined with Vrentas-Duda free volume theory	Grassi et al. (2009)
Chocolate	Hazelnut oil	2×10^{-10}	Combined Fickian diffusion and Vrentas-Duda free volume theory	Galdámez, Szlachetka, Duda, and Ziegler (2009)
Broccoli florets and stalks at 20–50 °C and moisture content of 2 kg water/kg dry matter	Water	Florets: 1.1×10^{-9} to 2.3×10^{-9} Stalks: 0.8×10^{-9} to 1.7×10^{-9}	Combined Fickian diffusion and Vrentas-Duda free volume theory	Jin, van der Sman, & van Boxtel (2011)
2%HM pectin +77.6% polydextrose at −20 °C (slab geometry)	Ascorbic acid (Vit C)	8.2×10^{-8}	Combined Fickian diffusion and modified WLF theory	Panyoyai et al. (2016a)
2% κ-carrageenan/82% glucose syrup	Thiamin hydrochloride (Vit B1)	7.06×10^{-10}	Combined Fickian diffusion and modified WLF theory	Panyoyai et al. (2015)
WPI microcapsules	Nicotinic acid (Vit B3)	8.99×10^{-15}	Combined Fickian diffusion and modified WLF theory	Panyoyai et al. (2016b)
Waxy maize starch microcapsules	Tocopheryl acetate (Vit E)	9.16×10^{-14}	Combined Fickian diffusion and modified WLF theory	Panyoyai et al. (2017)
2% κ-carrageenan +82%polydextrose at −16 °C (slab geometry)	α-linolenic acid	7.36×10^{-10}	Combined Fickian diffusion and modified WLF theory	Paramita et al. (2015)
3% HM pectin+81% glucose syrup at −16 °C (slab geometry)	Oleic acid	22.6×10^{-10}	Combined Fickian diffusion and modified WLF theory	Paramita et al. (2016a)
79% WPI + glucose syrup at −16 °C (slab geometry) WPI/gs ratio:	Linoleic acid		CombinedFickian diffusion and modified WLF theory	Paramita et al. (2017)
100:0		1.63×10^{-10}		
80:20		1.70×10^{-10}		
70:30		1.86×10^{-10}		
60:40		2.04×10^{-10}		
40:60		2.31×10^{-10}		
0:100		2.50×10^{-10}		

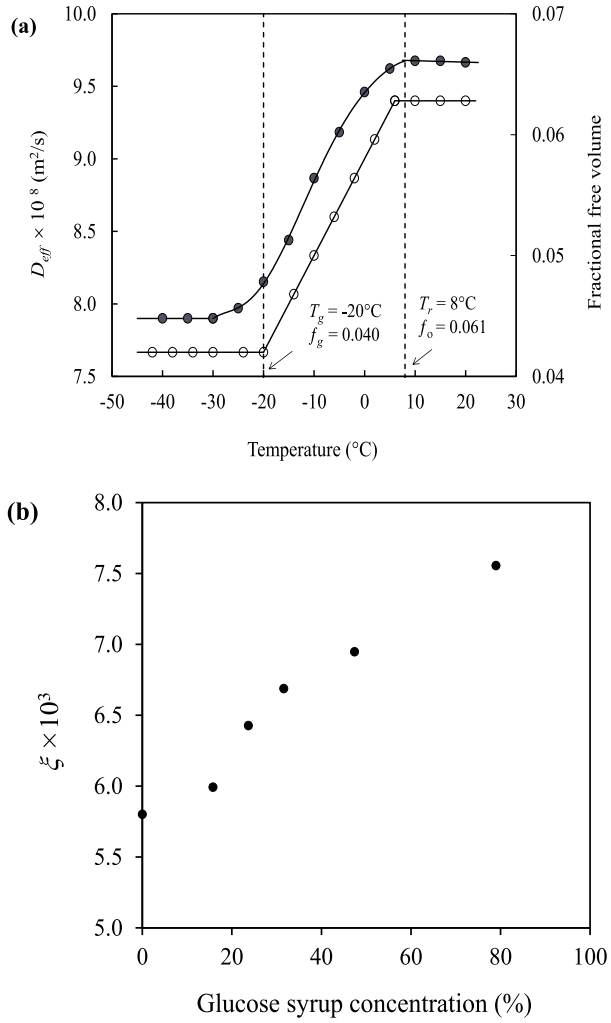

Fig. 6. (a) Temperature variation of the effective diffusion coefficient (D_{eff}) of ascorbic acid from a matrix of 2% high-methoxy pectin +77.6% polydextrose (closed symbols) in relation to the fractional free volume of the system (open symbols) (adapted from Panyoyai et al., 2016a, with permission) and (b) Coupling parameter (ξ) of linoleic acid release from whey protein/glucose syrup matrices as a function of co-solute concentration (adapted from Paramita & Kasapis, 2018b, with permission), with T_r and T_g being the temperatures at the rubbery state and glass transition, and f_o and f_g the fractional free volumes at the rubbery state and glass transition.

high-solid biopolymer networks in the glass transition region and may support further explorations for extensive application in bio-functional embodiments.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodhyd.2018.09.007.

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