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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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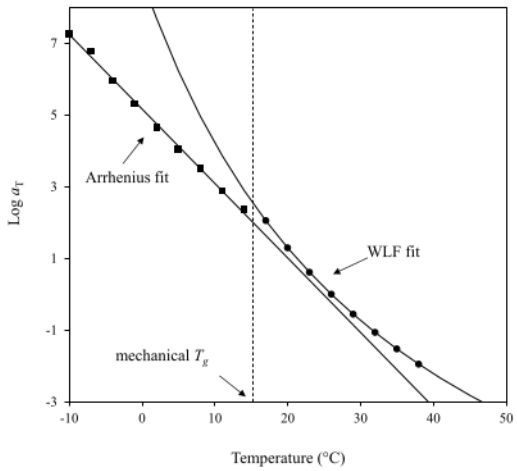

Fig. 4. Modified Arrhenius and WLF fits for 80% gelatin, plotted as a function of temperature and shift factor (adapted from Kasapis & Sablani, 2005, with permission).

& Palmen, 1998) to produce a set of shift factors (a_T), which is associated with molecular relaxation phenomena around T_g (Kasapis, Desbrières, Al-Marhoobi, & Rinaudo, 2002). Plotting the shift factors against experimental temperature often reveals a discontinuity, as illustrated in Fig. 4 for a sample of 80% (w/w) gelatin. Non-linear viscoelastic functions in the upper temperature range can be modelled with the WLF equation unveiling a free volume effect on the glass transition region of the system. At the lower temperature range, changes in viscoelasticity are better followed by the modified Arrhenius equation according to the predictions of the reaction rate theory. The meeting point of the two theoretical predictions (around 15 °C here) is identified as a system-dependant "critical temperature" (Karmas et al., 1992), which is known as the mechanical glass transition temperature of the biomaterial (Kasapis, 2005).

Mechanical T_g often deviates from the predictions of DSC T_g between 10 and 25 °C depending on the ability of the biopolymer to form a network in terms of molecular weight, electrostatic interactions with counterions, pH, etc., hence it is also known as the network T_g (Kasapis, Al-Marhoobi, & Mitchell, 2003c; Paramita et al., 2016a). This discrepancy in T_g predictions has been attributed to the nature of the measurement, with the former measuring the macromolecular properties of a glassy structure, whereas the latter focuses on the mobility of small molecule co-solute in the mixture (Kasapis & Sablani, 2005). Furthermore, metastable properties of biopolymer networks in the glass transition region affect significantly the diffusion kinetics of bioactive compounds incorporated in these high-solid matrices. And the relationship between matrix structure and transport phenomena of bioactive compounds will be reviewed next, once the various aspects of the diffusion theory have been dealt with.

5. Diffusion in high-solid biopolymer matrices and foods

5.1. Classical diffusion theory

The basic theory of diffusion was first introduced by Thomas Graham (1833) who concluded that gas in a closed chamber diffuses according to the square root of its density, with changes (contraction or expansion) in its volume being affected by the fractional resistance of channels in the experimental device. In 1855, Adolph Fick published his observations on salt diffusion through a porous membrane in water, which is proportional to the concentration difference in the two phases and inversely proportional to the distance of one element relative to the other. He then postulated the first law of diffusion where the transfer rate of the diffusant through a defined area is proportional to the change in the concentration gradient, as presented in the relation (Crank, 1975; Peppas & Narasimhan, 2014):

$$F = -D\frac{\partial C}{\partial x} \tag{15}$$

where, F is the flux (also noted as J) in mol m^{-2} s^{-1}, ∂C is the change in concentration of a diffusing substance in mol m^{-3}, ∂x is the variation in space coordinate in m, and D is the diffusion coefficient in m^2 s^{-1}. The negative symbol denotes the opposite direction of diffusion relative to the intensifying concentration of the substance.

Fick's First Law of diffusion only applies when diffusion occurs in a steady state, where concentration remains fixed, creating a uniform system that allows constant accumulation of the bioactive compound in the release medium, regardless of the time of observation. In normal circumstances, however, the concentration of diffusant decreases as a function of time creating a concentration or diffusion profile that describes an unsteady state. To follow transport kinetics in this case, Fick proposed the Second Law of diffusion, as follows (George & Thomas, 2001):

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{16}$$

where, ∂t is the variation in time, with the diffusion coefficient being affected by concentration changes.

The aforementioned theoretical principles guide the transport behaviour of small molecules in a biopolymer network. This can be classified as Fickian (Case I), non-Fickian (Case II), or anomalous diffusion that relates to a mixture of concentration dependent diffusion and structural relaxation of the supporting matrix (Alfrey, Gurnee, & Lloyd, 1966). An expedient approach to examine the rates of many transformations in a multi-species system is afforded by the empirical power-law equation of Ritger and Peppas (1987):

$$\frac{M_t}{M_\infty} = kt^n \tag{17}$$

where, M_t and M_∞ are the cumulative amounts of diffusant at a particular time (t in s) and at time approaching infinity, k is the structural or geometric constant for a particular system, and n is the diffusion exponent of the entrapped compound/ingredient. Table 2 summarizes the values of n that depend on the geometric characteristic of the system being a slab, cylinder or sphere (Lao, Peppas, Boey, & Venkatraman, 2011; Masaro & Zhu, 1999; Siepmann & Peppas, 2011).

Literature utilised the concept of diffusion exponent to model the Fickian, anomalous and Case II transport but, recently, this concept has been extended to include other release mechanisms, i.e. the Pseudo or Less Fickian diffusion, where $n < 0.5$, and the Supercase II diffusion, where $n > 1.0$ (Sperling, 2006). Less Fickian (and Fickian, where $n = 0.5$ for slabs) diffusions are often assumed to be molecular processes of a rather slow solute transport, where the rate of diffusivity is lower than the rate of structural relaxation in the polymer network ($R_D < R_R$). Approximately equal diffusion and relaxation rates are

Table 2
Diffusion exponents describing the release mechanism of bioactive compounds from various polymer matrix geometries.

Diffusion exponent (n)			Release mechanism
Slab (thin film)	Cylinder	Sphere	
0.5	0.45	0.43	Fickian diffusion (Case I transport)
$0.5 < n < 1.0$	$0.45 < n < 0.89$	$0.43 < n < 0.85$	Anomalous transport or non-Fickian diffusion
1.0	0.89	0.85	Case II transport

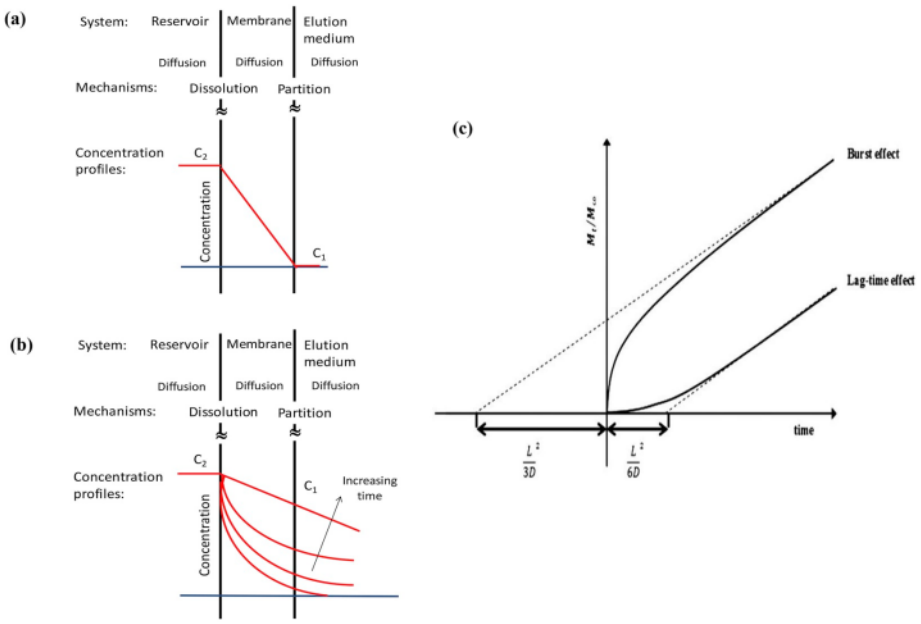

Fig. 5. (a) Steady state *versus* (b) unsteady state diffusion through membrane (modified from Cussler, 2009; Fan & Singh, 2012), and (c) lag time *versus* burst effects at steady-state diffusion (adapted from Siepmann & Siepmann, 2012), with C_2 and C_1 being the initial high and final low concentrations of the diffusing species, M_t/M_∞ the fraction of the released compound at time (t) and infinite time (∞), L the distance travelled, and D the diffusion coefficient.

characterised by an anomalous transport ($R_D \sim R_R$), where $0.5 < n < 1.0$ for slabs. Finally, Supercase II (and Case II, where $n = 1.0$ for slabs) processes reflect high rates of diffusion transport, as compared to the rate of structural relaxation ($R_D > R_R$) (Siepmann & Siepmann, 2008).

5.2. Improved diffusion theory

Besides the empirical approach of Ritger and Peppas (1987) presented in the preceding section, it was felt that transport phenomena should be described explicitly as a function of the geometry of the delivery device beyond the values obtained for k in equation (17). Regarding the First Law of diffusion, derivations were based on the concept of "free" diffusion where molecules move freely in any direction with only neighbouring molecules blocking their mobility. Here the rate of diffusion is faster than the rate of dissolution and it is time independent. A diffusion coefficient develops from the change in concentration along the space coordinate of the matrix where the flux of molecules across the membrane moves from high-concentrated to low-concentrated regions shown in Fig. 5a (Floury, Jeanson, Aly, & Lotal, 2010). Equation (15) that generalises Fick's First Law can then be recast to express diffusion at a steady-state in any coordinate system (Friedman, 2008), which provides equations for specific geometries in one dimension of the flux vector (F), as summarized in Table 3.

Literature then dealt with the more realistic case of Fick's Second Law in relation to the excipient geometry. In doing so, Fick's First Law was combined with the concept of mass balance to rationalise transport phenomena as a function of both distance or position and release time known as the unsteady-state diffusion (Fig. 5b). For the standard geometry of slab or thin film, the generalised form of Fick's Second Law shown in equation (16) was reworked with boundary constrains to yield the following equation (Peppas & Narasimhan, 2014; Ritger & Peppas, 1987):

Table 3
Steady-state diffusion equations in different geometries derived from Fick's law of diffusion.

Geometry	Steady-state expression	Equation
A solid slab	$D\frac{d^2C}{dx^2} = 0$	$F = D\frac{(c_2 - c_1)}{(L_2 - L_1)}$
A solid hollow cylinder	$\frac{D}{r}\frac{d}{dr}\left(r\frac{dc}{dr}\right) = 0$	$F = D(c_2 - c_1)\left(\frac{2\pi L}{\ln\frac{r_2}{r_1}}\right)$
A solid hollow spherical shape	$\frac{D}{r^2}\frac{d}{dr}\left(r^2\frac{dc}{dr}\right) = 0$	$\frac{F}{4\pi}\left(\frac{1}{r_1} - \frac{1}{r_2}\right) = D\,(c_2 - c_1)$

Note: c_1 and c_2 are solute concentrations at the opposite sites of the slab, cylinder or sphere; L_1 *and* L_2 are distances (m) at concentrations c_1 and c_2, respectively; L is the length of the cylinder; r_1 and r_2 are the inner and outer radii of a hollow cylinder or hollow sphere.

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} exp\left[\frac{-(2n+1)^2\pi^2 D}{L^2}t\right] \tag{18}$$

where, M_t/M_∞ is the fraction of the released compound, t is in seconds, L is the distance travelled (m), n is a dummy variable, and D is the diffusion coefficient in $m^2\ s^{-1}$. For short experimental times, the above approximation function can be rewritten as an error function (Siepmann & Peppas, 2012):

$$\frac{M_t}{M_\infty} = 4\left[\frac{Dt}{L^2}\right]^{1/2}\left[\frac{1}{\pi^{1/2}} + 2\sum_{n=1}^{\infty}(-1)^n ierfc\frac{nL}{2\sqrt{Dt}}\right] \tag{19}$$

with experimental evidence arguing that under these conditions, the error function $ierfc\ nL/2(Dt)^{0.5}$ won't significantly affect results if is taken to be close to zero. Therefore, the diffusion equation for a slab/thin film (so that it minimises edge effects) is given as (Wang, Wu, & Lin, 2008; Yusheng & Poulsen, 1988):

$$\frac{M_\infty - M_t}{M_\infty - M_i} = 4\left(\frac{Dt}{\pi L^2}\right)^{1/2} \quad (20)$$

where, data that follow at least partially, most commonly at $M_t/M_\infty \leq 0.6$ the "half-time" diffusion of $t^{1/2}$, indicate a Fickian release profile (Peppas & Peppas, 1994).

The well-defined geometry of a single sphere was also considered, and bioactive compound transport from a completely sunk spherical matrix under defined boundary restrictions was found for the early part ($M_t/M_\infty < 0.4$) of the experiment to be (Peppas & Peppas, 1994; Ritger & Peppas, 1987):

$$\frac{M_t}{M_\infty} = 6\left(\frac{Dt}{\pi R^2}\right)^{1/2} - 3\left(\frac{Dt}{R^2}\right) \quad (21)$$

Towards equilibrium conditions ($M_t/M_\infty > 0.6$), transport phenomena are better described by the following equation (Siepmann & Siepmann, 2012):

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\exp\left(-\frac{\pi^2 Dt}{R^2}\right) \quad (22)$$

In addition to film and spherical geometries, the diffusion of penetrants in a cylindrical polymer structure is also of interest, and this is given, respectively, for short ($M_t/M_\infty \leq 0.4$) and long ($M_t/M_\infty > 0.6$) experimental times as follows:

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi R^2}\right)^{1/2} - \frac{Dt}{R^2} \quad (23)$$

$$\frac{M_t}{M_\infty} = 1 - \frac{4}{(2.405)^2}\exp\left(-\frac{(2.405)^2 Dt}{R^2}\right) \quad (24)$$

where, R is the radius of the sphere or cylinder. The above protocol is applicable to conditions of constant diffusion for bioactive compounds that are uniformly distributed within a polymeric matrix, with their concentration being lower than their solubility limit in the matrix (state of a monolithic solution).

For the sake of completion, we wish to refer in this juncture to the early model of Higuchi that provided the first example of a mathematical model to describe drug release from a matrix system (Higuchi, 1961 &, 1963; Siepmann & Peppas, 2011). This is a pseudo-steady state diffusion where the active compound is homogenously distributed and its size is much smaller than the thickness of the matrix. The model requires that the concentration of the loaded compound is much higher than the solubility limit in the matrix hence its diffusion is constant with time and independent of its position in the delivery vehicle. The above conditions, in combination with a system that does not swell or disintegrate during the diffusion process, produce the Higuchi equation:

$$\frac{M_t}{A} = \sqrt{D(2C_0 - C_s)C_s t} \text{ for } C_0 > C_s \quad (25)$$

where M_t is the cumulative amount of entrapped compound at time t, A is the surface area of the controlled release device exposed to the release medium, D is the diffusion coefficient of the compound within the polymeric matrix, and C_o, C_s are the compound initial concentration and solubility concentration in the matrix, respectively. Clearly the basic equation of Higuchi describes the empirical power-law equation of Ritger and Peppas (17) in the idealised condition of a Fickian diffusion, where $n = 0.5$ (Lao et al., 2011).

In practice, the diffusion of bioactive compounds does not follow the ideal release behaviour, upon exposure to the release medium, described by the Higuchi equation for Case I transport. Countercurrent diffusion of the solvent, which is thermodynamically compatible with the polymeric matrix, often causes volume expansion and swelling leading to a moving boundary condition. Bioactive compound release is no longer a pure diffusion–controlled process, and is both affected by a concentration gradient and the relaxation of the polymeric network according to the osmotic flow of the solvent (Peppas, 1984).

A heuristic model developed by Peppas and Sahlin (1989) aims to address this complex problem in a rather straightforward manner:

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \quad (26)$$

where, k_1, k_2 and m are constants and t is time. The first term on the right hand side of the equality sign represents the Fickian diffusion contribution, F, whereas the second term is the case-II contribution from polymer relaxation, R. The ratio of both contributions can be calculated to provide an idea of the interplay between the two molecular processes during experimentation (Siepmann & Peppas, 2012):

$$\frac{R}{F} = \frac{k_2}{k_1} t^m \quad (27)$$

In systems with a protective membrane covering the surface of the biopolymer/bioactive compound composite, diffusion in the release medium won't occur immediately. There is a delay time before the active compound can penetrate the membrane and diffuse, which is called the "lag-time" (Fig. 5c). For membrane-controlled reservoir devices, equations (17) and (26) can be recast into the lag-time effect for Peppas equation and lag-time effect for Peppas-Sahlin equation, respectively (Ford et al., 1991; Ma et al., 2018):

$$\frac{M_t}{M_\infty} = k(t - l)^n \quad (28)$$

$$\frac{M_t}{M_\infty} = k_1(t - l)^m + k_2(t - l)^{2m} \quad (29)$$

where, t is in seconds, l is the lag time and the remaining parameters have been described earlier.

In contrast to the lag-time effect, the release profile of a bioactive compound can show a drastic increase in gradient concentration, immediately after exposing the system to the release medium. This phenomenon is known as the "burst effect" and is also illustrated in Fig. 5c. The appropriate equation to accommodate the burst effect is written as follows (Lao et al., 2011; Lindner & Lippold, 1995):

$$\frac{M_t}{M_\infty} = kt^n + b \quad (30)$$

where, b is the burst effect at a particular time. Such patterns are observed when the membrane is saturated with an active ingredient due to its accumulation in the membrane over a long period of time during storage of the bio-functional product (Siepmann & Siepmann, 2012).

6. Factors affecting diffusion in biomaterials and food systems

6.1. General matrix effects

The structural properties of biomaterials, as determined by molecular assembly and concentration, are critical for the diffusion of bioactive compounds from single or composite preparations (Contreras-Lopez, Champion, Hervet, Blond, & Le Meste, 2000; Duda, 1985). For example, a combination of silk-like and elastin-like amino acid sequences demonstrated the effect of protein concentration and specific ratio of these amino acid blocks on the release behaviour of entrapped bioactive compounds (Cappello et al., 1998). Their transport phenomena are further dependent on the vitrification properties of the high-solid matrix recorded for several preparations of natural polymers plasticised with small molecule co-solute (Panyoyai & Kasapis, 2016; Paramita & Kasapis, 2018b).

Material composites are generally preferred to yield the required techno-functionality that underpins bio-functionality *via* controlled drug release. Mixing of natural polymers results in binary systems with a phase-separated or associated network topology (Bates, 1991; Shi & Weitz, 2017). The former is a likely scenario in mixing two biopolymers, where there is no overriding drive for thermodynamic heterotypic

associations, and the behaviour of segregated phases can be further manipulated by the degree of branching in side chains (Bates, 1991). The viscosity of gelatin in mixture with polydextrose was varied as a function of increasing co-solute concentration to reach solids levels up to 80 (w/w), which influenced the permeability and mechanical properties of the high solids film and created a glass transition temperature of −22 °C, as compared to single polydextrose preparations at this solids level, $T_g = -30$ °C (Almrhag et al., 2012). Table 1 summarizes estimates of the glass transition temperature for a wide range of natural polymers (polysaccharides and proteins) and in mixture with polyhydroxy co-solute using the combined framework of WLF equation and free volume theory. These were confirmed experimentally with thermomechanical analysis to delineate the transition from glassy state to a rubbery plateau leading to increased segmental mobility that affects drug diffusion in these excipients (George & Thomas, 2001).

Since the bioactive compound diffusion occurs through the microscopic or macroscopic channels defined by the integrity of the polymeric network, voids or free volume between adjacent structural knots can significantly impact the quality of the film in terms of its function as a delivery vehicle (Karel & Saguy, 1991). The diffusion kinetics of caffeine, as a pharmacotherapeutic, was monitored in films made of glucose syrup alone or κ-carrageenan/glucose syrup mixtures to confirm a considerable restriction in its mobility due to the increase in the mechanical T_g of the mixture (Jiang & Kasapis, 2011). Change in the kinetic rates of essential fatty acids from high-solid whey protein matrices was also recorded, with increasing plasticisation of the protein network by co-solute (glucose syrup) leading to a transformation from classic Fickian to anomalous transport (Paramita et al., 2017). Multilayer designs of chitosan and fucoidan were used to follow this change from Fickian to anomalous diffusion of poly-L-lysine, where structural relaxation was manipulated with pH leading to changes in the ionic interactions between drug and polymer (Pinheiro et al., 2015).

6.2. Effect of molecular weight of polymer and diffusing species

Discussion in the preceding paragraph indicates that the nature of the polymeric network should also be a critical aspect in molecular transport. The mesh size of the holding structure shaped up *via* mechanical relaxation and chain reptation will determine diffusant mobility (Langer & Peppas, 2003). In high-solid preparations, variation in the apparent diffusion coefficient is regulated by the glass-to-rubber transition, as already reviewed (Korsmeyer & Peppas, 1981; Lourdin, Coignard, Bizot, & Colonna, 1997). The influence of T_g on polymeric molecular weight has also been examined (Holowka & Bhatia, 2014, pp. 7–58) and, for example, in high-solid gelatin/sucrose/glucose syrup (80% w/w) decrease in molecular weight of the protein caused considerable delay in the coil-helix transition and vitrification of the system (Kasapis et al., 2003b).

Low molecular-weight viscous components increase free space in the matrix, lower the activation energy of conformational rearrangements from one state to another, and accelerate diffusion kinetics (Paramita et al., 2017). In contrast, a high molecular weight polymer creates entanglements in the form of a cage-like structure that restricts the movement of diffusing materials (Hoare & Kohane, 2008; Langer & Peppas, 2003). Such demonstration has been reported for caffeine release from complex protein/polysaccharide matrices that systematically increased the elastic property, *via* higher polymeric molecular weight, to retard the release of the pharmacotherapeutic (Hernández-Marín, Lobato-Calleros, Román-Guerrero, Alvarez-Ramirez, & Vernon-Carter, 2016).

Aside from the structural properties of the macromolecule, dimension of diffusing species also influences transport. Displacement of bioactive compound in the polymeric system needs to navigate the entangled structure of chains or defined topological locus formed by neighbouring molecules (Klein, 1981). The molecular weight dependence of this diffusion phenomenon is expected to comply with the following relationship:

$$D \sim M^{\alpha} \tag{31}$$

where, D is the apparent diffusion coefficient, M is the molecular weight of diffusing substance and α is a constant (Bachus & Kimmich, 1983). The value of α varies from 0.5 to 2.0 depending on diffusion mechanism; α is 0.5 for a bead-shaped molecule, 1.0 for molecules comprising up to 30 beads, and 2.0 for more than 30 beads (Bachus & Kimmich, 1983; Fang & Vitrac, 2017). This condition is only valid for systems without steric or other constrains and if the active agent is self-diffusing (Fang & Vitrac, 2017). In broad agreement with the above, Lavoine, Guillard, Desloges, Gontard, and Bras (2016) have shown a 65-time faster diffusion of caffeine (M_w = 194 g/mol) compared to chlorhexidine digluconate (M_w = 898 g/mol) from cellulose nanofiber samples. Similar outcomes were also reported by Cappello et al. (1998) and Kolakovic et al. (2013) using dextran-fluorescein and several drugs with various molecular weights upon diffusion from protein and cellulose matrices.

6.3. Effect of crosslinking

Formation of a three-dimensional lattice for the targeted delivery of bioactive compounds is fine-tuned by the density and stability of intermolecular associations that can be physical or chemical in nature (Charlesby, 1990; Holowka & Bhatia, 2014, pp. 7–58). The former has been extensively discussed in the preceding sections and chitosan, for example, utilises such self-associations to form an interpenetrating structure that can accommodate, *via* ionic bonds, small penetrants or co-solute (Berger et al., 2004). In order to withstand the harsh conditions of the human gastrointestinal tract, cross linking agents are often introduced in the polymeric matrix (Peppas, Huang, Torres-Lugo, Ward, & Zhang, 2000).

1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) is a low toxicity crosslinking agent that has been used to create guar gum films. These were characterised by high rigidity as a function of the degree of crosslinking due to the formation of dense networks with a plethora of structural knots to store shear energy (Holowka & Bhatia, 2014, pp. 7–58). Accordingly, the DSC T_g values of the films were higher than the uncrosslinked preparations (Banegas, Zornio, Borges, Porto, & Soldi, 2013). Water absorption of the crosslinked films with 30% EDC was lower than the 10 and 20% samples owing to the relative unavailability of hydroxyl groups to form hydrogen bonding with water molecules. Finally, Peters, Luyten, Alting, Boom, and van der Goot (2015) documented the increasing water-holding capacity of whey protein microparticles from six to nine grams water per gram of protein in the presence of dithiothreitol (DTT), which decreased the disulphide-bridge/crosslinking density of the network.

Crosslinking agents for oral administration include genipin, anhydrous tripolyphosphate, citric acid, transglutaminase and glutaraldehyde. They have been utilised to manipulate the structural characteristics of delivery vehicles *via* binding with opposite-charged polymeric chains or an enzyme-mediated crosslinking process (Aramwit, Ekasit, & Yamdech, 2015; Orban et al., 2004; Song, Zhang, Yang, & Yan, 2009). Genipin is considered to be non-toxic and finds increasing application in functional foods and pharmaceutical dosage forms. In the presence of oxygen, genipin reacts with two lysine amino groups from adjacent protein segments to form stable associations (Song et al., 2009). In the case of alfuzosin hydrochloride, a pharmaceutical drug used to treat benign prostatic hyperplasia, gradual release was achieved according to therapeutic requirements from spray dried genipin/casein nanoparticles prepared at drug-polymer concentrations of 1:5 (Elzoghby, Samy, & Elgindy, 2013).

Table 4 summarizes the outcomes of some delivery studies in terms of natural polymer, crosslinking agent, bioactive compound/drug, device geometry and type/kinetics of release. Crosslinking between bioactive compound and macromolecule might also affect release

Table 4
Release studies of bioactive compounds using biopolymers and natural crosslinkers.

Biopolymer	Crosslinker	Bioactive compound	Geometry of the system	Summary of findings	References
Chitosan	Genipin	Albumin	Microspheres	(1) The degree of cross-linking of chitosan microspheres increased with cross-linking time or genipin concentration (2) The swelling ratio decreased with increased cross-linking time or genipin concentration (3) Chitosan microspheres crosslinked with genipin released albumin more slowly than non-crosslinked microspheres (4) Controlled release was governed by: (a) Genipin being available to react with the NH_2 groups of albumin as well as those of the chitosan (b) Interaction between albumin and chitosan	Yuan et al. (2007)
Chitosan	Genipin	Nerve growth factor (NGF)	Conduits	Controlled release of NGF was controlled by: (a) Concentration gradient (b) Degradation of chitosan (c) Intermolecular crosslinking of genipin with chitosan to entrap NGF	Yang et al. (2011)
Chitosan	Anhydrous tri-polyphosphate	Sericin	Microspheres	(1) Controlled release was governed by: (a) Strong ionic interactions of the positively charged chitosan with the negatively charged sericin (b) Degradation rate of microspheres *via* enzymatic hydrolysis (2) *In-vitro* release study indicated optimum ratio of drug to polymer of 1:1 after 72 h release at 37 °C	Aramwit et al. (2015)
Chitosan-g-poly(methacrylamide) (CS-g-PMAAm)	Glutaraldehyde	Enalapril maleate (ENAM)	Microspheres	(1) Release profiles were governed by the effect of concentration of bioactive compound and amount of crosslinking agent, with high amount of drug (15%) resulting in increase in ENAM diffusivity (2) The '*n*' value indicates a diffusion mechanism ranging from 0.30 to 0.50 for a Less (Pseudo) Fickian and Fickian drug release	Swamy et al. (2013)
Chitosan	Glutaraldehyde	Bovine serum albumin (BSA)	Hydrogel beads	BSA adsorption capacity to the hydrogel was reduced at acidic pH due to the repulsive force created by the positive charged chitosan and BSA, but adsorption and subsequent diffusion improved as the pH increased above 5.0 due to the electrostatic interaction between biopolymer (chitosan) and penetrant (BSA)	Mondal et al. (2015)
Chitosan	Genipin	Salidroside	Microspheres	A burst release of salidroside from chitosan-genipin microspheres followed a Fickian model ($0.43 < n < 0.85$) at the early stage of diffusion (< 10 h), which was followed by a sustained release of a less Fickian diffusion mechanism ($n < 0.43$) at 10–72 h	Luo et al. (2015)
κ-Carrageenan/polyvinyl alcohol	Genipin	β-Carotene	Film	(1) Addition genipin allowed structural modification and minimised the burst release of β-carotene from a κ-carrageenan/polyvinyl alcohol film (2) Burst release of the bioactive compound was affected by the degree of crosslinking and the mesh space available for diffusion (3) Increasing crosslinker concentration (0.1–1.0 mM of genipin) reduces the diffusivity coefficient of β-carotene	Hezaveh and Muhamad (2013)
κ-Carrageenan/sodium carboxymethylcellulose (CCMC)	Genipin	β-Carotene	Spherical beads	(1) β-Carotene release was reduced after CCMC was cross-linked with genipin (from 0.5 to 1.5 mM) due to increasing degree of polymer crosslinking and network density (2) The release rate was higher at near neutral pH (7.4) compared to in acidic condition (pH 1.2) by 2.5 times	Muhamad et al. (2011)
Alginate–montmorillonite composite	Calcium or barium	Riboflavin	Beads	Release rate was significantly low for alginate beads with high amount of montmorillonite (0.2%) leading to less Fickian diffusion ($n < 0.43$) in simulated gastric or intestinal fluid	Kaygusuz, Uysal, Adımcılar, and Erim (2015)
Guar gum (GG)	1,2,3,4-butanetetracarboxylicdianhydride (BTCA).	Bovine Serum Albumin (BSA) and egg white lysozyme	Granulated hydrogels	(1) Transport profiles of BSA and lysozyme were modified based on the pH of the system, with maximum adsorption of BSA occurring at pH where BSA and GG were oppositely charged and similarly for the oppositely charged lysozyme and GG at pH 6-11 (2) In the first hour of the release study, BSA/lysozyme diffusion was 30–50% of the loaded protein *via* a burst effect but later, diffusion was less rapid because the protein was bound to the gel network *via* strong interactions	Kono et al. (2014)

(*continued on next page*)

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 (9.76×10^{-11} m^2/s) compared to a sorbitol-beewax composite plasticiser (8.34×10^{-11} m^2/s), whereas inclusion of a liquid sugar fraction yielded a diffusion coefficient of 4.44×10^{-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:

$$f = f_g + \alpha_f (T - T_g) \quad (39)$$

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

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

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 $\times 10^{-8}$ 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 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	$(8.07 \pm 0.85) \times 10^{-6}$	Peppas diffusion equation combined with Vrentas-Duda free volume theory	Grassi et al. (2009)
	Vitamin B12	$(3.67 \pm 0.22) \times 10^{-6}$		
	Myoglobin	$(1.21 \pm 0.21) \times 10^{-6}$		
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}		

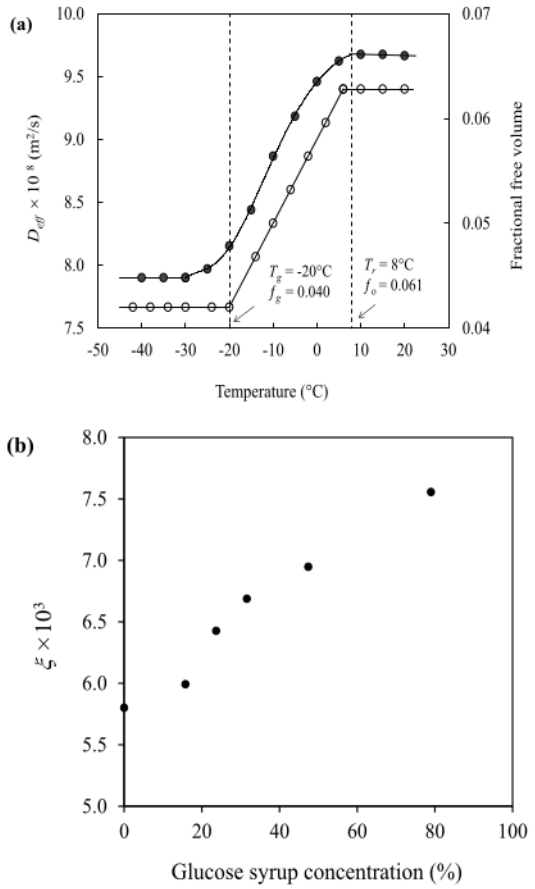

Fig. 6. (a) Temperature variation of the effective diffusion coefficient (D_{eff}) of ascorbic acid from a matrix of 2% high-methoxy pectin +77.6% polydextrose (closed symbols) in relation to the fractional free volume of the system (open symbols) (adapted from Panyoyai et al., 2016a, with permission) 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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