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Polyphenols encapsulation – application of innovation technologies to improve stability of natural products

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1 Introduction

1.1 Microencapsulation in the food industry

Microencapsulation – developed approximately 65 years ago – is defined as a technology of packaging solids, liquids, or gaseous materials in miniature, sealed capsules that can release their contents at controlled rates under specific conditions [1]. The main objective of encapsulation is to protect the core material from adverse environmental conditions, such as undesirable effects of light, moisture, and oxygen, thereby contributing to an increase in the shelf life of the product, and promoting a controlled liberation of the encapsulate [2]. In the food industry, the microencapsulation process can be applied for a variety of reasons, summarized by Desai and Park [1] as follows:

- protection of the core material from degradation by reducing its reactivity to its outside environment;
- reduction of the evaporation or transfer rate of the core material to the outside environment;
- modification of the physical characteristics of the original material to allow easier handling;
- tailoring the release of the core material slowly over time, or at a particular time;
- to mask an unwanted flavor or taste of the core material;
- dilution of the core material when only small amounts are required, while achieving uniform dispersion in the host material;
- to help separate the components of the mixture that would otherwise react with one another.

Food ingredients of acidulates, flavoring agents, sweeteners, colorants, lipids, vitamins and minerals, enzymes and microorganisms, are encapsulated using different technologies [3].

2 Polyphenols

The results of studies outlined in several reviews provide a current understanding on the biological effects of polyphenols and their relevance to human health. These compounds show a wide spectrum of biological properties such as antioxidant, anti-inflammatory, antibacterial and antiviral activities [4]. Antioxidant properties make polyphenols potential therapeutic agents against serious diseases, like cancer, diabetes and cardiovascular disorders [5], acting against reactive oxygen species generated by exogenous chemicals or endogenous metabolism [6] and preventing cell damages caused by oxidative stress [7]. Polyphenols offer great hope for the prevention of chronic human diseases.

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They are a large family of substances, ranging from simple molecules to complex structures. Several thousand molecules with a polyphenol structure (i.e. several hydroxyl groups on aromatic rings) have been identified in higher plants, and several hundred are found in edible plants. These molecules are secondary metabolites of plants and are generally involved in defense against ultraviolet radiation or aggression by pathogens. These compounds may be classified into different groups as a function of the number of phenol rings that they contain and of the structural elements that bind these rings to one another. Distinctions are thus made between the phenolic acids, flavonoids, stilbenes, and lignans (see Figure 1). The flavonoids, which share a common structure consisting of two aromatic rings (A and B) bound together by three carbon atoms that form an oxygenated heterocycle (ring C), may themselves be divided into four subclasses as a function of the type of heterocycle involved: flavonols, flavones, isoflavones, and flavanones (Figure 2). In addition to this diversity, polyphenols may be associated with various carbohydrates and organic acids and with one another.

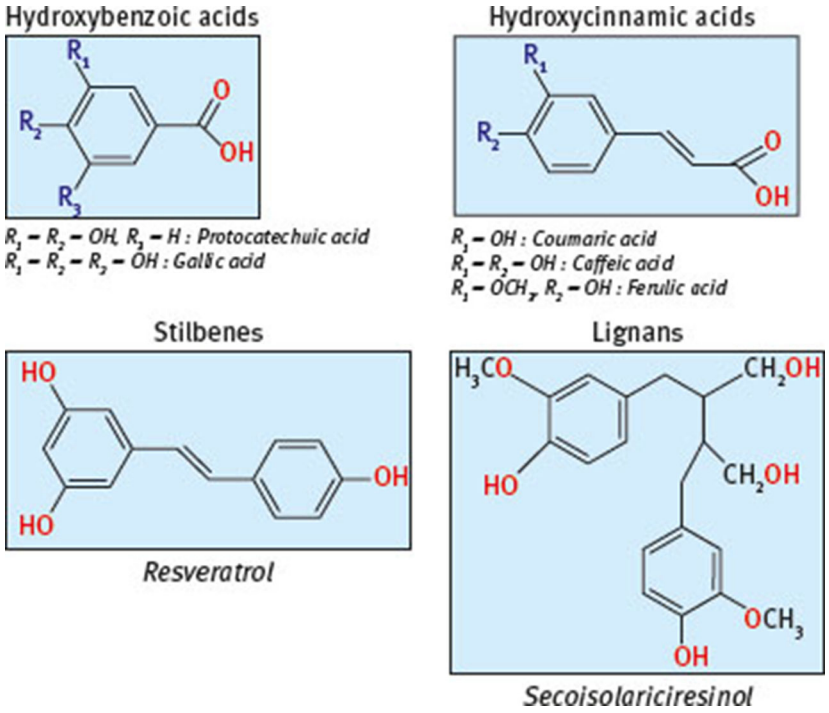

Figure 1: Structures of phenolic acids, flavonoids, stilbenes, and lignans.

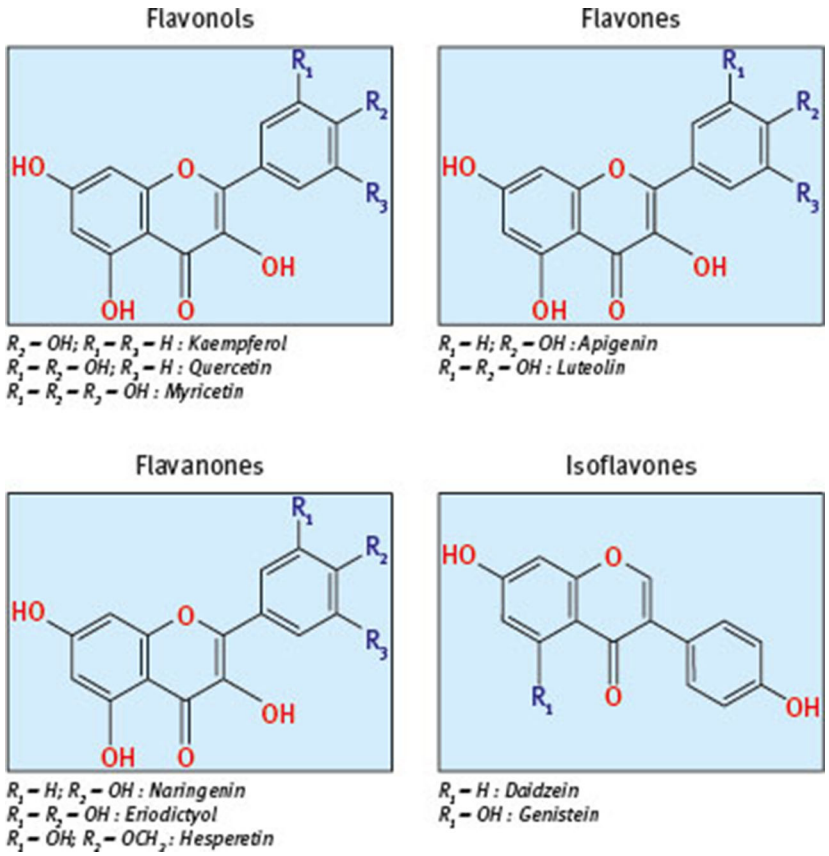

Figure 2: Structures of flavonols, flavones, isoflavones, and flavanones.

2.1 Phenolic acids

Two classes of phenolic acids can be distinguished: derivatives of benzoic acid and derivatives of cinnamic acid. The hydroxybenzoic acid content of edible plants is generally very low, with the exception of certain red fruits, black radish, and onions, which can have concentrations of several tens of milligrams per kilogram fresh weight [8]. Tea is an important source of gallic acid: tea leaves may contain up to 4.5 g/kg fresh wt. [9]. Furthermore, hydroxybenzoic acids are components of complex structures such as hydrolyzable tannins (gallotannins in mangoes and ellagitannins in red fruit such as strawberries, raspberries, and blackberries). Because these hydroxybenzoic acids, both free and esterified, are found in only a few plants eaten by humans, they have not been extensively studied and are not currently considered to be of great nutritional interest [10].

The hydroxycinnamic acids are more common than are the hydroxybenzoic acids and consist chiefly of *p*-coumaric, caffeic, ferulic, and sinapic acids. These acids are rarely found in the free form, except in processed food that has undergone freezing, sterilization, or fermentation. The bound forms are glycosylated derivatives or esters of quinic acid, shikimic acid, and tartaric acid. Caffeic and quinic acid combine to form chlorogenic acid, which is found in many types of fruit and in high concentrations in coffee: a single cup may contain 70–350 mg chlorogenic acid [11]. The types of fruit having the highest content (blueberries, kiwis, plums, cherries, apples) contain 0.5–2 g hydroxycinnamic acids/kg fresh wt.

Caffeic acid, both free and esterified, is generally the most abundant phenolic acid and represents 75–100% of the total hydroxycinnamic acid content of most fruit. Hydroxycinnamic acids are found in all parts of the fruit, although the highest concentrations are seen in the outer parts of ripe fruit. Concentrations generally decrease during the course of ripening, but total quantities increase as the fruit increases in size [12].

Ferulic acid is the most abundant phenolic acid found in cereal grains, which constitute its main dietary source. The ferulic acid content of wheat grain is ≈0.8–2 g/kg dry wt., which may represent up to 90% of total polyphenols [13]. Ferulic acid is found chiefly in the outer parts of the grain. The aleurone layer and the pericarp of wheat grain contain 98% of the total ferulic acid. The ferulic acid content of different wheat flours is thus directly related to levels of sieving, and bran is the main source of polyphenols. Rice and oat flours contain approximately the same quantity of phenolic acids as wheat flour (63 mg/kg), although the content in maize flour is about three times as high. Ferulic acid is found chiefly in the *trans* form, which is esterified to arabinoxylans and hemicelluloses in the aleurone and pericarp. Only 10% of ferulic acid is found in soluble free

form in wheat bran. Several dimers of ferulic acid are also found in cereals and form bridge structures between chains of hemicellulose [14, 15].

2.2 Flavonoids

Flavonols are the most ubiquitous flavonoids in foods, and the main representatives are quercetin and kaempferol. They are generally present at relatively low concentrations of ≈15–30 mg/kg fresh wt. The richest sources are onions (up to 1.2 g/kg fresh wt.), curly kale, leeks, broccoli, and blueberries. Red wine and tea also contain up to 45 mg flavonols/L. These compounds are present in glycosylated forms. The associated sugar moiety is very often glucose or rhamnose, but other sugars may also be involved (e.g. galactose, arabinose, xylose, glucuronic acid). Fruit often contains between five and ten different flavonol glycosides [16]. These flavonols accumulate in the outer and aerial tissues (skin and leaves) because their biosynthesis is stimulated by light. Marked differences in concentration exist between pieces of fruit on the same tree and even between different sides of a single piece of fruit, depending on exposure to sunlight [17]. Similarly, in leafy vegetables such as lettuce and cabbage, the glycoside concentration is ≥10 times as high in the green outer leaves as in the inner light-colored leaves [18]. This phenomenon also accounts for the higher flavonol content of cherry tomatoes than of standard tomatoes, because they have different proportions of skin to whole fruit.

Flavones are much less common than flavonols in fruit and vegetables. Flavones consist chiefly of glycosides of luteolin and apigenin. The only important edible sources of flavones identified to date are parsley and celery. Cereals such as millet and wheat contain *C*-glycosides of flavones [19]. The skin of citrus fruit contains large quantities of polymethoxylated flavones: tangeretin, nobiletin, and sinensetin (up to 6.5 g/L of essential oil of mandarin). These polymethoxylated flavones are the most hydrophobic flavonoids [20].

In human foods, flavanones are found in tomatoes and certain aromatic plants such as mint, but they are present in high concentrations only in citrus fruit. The main aglycones are naringenin in grapefruit, hesperetin in oranges, and eriodictyol in lemons. Flavanones are generally glycosylated by a disaccharide at position 7: either a neohesperidose, which imparts a bitter taste (such as to naringin in grapefruit), or a rutinose, which is flavorless. Orange juice contains between 200 and 600 mg hesperidin/L and 15–85 mg narirutin/L, and a single glass of orange juice may contain between 40 and 140 mg flavanone glycosides. Because the solid parts of citrus fruit – particularly the albedo (the white spongy portion) and the membranes separating the segments – have a very high flavanone content, the whole fruit may contain up to five times as much as a glass of orange juice [21, 22].

Isoflavones such as genistein and daidzein are commonly regarded to be phytoestrogens because of their estrogenic activity in certain animal models. A major dietary source of isoflavonoids is soy products. There are at least 12 known isoflavone compounds in soybeans (three aglycones, three glucosides, three acetyl-ester glucosides, and three malonyl-ester glucosides). Significant amounts of the isoflavone genistein as its glucosyl glucoside have also been reported in the tubers of the American groundnut (*Apios americana*) [23]. Mazur et al. [24] estimated the isoflavone concentrations in 68 cultivars of 19 common leguminous food species and four forage legumes. The highest total isoflavone concentration was found in kudzu root (*Pueraria lobata*) (>2 mg/g dry weight). Puerarin has been reported to be the major isoflavonoid in kudzu dietary supplements [25].

2.3 Lignans

Lignans are naturally occurring plant phenols that are derived biosynthetically from phenylpropanoids. Most lignans occur freely in plants, but a small proportion co-exist with sugars to form glycosides in wood and resin of plants. Lignans are commonly referred to as dimers, with complex skeletons and characteristic chemical functions, but a few are trimers or tetramers. The widely distributed lignans are important components of food and medicine that are derived from plants, and they have been target compounds for organic synthesis and biological-function research because of the many types of bonding of the C6–C3 units, and oxidation of the structures. Lignans, which occur almost in all morphological parts of the plants including xylem, roots, leaves, flowers, fruits, rhizomes, stems, and seeds, are secondary metabolites with low molecular weight. Lignans can be classified into five main types according to their structures: lignans, neolignans, norlignans, hybrid lignans, and oligomeric lignans. Various types of lignans have attracted considerable attention because of their numerous pharmacological features such as the antitumor, hepatoprotective, platelet-activating factor antagonistic, insecticidal and estrogenic, antifungal, antihypertensive, sedative, antioxidant activities. Plants with high lignan contents have been used as folk medicine in China, Japan, and the Eastern World for approximately 1000 years. Nowadays, their extensive use in traditional medicine makes lignans an important family of lead compounds for the development of new therapeutic agents based on structural modifications [26, 27].

2.4 Stilbenes

Stilbenes are found in only low quantities in the human diet [28]. One of these, resveratrol, for which anticarcinogenic effects have been shown during screening of medicinal plants and which has been extensively studied, is found in low quantities in wine (0.3–7 mg aglycones/L and 15 mg glycosides/L in red wine). However, because resveratrol is found in such small quantities in the diet, any protective effect of this molecule is unlikely at normal nutritional intakes [27, 29].

3 Encapsulation of polyphenols

The biological activity of natural polyphenols, related to scavenging free radicals and interaction with proteins, makes them potentially interesting for a variety of applications, whose realization is limited by the inherent instability of these phytochemicals. Instability is observed as degradation during processing and storage (temperature, oxygen, light), or within *in vivo* administration (pH, enzymes in the gastrointestinal tract). Encapsulating polyphenols (usually plant extracts) aims to preserve the biological activity and to improve the stability of the active compounds, as well as to ensure controlled release of the latter. Encapsulation has the advantage of being a nonthermal stabilization approach, suitable for temperature-sensitive natural biologically active compounds, as the ones extracted from different plants with medical applications. The wall material usually improves the stability of the active compounds by protecting them from direct exposure to air and light. In this way the polyphenols' inherent antioxidant activity is preserved and even improved [30]. Encapsulation and co-encapsulation of different biologically active substances is investigated on micro-and nanoscale levels [5, 30–33], the former being the focus of this review. It is a promising approach to improve the performance of medicines, as the capsules exhibit controlled release profile for the contained polyphenols, leading to better bioavailability.

Encapsulation allows us to solve two main reasons for the low bioavailability of polyphenols as free compounds and the need to administer higher concentrations of molecules of interest: the impossibility of maintaining the active molecular form until the time of consumption and the insufficient gastric residence time, which usually leads to concentrations of an order of magnitude lower than the effective ones, determined from *in vitro* assays [34, 35]. The investigations concern mainly *in vitro* studies, many of them under conditions that best simulate the expected *in vivo* environment (see Table 1), but the number of *in vivo* studies reporting improved bioavailability within oral administration of bioactive compounds and extracts is increasing [32, 35–37]. By nanoencapsulation the nanoparticles can also be used for intravenous injection (when their average diameter is less than 200 nm). In general, regulating the particle size enables targeted delivery to different organs [5].

Table 1 Investigations dealing with polyphenols release kinetics from microcapsules.

Coating material	Method of encapsulation	Source material/extraction method	Reference	Release data			
				Release time	Experimental Particle size distribution	Release media	Modeling
Ethyl cellulose	Emulsion phase separation	Bayberry, microwave extraction with 80 % ethanol	[45]	40 min	17 μm to 93 μm	Simulated-intestinal fluid	–
Whey protein	Spray-drying	Blueberry pomace extract with 80 % ethanol	[44], [52]		48.5 μm volumetric mean diameter (D4,3)		
Sodium alginate	Emulsification/internal gelation	Cocoa extract	[46]	1500 min	39 to 321 μm	Polyoxyethylene sorbitan monolaurate (Tween_20)	Peppas - Sahlin eq.
Whey protein, carboxymethyl cellulose (CMC) and pectin	Film formation (according to simplex centroid experimental design)	Roselle extract (aqueous extract of Roselle calyx)	[51]	500 min (300 min to reach the plateau)	1 cm^2 pieces with an approximate weight of 0.1 g	NaCl aqueous solution	Peppas eq.
Sucrose matrix Calcium alginate hydrogel Calcium alginate–chitosan	Entrapment by cocrystallization Encapsulation by ionic gelation	Aqueous extracts of yerba mate	[50] [53] [54] [55]	45 s dissolute 200 min release (40 min to reach the plateau) 800 min	0.2 and 2 mm	Water gastric and intestinal simulated fluids	Peppas eq. Kopcha, Lordi eq.
Cellulose–lignin hydrogels	Immersion of dried hydrogel in the extract and swelling	Extract of grapes seeds from chambourcin with ethanol	[56]	550 min	– Pore size given: 169 and 431 μm	Water-ethanol	Peppas (Korsmeyer-Peppas
Poloxamers	Coprecipitation by supercritical antisolvent process	Ethanolic extract of rosemary leaves	[47]	1 h	<1 μm agglomerates 5 to 20 μm	Aqueous	–
Poly-ε-caprolactone	High pressure antisolvent coprecipitation	Green tea extract in acetone	[48]	90 h (20 h to reach he plateau)	3–5 μm High degree of agglomeration	Phosphate buffer	–

Polyethyleneglycol	Ionic gelification	Ethanolic extract of anthocyanins from jabuticaba skins (*Myrciaria cauliflora*)	[39]	30 min	2.8–3.2 mm	Hydrochloric acid/potassium chloride buffer	First order kinetics
Alginate–chitosan microbeads	Electrostatic extrusion	Raspberry leaf, hawthorn, nettle, yarrow, ground ivy, olive leaf	[40]	30 min	781–1785 μm	Water	–
Whey protein gels		Bilberry extract from *Vaccinium myrtillus*	[41]	300 min	5 mm	Simulated gastric fluid	Peppas (Ritger Peppas)

3.1 Improved stability

The improved stability of the active substances after encapsulation is in the focus of a number of studies concerning polyphenols encapsulation [38–42]. These results are important for enlarging commercial applications, requiring longer storage with preserved biological activities. Usually encapsulation is applied in solid microcapsules, but there are also attempts to encapsulate bioactive flavonoids (e.g. Rutin) and anthocianins in multiple emulsions using a spinning disc reactor (SDR) [43].

The effect of the encapsulation method, the choice of the carrier, particles size or size distribution, shape and smoothness of the outer surface as well as swelling behavior, are important factors affecting many properties of the microcapsules, among which are storage stability, core material retention (encapsulation efficiency) and controlled release. Spray-drying [38, 44], phase separation [45], emulsification/internal gelation [39, 46], SAS (supercritical antisolvent) – precipitation and coprecipitation [47, 48], rapid expansion of supercritical solution (RESS) [39], and electrostatic extrusion in microbeads [40] are some of the methods used for polyphenols encapsulation, comparative reviews on the subject being given in [34, 49].

The possibility to obtain higher retention of phenolics within the capsules is discussed in view of the encapsulating material, as well as the solvent used for extraction (aqueous or ethanolic) [44]. The reported stability data concern light, temperature, oxygen and moisture exposure. Cocrystallization with sucrose is investigated in order to improve the properties of antioxidant powders obtained from plant extracts with better physicochemical stability during storage [50]. The small size of the particles (3–5 μm) with a narrow particle size distribution usually lead to high degree of agglomeration [48], which is to be avoided by encapsulation. By nanoscale applications (e.g. lipid-core nanocapsules) the formation of very stable colloidal suspensions is reported [32] with unchanged particle size characteristics, polydispersity index, zeta potential and drug loading.

There are extensive reviews available in the literature on recent advances in the encapsulation of polyphenols [34, 49], where the whole spectrum of biological activities is discussed, as well as accent given on the methods of encapsulation, coating materials and achieved encapsulating efficiencies. The encapsulation techniques are discussed in relation to the degree of stabilization achieved [49].

4 Controlled release

Controlled release means not constant, but rather slowed down release (compared to the direct application of polyphenols containing extracts), which can be predicted adequately and used in the appropriate way for the human body. The slowed down release is due to the fact that instead of a pure dissolution process, diffusion through the capsules wall is taking place, whose rate coefficient (the internal diffusion coefficient through the pores of the encapsulating material) is essentially lower than the value of the molecular diffusion coefficient. Furthermore, the release can be controlled by the characteristic diffusion time, which includes the square of the characteristic particle size and the rate coefficient (the effective diffusion coefficient in the solid capsule). Diffusion can be coupled with erosion and partial dissolution of the encapsulating material, resulting in a transport rate between that of pore diffusion in the solid and molecular diffusion in the free volume of the surrounding liquid. Swelling or shrinking of the encapsulating material contributes to the complexity of the mass transfer mechanism, especially for polymeric encapsulating materials like hydrogels.

Crude extracts are multicomponent in nature and their encapsulation is limited by the differences in solubility, distribution, and potential interaction among the contained biologically active compounds. The present review deals with *in vitro* investigations of the release kinetics of encapsulated natural extracts of polyphenols and flavonoids. They are illustrated by a typical kinetic curve, giving the increase of the concentration of the target compounds in the liquid around the microcapsules vs. time. These curves in general start with a steep initial slope (burst effect), followed by much lower and eventually constant rate of increasing concentrations (sustained release) and ending by a plateau, which corresponds to the equilibrium for a given set of experimental conditions (temperature, particle size, solid to liquid ratio). The experimental kinetic curves are either reported in terms of the contact time required to reach the plateau, respectively the final value of the released compounds concentration, or are further treated mathematically by simple semi-empirical models to define the value of the rate coefficients.

Table 1 gives a summary of recent data on the release of encapsulated polyphenols from natural extracts in view of the experimental conditions employed. Factors controlling the release kinetics are: the amount of incorporated polyphenols and the composition of the coating material [51]; and the size of the microcapsules; the temperature and pH of the release media (being especially important for pH- or temperature-sensitive hydrogels). Surface diffusion and the so-called burst effect are observed, especially with smaller sizes (micro- or nano-scale) of the encapsulated particles [5].

The various techniques used for encapsulation also concern the diversity of microcapsules morphologies, which is important for the adequate mathematical modeling of the release process through them [34].

4.1 Mechanism of mass transfer and modeling

The increasing diversity of controlled delivery systems requires an adequate mathematical modeling of the release process to help reveal the mechanism(s) of bioactive release and to facilitate the optimization of the carrier systems by avoiding excessive experimentation [56]. Two major groups of models are observed:

i. Semi-empirical, geometry independent, based on simple mathematical functions (power or exponential) and accounting for one or two (additive) controlling release mechanisms.

ii. Detailed models with larger physical basis, based on analytical or rather numerical solutions of a set of differential equations for different geometry and different boundary conditions. Here two- and three-dimensional solutions are also of interest.

The mathematical apparatus developed for controlled drug delivery is also used in the particular case of polyphenols release. Furthermore, the same approach for understanding the release kinetics and its mathematical modeling is applied to nanoencapsulation of polyphenols [33, 56].

The majority of the investigations concerning encapsulated polyphenols release report diffusional mechanism – Fick's type or case 2 anomalous diffusion according to the semi-empirical power-law equation, known as Peppas equation [53]:

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

Here M_t and M_∞ denote the cumulative amount released at time t and infinite time, respectively, concentration.

The mechanism of transfer is revealed in the value of the exponent n, obtained by regression analysis on the experimental data: $n = 0.5$ indicates Fickian diffusion mechanism (Higuchi model [57]):

$$\frac{M_t}{M_\infty} = k_H\sqrt{t} \tag{2}$$

while a value $0.5 < n < 1$ indicates an anomalous or non-Fickian behavior, as observed for gallic acid encapsulation [42]. When $n = 1$ a case II transport mechanism is involved, where the rate is largely determined by swelling and relaxation of the polymer chains, while $n > 1$ is known as special (or super) case II transport. The latter is related to the plasticization of the polymer system and increased mobility, facilitating the active compound release. Super case II transport was observed during natural extract release from chitosan microcapsules [54]. Many authors obtain values of the exponent lower than 0.5 (or 0.45 which is theoretically expected for sphere geometry). Prof. Kulozik and Prof. Martin, in their publications, comment $n < 0.45$ as diffusional mechanism [41, 58], but attention should be paid also to the relation between n and the rate constants, obtained by regression. Keeping the same rate constants, the authors [41] recalculate the value of n to be much closer to 0.45. Others [46] attribute this fact to the influence of a relaxation/dissolution mechanism, which suggests that relaxation has influence on the release process (example with polyphenols release from alginate microspheres in an aqueous medium). Such observations were made also by numerical simulation of the release kinetics from particles with pronounced deformation due to swelling or shrinking. The power-law equation was used to study the mechanism of diffusion of quercetin or rutin into the skin following release from liposome/hydrogel complex system [42]. Numerous applications of eq. (1) are found in studies concerning polyphenols release from encapsulated natural extracts (Roselle [51], grapes seeds [56] bilberry [41]).

When the remaining in the solid amount is considered, the respective form of the power-law dependence (1) becomes:

$$(M_0 - M_t)/M_0 = kt^a \tag{3}$$

M_0 and M_t corresponding to initial 0 and at time t solid phase content. Considering the mechanism of transfer this relation is used for diffusion-controlled release of antioxidants (carnosine and gallic acid) together with the parabolic diffusion model [59]:

$$(1 - M_t/M)/t = kt^{-0.5} + b \tag{4}$$

Both expressions are single kinetics models supposing one rate-determining mechanism of release. They are used to treat the release data of antioxidants (e.g. gallic acid) controlled by intraparticle or surface diffusion [57].

Empirical kinetic models for more than one controlling release mechanisms are illustrated by the following examples.

- An intercept like the term 'b' in eq. (4) can be included in the semi-empirical power-law eq. (1) to account for the release due to the initial burst effect, considered as time-independent. This approach is employed in both diffusion-controlled and swelling-controlled release systems [59] including antioxidants from encapsulated natural extracts (yerba mate) in food additives [60].
- An alternative to eq. (1) simple mathematical description of the release kinetics is the monoexponential relation. In the form of eq. (5) it was used to calculate the concentration of a bioactive compound entrapped within a nanocarrier [58]:

$$C = C_0 e^{-kt} \tag{5}$$

as well as its two-step version – the biexponential equation:

$$C = ae^{-k_1 t} + be^{-k_2 t} \tag{6}$$

- where the rate constants k_1 and k_2 are related to burst and sustained release, respectively.
- In the case of hydrogels an anomalous transport mechanism is preferred, coupling Fickian diffusion with relaxation of the hydrogel network. The Peppas and Sahlin equation supposes diffusional mechanism in the first term, whereas the second one stands for the "case II transport" contribution [36]:

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \tag{7}$$

- This semi-empirical expression is supposed to have better a chance of treating experimental data with contributions of Fickian diffusion and matrix relaxation/dissolution. Examples are found in release data of polyphenols from natural extracts (yerba mate [53], cocoa extract [46]) encapsulated in microspheres.
- In the case of yerba mate extract encapsulated in calcium alginate beads, a release mechanism combining erosion and diffusion was observed [58], and is described by the semi-empirical model of Kopcha and Lordi [53]:

$$M = At^{1/2} + Bt \tag{8}$$

- Where M is the percentage of polyphenols released at time t, while A and B are the diffusion and erosion terms, respectively. This simple expression combines two additive time-dependent power terms – a diffusion term (like in the Higuchi equation $n = 0.5$) and an erosion term, $n = 1$.

Analytical and numerical solutions, based on Fickian diffusion for different particle geometries [61], available in the field of controlled drug delivery, are rarely used for polyphenols release from micro- and nanocapsules. Such models are successfully developed as two-dimensional ones [60, 62] complicated by moving boundary conditions reflecting swelling/shrinking [60, 62] and/or variable diffusion coefficients to describe more sophisticated internal diffusional transport [60].

5 Conclusions

Activity preservation and controlled release are the keywords for the importance of the encapsulation method. Polyphenols represent a wide area of application because of their diversity and wealth of bioactive properties, as well as the inherent limited stability and/or solubility, which results in restricted commercial application.

Microencapsulation is an innovative approach allowing protection against oxidation and thermal degradation, and improving their bioavailability *in vivo* and *in vitro*.

Numerous investigations of the latter are reported, but studies on release *in vivo* conditions are constantly increasing, answering the challenge of testing the release in a specific surrounding environment. Nanoencapsulation of polyphenols with therapeutic importance offers a way to obtain a minimally invasive delivery of sustained concentrations to a specific site. The future of encapsulated polyphenols and site-specific carrier targeting is promising in order to improve the performance of medicines and functional foods and use to the best effect the health benefits of these bioactives. Natural extracts with their unique multicomponent composition, as well as individual polyphenols have been an object of encapsulation and extensive study concerning the material of the carrier and the potential of the different encapsulation methods to obtain high amounts of entrapped polyphenols and a desired kinetic of their release. Co-encapsulation methodologies, where two or more bioactive ingredients can be combined to have a synergistic effect, are also gaining interest. Providing controlled amount and rate of active compounds release, the encapsulating of naturally derived polyphenolics is of primary interest for the food industry, as well as for pharmaceutical and cosmetic purposes, thus answering the demand for healthy products and foods containing naturally derived preservation ingredients.

Mathematical modeling has a significant role in understanding the release mechanisms and to quantify the rate parameters of the process. Models of different complexity require reliable experimental validation in order to reveal the detailed phenomena and to possess a predictive capability, which can be particularly fruitful if integrated in the process of product development.

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References

[1] Desai, K. G. H., Jin Park, H., Recent developments in microencapsulation of food ingredients, Dry Technol 23 (2005) 1361–1394.
[2] Shahidi, F., Han, X. Q., Encapsulation of food ingredients, Crit Rev Food Sci 33 (1993) 501–547.
[3] Ranadheera, C. S., Evans, C. A., Adams, M. C., Baines, S. K., Microencapsulation of Lactobacillus acidophilus LA-5, Bifidobacterium animalis subsp. lactis BB-12 and Propionibacterium jensenii 702 by spray drying in goat's milk, Small Ruminant Res 123 (2015) 155–159.
[4] Aliakbarian, B., Casazza, A. A., Perego, P., Valorization of olive oil solid waste using high pressure-high temperature reactor, Food Chem 128 (2011) 704–710.
[5] Kumari, A., Yadav, S. K., Pakade, Y. B., Kumar, V., Singh, B., Chaudhary, A., et al., Nanoencapsulation and characterization of Albizia chinensis isolated antioxidant quercitrin on PLA nanoparticles, Colloids Surfaces B: Biointerfaces 82 (2011) 224–232.
[6] Georgetti, S. R., Casagrande, R., Souza, C. R. F., Oliveira, W. P., Fonseca, M. J. V., Spray drying of the soybean extract: effects on chemical properties and antioxidant activity, LWT – Food Sci Technol 41 (2008) 1521–1527.
[7] Moure, A., Cruz, J. M., Franco, D. J. M., Dominguez, J. M., Sineiro, J. H., Dominguez, H., et al., Natural antioxidants from residual sources, Food Chem 72 (2001) 145–171.
[8] Herrmann, K., Nagel, C. W., Occurrence and content of hydroxycinnamic and hydroxybenzoic acid compounds in foods, Crit Rev Food Sci **28** (1989) 315–347.
[9] Tomás-Barberán, F. A., Clifford, M. N., Dietary hydroxybenzoic acid derivatives – nature, occurrence and dietary burden, J Sci Food Agr **80** (2000) 1024–1032.
[10] Chagne, D., Krieger, C., Rassam, M., Sullivan, M., Fraser, J., Andre, C., et al., QTL and candidate gene mapping for polyphenolic composition in apple fruit, BMC Plant Biol **12** (2012) 12
[11] Clifford, M. N., Chlorogenic acids and other cinnamates – nature, occurrence and dietary burden, J Sci Food Agr **79** (1999) 362–372.
[12] Rodríguez, H., Landete, J. M., de las Rivas, B., Muñoz, R., Metabolism of food phenolic acids by Lactobacillus plantarum CECT 748T, Food Chem **107** (2008) 1393–1398.
[13] Lempereur, I., Rouau, X., Abecassis, J., Genetic and agronomic variation in arabinoxylan and ferulic acid contents of durum wheat (*Triticum durum L.*) grain and its milling fractions, J Cereal Sci **25** (1997) 103–110.
[14] Manach, C., Scalbert, A., Morand, C., Rémésy, C., Jiménez, L., Polyphenols: food sources and bioavailability, Am J Clin Nutr **79** (2004) 727–747.
[15] C. Manach, C., Williamson, G., Morand, C., Scalbert, A., Remesy, C., Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies, Am J Clin Nutr **81** (2005) 230S–242S
[16] Chang, Y. L., Enzymatic Oxidation of phenolic compounds in fruits, in phenolic compounds in food and their effects on health, I, J Am Chem Soc (1992) 305–317.
[17] Price, S. F., Breen, P. J., Valladao, M., Watson, B. T., Cluster sun exposure and quercetin in pinot noir grapes and wine, Am J Enol Viticult **46** (1995) 187–194.
[18] Herrmann, K., Flavonols and flavones in food plants: a review, Int J Food Sci Tech **11** (1976) 433–448.

[19] Sartelet, H., Serghat, S., Lobstein, A., Ingenbleek, Y., Anton, R., Petitfrère, E., et al., Flavonoids extracted from fonio millet (Digitaria exilis) reveal potent antithyroid properties, Nutrition **12** (1996) 100–106.
[20] Drewnowski, A., Gomez-Carneros, C., Bitter taste, phytonutrients, and the consumer: a review, Am J Clin Nutr **72** (2000) 1424–1435.
[21] Gil, E. S., Couto, R. O., Flavonoid electrochemistry: a review on the electroanalytical applications, Rev Bras Farmacogn **23** (2013) 542–558.
[22] Crozier, A., Jaganath, I. B., Clifford, M. N., Dietary phenolics: chemistry, bioavailability and effects on health, Nat Prod Rep **26** (2009) 1001–1043.
[23] Barnes, S., Wang, C. C., Kirk, M., Smith-Johnson, M., Coward, L., Barnes, N. C., et al., HPLC-Mass Spectrometry of Isoflavonoids in Soy and the American Groundnut, Apios Americana, in Buslig, B., Manthey, J., (editors). Flavonoids in Cell Function. Springer US (2002) 77–88.
[24] Mazur, W. M., Duke, J. A., Wähälä, K., Rasku, S., Adlercreutz, H. Isoflavonoids and lignans in legumes: Nutritional and health aspects in humans, J Nutr Biochem **9** (1998) 193–200.
[25] Prasain, J. K., Jones, K., Kirk, M., Wilson, L., Smith-Johnson, M., Weaver, C., et al., Profiling and quantification of isoflavonoids in kudzu dietary supplements by high-performance liquid chromatography and electrospray ionization tandem mass spectrometry, J Agr Food Chem **51** (2003) 4213–4218.
[26] Zhang, J., Chen, J., Liang, Z., Zhao, C., New lignans and their biological activities, Chem Biodivers **11** (2014) 1–54.
[27] Ignat, I., Volf, I., Popa VI. A critical review of methods for characterisation of polyphenolic compounds in fruits and vegetables, Food Chem **126** (2011) 1821–1835.
[28] Fernández-Marín, M. I., Guerrero, R. F., García-Parrilla, M. C., Puertas, B., Richard, T., Rodriguez MA-Werner, et al., Isorhapontigenin: a novel bioactive stilbene from wine grapes, Food Chem **135** (2012) 1353–1359.
[29] Soleas, G. J., Diamandis, E. P., Goldberg, D. M., Resveratrol: a molecule whose time has come? And gone? Clin Biochem **30** (1997) 91–113.
[30] Coradini, K., Lima, F. O., Oliveira, C. M., Chaves, P. S., Athayde, M. L., Carvalho, L. M., et al., Co-encapsulation of resveratrol and curcumin in lipid-core nanocapsules improves their in vitro antioxidant effects, Eur J Pharm Biopharm **88** (2014) 178–185.
[31] Asanuma, H., Liang, X., Nishioka, H., Matsunaga, D., Liu, M., Komiyama, M., Synthesis of azobenzene-tethered DNA for reversible photoregulation of DNA functions: hybridization and transcription, Nat Protoc **2** (2007) 203–212.
[32] Zanotto-Filho, A., Coradini, K., Braganhol, E., Schröder, R., de Oliveira, C. M., Simões-Pires, A., et al., Curcumin-loaded lipid-core nanocapsules as a strategy to improve pharmacological efficacy of curcumin in glioma treatment, Eur J Pharm Biopharm **83** (2013) 156–167.
[33] Wu, T. H., Yen, F. L., Lin, L. T., Tsai, T. R., Lin, C. C., Cham, T. M., Preparation, physicochemical characterization, and antioxidant effects of quercetin nanoparticles, Int J Pharm **346** (2008) 160–168.
[34] Fang, Z., Bhandari, B., Encapsulation of polyphenols – a review, Trends Food Sci Tech **21** (2010) 510–523.
[35] Ting, Y., Jiang, Y., Ho, C.-T., Huang, Q., Common delivery systems for enhancing in vivo bioavailability and biological efficacy of nutraceuticals, J Funct Foods **7** (2014) 112–128.
[36] Arifin, D. Y., Lee, L. Y., Wang, C.-H., Mathematical modeling and simulation of drug release from microspheres: Implications to drug delivery systems, Adv Drug Deliver Rev **58** (2006) 1274–1325.
[37] Grassi, M., Lamberti, G., Cascone, S., Grassi, G., Mathematical modeling of simultaneous drug release and in vivo absorption, Int J Pharm **418** (2011) 130–141.
[38] Mahdavi, S. A., Jafari, S. M., Ghorbani, M., Assadpoor, E., Spray-drying microencapsulation of anthocyanins by natural biopolymers: a review, Dry Technol **32** (2014) 509–518.
[39] Santos, D. T., Albarelli, J. Q., Beppu, M. M., Meireles, M. M. A., Stabilization of anthocyanin extract from jabuticaba skins by encapsulation using supercritical CO_2 as solvent, Food Res Int **50** (2013) 617–624.
[40] Belaak-Cvitanovi, A., Stojanovi, R., Manojlovi, V., Komes, D., Cindri, I. J., Nedovi, V., et al., Encapsulation of polyphenolic antioxidants from medicinal plant extracts in alginate chitosan system enhanced with ascorbic acid by electrostatic extrusion, Food Res Int **44** (2011) 1094–1101.
[41] Betz, M., Kulozik, U., Whey protein gels for the entrapment of bioactive anthocyanins from bilberry extract, Int Dairy J **21** (2011) 703–710.
[42] Park, S. N., Lee, M. H., Kim, S. J., and Yu, E. R., Preparation of quercetin and rutin-loaded ceramide liposomes and drug-releasing effect in liposome-in-hydrogel complex system, Biochem Bioph Res Co **435** (2013) 361–366.
[43] Akhtar, M., Murray, B. S., Afeisume, E. I., and Khew, S. H., Encapsulation of flavonoid in multiple emulsion using spinning disc reactor technology, Food Hydrocolloid **34** (2014) 62–67.
[44] Flores, F. P., Singh, R. K., Kong, F., Physical and storage properties of spray-dried blueberry pomace extract with whey protein isolate as wall material, J Food Eng **137** (2014) 1–6.
[45] Zheng, L., Ding, Z., Zhang, M., Sun, J., Microencapsulation of bayberry polyphenols by ethyl cellulose: preparation and characterization, J Food Eng **104** (2011) 89–95.
[46] Lupo, B., Maestro, A., Porras, M., Gutiérrez, J. M., González, C., Preparation of alginate microspheres by emulsification/internal gelation to encapsulate cocoa polyphenols, Food Hydrocolloid **38** (2014) 56–65.
[47] Visentin, A., Rodríguez S-Rojo, S., Navarrete, A., Maestri, D., Cocero, M. J., Precipitation and encapsulation of rosemary antioxidants by supercritical antisolvent process, J Food Eng **109** (2012) 9–15.
[48] Sosa, M. V., Rodríguez-Rojo, S., Mattea, F., Cismondi, M., Cocero, M. J., Green tea encapsulation by means of high pressure antisolvent coprecipitation, J Supercrit Fluid **56** (2011) 304–311.
[49] Cavalcanti, R. N., Santos, D. T., Meireles MAA., Non-thermal stabilization mechanisms of anthocyanins in model and food systems—an overview, Food Res Int **44** (2011) 499–509.
[50] López-Córdoba, A., Deladino, L., Agudelo-Mesa, L., Martino, M., Yerba mate antioxidant powders obtained by co-crystallization: Stability during storage, J Food Eng **124** (2014) 158–165.
[51] Ciolacu, D., Oprea, A. M., Anghel, N., Cazacu, G., Cazacu, M., New cellulose–lignin hydrogels and their application in controlled release of polyphenols, Mater Sci Eng **32** (2012) 452–463.
[52] Flores, F. P., Singh, R. K., Kerr, W. L., Pegg, R. B., Kong, F., Total phenolics content and antioxidant capacities of microencapsulated blueberry anthocyanins during in vitro digestion, Food Chem **153** (2014) 272–278.

[53] Kopcha, M., Lordi, N. G., Tojo, K. J., Evaluation of release from selected thermosoftening vehicles, J Pharm Pharmacol **43** (1991) 382–387.
[54] Deladino, L., Anbinder, P. S., Navarro, A. S., Martino, M. N., Encapsulation of natural antioxidants extracted from Ilex paraguariensis, Carbohyd Polym **71** (2008) 126–134.
[55] Peppas, N. A., Analysis of Fickian and non-Fickian drug release from polymers, Pharm Acta Helv **60** (1985) 110–111.
[56] Fathi, M., Mozafari, M. R., Mohebbi, M., Nanoencapsulation of food ingredients using lipid based delivery systems, Trends Food Sci Tech **23** (2012) 13–27.
[57] Kong, X., Jin, L., Wei, M., and Duan, X., Antioxidant drugs intercalated into layered double hydroxide: Structure and in vitroin vitro release, Appl Clay Sci **49** (2010) 324–329.
[58] López Córdoba, A., Deladino, L., Martino, M., Effect of starch filler on calcium-alginate hydrogels loaded with yerba mate antioxidants, Carbohyd Polym **95** (2013) 315–323.
[59] Naddaf, A. A., Tsibranska, I., and Bart, H. J., Kinetics of BSA release from poly (N-isopropylacrylamide) hydrogels, Chem Engin Process: Process Intensification **49** (2010) 581–588.
[60] Deladino, L., Navarro, A. S., Martino, M. N., Carrier systems for yerba mate extract (Ilex paraguariensis) to enrich instant soups. Release mechanisms under different pH conditions, LWT – Food Sci Technol **53** (2013) 163–169.
[61] Siepmann, J., Podual, K., Sriwongjanya, M., Peppas, N. A., Bodmeier, R., A new model describing the swelling and drug release kinetics from hydroxypropyl methylcellulose tablets, J Pharm Sci **88** (1999) 65–72.
[62] Siepmann, J., and Siepmann, F., Mathematical modeling of drug delivery, Int J Pharm **364** (2008) 328–343.