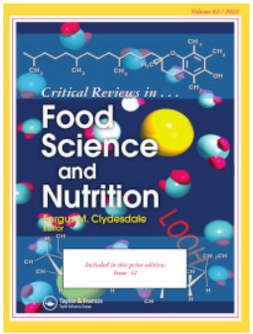

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REVIEW

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Caffeine-loaded nano/micro-carriers: Techniques, bioavailability, and applications

Rezvan Shaddel[a], Safoura Akbari-Alavijeh[a], Ilaria Cacciotti[b], Shima Yousefi[c], Merve Tomas[d], Esra Capanoglu[e], Ozgur Tarhan[f], Ali Rashidinejad[g], Atefe Rezaei[h], Mohammed Bhia[i,j] and Seid Mahdi Jafari[k,l,m]

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ABSTRACT

Caffeine, as one of the most consumed bioactive compounds globally, has gained considerable attention during the last years. Considering the bitter taste and adverse effects of high levels of caffeine consumption, it is crucial to apply a strategy for masking the caffeine's bitter taste and facilitating its programmable deliverance within a long time. Other operational parameters such as food processing parameters, exposure to sunlight and oxygen, and gastrointestinal digestion could also degrade the phenolic compounds in general and caffeine in special. To overcome these challenges, various nano/micro-platforms have been fabricated, including lipid-based (e.g., nanoliposomal vehicles; nanoemulsions, double emulsions, Pickering emulsions; microemulsions; niosomal vehicles; solid lipid nanoparticles and nanostructured lipid carriers), as well as biopolymeric (e.g., nanoparticles; hydrogels, organogels, oleogels; nanofibers and nanotubes; protein-polysaccharide nanocomplexes, conjugates; cyclodextrin inclusion complexes) and inorganic (e.g., gold and silica nanoparticles) nano/micro-structures. In this review, the findings on various caffeine-loaded nano/micro-carriers and their potential applications in functional food products/supplements will be discussed. Also, the controlled release and bioavailability of encapsulated caffeine will be given, and finally, the toxicity and safety of encapsulated caffeine will be presented.

KEYWORDS

Bioavailability; caffeine; encapsulation; functional foods; nano/micro-delivery systems

Introduction

Encapsulation is a method for coating one material or creating an external membrane over another material which is used to preserve and/or protect the target bioactive compound from thermal and biochemical deterioration (Comunian et al. 2022). Nano-capsules and microcapsules are the most functional and favorable size in encapsulation processing. Nevertheless, nanoscale and microscale refer to 1-1000 nm and 1-1000 μm, respectively, nano-encapsulation ranges the capsule size from 1 nanometer to several hundred nanometers in diameter, and microencapsulation ranges from 1 micrometer to several hundred micrometers in diameter (Saifullah et al. 2019; Katouzian and Jafari 2016). Between them, nanotechnology could provide novel nanoscale materials in the realm of food/medicine with the beneficial features of reducing the risk of diverse ailments, including diabetes (Veiseh et al. 2015), cancer (Shamsi et al. 2019; Youn and Bae 2018), cardiovascular (Godin et al. 2010; Lobatto et al. 2011), and infectious diseases (Zhu et al. 2014). Nano-engineered delivery systems have predominantly emerged in response to the pressing need for counteracting the main pharmacokinetic impediments in the absorption and bioavailability of encapsulated bioactives (Akbari-Alavijeh, Shaddel, and Jafari 2020; Assadpour and Jafari 2019). In this regard, a potent vehicle requires to counteract legions of biophysical obstacles within the biological milieu to offer an efficient delivery to the targeted sites and provide sustained release of the bioactive therein (Falsafi, Rostamabadi, and Jafari 2020; Shamsi et al. 2019). The purpose of developing nano/micro-delivery devices is to boost the pharmacokinetics,

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biodistribution and bioavailability of their bioactive load, protect it from distinct degradative enzymes and promote the controlled release of the labile molecule via acting as a bioactive reservoir across the cells/tissues (Assadpour, Rostamabadi, and Jafari 2020; Rostamabadi, Falsafi, and Jafari 2020).

Caffeine is one of the most consumed bioactive compounds globally, which can improve mental proficiency, release exhaustion and diminish depression. This bioactive agent, commonly found in tea, chocolate, coffee, etc., is part of the methylxanthine class (Baratloo et al. 2016). Pure caffeine is odorless and has a bitter taste and a mixture of sucrose and other flavors is usually used to mask the bitter taste of caffeine. In addition, high loads of caffeine consumption have adverse health effects on the cardiovascular and nervous systems (Islam et al. 2016; Katouzian and Jafari 2019; Zulli et al. 2016). Considering the bitter taste and adverse effects of high levels of caffeine consumption, it is crucial to apply a strategy for masking the caffeine's bitter taste and facilitating its programmable deliverance within a long time. Furthermore, naturally occurring features of caffeine or its food/drug applicability maybe unavoidably alter upon the food/drug processing adverse conditions (e.g., shear stress, high temperature, and transporting conditions), exposure to sunlight and oxygen, or through its passage from the gastrointestinal tract (GIT) (Madadlou, Jaberipour, and Eskandari 2014). To overcome these challenges, various nano/micro-platforms have been fabricated to mask the bitter taste of caffeine, efficaciously assure the caffeine safe journey through the GIT and its successive sustained/controlled secretion at the desired locus via its protecting inside an appropriate nanocarrier (Solghi et al. 2020).

Nano/micro-carriers have displayed an unprecedented potential for caffeine delivery and could coarsely be classified as lipid-based (e.g., nanoliposomal vehicles; nanoemulsions, double emulsions, Pickering emulsions; microemulsions; cubosomes, hexosomes; niosomal vehicles; solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs)), as well as biopolymeric (e.g., nanoparticles (NPs); hydrogels, organogels, oleogels; nanofibers and nanotubes; protein-polysaccharide nanocomplexes, conjugates; cyclodextrin inclusion complexes), and inorganic (e.g., graphene/graphene oxide, carbon nanotubes, gold and silica NPs) nano/micro-structures. These nano/micro-carriers, especially nano-formulations, facilitate the fabrication of caffeine-based formulations of declined degradation throughout the circulatory system, develop solubility in food/drug formulations, improve release and purposed delivery, and promote biostability/bioavailability (Seyedabadi et al. 2021).

In this review article, we provide a comprehensive discussion of the following aspects: i) a brief summary of caffeine in terms of its properties and chemical structure, sources and applications, extraction and purification, as well as health benefits; ii) up-to-date nano/micro-carriers for the delivery of caffeine alongside their distinct characteristics; iii) a categorized collection of the literature focusing on the encapsulation of caffeine within different nano/micro-carriers; v) illuminating the factors affecting the release and bioaccessibility of the encapsulated caffeine; vi) potential applications of caffeine-loaded nano/micro-carriers in functional food products/supplements; ultimately, vii) current toxicity and safety challenges for the development of caffeine-loaded formulations.

An overview of caffeine

Caffeine (1,3,7–trimethylxanthine), a purine alkaloid, is an essential constituent of many prominent beverages, including coffee and tea. Caffeine and its catabolic products, theobromine and xanthine, showed antioxidant and prooxidant properties (Azam et al. 2003; Cacciotti et al. 2018). Caffeine is naturally present in the seeds, nuts, or leaves of certain plants, but most commonly found in coffee beans, tea leaves, soft drinks, chocolate, cocoa and energy drinks (Fulgoni, Keast, and Lieberman 2015). Its concentration varies depending on the environmental and agronomic factors, processing parameters, and product type (de Mejia and Ramirez-Mares 2014). Moreover, caffeine is commonly consumed by various population groups, including children, adolescents and adults (Kumar et al. 2018).

Various extraction techniques like heat reflux or Soxhlet utilizing organic solvents have been used to extract caffeine from its sources (Bravo et al. 2013). However, the use of organic solvents is not preferred due to the unwanted effects on human health and environmental pollution. Thus, efficient decaffeination methods and nontoxic alternatives have been extensively investigated in recent years. Supercritical fluid extraction (SFE) by CO_2, which is a nontoxic and environmentally friendly method, is one of the most widely used methods (Herrero et al. 2010; Kim et al. 2008). Caffeine was extracted from green tea by SFE with CO_2 and water as a cosolvent. The extraction yield was 54% under the following optimized conditions: 40 °C, 40 MPa and 7 wt% water content (Kim et al. 2008). In another study, Mumin et al. (2006) extracted caffeine from soft drinks, green tea, black tea, and coffee using solid-phase extraction and performed some characterization analysis. Both of the proposed purification and characterization techniques had significant advantages over the traditional purification techniques, as well as spectrophotometric and other HPLC techniques.

On the other hand, Tello, Viguera, and Calvo (2011) investigated the extraction of caffeine from coffee husks using SFE with CO_2. The maximum extraction yield was 84% when working at 99.85 °C and 30 MPa, using 197 kg CO_2/kg husks. In addition, static and dynamic SFE of caffeine from green tea using pure CO_2 and green cosolvents, including ethanol, ethyl lactate, and ethyl acetate, studied at 30 MPa and 343 K (Bermejo et al. 2016). The order of solvents concerning caffeine yield was as follows: ethyl lactate in both static and dynamic extractions (13.0 and 14.2 mg/g of tea, respectively) > ethanol (10.8 mg/g with the static method and 8.8 mg/g with the dynamic method) > ethyl acetate (both extraction types was lower than 7 mg/g). Optimum extraction of caffeine from green tea observed in the following conditions: the pressure of 25 MPa, the temperature of 60 °C and extraction time of 3 h (Sökmen, Demir, and Alomar 2018). Deep eutectic solvents are also uncomplicated and environmentally friendly, with high extraction

efficiency and low cost (Cai et al. 2019). The optimum caffeine extraction from Chinese dark tea was at 58 °C, 38 min period, 29:1 liquid-solid ratio, and 69 wt% deep eutectic solvent concentration (Cai et al. 2019). Additionally, the caffeine extraction yield found to be 26.78 mg/g. In another study, caffeine from green tea leaves extracted using the microwave-assisted extraction (MAE) method (Pan, Niu, and Liu 2003). According to the results, the yield of caffeine with MAE for 4 min (30 and 4%) was higher than that of extraction at room temperature for 20 h, heat reflux extraction for 45 min (28 and 3.6%), and ultrasonic-assisted extraction (UAE) for 90 min, respectively.

Caffeine is one of the many constituents in foods that can exert various health benefits, including lower risks of diabetes, Alzheimer's, Parkinson's, cardiovascular diseases, a potential role in weight loss, a favorable effect on liver function, protection against certain cancers, increased in energy availability and expenditure, enhancement in wakefulness, alertness, and feelings of energy (de Mejia and Ramirez-Mares 2014; Glade 2010; Heckman, Weil, and De Mejia 2010; Kumar et al. 2018).

Caffeine may also be an alternative for healthy weight loss. Systematic review and meta-analysis of randomized controlled trials showed that caffeine intake promoted weight, body mass index (BMI), and body fat reduction (Tabrizi et al. 2019). Parkinson's disease is a progressive neurological disorder. Increased caffeine consumption showed a lower risk of developing Parkinson's disease (Ren and Chen 2020). Smith (2005) investigated the influence of caffeine consumption on changes in alertness and performance over the working day (110 volunteers). The author reported that the higher levels of caffeine consumption significantly enhanced the alertness over the working day. In another study, caffeine examined for its anti-degranulation activity using in vitro and in vivo studies (Nugrahini et al. 2019). Caffeine significantly inhibited antigen-induced degranulation by RBL-2H3 cells in a dose-dependent manner. Moreover, caffeine hindered FcεRI-mediated intracellular signaling pathways, suppressing phosphorylation of Btk, Syk, PI3K, PLCγ1, and Akt in antigen-stimulated RBL-2H3 cells. Oral caffeine administration quickly decreased both brain and plasma Aβ levels. "Caffeinated" coffee enabled to quickly reduce plasma Aβ levels in Alzheimer's disease mice, but not the "decaffeinated" one, concluding that moderate caffeine intake (about 5 cups of coffee per day) may protect against Alzheimer's disease or treat it in a mouse model (Arendash and Cao 2010).

On the other hand, excessive caffeine intake has also been connected with nausea, headaches, anxiety, restlessness, and hypertension (de Mejia and Ramirez-Mares 2014). However, the routine daily consumption of caffeine up to 1000 mg (about 10 cups of coffee daily) posed no risks to human health (Bonita et al. 2007). More recently, the effect of caffeinated beverage consumption on sleeping quality was investigated among College Students in Korea (Choi 2020). Caffeinated beverage consumption did not show a significant effect on sleeping quality. It can be concluded that the amount of caffeine that may result in adverse effects varies from person to person, depending on age, weight, sex, and differences in susceptibility (Kumar et al. 2018).

Different carriers for the delivery of caffeine

The use of caffeine in specific food applications is precluded, taking into account its characteristic astringency and bitterness (Belščak-Cvitanović et al. 2015), which make the addition of sugar or flavors mandatory (Fuciños et al. 2017), its short immediate intake into the blood flow and prompt impact on the central nervous system (Martínez-López et al. 2014), and the gastrointestinal problems associated to its ingestion in high doses (Belščak-Cvitanović et al. 2015). Besides the food applications of caffeine, also the employment of caffeine in the cosmetic sector, due to its stimulating effect and lipolytic activity (Ryu et al. 2001), is limited by the fact that it is an approximately polar substance with low solubility in both oil or water (Kim et al. 2002). Thus, due to its hydrophilicity, its penetration through the stratum corneum, the outermost layer of the skin that acts as a barrier to water loss by evaporation and as protection versus the penetration of foreign chemical, physical and pathogenic ingredients from the surroundings (Rubio et al. 2011) is very complicated (Dias et al. 1999).

For all these reasons, the encapsulation of caffeine has been proposed to overcome these criticisms related to its consumption (Matoušková et al. 2012), also ensuring its controlled release with consequent reduced gastrointestinal diseases.

Lipid-based carriers

Several kinds of lipid-based carriers, such as nanoliposomes, nanoemulsions, SLNs, niosomes, and NLCs, have been reported as promising carriers for caffeine. Their compositions and main features are summarized in Table 1 and described in the following sections.

Nanoliposomal vehicles

Nanoliposomes consists of globular particles formed by the phospholipid molecules aggregation by a source of energy in aqueous media, which can synthesize in various forms (e.g., powder, suspension, semi-solid state) (Katouzian et al. 2017). For instance, Seyedabadi et al. (2021) reported the nanoencapsulation of caffeine in chitosan-coated nanoliposomes, so-called chitosomes, through the thin-film hydration method. Indeed, their work aimed to overcome the main challenge of nanoliposomes, i.e., the tendency to degrade by hydrolysis or oxidation and aggregation and fusion phenomena, which can result in the system leakage and sudden release of payload (Sarabandi and Jafari 2020). Indeed, a possible approach is related to the nanoliposomal surface modification through biopolymeric coatings, such as chitosan film, taking into account that chitosan is easily and widely available, owns a positive charge, and leads to the decrease of membrane fluidity and diminishes the aggregation rate of the assembled nanocarriers (Hasan et al. 2016; Shishir et al. 2019). The obtained nanoliposomes were spherical, presented smooth surfaces and homogenous distribution and had surface charges of −25 and 31.9 mV for nanoliposome and chitosome particles, respectively, suggesting a

Table 1. Types, components and main features of lipid-based nanocarriers for caffeine delivery.

Nanocarrier	Components	Release and bioavailability	Other findings	Reference
Nanoliposomes	Lecithin, cholesterol Tween® 80 (chitosan for the coating)	• The diffusion-based release system and Kopcha model was the chosen model to explain the release behavior of caffeine from developed chitosomes in the simulated digestive media (gastric and small intestine environment) • Slower release rate in the simulated digestive system (gastric and small intestine media) for chitosan-coated nanoliposomes than that of the uncoated system indicates the higher retention and stability of caffeine inside chitosome systems	• Spherical nanoliposomes with a homogenous distribution and smooth surfaces • Surface charges of −25 and 31.9 mV for nanoliposome and chitosome particles, respectively • A relatively stable nanocarrier	Seyedabadi et al. (2021)
Emulsion	Glycerin, PEG-24 glyceryl stearate, glyceryl stearate, cetostearyl alcohol, octyl stearate, methyl isothiazolinone, methyl-chloro-isothiazolin-one, imidazolidinylurea and water (perfluoropolymethylisopropylether (1, 3 or 5% w/w) in some formulations)		• No influence of the perfluoropolymethylisopropylether on caffeine penetration • Steady-state flux values of caffeine lower than 1.6 mg/cm2/h and around 0.2 mg/cm2/ h for the 0.1% and 0.01% caffeine emulsions, respectively	Bonina et al. (1992)
O/W emulsion	Water, polyoxyethylene glycol stearate, stearyl alcohol, petroleum and ethanol		• Remarkably higher amounts of caffeine deposited in skin due to the application of the emulsion versus acetone	Chambin-Remoussenard et al. (1993)
O/W and W/O emulsions	• Silicone/almond oil as the oil phases • For O/W emulsion sorbitan tristearate and PEG-40 stearate as emulgents • For W/O emulsion cetyl dimethicone dipolyol and methyl glucose dioleate as emulgents		• No significant differences in terms of caffeine skin penetration among the considered formulations	Dreher et al. (2002)
Pickering W/O emulsion	• Wheat germ oil (WGO) as the external continuous oily phase • MgO NPs as solid stabilizers	• The caffeine release that reached 70% within 48 h followed zero order kinetics	• Obtainment of nanodroplets (average size 665.9 ± 90 nm) • Caffeine safe levels without the risk of burst effect and consequent dangerous blood level spikes • Remarkable hepatoprotective action against liver damage induced by CCl4 in rats	Elmotasem, Farag, and Salama (2018)
Multiple emulsions	• Carboxymethylcellulose: Whey peptides paired solvable complexes • Whey peptides:carboxymethylcellulose: whey protein triplex solvable complex.	• A correlation between the emulsion bulk viscoelastic properties and release kinetics: higher viscoelastic moduli led to gradual caffeine release • When whey protein was the main component in soluble complexes, caffeine release was slower • When the complexes contained whey peptides, a faster caffeine release was evidenced • Study of the caffeine release from multiple emulsions incorporated into yogurt during 21 days of storage, under bile and acid salts	• Incorporation of caffeine loaded multiple emulsions in partial substitution of milk-fat to develop reduced milk-fat yogurts variations	Hernández-Marín et al. (2016)
Microemulsions and emulsions	• Isostearyl isostearate, cyclomethicone and diisopropyl adipate as lipophilic components for both emulsion and MEs • Addition of propylene glycol (PG, 2 %) in MEs	–	• The highest cumulative level of caffeine can permeate the skin for the MEs formulation, as well as the highest content of caffeine delivered to the hypodermis • No influence of the higher surfactant content in the MEs formulations on the barrier function of skin samples	Bolzinger et al. (2008)
Three types of microemulsions (i.e., O/W, W/O and bicontinuous)	• Quaternary mixtures of Polysorbate 21 (Tween®21) and Sorbitan monolaurate (Span®20) surfactants, isononyl isononanoate oil and water	–	• Progressively higher cumulative permeation in the following order: O/W MEs > bicontinuous MEs > W/O MEs = caffeine solution.	Naoui et al. (2011)

Different kinds of microemulsions (bicontinuous, O/W and W/O),	• Labrasol1, Cremophor1 EL and isopropyl myristate as the oil, surfactant and co-surfactant ingredients, respectively • Bromo-iminosulfurane or azone1 is further added in some formulations as permeation enhancers	–	• The highest caffeine cumulative amounts permeated for the O/W MEs • No influence of the penetration enhancers addition	Zhang and Michniak-Kohn (2011)
Microemulsions	• Isopropyl palmitate as the oil phase, glyceryl oleate and Labrasol1 as surfactants, propylene carbonate and different water proportions	–	• Remarkably higher skin penetration ability for both the W/O liquid emulsion and the MEs gel with respect to the caffeine solution used as control.	Sintov and Greenberg (2014)
Microemulsion	• Labrafil M 1944 CS (5% (w/w)) as oil phase, Smix (Cremophor EL as surfactant:tetraglycol as cosurfactant 2:1) (15% (w/w)), and water (80% (w/w))	–	• Skin location amount of caffeine nearly 3-fold higher than control ($P < 0.05$), as well as the amount permeated through the skin. • A remarkable increment of apoptotic sunburn cells ($P < 0.05$) with respect to control.	Ma et al. (2015)
Concentrated W/O emulsions	• Isohexadecane and emulsifier as oil phase	• Higher release of caffeine after 15 h only for one emulsifier • No influence of the emulsifier level on the caffeine release • Increment of the caffeine diffusion with the internal water phase percentage	• Decrement of the droplet diameter, increment of the apparent viscosity and changes the shape of the droplet from spherical to polyhedral increasing the dispersed phase percentage	Clément, Laugel, and Marty (2000)
SLNs	Softisan 100/ethanol/water as oil phase Pluronic F68 as surfactant		• Particles with an average size of (182.6 nm) • Good encapsulation efficiency and yield. • Increased caffeine permeation through skin	Puglia et al. (2016)
SLNs	Precirol® as lipid phase	• A sustained drug release over 24 h of storage at room temperature	• Nanosized particles (mean size of 94 nm) • Good encapsulation efficiency (86 %) and loading efficiency (28%) • Good stability within the storage for 12 months at room temperature • Good caffeine dispersion within the produced SLNs in an amorphous state • Higher drug accumulation in the skin with caffeine-SLN-hydrogel in comparison to the caffeine hydrogel • Flux value of caffeine through rat skin in caffeine-SLN-hydrogel 3.3 times < caffeine hydrogel • Whole lysis of adipocytes by administration of caffeine-SLN-hydrogel in deeper skin layers	Hamishehkar et al. (2015)
NLCs	• Polysorbate 60 as surfactant • Caffeine extracted from Coffee Silverskin	• Biphasic compound release profile, with a quick-release initial phase followed by a prolonged phase release until 8 h	• Nanocarriers (<200 nm) with a low PDI (<0.25) • Zeta potential around −30 mV • Caffeine association efficiency of about 30% at production time and after storage • Storage stability up to 180 days at 25 °C and 65% relative humidity (RH) and 40 °C/75% RH • Improved penetration of caffeine from NLC-CS when compared to CS extract	Rodrigues et al. (2016)
SLNs	Softisan 100® and Span 20® mixture, Tween 20®	• Gradual caffeine release and controlled over a 6-h period, after an initial burst at 3 min	• Polydispersity index <0.3 • Sizes <210 nm • Encapsulation efficiency of 49.22%	Algul et al. (2018)
NLCs	Coconut oil as a liquid lipid and glyceryl behenate as a solid lipid	–	• High entrapment efficiency (62-99%) • Nanosized range (≈ 60-390 nm) • Low polydispersity index • High negative zeta potential (> −30 mV)	Manchun et al. (2019)
Neutral and positively charged multilamellar (MLV) niosomes	Sorbitan esters	–	• Reduced drug entrapment due to the positively charged molecules incorporation • Highest encapsulation efficiency for neutral formulation with Span 60 and cholesterol • Progressive and linear increase of the niosomes average size with the surfactant lipophilicity (HLB values) of surfactants	Khazaeli, Pardakhty, and Shoorabi (2007)

relatively stable nanocarrier. The authors studied the release profile of the caffeine in the simulated digestive system (gastric and small intestine media) from the developed nanoliposomes, evidencing a slower release rate in the case of chitosan-coated nanoliposomes for the uncoated ones. Thus, the developed chitosomes could be used for caffeine retention and controlled release in the digestive system and can be considered efficient nanocarriers for caffeine retention and delivery, to be applied for the development of functional foods, as well as for drugs formulations.

Interestingly, a commercial product based on caffeine-loaded liposomes, produced by Dermaviduals® (USA), is available to stimulate of microcirculation and mobilization of lipids and can be used for cellulite- and atrophy-prone skin. The basis of composition is on pure phosphatidylcholine and highly dosed caffeine in liposomal dispersion, mainly composed of phosphatidylcholine, used for injection lipolysis (fat melting injection). It can be employed as an additive for Dermaviduals® base creams, as well as for local skin treatment using the pure concentrate.

In brief, nanoliposomes can be regarded as promising nanocarriers for food and drug applications, considering the easiness of the related production techniques and the available raw materials. Moreover, their main disadvantages are the tendency to degrade by hydrolysis or oxidation and aggregation and fusion phenomena (Sarabandi and Jafari 2020). Some approaches aimed at overcoming the limitations of nanoliposomes have been proposed, such as coating with chitosan (Seyedabadi et al. 2021), obtaining structures suitable for caffeine retention, and controlled release in the digestive system.

Nanoemulsions/double emulsions/pickering emulsions

Emulsions have also been proposed as promising systems for caffeine delivery. Bonina et al. (1992) encapsulated caffeine (in two different concentrations, i.e., 0.001% and 0.1%) in emulsions based on glycerin, polyethylene glycol (PEG)-24 glyceryl stearate, glyceryl stearate, cetostearyl alcohol, methyl isothiazolin-one, octyl stearate, methyl-chloro-isothiazolin-one, imidazolidinylurea, and water. In some formulations, perfluoropolymethylisopropylether (1, 3, or 5% w/w) was also added, even if it did not influence on caffeine penetration. Penetration experiments were carried out on human skin, evidencing steady-state flux values of caffeine lower than 1.6 mg/cm^2/h and around 0.2 mg/cm^2/h for the 0.1% and 0.01% caffeine emulsions, respectively. Chambin-Remoussenard et al. (1993) prepared oil-in-water (O/W) emulsions with water, stearyl alcohol, polyoxyethylene glycol stearate, ethanol and petroleum and compared them with acetone solution. They evidenced remarkably higher amounts of caffeine delivered in the skin due to the utilization of emulsions versus acetone, even if the acquired data were probably influenced by the low surface tension of acetone which spread over the skin during its evaporation.

Dreher et al. (2002) prepared O/W and W/O emulsions loaded with caffeine and compared them with a caffeine-containing hydrogel (composed of ethanol, water, triethanolamine, Carbomer1, methylparaben and imidazolidinyl urea), at the same concentration (1% w/w). In the case of emulsions, the oil phases consisted of almond and silicone oils. For the O/W emulsions, PEG-40 stearate and sorbitan tristearate were utilized as emulgents, whereas for W/O emulsions, cetyl dimethicone dipolyol and methyl glucose dioleate. In terms of caffeine skin penetration, no significant differences were detected among the considered formulations.

The use of Pickering emulsions (PEs) for caffeine delivery has been attempted by the addition of solid particles to stabilize the oil and water interface, which was characterized by higher stability as compared to the emulsions stabilized with emulgents. For example, Elmotasem, Farag, and Salama (2018) formulated caffeine-loaded W/O PEs, based on wheat germ oil (WGO) and stabilized by MgO NPs, obtaining nanodroplets able to guarantee caffeine sustained release rate. Indeed, the caffeine release reached 70% within 48 h followed zero order kinetics. Caffeine was encapsulated within the internal aqueous phase of the emulsion in order to prolong the caffeine effect and reduce dosing frequency. WGO was employed as the external continuous oily phase of the emulsion, being a good source of unsaturated fatty acids and sterols, able to improve the lipid profile and decrease cholesterol levels (Anwar and Mohamed 2015), and also antioxidants like vitamin E, providing a protective action from free radical damaging effects (Paranich et al. 2000). MgO NPs were selected as solid stabilizers due to their anti-bacterial properties, particularly against food-born bacteria (Jin and He 2011; Patel et al. 2013). Thus, the obtained systems would allow safe caffeine levels without the risk of burst effects and consequent dangerous blood level spikes. Additionally, they demonstrated remarkable hepatoprotective action against liver damage induced by CCl_4 in rats. They could be employed for the treatment of specific serious liver problems, for example, associated with hepatitis C virus replication.

Finally, W/O/W double emulsions can be considered promising encapsulation systems since they allow to encapsulate the bioactive components within the inner water phase, the intermediate oil phase, or the outer water phase (Leal-Calderon, Schmitt, and Bibette 2007). Hernández-Marín et al. (2016) prepared caffeine-loaded multiple emulsions by carboxymethylcellulose: whey protein and carboxymethylcellulose: whey peptides paired solvable complexes, and a whey peptides: carboxymethylcellulose: whey protein triplex solvable complex. They investigated the physical characteristics of obtained multiple emulsions and incorporated them in partial substitution of milk-fat to develop reduced milk-fat yogurts variations and studied the release of caffeine under bile, acid and yogurt storage environments. They demonstrated a correlation between the emulsion bulk viscoelastic properties and their stability and release kinetics: higher viscoelastic moduli led to gradual caffeine release rates. Moreover, when whey protein was the main component in the soluble complexes, the caffeine release was slower since a more prominent protein: polysaccharide shell, wrapped the oil droplets. On the contrary, when the complexes

contained whey peptides, a faster caffeine release was evidenced due to lower viscoelastic properties for the complexes with whey protein concentrate. The caffeine release from multiple emulsions incorporated into yogurt was evaluated during 21 days of storage under bile and acid salts environments, evidencing that it is influenced by the composition of the soluble complexes building the interfacial layers.

Concerning the reported emulsion formulations, Pickering emulsions are characterized by caffeine higher stability than the emulsions stabilized with emulgents. W/O/W double emulsions can entrap the bioactive components within the inner water phase, the intermediate oil phase, or the outer water phase (Leal-Calderon, Schmitt, and Bibette 2007). The caffeine release is influenced by the composition of the soluble complexes building the interfacial layers: a slower caffeine release can be achieved using whey proteins as the main component in the soluble complexes, whereas a faster caffeine release for whey peptides (Hernández-Marín et al. 2016).

Microemulsions (MEs)

Another possible delivery system for caffeine is represented by MEs, which contain oils, water and surfactants, and assemble single-phase thermodynamically stable systems with a size range of < 100 nm (Santos et al. 2008). Bolzinger et al. (2008) compared the caffeine delivery from MEs, emulsions and hydrogel formulations. Both MEs and emulsion formulations were composed of the same lipophilic ingredients, i.e., diisopropyl adipate, cyclomethicone and isostearyl isostearate. In contrast, the MEs were characterized by the addition of propylene glycol (PG, 2%). The hydrogel was based on Carbomer1 and PG (2%). The highest cumulative amounts of caffeine able to permeate the skin were detected for the MEs formulation, as well as the highest content of caffeine delivered to the hypodermis. It was demonstrated that higher surfactant contents in the MEs formulations did not affect the barrier function of skin samples.

Comparable permeation data were collected by Naoui et al. (2011), applying the same experimental conditions. Naoui et al. (2011) analyzed three types of MEs (i.e., O/W, W/O, and bicontinuous) containing 0.8% (w/w) caffeine, comparing them with a caffeine aqueous solution used as a control. The skin permeation was observed for 24 h, evidencing progressively higher cumulative permeation in the following order: O/W MEs > bicontinuous MEs > W/O MEs = caffeine solution. Moreover, the Authors ascribed the possible penetration enhancement effects to the skin lipids solubilization by surfactant components. Similarly, Zhang and Michniak-Kohn (2011) investigated different kinds of MEs (bicontinuous, O/W and W/O), comprising caffeine (1% w/w), using Labrasol1, Cremophor1 EL and isopropyl myristate as the oil, surfactant and co-surfactant ingredients, respectively. Bromo-iminosulfurane or azone1 were further added in some formulations as permeation enhancers. In the skin penetration experiments, the highest caffeine cumulative contents permeated were recorded for the O/W MEs. It was noted that the penetration enhancers addition did not influence and improve the skin penetration.

On the other hand, Sintov and Greenberg (2014) fabricated caffeine-loaded MEs (1% w/w) based on isopropyl palmitate as the oil phase, glyceryl oleate and Labrasol1 as surfactants, propylene carbonate and different water proportions. Additionally, they prepared caffeine-containing MEs gels by incorporating amorphous silica into the formulation based on 20% water. A remarkably higher skin penetration ability was observed for the W/O liquid emulsion and the MEs gel for the caffeine solution used as control.

Ma et al. (2015) proposed an optimized MEs formulation based on Labrafil M 1944 CS (5% (w/w)) as oil phase, Smix (Cremophor EL as surfactant:tetraglycol as cosurfactant 2:1) (15% (w/w)), and water (80% (w/w)), for the topical delivery of caffeine to improve its skin retention and, thus, its therapeutic effect on UVB-induced skin carcinogenesis. They performed ex vivo skin permeation studies using a gel containing the same amount of caffeine (1%w/w) as the control. The skin location amount of caffeine from the optimized formulation was nearly 3-fold > control ($P < 0.05$), as well as the amount permeated through the skin. Moreover, a remarkable increment of apoptotic sunburn cells ($P < 0.05$) was evidenced to control.

Clément, Laugel, and Marty (2000) studied the effects of formulation parameters, i.e., water content, emulsifier type, and its concentration, in concentrated W/O emulsions on the release profile of caffeine. They evaluated several physicochemical factors influencing caffeine release, such as droplet size, viscosity, stability, and structure. For this aim, the authors used four emulsifiers, evidencing that only one gave a statistically higher release of caffeine after 15 h. Moreover, the emulsifier concentration did not influence the caffeine release significantly. On the other hand, caffeine release from concentrated W/O emulsions highly depends on the internal phase volume, increasing the caffeine diffusion with the internal water phase percentage. It was reported that increasing the dispersed phase percentage, the droplet diameter decreased, the apparent viscosity increased, and the droplet's shape changed from spherical to polyhedral. Thus, the caffeine flux was mainly influenced by dispersed phase percentage and the shape of the droplet (the polyhedral shape increased it), but not by viscosity, droplet diameter, surfactant type, or concentration.

To conclude, MEs (i.e., O/W, W/O, and bicontinuous) show the highest cumulative amounts of caffeine able to permeate the skin, as well as the highest content of caffeine delivered to the hypodermis (Bolzinger et al. 2008; Naoui et al. 2011; Sintov and Greenberg 2014; Ma et al. 2015).

Niosomal vehicles

Niosomes are considered promising alternatives to the conventional liposomes (Alsarra et al. 2005; Palozza et al. 2006). They consist of unilamellar/multilamellar spheroidal structures based on a mixture of cholesterol and nonionic surfactants (e.g., esters, alkyl ethers, amides) (Balakrishnan et al. 2009). In the case of topical applications, niosomes can favor an enhanced penetration, probably due to the detected structural alterations in the lipid interstitial spaces

of the stratum corneum upon disposal of the skin to niosomes (Hofland et al. 1994).

In this regard, Khazaeli, Pardakhty, and Shoorabi (2007) prepared both neutral and positively charged multilamellar (MLV) niosomes, including sorbitan esters, for caffeine encapsulation, observing a declined caffeine entrapment due to the positively charged molecules incorporation. Among the prepared formulations, neutral with Span 60 and cholesterol presented the highest encapsulation efficiency because of the solid-state nature of this surfactant's bilayers. Moreover, the average size of niosomes progressively and linearly increased with surfactant lipophilicity.

Therefore, concerning conventional liposomes, niosomes present several advantages, such as their higher chemical stability, lower cost reagents, lack of toxic solvents, a large amount of available surfactants, possible large-scale production (Alsarra et al. 2005; Palozza et al. 2006), as well as a higher penetration in the case of topical applications (Hofland et al. 1994).

Solid lipid nanoparticles/nanostructured lipid carriers

Lipid NPs, i.e., NLCs and SLNs, have been considered promising bioactive carriers. SLNs consist of colloidal carrier systems based on high melting point physiological and biodegradable lipids as a solid core and surfactants as the coating. NLCs represent the second generation of SLNs and consist of blends between solid and liquid lipids, forming an imperfect matrix within the amorphous nanostructure.

SLNs consist of colloidal carrier systems based on high melting point physiological and biodegradable lipids as a solid core and surfactants as the coating. NLCs represent the second generation of SLNs and consist of blends between solid and liquid lipids, with the formation of an imperfect matrix within the amorphous nanostructure. Thus, NLCs are characterized by high loading capacity, the lower water content of the particle suspension, and lesser degree of bioactive release, reducing/avoiding the possible premature release of the encapsulated bioactive compounds during storage.

For these reasons, their features make them suitable for biomolecule delivery (Puglia and Bonina 2012). Lipid NPs are also able to improve the chemical stability of light-sensitive compounds and inhibit the oxidation and hydrolysis of materials (Pardeike, Hommoss, and Müller 2009). For all their properties, SLNs can find applications in several sectors, including epidermal targeting (Liu et al. 2007), follicular delivery (Münster et al. 2005), controlled drug delivery (Muller, Radtke, and Wissing 2002) and photostability improvement of active pharmaceutical ingredients (Iannuccelli et al. 2006). SLNs can be produced using different kinds of lipids and surfactants/polymers (Muller, Radtke, and Wissing 2002), using homogenization, MEs, solvent emulsification or evaporation, ultrasonication, and solvent diffusion methods (Kazemi et al. 2014). In particular, the high-pressure homogenization method presents many advantages, such as straightforward scale-up, prevention of organic solvents, and short producing time (Pardeike, Hommoss, and Müller 2009).

Concerning caffeine delivery, Puglia et al. (2016) encapsulated caffeine within SLNs via a modification of the quasi-emulsion solvent diffusion method (QESD), obtaining particles with an average size of (182.6 ± 8.4 nm) and good payload value (75% ± 1.1). They compared the caffeine/SLNs dispersion loaded into a xanthan gel formula with a gel loaded with the exact caffeine content. The in vitro percutaneous absorption research with excised human skin membranes (i.e., Stratum Corneum Epidermis or SCE) evidenced the capability of the produced lipid NPs in increasing the caffeine permeation across the skin. Differential scanning calorimetry (DSC) results confirmed the successful drug incorporation. Similarly, Hamishehkar et al. (2015) synthesized caffeine-loaded SLNs for the treatment of cellulite, by hot homogenization technique using Precirol® as lipid phase. They obtained nanosized particles (94 nm), with a good encapsulation efficiency (86%) and loading efficiency (28%). In vitro studies demonstrated good physical stability within the storage for 12 months at room temperature in terms of clarity and phase separation, as well as mean volume diameter (MVD) and span value. The good caffeine dispersion within the produced SLNs in an amorphous state was demonstrated by differential scanning calorimetry (DSC) and X-Ray diffraction (XRD) analyses. In vitro permeation research highlighted higher caffeine accumulation in the skin with caffeine-SLN-hydrogel compared to the caffeine hydrogel. In particular, the flux value of caffeine through rat skin in caffeine-SLN-hydrogel was 3.3 times < caffeine hydrogel, exhibiting less systemic absorption. The histological studies revealed the whole lysis of adipocytes by administration of caffeine-SLN-hydrogel in the deeper skin layers, concerning caffeine hydrogel.

Rodrigues et al. (2016) prepared spherical NLCs (<200 nm) loaded with caffeine extracted from Coffee Silverskin (NLC-CS), a food by-product, for the topical therapy of cellulitis via double emulsion technique using polysorbate 60 as surfactant. The obtained NLCs presented a low polydispersity index (PDI) (<0.25), zeta potential values around −30 mV, association efficiency (AE) of caffeine of about 30% at production time and after storage period, storage stability up to 180 days at 25 °C and 65% relative humidity (RH) and 40 °C/75% RH. Algul et al. (2018) produced caffeine-loaded SLNs using the double emulsion method with homogenization and ultrasonication, obtaining particles with a PDI <0.3, sizes <210 nm and encapsulation efficiency of 49.22%. Manchun et al. (2019) prepared caffeine-loaded NLCs by the ultrasonic emulsification method, using coconut oil as a liquid lipid and glyceryl behenate as a solid lipid. The produced nanocarriers presented a high entrapment efficiency (62-99%), a nanosized range (≈ 60-390 nm), a low PDI and high negative zeta potential values (over −30 mV).

As final considerations for the liposomes, lipid NPs, i.e., NLCs and SLNs, present many benefits: high physical stability, absence of organic solvents in the preparation process, low toxicity, high tolerability, rapid biodegradation, high bioavailability, high loading capacity, low cost and ease of scale-up and manufacturing (Fang, A Al-Suwayeh, and Fang, Al-Suwayeh, and Fang 2013; Muller, Radtke, and Wissing

2002), as well as the capability to improve the chemical stability of light-sensitive compounds and to inhibit the oxidation and hydrolysis of materials (Pardeike, Hommoss, and Müller 2009). In particular, NLCs are characterized by high loading capacity, the lower water content of the particle suspension and lesser degree of bioactive release, reducing/avoiding the possible premature release of the encapsulated bioactives during storage. SLNs could finely disperse caffeine in an amorphous state to increase the caffeine permeation across the skin leading to its higher accumulation (Puglia et al. 2016) and stabilizing it (> 12 months) (Hamishehkar et al. 2015). Thus, NLCs and SLNs features make them suitable for biomolecules delivery (Puglia and Bonina 2012), finding applications in several sectors, including epidermal targeting (Liu et al. 2007), follicular delivery (Münster et al. 2005), controlled drug delivery (Muller, Radtke, and Wissing 2002) and photostability improvement of active pharmaceutical ingredients (Iannuccelli et al. 2006).

Biopolymeric nano-carriers

In the last two decades, rapidly emerging technologies have induced promising approaches for developing biopolymeric delivery vehicles facilitating efficient encapsulation and transport of bioactive compounds such as caffeine in food systems and pharmaceuticals. Both natural (i.e., polysaccharides and proteins) and synthetic (i.e., PVP, polyvinylpyrrolidone, PLA, polylactic acid, and PVA, polyvinyl alcohol) biodegradable polymers loaded with caffeine in nanoscale formulations are effectively used for delivery purposes (Li et al. 2013; Madadlou, Jaberipour, and Eskandari 2014; Ravichandran et al. 2011; Shao et al. 2021; Sundar, Kundu, and Kundu 2010). Although non-biodegradable synthetic polymers have limitations for use in foods, some of them (e.g., polyethylene glycol, PEG) can be used in caffeine delivery systems as well (Artusio et al. 2019).

Bioactive-loaded nanocarriers of natural biopolymers, including proteins and polysaccharides, are considered safe materials and offer several advantages such as ease of preparation, considerable stability, sustainable transportation, and target release purposing to improve bioavailability upon delivery. Regarding this, the particle size of nanocarriers has been considered a critical parameter affecting loading capacity, solubility and delivery properties of the active material. Decreased particle size due to preparation method and formulation increases the surface area by improving bioavailability and sensory attributes of food ingredients such as caffeine (Bagheri et al. 2014a; Hassan et al. 2018). Biopolymeric nanocarriers formulated as NPs, nanohydrogels, nanofibers and nanotubes, and β-cyclodextrin inclusions have been regarded as successful matrices currently investigated for caffeine loading (Bagheri et al. 2014a; Bourbon, Cerqueira, et al. 2016; Bourbon et al. 2018; Fuciños et al. 2017; Gunasekaran, Ko, and Xiao 2007; Hassan et al. 2018; Kwak et al. 2017; Noor et al. 2018; Panda and Nayak 2018). Examples of current biopolymeric nanocarriers used for caffeine encapsulation and delivery are represented in Figure 1, and discussed in the following sections.

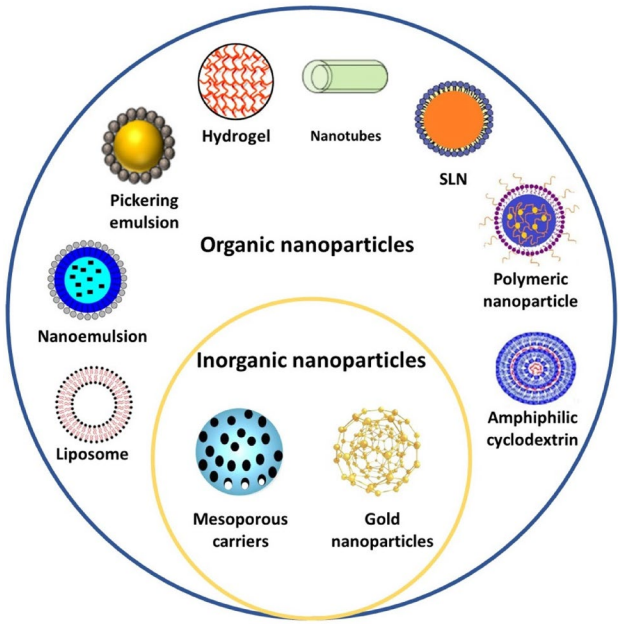

Figure 1. Different types of nanocarriers used for the delivery of caffeine.

Biopolymeric nano-particles

Proteins comprise various functional groups along with their natively folded polymer chain and those groups are exposed to the surface when protein is unfolded and/or partially unfolded through some processes such as enzymatic, thermal, and mechanical treatments. Exposed groups then interact with each other and different molecules to form varying-sized NPs capable of entrapping hydrophilic and hydrophobic bioactive ingredients (Fathi, Donsi, and McClements 2018; Madadlou, Jaberipour, and Eskandari 2014). Similarly, polysaccharides can be structured to form NPs with the help of some the above-mentioned treatments and crosslinking agents (Hassan et al. 2018). Resultant biopolymeric NPs exhibit different characteristics promising to achieve a favorable encasing and targeted caffeine delivery. Whey proteins and chitosan are popular biopolymers extensively studied for forming NPs aiming for bioactive agent loading, such as caffeine. For instance, heat denaturation-based and highly stable β-lactoglobulin (β-lg) NPs with ~200-300 nm in size were loaded by caffeine and resultantly, β-lg/caffein NPs reached ~350 nm in size with a maximum encapsulation efficiency of 13.54% (50:1 molar ratio of caffeine to β-lg) (Guo et al. 2017). Enzymatically cross-linked and developed whey protein NPs, ~ 118 nm, were reported as appropriate vehicles to carry caffeine (Madadlou, Jaberipour, and Eskandari 2014). Caffeine was also successfully incorporated in tripolyphosphate-crosslinked chitosan NPs (Hassan et al. 2018). They reported higher stability of caffeine-loaded chitosan NPs at refrigerator temperature compared to the control formulation, which is an aqueous caffeine solution. Besides, caffeine has been administrated to the other polymer-based NPs successfully as well (Hodali, Rawajfeh, and Allababdeh 2017).

Cashew and maltodextrin microparticles (MPs) presented the considerable potential to encapsulate green tea phenolics,

including caffeine, for fortification purposes in food processing (Silva et al. 2018).

Biopolymeric hydrogels/organogels/oleogels

Hydrogel matrices have been considered as innovative delivery systems with their viscoelastic nature and tunable pore size, which successfully entrap bioactive molecules. Nano-scale pores provide a larger surface area and the ability to encase high amounts of active agents in the nanohydrogel matrix. Protein and polysaccharide-based nanohydrogels promise to be an excellent vector for encapsulation and controlled release of caffeine (Belščak-Cvitanović et al. 2015; Bourbon, Cerqueira, et al. 2016; Gunasekaran, Ko, and Xiao 2007; Morrish et al. 2020; Zand-Rajabi and Madadlou 2016). In a study, alginate hydrogels with a size of ~ 6–7 nm were used to entrap caffeine which then exhibited a sustained release (Morrish et al. 2020). Bourbon, Cerqueira, et al. (2016) reported that caffeine was successfully entrapped in lactoferrin-glycomacropeptide nanohydrogels with a size of ~ 120 nm and high encapsulation efficiency (> 90%). Crosslinking and coating agents integrated into the biopolymer matrix significantly developed network integrity and release behavior of bioactive compounds. Chitosan-coated electrosprayed calcium-alginate microhydrogels designed to encase caffeine exhibited more strengthen gel network possessing high retention and controlled release of caffeine while maintaining gel integrity due to electrostatic interactions between chitosan and alginate (Nikoo et al. 2018). In another research work, chitosan or pectin coated, protein-reinforced alginate microhydrogel formulations used to encapsulate caffeine revealed that chitosan or pectin could not enhance the physicochemical properties or encapsulation efficiency but improved release profile of caffeine (Belščak-Cvitanović et al. 2015).

Organogels and oleogels comprising structured edible oils in a three-dimensional network formed by organogelators can also be served as efficient matrices to entrap, protect and release bioactive food ingredients and drugs (Mao et al. 2020; Qureshi et al. 2021). At the moment, there are no studies on caffeine-loaded organogels and oleogels.

Nanofibers and nanotubes

Electrospinning, self-assembly and layer-by-layer assembly approaches are well-described in producing nanofibers and nanotubes capable of encasing active agents and drugs (Katyal, Meleties, and Montclare 2019; Sharifi et al. 2016). Electrospun protein nanofibers (NFs) have superior properties through their extensive surface area and porosity, which could promote the transport and rapid delivery of bioactive materials (Sharifi et al. 2016). Besides well-known synthetic polymers (e.g., PVA and PVP), nanofibers developed from natural proteins can be served as promising candidates for caffeine loading. Kwak et al. (2017) studied caffein-loaded nanofibers based on electrospun fish gelatin and demonstrated ultrafast integration and release of caffeine from these nanofibers compared to the other caffeine-integrated polymer nanofibers. Moreover, fish gelatin nanofibers exhibited higher caffeine loading capacity than the other conventional nanofibers. These findings strongly suggest the use of gelatin nanofibers for the efficient encapsulation and fast delivery of hydrophilic compounds (Kwak et al. 2017).

Different from nanofibers, protein nanotubes are hallowed nanostructures and are capable of holding bioactive materials in their cavity, or binding through their surface or entrapping in the gel matrix formed during nanotubular growth (Graveland-Bikker and De Kruif 2006; Tarhan, Hamaker, and Campanella 2021). Fuciños et al. (2017) reported that whey-based α-lactalbumin nanotubes were highly influential for loading caffeine, providing high nanotube stability and a desirable caffeine release profile (Fuciños et al. 2017). The results showed the high stability of nanotubes against freeze drying and enhanced caffeine release by nanotube disassembly.

Protein-polysaccharide nano-complexes/conjugates

In recent years, most aqueous delivery systems for the protection (chemical or physical) and delivery of bioactive compounds have focused on the physical or chemical complexation or binding of the bioactive ingredient to molecular (or supramolecular) structures such as proteins and polysaccharides (Sagalowicz and Leser 2010). The formation of protein-polysaccharide complexes/conjugates (PPCs) can be promoted by non-covalent complexation and covalent interactions, respectively (Zhang et al. 2021). These complexes can be fabricated using both top-down (e.g., emulsion-based homogenization) and bottom-up (e.g., pH-driving encapsulation, self-assembly, liquid antisolvent precipitation, and heating or ionic gelation) approaches, with each approach exhibiting its unique advantages in terms of controlled release, stability, and functional characteristics of bioactive compounds. Generally speaking, the bottom-up approaches exhibit more advantages for the development of such nanocarriers, which is primarily due to their simplicity (Zhang et al. 2021).

Due to a synergistic combination of functional structures of both macromolecules (i.e., the protein and the polysaccharide), the formation of non-covalent electrostatic complexes/conjugates between proteins and polysaccharides could result in the appearance of different functional characteristics that those of the two individual biopolymers (McClements 2006; Schmitt and Turgeon 2011). Such functional properties may be beneficial for the stability and delivery of bioactives such as caffeine. In terms of the characterization of the nanocarriers fabricated using PPCs, the aspects of encapsulation profiles, formation mechanisms, and micromorphological properties can be investigated, for example, using spectroscopic and electron microscopic techniques (Hosseini et al. 2015; Zhang et al. 2021). Of course, like every other nanocarrier system, safety issues, as well as the targeted application, should be carefully considered during the manufacture and processing of the functional food formulations or nutraceuticals containing bioactives encapsulated using PPCs.

In recent years, some researchers have investigated the potential applications of both soluble and insoluble PPCs for the encapsulation of various bioactives (Emamverdian et al. 2020; Hosseini et al. 2015; Santos, da Costa, and Garcia-Rojas 2018; Zhang et al. 2021). Proteins such as milk proteins (e.g., whey proteins) and polysaccharides such as chitosan have been chiefly used for this purpose. Nevertheless, to the best of our knowledge, there is no information on whether the complexes and/or conjugates of proteins and polysaccharides can be used for the encapsulation of caffeine, although this compound (i.e., caffeine) has been encapsulated using the individual proteins or polysaccharides (Bagheri et al. 2014b; Fuciños et al. 2017; Madadlou, Jaberipour, and Eskandari 2014; Shao et al. 2021). Previous researchers (Gunasekaran, Ko, and Xiao 2007; Madadlou, Jaberipour, and Eskandari 2014) have reported that caffeine may not bind with some specific proteins (e.g., whey proteins), meaning that the encapsulation of caffeine using complexation with such proteins alone may not be successful; Methods such as physical entrapment (e.g., caffeine-loaded nanotubes) could be a solution (Fuciños et al. 2017). Besides, protein structure can affect the interaction thermodynamics between protein and caffeine during complexation. The native and thermally unfolded β-lg examined for binding caffeine revealed that the best interaction occurred at the hydrophobic sites of protein in both cases and thermal denaturation increases the structural flexibility to protein (Santa Rosa et al. 2021).

Microfluidic techniques facilitating electrostatic complexation between at least two oppositely charged polymers, eg. chitosan and gellan gum nanocomplex serve high efficiency in entrapment and carry caffeine (Fonseca et al. 2022).

Cyclodextrin inclusion complexes

β-Cyclodextrins (β-CD) are nontoxic macrocyclic oligosaccharides, which consist of (α-1,4)-linked α-l-glucopyranose units, where the outer side and inner side of the cavity being hydrophilic and hydrophobic, respectively. These properties of cyclodextrins (CDs) allow the encapsulation of bioactive compounds, such as caffeine to form host-guest complexes of supramolecular species (Prabu et al. 2015). The supramolecular chemistry of CDs is well-known and such a discipline of chemistry involves all intermolecular interactions, where no covalent bond is recognized between the interacting species (Harata, Xin Song, and Morii 2000; Rusa, Luca, and Tonelli 2001). However, most of these interactions are the host-guest interactions, which are determined by several weak forces; hydrophobic dipole-dipole, Van der Waals, and hydrogen bonding interactions (Hamdi, Abderrahim, and Meganem 2010; Harata, Xin Song, and Morii 2000). An extensive aspect of CDs is that they can form solid inclusion complexes by a molecular complexation with a very wide range of compounds from solids to liquids and gases.

CDs glucopyranose units in a torus-like macro-rings format can form inclusion complexes with a broad range of guest molecules containing bioactive compounds like caffeine (Prabu et al. 2015; Song et al. 2011). Therefore, such inclusion complexation can result in some favorable changes in the physicochemical properties of the guest molecule; e.g., improvement in its stability, solubility, dissolution rate, and bioavailability (Chen and Liu 2010; Liu et al. 2013; Qiu et al. 2014; Zhang et al. 2013).

Prabu et al. (2015) confirmed the spontaneous formation of the inclusion complex of caffeine as the guest molecule with β-CD in solution state (1:1 stoichiometric ratio), and the crystal structure modification of such a solid inclusion complex observed under a scanning electron microscope. The molecular docking studies also confirmed the findings obtained through various experimental methods, meaning that the formation of the inclusion complex between caffeine and β-CD was reproducible, possibly through the inclusion of the imidazole ring and pyrimidine ring of caffeine in the cavity of β-CD (Prabu et al. 2015). In another study published long ago (Gaffney et al. 1986), the interactions between polyphenols in aqueous media and caffeine with both α- and β-CDs studied in both binary and ternary systems. ^{1}H NMR (nuclear magnetic resonance) spectroscopy and microcalorimetry techniques revealed a significant modification of the complexation of polyphenols with caffeine in the presence of CDs. These results were also confirmed by Cai et al. (1990), who later investigated the complexation of a range of phenolic compounds with caffeine in aqueous media and related heterocycles with both α- and β-CDs.

Noor et al. (2018) encapsulated caffeine in various polysaccharide-based delivery systems, including β-CDs. The results showed that the smallest particle size distribution corresponded to that of the β-CDs system, although the other systems, including β-glucan showed a higher decline in the release of caffeine (when compared to CDs) under the simulated stomach conditions (Noor et al. 2018).

Inorganic nanocarriers

Inorganic NPs are a subset of nanocarriers comprising of metal, metal alloys, and inorganic nonmetallic materials which can be used as nanocarriers for delivery and encapsulation of different molecules, offering a wide range of optical and magnetic features with many different categories of delivery systems such as the NPs of iron oxide, gold, silica, silver, quantum dots, zinc oxide, carbon. These unique NPs employ their unmatched features such as high surface-volume ratio, antimicrobial activities, intrinsic magnetism, simplicity to functionalize, optical responsiveness, adjustable size and shape, and long-term stability can be used for effective delivery of cargos for therapeutic, imaging, cosmetic, and food applications (Jiao et al. 2018; Luther et al. 2020; Meena et al. 2020). The great potential of inorganic NPs is demonstrated with more than 25 marketed products for biomedical applications (Huang et al. 2020). Moreover, inorganic NPs can be prepared by using a composite of different inorganic materials, which can help utilize the different features of the materials used to achieve several benefits and more sensitivity, such as their use in multimodal imaging in atherosclerosis (Dai et al. 2020). However, it is crucial to keep in mind that there is limited knowledge

about their chronic toxicity; therefore, there is a need to carefully assess the toxicity and biocompatibility of inorganic NPs before advancing them in advanced preclinical models or clinical trials (Mohammadpour et al. 2019).

Gold NPs are one of the most prevalent inorganic delivery systems (Daraee et al. 2016). The use of gold NPs was reported for loading caffeine to enhance its anti-inflammatory activity (Kamalakannan et al. 2017). For the green synthesis of gold NPs, the study reports isolating caffeine molecules from coffee beans by solvent extraction technique used as a stabilizer and reducing agent. Subsequently, the delivery system was prepared by conjugating caffeine-loaded gold NPs to poly(lactic acid)-polyethylene glycol-poly(lactic acid) (PLA-PEG-PLA) copolymer matrix. The conjugation occurred by employing solvent evaporation and W/O emulsification methods through the synergic p-bond between the ester carbonyl group of the polymers and the gold NPs (Figure 2). Caffeine showed strong interactions with back bonded ester carbonyl oxygen as well as showing improved anti-inflammation properties. Physicochemical properties of the nanocarriers were evaluated through X-ray photoelectron spectroscopy (XPS), energy dispersive spectroscopy (EDS), X-ray diffraction (XRD), UV–vis absorption spectroscopy, selected area electron diffraction (SAED), and transmission electron microscopy (TEM). These evaluations confirmed the presence of caffeine and the formation of gold NPs. The polymeric matrix was shown to have a sheet-like shape (356 nm length and 216 nm width) with a uniform distribution of gold NPs throughout the sheet. The presence of the sheet-like structure could be explained because polyvinyl alcohol was not used in the emulsification process, which using polyvinyl alcohol typically would result in a spherical copolymer matrix (Agrawal et al. 2008). Subsequently, the EDS technique confirmed the presence of carbon (in the polymeric matrix), gold, oxygen (in the polymeric matrix) and nitrogen (in caffeine) atoms. Moreover, the triblock copolymer matrix showed crystalline properties, and the p-back bonds in the nanoconjugates were confirmed. Further in vitro tests revealed that the developed nanoconjugates improved protein denaturation and the stability of red blood cells' membranes. Due to the poor solubility of pure caffeine in salt solutions, the prepared nanocarriers helped to improve the anti-inflammatory effects of caffeine through the higher dispersion and affinity of the caffeine-loaded NPs. This study indicated the extent of inorganic NPs' benefits when loading caffeine (Kamalakannan et al. 2017).

Mesoporous silica nanoparticles (MSNs) are a subset of inorganic nanomaterials used as drug delivery systems because of their high loading efficiency, large surface area, biocompatibility, controlled release, stability, and tunable pore sizes and volumes (Abeer et al. 2020). To overcome the challenges of therapeutic applications of caffeine, such as its poor bioavailability and high clearance rate, MSNs were employed as a nanocarrier for the delivery of caffeine for anti-inflammatory applications. The prepared NPs had a loading efficiency of 28%, which was confirmed by High-Performance Liquid Chromatography (HPLC). Additionally, several anti-inflammatory tests (assays of COX, 5-lipoxygenase, Myeloperoxidase (MPO) activity cell, iNOS) were used to determine the anti-inflammatory effects of caffeine-loaded MSNs. These assays demonstrated that the developed formulation had higher anti-inflammatory effects in inhibiting inflammatory markers compared to caffeine on lipopolysaccharide (LPS) activated macrophage cells. Additionally, the scratch wound healing assay showed a higher reduction in wound area when caffeine-loaded MSNs were used compared to free caffeine or untreated cells. These results are promising, suggesting that MSNs can be utilized as nanocarriers for caffeine and improve its anti-inflammatory activities (Babu et al. 2018). In another evaluation, **Mobil Crystalline Material (MCM-48 and MCM-41) MSNs** were used to load caffeine and study its release profile. The main key finding of mesoporous silica release studies showed initial burst release, diffusion as the predominate dissolution mechanism, faster release with NPs than microparticles, and larger pore sizes showed a faster release profile (Hodali, Rawajfeh, and Allababdeh 2017).

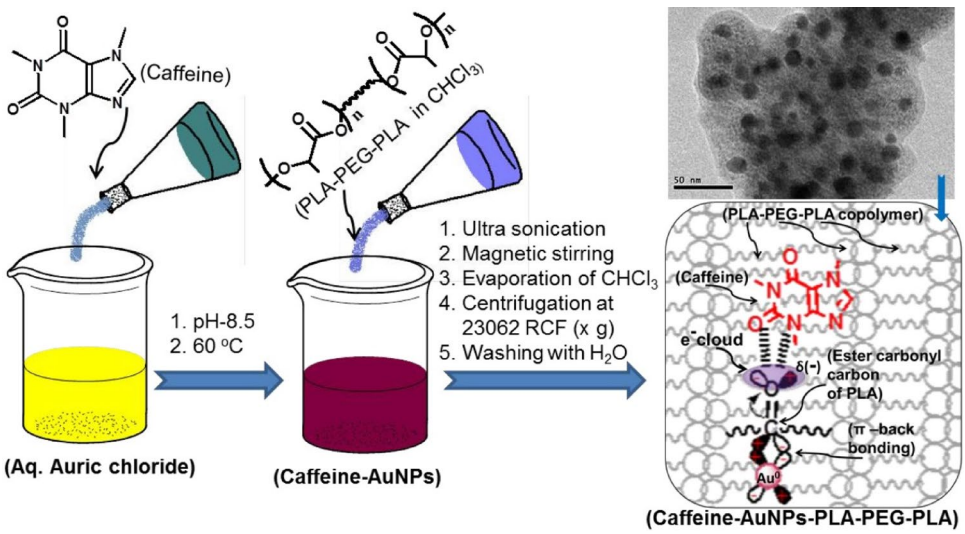

Figure 2. The preparation of caffeine-loaded gold nanoparticles conjugated to triblock copolymer matrix. Reproduced with permission from (Kamalakannan et al. 2017).

In another approach, **Fe_3O_4 NPs** were employed to build a magnetic microsphere composite. The composite comprised cross-linked pH-responsive poly(methacrylic acid-co-N-vinyl pyrrolidone) P(MAA-co-NVP) copolymers that covalently attached Fe_3O_4 NPs, which then was loaded with caffeine. Fe_3O_4/P(MAA-co-NVP) microspheres had an 800 nm mean diameter. They displayed a spherical shape with superparamagnetic features, while Fe_3O_4 NPs alone exhibited an aggregated spherical form with 12 nm as an average diameter. Moreover, the prepared microspheres showed a slower release of caffeine at pH= 1.4 compared to pH= 7.4. Subsequently, the results demonstrated that the developed microspheres followed a Fickian diffusion model. This study displayed the potential of inorganic NPs in modifying the release profile of caffeine (Di et al. 2011). Further studies can utilize these magnetic microspheres for theranostics and imaging purposes to track caffeine distribution in vivo settings.

There is still a limited number of studies using inorganic nanocarriers for caffeine encapsulation, and there is still a considerable way to design and evaluate different inorganic NPs. For instance, a few subsets of inorganic NPs have been employed for caffeine encapsulation. Even though several studies have utilized inorganic nanomaterials for biosensing and removal of caffeine, such as iron NPs, copper NPs, silver NPs, carbon nanotubes, graphene oxide, Fe_3O_4 NPs, quantum dots, gold NPs, and zinc oxide NPs, these nanobiosensors can be used for various applications in the food industry, such as removal of caffeine from the desired media, detection of caffeine, and determination of caffeine quantities (Abdel-Aziz, Farag, and Abdel-Gawad 2020; Jagadish et al. 2017; Mulyasuryani, Tjahjanto, and Andawiyah 2019; Ören and Anık 2017; Raj and Goyal 2019; Serrano et al. 2019; Shehata, Azab, and Fekry 2020; Ulusoy, Yılmaz, and Soylak 2019). However, these studies did not focus on caffeine encapsulation but showed that inorganic nanomaterials could be applied to deliver and encapsulate caffeine rather than just developing caffeine biosensors. Multiple studies reported the use of another exciting approach by using inorganic molecules such as gold, zinc halide, copper, cadmium halide, and silver to complex with caffeine (Altun and Şuözer 2019; Cannon et al. 2009; Rukk et al. 2019; Trommenschlager et al. 2018).

In addition, two of the reported studies in this section did not use a pure inorganic nanocarrier. However, they employed polymer materials to add additional functionalities to these carriers, which some may consider them as hybrid organic/inorganic nanomaterials. Thus, there is a need for future studies to explore and compare hybrid nanocarriers and pure inorganic nanocarriers head-to-head. Future research should keep in mind that for better marketing potential, it would be beneficial to design simple and effective formulations rather than complex systems that are hard to scale up. Moreover, there is a vast design space to employ a wide range of inorganic NPs for caffeine delivery. Future studies could explore using carbon nanotubes, graphene oxide, metal–organic framework (MOFs), MXenes, dentritic MSNs, and other novel inorganic nanocomposites. Finally, the current literature is limited regarding the application of these carriers; There is room for more comprehensive research in the food industry, in vivo settings, therapeutics potential, toxicology profile, bioavailability analysis, imaging applications, and theranostics applications of caffeine-loaded inorganic NPs.

Controlled release and bioavailability of the nanoencapsulated caffeine

The principle purpose of applying nanoencapsulation methods in the food industry is to supply the bioaccessibility and subsequent absorption of bioactives in a distinct organ using these delivery nanocarriers (Akbari-Alavijeh, Shaddel, and Jafari 2020; Jafari, Esfanjani, et al. 2017). Therefore, the controlled and targeted release of the bioactives is critical. One or a mixture of different release mechanisms may control the release behavior of bioactive food compounds from nanocarriers in which the release profile of encapsulated materials could be governed by the type of a release mechanism. The proposed procedures for delivery of the bioactive ingredients include dissolution, diffusion, osmosis, partitioning, swelling, and erosion (Jafari, Esfanjani, et al. 2017; Raval, Parikh, and Engineer 2010).

The burst release of the nanoencapsulated food bioactives is likely to cause uncontrolled and untargeted release and subsequently decrease the absorption process within the gastrointestinal lumen. Thus, developing the formulations with extended-release behavior is the primary objective of boosting the bioavailability of the encapsulated compounds (Akbari-Alavijeh, Shaddel, and Jafari 2020; Gaonkar et al. 2014). The kind of bioactive compounds, the system of encapsulation, and environmental parameters like temperature, a_w, and dissolution features could affect the release rate and behavior of the nanoencapsulated bioactive compound. Different external/internal triggers make conformational alterations of controlled release structures and initiate the release of nutraceuticals in food formulations or the human GIT. However, it is essential to design a wide range of encapsulation systems with various biological and physicochemical characteristics to have a programmed and controlled release to the definite place of the GIT over a prolonged period (Jafari, Katouzian, et al. 2017).

Various nanocarriers with resistance ability versus the physiological condition of GIT have been designed. Among them, biopolymeric and lipid-based nanocarriers are highly suggested to boost the bioavailability via improving the ratio of surface to volume and thus, elevate mucoadhesive anticipation in the small intestine via enhancing the intermingling viability with metabolic parameters or enzymes (Esfanjani and Jafari 2016; Jafari and McClements 2017). The reason for these properties is the easy penetration of nano-delivery developed systems within the cell wall and correctly approaching and releasing of their contents to the definite cells (Jain et al. 2016; Penalva et al. 2015). Caffeine entrapment into biopolymeric as well as lipids-based nanocarriers could be a probable scenario for their transformation through the micelle phase and increase their

bioaccessibility and bioavailability (Tan et al. 2016; Tydeman et al. 2010) by prompt dissolution, extended-release and increasing solubilization (Fu et al. 2019; Hsu et al. 2019). The biological fate of orally delivered nanoencapsulated caffeine is illustrated in Figure 3. The prolonged-release process of encapsulated caffeine has two main effects. First, suppression of bitter taste receptors on oral mucosa can lead to lower bitterness sensing in the cortical region of the brain. Second, the extended-release process of caffeine through GIT helps to get its beneficial effects on all human body organs while avoiding its adverse effects caused by overdosing (Shao et al. 2021; Jafari, Katouzian, et al. 2017).

Followings are some of the current research which have been done on the release and bioavailability of various caffeine-loaded nanocarriers fabricated by different encapsulation approaches. In this case, Seyedabadi et al. (2021) encapsulated caffeine by chitosan-coated nanoliposomes using Tween 80 as a surfactant to investigate caffeine release behavior and bioavailability in the simulated digestive media (gastric and small intestine environment). According to their results, most of the caffeine released in the small intestine and chitosan-coated nanoliposomes displayed a higher retention and stability of caffeine inside chitosome systems compared to the nanoliposomal system. In detail, 16.2% and 9.3% of caffeine were released in simulated gastric fluid (SGF), 27.99 and 20.62% in simulated intestinal fluid (SIF), and 29.92% and 44.19% in digestion fluid simulants from nanoliposomes and chitosomes, respectively. Kopcha model was the chosen model to explain the diffusion-based behavior of caffeine from developed chitosomes. In another study which was done by Hamishehkar et al. (2015), formulation and histopathological assessment of caffeine-loaded SLNs as an efficient treatment of cellulite using Precirol® as lipid phase have been investigated. As their findings, a sustained drug release of caffeine-loaded SLN incorporated into carbopol-made hydrogel (caffeine-SLN-hydrogel) was observed in comparison to the caffeine hydrogel over 24 h of storage at room temperature upon in vitro drug release studies.

Rodrigues et al. (2016) prepared nanostructured spherical lipid carriers loaded with caffeine extracted from Coffee Silverskin (NLC-CS) as formerly described using polysorbate 60 as a surfactant. They showed a biphasic compound release profile, with a quick-release initial phase followed by a prolonged phase release until 8 h. The in vitro skin permeation study, carried out on Franz diffusion cells using pig skin ear as permeation membrane, demonstrated an improved penetration of caffeine from NLC-CS compared to CS extract. The in vitro release studies of produced caffeine-loaded SLNs by Algul et al. (2018) showed that after an initial burst at 3 min, the caffeine release was gradual and controlled over a 6-h period. Bourbon, Cerqueira, et al. (2016) achieved encapsulation of caffeine in lactoferrin-glycomacropeptide (LF-GMP) nanohydrogels. They revealed that the release of caffeine is dependent on pH, which could affect the texture of the nanogel matrix and at low pH, the release was triggered (Bourbon, Cerqueira, et al. 2016). Later, these researchers also revealed a slight increase in the bioaccessibility of caffeine when incorporated in chitosan-coated protein nanohydrogels in comparison to uncoated ones and chitosan-coated nanohydrogels remained intact longer during gastric digestion (Bourbon, Pinheiro, et al. 2016, Bourbon et al. 2018).

Similarly, caffeine nanohydrogels fabricated by Artusio et al. (2019) using poly(ethylene glycol) diacrylate and inverse miniemulsion polymerization method showed that caffeine was magnificently released from the nanohydrogels, approving the suitability of such a system for controlled and sustained release of various drugs. The ex vivo release experiments must be performed to carry the fabricated nanohydrogel suspensions one step closer to the transdermal release applications (Artusio et al. 2019). In another attempt, Puglia et al. (2016) prepared SLNs loaded with caffeine using softisan 100, ethanol, and water via quasi-emulsion solvent diffusion technique. The in vitro results highlighted that lipid NPs could significantly enhance the caffeine permeation rate across the skin. Then, it can be used for therapeutic applications.

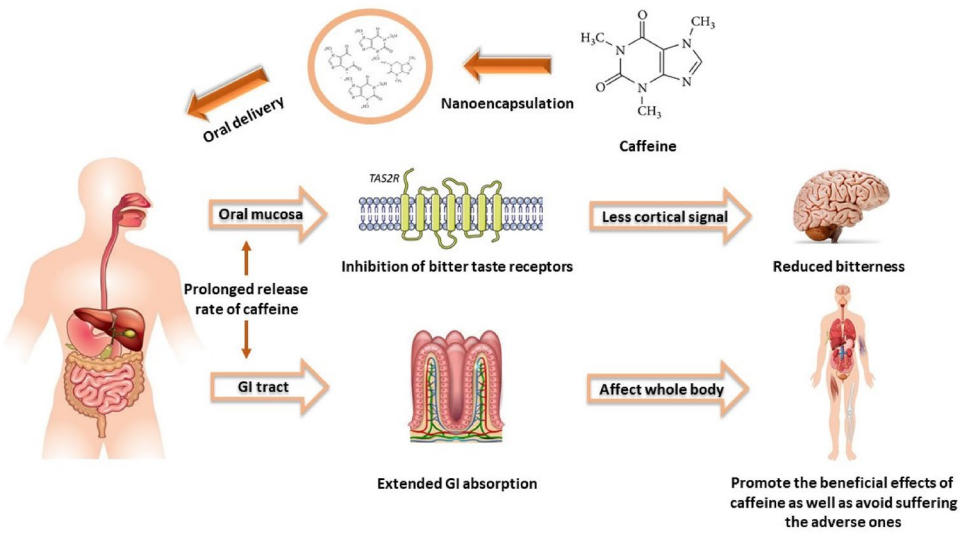

Figure 3. Biological fate of nanoencapsulated caffeine by oral delivery.

Biopolymeric nanocarries for caffeine delivery have also been fabricated in different literature to study their release behavior. In this case, Bagheri et al. (2014a) fabricated peptide NPs for caffeine loading from hydrolyzed whey proteins subsequently cross-linked with transglutaminase. Successfully encapsulated caffeine in particulate whey peptides exhibited a sustainable controlled release in a simulated gastric medium (Bagheri et al. 2014a). In another study (Hassan et al. 2018), caffeine-loaded tripolyphosphate-crosslinked chitosan NPs enhanced the release of caffeine from chitosan NPs when compared to the control formulation, which is an aqueous caffeine solution. Alginate hydrogels containing caffeine were found to be promising delivery systems with high sustained caffeine release attributes (Morrish et al. 2020). According to the results of Fuciños et al. (2017), enhanced caffeine release by nanotube disassembly was observed upon nanoencapsulation of caffeine by α-la nanotubes. Moreover, Noor et al. (2018) achieved that βCD increased the release rate of caffeine in comparison to the other two polymers when encapsulated caffeine by βCD, β-glucan and starch.

More details of published studies on bioavailability and intestinal absorption of caffeine loaded in various nanocarriers have been summarized in Tables 1 and 2 (release and bioavailability section) as well as Table 3 (stability and release section).

Potential applications of caffeine-loaded nanocarriers in different industries

Caffeine has been widely applied in food and medical products, including beverages, chocolates, and pain-relieving medicines (Quinlan, Lane, and Aspinall 1997). Additionally, the extreme bitterness of caffeine causes an unpleasant aftertaste, which limits its application in food and drinks formulations (Tenney et al. 2017). Therefore, we need a way to consume caffeine that can suppress its bitterness as well as provide benefits over a more extented time. Encapsulation of caffeine using odorless/tasteless substances, especially biopolymers, can be a better option for suppressing caffeine bitterness without presenting an unrequited flavor/odor (Keast 2008). To date, various wall materials have been used to encapsulate caffeine, such as alginate hydrogels combined with pectin, carrageenan, chitosan and psyllium (Belščak-Cvitanović et al. 2015), β-glucan (Noor et al. 2018), starch matrices (Shao et al. 2021) and β-cyclodextrin (β-CD) (Panda and Nayak 2018). Although pectins could suppress caffeine bitterness, the obtained caffeine-loaded beads still showed some flaws in chewiness during oral processing (Belščak-Cvitanović et al. 2015).

Generally, it is not easily possible to incorporate bioactive compounds into various foods mainly due to their undesirable effects on sensory attributes of the product as well as their deterioration under the adverse operational parameters or gastrointestinal digestion as described above, which could be solved by encapsulation as an appropriate solution. Regarding the literature, a few studies worked on practical applications of micro-or nano-encapsulated caffeine for food, drug, and nutraceutical industries, while most of the literature focused on potential applications.

Chewing gum is introduced as a suitable carrier for many active ingredients and stimulants like caffeine (Cacciotti et al. 2021). Sweeteners, as well as stimulant agents such as caffeine, are components that need to be covered by encapsulants to guarantee their controlled release in chewing gum during chewing and gastrointestinal digestion. Non-protected caffeine could release in chewing gum as fast as the release of stimulants in energy drinks and beverages, resulting in the formation of an unpleasant bitter taste caused by the quick release of caffeine. Nanoencapsulation can tune up the release rate of caffeine by prolonging its release, avoiding gastrointestinal suffering, and moderating taste issues (Gudas et al. 2000). Chewing gum is inherently able to control the release rate of caffeine during gastrointestinal digestion. Further, nanoencapsulation would be capable of controlling

Table 2. Biopolymeric nanocarriers for caffeine delivery.

Nanocarrier	Particle size / Efficiency	Stability and Release	Reference
Nanoparticles			
Peptide nanoparticles (PNPs)	52 – 348 nm / 89.60 %	Transglutaminase crosslinking increased stability of caffeine-loaded NPs and slowed down release rate in gastric fluid	Bagheri et al. (2014a)
Chitosan nanoparticles (CNPs)	50 – 150 nm / 60.69 %	High degradation rate at room temperature and triggered release of caffeine when encased in chitosan NPs	Hassan et al. (2018)
Nano-hydrogels/ organogels/oleogels			
Alginate hydrogels	6 – 7 nm / –	Calcium crosslinking altered microstructure and diffusion parameters of alginate gels, and sustained release of caffeine was achieved	Morrish et al. (2020)
Lactoferrin glycomacropeptide (LF-GMP) nanohydrogels	126 nm / > 90 %	Caffeine release was pH-dependent and it increased at low pH (2.0) due to the relaxation of the nanogel matrix	Bourbon, Cerqueira, et al. (2016)
Nanofibers and nanotubes			
Fish gelatin nanofibers (FGNFs)	200 – 220 nm / –	Ten times faster caffeine release was achieved through FGNFs than other caffeine-loaded polymers	Kwak et al. (2017)
α-lactalbumin nanotubes	20 nm / ~100 %	High stability of nanotubes against freeze drying and enhanced caffeine release by nanotube disassembly	Fuciños et al. (2017)
Cyclodextrin inclusion complexes			
β-cyclodextrin, β-glucan, starch	– / 74 %	β-cyclodextrin increased the release rate of caffeine in comparison to the other two polymers	Noor et al. (2018a)
β-cyclodextrin	–	Complexation with β-cyclodextrin increased the release profile of caffeine	Panda and Nayak (2018)

Table 3. The potential applications of various caffeine-loaded nanocarriers.

Nanocarrier	Encapsulant (s)	Encapsulation approach	Release and bioavailability	Findings/applications	Reference
Nanoliposomes	Chitosan	Thin-film hydration	The chitosome nanocarriers presented a sustained release in comparison with nanoliposomes deprived of chitosan, underlining the improved retention and stability of caffeine-loaded chitosomes.	They concluded that such caffeine nanovehicles could be used in food and pharmaceutical areas to produce functional foods and drugs.	Seyedabadi et al. (2021)
Calcium-alginate hydrogels	Chitosan	Electrospraying	They suggested that the chitosan-coated microhydrogels can be used as potential carrier systems guaranteeing a controlled release	The results showed that chitosan-alginate NPs could be used as efficient entrapments for caffeine and other bioactives.	Nikoo et al. (2018)
Microcapsules	β- cyclodextrin, resistant starch, and β- glucan	Lyophilization	–	The smallest and largest capsules were found in formulations containing resistant starch and β-CD. The maximum encapsulation efficiency of caffeine belongs to the β-glucan nanocarriers, which make it a potential vehicle for delivering caffeine in food and pharmaceutical applications.	Noor et al. (2018a)
Nanohydrogels	Lactoferrin-glycomacropeptide (LF-GMP)	Thermal gelation	The prolonged delivery system for caffeine	LF-GMP nanohydrogels are capable of encapsulating caffeine and other bioactive compounds as safe and GRAS ingredients, making them exciting candidates as nanocarriers for food and pharmaceutical applications.	Bourbon, Cerqueira, et al. (2016)
Supercritical CO_2 ($SC\text{-}CO_2$)	Carboxylate-based metal-organic frameworks (MOFs)	Impregnation	It can guarantee the targeted delivery of heat-sensitive and unstable bioactives for various food, cosmetic, drug, and pharmaceutical applications.	This green procedure could be potentially used in all hydrophilic compounds, such as caffeine, in $SC\text{-}CO_2$.	Monteagudo-Olivan et al. (2019)
Nanohydrogels	Poly(ethylene glycol) diacrylate	Inverse miniemulsion polymerization	Caffeine was magnificently released from the nanohydrogels, approving the suitability of such a system for controlled and sustained release of various drugs.	The ex vivo release experiments need to be performed to carry the fabricated nanohydrogel suspensions one step closer to the transdermal release applications.	Artusio et al. (2019)
Microemulsions	Enzymatically cross-linked whey proteins	Nanoparticulation through micro emulsification/ heat gelation procedure	–	Whey proteins are proper nominees to produce nanospheres and nanocapsules in order to provide nanovehicles transferring various nutraceuticals. Transglutaminase cross-linked whey proteins led to the formation of monodisperse and smaller nanodroplets.	Madadlou, Jaberipour, and Eskandari (2014)
Nanotubes	α-lactalbumin	Physical entrapment	–	Enzymatically hydrolyzed α-lactalbumin in the presence of divalent ions results in the construction of compatible food-grade nanotubes, with an excellent potential for cosmetic and food sectors.	Fuciños et al. (2017)
Solid lipid nanoparticles (SLNs)	Softisan 100, ethanol, and water	Quasi-emulsion solvent diffusion technique	The *in vitro* results highlighted that lipid nanoparticles could significantly enhance the caffeine permeation rate across the skin.	SLNs were efficient in encapsulation of caffeine with suitable encapsulation efficiency. According to the bioavailability results, it can be used for therapeutic applications.	Puglia et al. (2016)
Nanocapsules	Alginate and chitosan	Layer-by-layer adsorption	–	In this study, the caffeine molecules were incorporated into the polysaccharide shell with the encapsulation efficiency reliant on the quantity of adsorbed polymer layers and the chitosan characteristics. Regardless of the low encapsulation efficiency of the drug (caffeine), the quantity of caffeine loaded into the film layers was high enough, and pharmacological dosages were attained with very low volumes of dispersion.	Milkova and Goycoolea (2020)
Inorganic nanoparticles	Mesoporous silica nanoparticles	Sol-gel process	–	Anti-inflammatory effect was achieved by caffeine-loaded mesoporous silica nanoparticles on lipopolysaccharide-activated macrophage cells	Babu et al. (2018)
Inorganic nanoparticles	Gold nanoparticles conjugated with PLA-PEG-PLA	Ultra-sonication-induced W/O emulsification and solvent evaporation	–	Caffeine-loaded gold nanoparticles conjugation to PLA-PEG-PLA copolymer was made possible by π-back bonding. Moreover, the biocompatibility of the developed platform was confirmed on African green monkey's kidney cells. Furthermore, anti-inflammatory effects were shown by the stabilization of red blood cells membrane activity and the suppression of protein denaturation	Kamalakannan et al. (2017)
Inorganic nanoparticles	SBA-15 type, non-ordered silica, and PEO-PPO-PEO copolymer	*In situ* method	Caffeine was released from SBA-15 nanoparticles after half day, while in the non-ordered silica the full release occurred after 1 day	This study used a one-step preparation technique to encapsulate caffeine-PEO-PPO-PEO micelles in the pores of two types of mesoporous silica nanoparticles (SBA-15 and non-ordered silica). Thermal stability and improved drug release achieved due to the formation of hydrogen bonds between caffeine and silica hydroxyls. Moreover, the SBA-15 platform showed a better encapsulation rate.	Liedana et al. (2013)

the release rate as well as avoid the caffeine degradation/release over the product shelf life. For instance, in a human study conducted by Kimamori et al. (Kamimori et al. 2002), the absorption rate and bioavailability of caffeine-loaded capsules (50, 100, and 200 mg dosages) were investigated in the formulation of commercial chewing gum (Stay Alert®) in comparison with the control sample. The results showed that the relative bioavailability of the encapsulated caffeine was about 13% higher than the free caffeine, so that the bioavailability percent of chewing gum loaded with encapsulated caffeine reached 97% in 200 mg concentration, while 77% in the chewing gum loaded with free caffeine. They also stated the accelerated absorption rate in the chewing gums containing free caffeine compared to the encapsulated form, most probably due to the faster absorption through the buccal mucosa. According to their findings, chewing gum could be employed as a suitable candidate to encapsulate caffeine for pharmacological applications because of generating a controlled release of caffeine to keep alertness and boost cognitive performance.

It is predicted that about two-thirds of the daily caffeine intake derives from coffee. This made coffee a proper medium to deliver caffeine. In this regard, caffeine administration in various oral forms (cola, dark chocolate, and caffeine capsules) was investigated by Mumford et al. (1996) to monitor the caffeine uptake in plasma. The capsule form of caffeine showed a peak concentration in plasma in a short time (30 min). In comparison, the caffeine plasma concentration peaked after 90-120 min in both dark chocolate and cola samples, indicating the suitability of these products to guarantee the controlled release of caffeine during ingestion. It shows that dark chocolate ingredients, for instance, are better choices to encapsulate or cover caffeine during ingestion than caffeine capsules. Similar findings regarding cola are reported in energy drinks in which a large amount of the administered beverage could postpone the gastric emptying time resulting in an extended caffeine absorption (Laizure et al. 2017; Martínez-López et al. 2014).

Guo et al. (2017) loaded caffeine into β-lactoglobulin (Blg) NPs by a green approach using a simple heat-induced denaturation method. A formulation containing 2% Blg prepared at pH= 6 by heating at 75 °C for 45 min was identified as the optimal treatment with suitable stability, monodispersity (200-300 nm in size), and aggregation efficiency (>90%). The maximum caffeine entrapment efficiency was found at the caffeine to Blg molar ratio of 50:1. Gastric digestion of nanocarriers showed a fast degradation of Blg NPs, while the release of caffeine was insignificant. The total release of caffeine occurred in the intestine condition. Caffeine adsorption (affinity) to the partially denatured Blg was about three times higher than the native Blg, signifying the influence of conformational alteration due to heat denaturation on Blg affinity to caffeine. The possible reason for increasing caffeine affinity could be associated with the greater exposure of hydrophobic groups as a result of heat denaturation, allowing Blg to carry more caffeine compared to the native Blg (Santa Rosa et al. 2021). Recently, caffeine-loaded gold nanostructures were developed for the treatment of bacterial infections. These nanoarchitectures demonstrated potential in suppressing biofilm generation, dispersing mature biofilms and eliminating Gram-positive/negative bacteria (Khan et al. 2021).

Chitosan nanocarrier, as a promising biopolymeric vehicle, was employed to entrap caffeine as a commonly used drug in treating cellulite (Abosabaa, ElMeshad, and Arafa 2021). The effect of various parameters, including chitosan concentration, pH, and chitosan to tripolyphosphate ratio, was investigated on caffeine loading efficiency, particle size distribution and stability of the constructed nanocarriers. The results showed that chitosan concentration had a positive impact on caffeine encapsulation efficiency. In contrast, higher solution pH and higher chitosan to tripolyphosphate ratio had the opposite impact on encapsulation efficiency. The optimal condition was obtained using the Box-Behnken design with high desirability (0.805). Regardless of obtaining a successful nanocarrier with a particle size of 173 nm and zeta-potential of +41.7 mV, a relatively low caffeine encapsulation efficiency was observed mainly due to the alteration of several parameters disturbing the caffeine hydrophilicity and its molecular weight.

The transdermal delivery of caffeine as an anticancer drug was also performed by Shakeel and Ramadan (Shakeel and Ramadan 2010) using a W/O nanoemulsion system. The oil phase titration approach was a safe method to produce thermodynamically stable caffeine-loaded nanoemulsions to support the skin from skin cancer initiated by sunlight exposure. The rat skin-incorporated Franz diffusion cell was used as the permeation membrane to plot the skin permeation profile of nanoencapsulated caffeine in comparison with caffeine aqueous solution. A significantly higher permeation rate was observed in nanoencapsulated caffeine formulations compared to the aqueous solution containing free caffeine. The tablets are also displayed a suitable potential as caffeine carriers. Because of that, casein gel tables were fabricated to encapsulate caffeine to generate a controlled release system lasting from a couple of minutes to a few days (Tan, Ebrahimi, and Langrish 2019). The acidified casein gel was used as an insoluble control-releasing matrix and spray-dried with coffee to microencapsulate the caffeine. The pressurized controlled release was employed to achieve the release rate of 80% for 24 h at 8 MPa. It can be applied for drug and pharmaceutical uses.

Abd, Roberts, and Grice (2016) studied the permeation and penetration of caffeine (as a hydrophilic drug) through and into the human epidermis using various vesicular carriers. These vesicles can protect caffeine against degradation and facilitate its skin penetration, causing higher efficiency. Oleic acid and eucalyptol were used in the formulations as penetration promoters. 2% w/v caffeine was loaded into five vesicle formulations, namely conventional liposome (L), L + oleic acid (LOA), L + eucalyptol (LEU), in addition to noisome (N) and transferosome (T) as the modified liposomes, and finally, a water solution containing the same amount of caffeine was used as the control. The average particle size of the fabricated nanocarriers ranged between 128-158 nm with a low polydispersity index (ranged from 0.06-0.15). The encapsulation efficiency of the vesicles was

found to be between 46-66%, so LEU showed the highest efficacy. High-performance liquid chromatography detected caffeine permeation and penetration in the skin. Transferosomes and niosomes were found as the most efficient nanocarriers to increase the caffeine penetration into the skin and permeation through the stratum corneum. Furthermore, LOA and transferosomes were introduced as caffeine penetration boosters into the hair follicles. They concluded that nano-size vesicles are suitable nominees for the targeted delivery of caffeine into the skin as anticancer drugs. In another study, Ramezani et al. (Ramezani et al. 2018) employed transferosomes to encapsulate caffeine and minoxidil to overcome hair loss (alopecia) by improving their delivery to the hair follicles. The results revealed that using 9.3% polysorbate 20 and 22.2% polysorbate 80 in the transferosome formulations as the edge activators could improve the drug delivery to the skin.

NLCs constructed with argan oil were also engaged as a novel approach to deliver caffeine to stratum corneum and hair follicles (Shiehzadeh et al. 2021). The concentration of lipid, caffeine, and surfactant, as well as Span to Tween and stearic acid to argan oil ratios, were investigated as main variables to monitor the caffeine encapsulation efficiency. A formulation containing 2% argan oil, 2% surfactant, Span to Tween of 1.25, and stearic acid to argan oil ratio of 3.5 was chosen as the most efficient treatment for caffeine encapsulation with an encapsulation efficiency of 89%. Then, the penetration of caffeine-loaded NLCs was scrutinized by transcellular and transfollicular pathways in an in vivo model. The caffeine loss of the caffeine-loaded NLC solution was significantly lower than the free caffeine solution in the hair follicle on the third and sixth days of treatment compared to the first day of treatment, representing a stable and targeted drug delivery in encapsulated caffeine. The potential applications of various caffeine-loaded nanocarriers are presented in Table 3.

Toxicity and safety of nanoencapsulated caffeine

Although caffeine has many positive effects on health, there have been some reports about the toxicity at high dose levels consumption of caffeine. The studies on animal and human toxicity of caffeine affirmed the safety of caffeine in moderate consumption. Caffeine may have preventive effects on some diseases such as Parkinson's disease and cancers. There are many studies about the animal toxicity of caffeine for different durations (acute, subchronic, chronic, and lifetime exposure). It is confirmed that caffeine could be well-sustained at high dose intake. The studies about the acute toxicity of caffeine in animals indicated that a high dose intake of 185 mg/kg body weight induces low acute toxicity in some species. The animal species indicated dejected activity for around 2 days that was pursued by repetitive motions such as running back. Furthermore, there are some reports about the increased weights in adrenal and thymus glands at high dose intake (Roberts 2021). The developmental and reproductive risks of caffeine were assessed by Brent, Christian, and Diener (2011) and the NOAEL of caffeine in rodents was reported to be around 80-120 mg/kg body weight per day (Brent, Christian, and Diener 2011).

The World Health Organization's International Agency for Research on Cancer (WHO IARC) has reported insufficient proof supporting that caffeine is carcinogenic (IARC 1990). The epidemiological studies indicated that regular intake of coffee could decrease the risk of kidney and liver cancers and, to a lesser extent, colon and breast cancers (Nkondjock 2009). The in vitro studies of caffeine at high doses indicated some pro-convulsive effects and also produced seizures in animals (Chrościńska-Krawczyk et al. 2011). Moreover, some concerns, such as malformation and decreased fetal weight, are detected only at high dose levels and in the presence of caffeine toxicity in the mother (Roberts 2021). Many human studies about the safety of caffeine that have deliberated the effects of caffeine on different physiological parameters such as arrhythmia, heart rate, blood pressure, glucose tolerance, and calcium balance. Epidemiological investigations have investigated different effects of caffeine consumption on cardiovascular disease, cancer, pregnancy outcomes, and diabetes. There are rare reports about caffeine intoxication. Symptoms of caffeine toxicity manifest as gastrointestinal symptoms, restlessness, excitement, facial flushing, insomnia, nervousness, and diuresis. The toxicity associated with these symptoms occurs when the plasma concentration is greater than 30 µg/mL (equivalent to 150 µmol/L) (Sawynok 1995). The high dose levels consumption of caffeine that induces blood caffeine concentrations higher than 80 µg/mL may result in fatal reactions (Moffat et al. 2011). A meta-analysis by Cheng et al. (2014) showed a reduced risk related to caffeine intake and atrial fibrillation (Cheng et al. 2014).

Caffeine daily intake comes from caffeinated beverages such as tea, coffee, and carbonated soft drinks. The average caffeine intake for adults (19 years or older) approximated at 186 mg/day and for real caffeine consumers of the same age was 211 mg/day (Fulgoni, Keast, and Lieberman 2015). Most caffeine-related adverse health effects are related to the intake of dietary supplements, caffeine tablets, and caffeine-containing pharmaceuticals (Roberts 2021). The standard guidance recommended by regulatory agencies for the consumption of caffeine is 400 mg/day in healthy adults that don't have adverse health effects (Nawrot et al. 2003). EFSA offers the value of 200 mg/day for lactating women and pregnant (EFSA Panel on Dietetic Products and Nutrition and Allergies (NDA)) 2015). A systematic review of the adverse health effects of caffeine intake in healthy adults, adolescents, children, and pregnant women have been published by Wikoff et al. (2017). Their results confirmed that consumption of up to 400 mg caffeine/day in healthy adults, 300 mg caffeine/day in healthy pregnant women, and 2.5 mg caffeine/kg body weight/day in children and adolescents were safe and generally not related to the adverse health effects. Although, data obtained for child and adolescent populations were limited (Wikoff et al. 2017).

Despite many recent studies on caffeine toxicity and safety, there is limited study about the toxicity and safety of encapsulated caffeine. Silva Faria et al. (2020) evaluated

the oral toxicity of encapsulated and non-encapsulated green coffee fruit extracts (GCFE). They indicated that encapsulated extracts from green coffee fruit might induce lower intoxication in comparison to non-encapsulated caffeine at the same dose intake due to the delayed release of caffeine and other bioactives from the extract. The results of the acute test for a period of 14 days indicated no adverse effect on both male and female mice for single oral dosage up to 1000 mg/kg per body weight. The comparison of the lethal doses of encapsulated and non-encapsulated GCFE revealed that for encapsulated GCFE, it was not detectable, while for non-encapsulated GCFE, it was determined to be 5000 mg/kg per body weight. According to the results of the no-observed-adverse-effect level (1000 mg/kg per body weight/day), the authors estimated a dose of 189 mg/kg per body weight/day of encapsulated GCFE for human consumption (Silva Faria et al. 2020).

In another study, researchers evaluated the hepatoprotective effect of caffeine-loaded W/O Pickering emulsions (37.5 mg/kg/day caffeine for 14 days) against CCl4 intoxicated rats. The histopathological results showed significant hepatoprotection (Elmotasem, Farag, and Salama 2018). Furthermore, the blood circulation time of encapsulated compounds (especially nanoencapsulated samples) was higher than non-encapsulated compounds and can reduce liver accumulation (Gref et al. 1994). Liu et al. (2020) encapsulated R837 and caffeine into the nano-immunomodulator systems (nIMs) and assessed their cytotoxicity against murine breast cancer 4T1 or murine macrophage-like RAW 264.7 cells. The results indicated no apparent cytotoxicity in the free R837 and free caffeine groups, while minor cytotoxicity of nIMs was detected at slightly high concentrations (30 μM R837 and 33.3 μM caffeine) that was attributed to the use of surfactant in nIM preparation (Liu et al. 2020).

It is worth mentioning that the safety of the carrier used for encapsulation is essential and also affects the release rate of the encapsulated compound. Encapsulated bioactive compounds in nanocarriers may have three different biological fates after ingestion depending on the type of carrier, a) may be fully digested and absorbed, b) may be resistant to digestion, or c) may be partially digested and absorbed. Each of the suggested pathways may cause toxicity or immunological responses (Rezaei, Fathi, and Jafari 2019). Although the safety of nanostructured compounds has not yet been fully validated and further studies are needed, one of the concerns is the high bioavailability of nanostructured compounds that can lead to high uptake and cytotoxicity. In brief, based on the reported studies related to the safety and cytotoxicity of encapsulated caffeine, there is not sufficient data to certainly determine the safe dose of encapsulated caffeine, and more extensive studies are needed.

Conclusions and future perspectives

The incorporation of caffeine with various health bienefits in the food industry has been attaining immense importance nowadays. Despite numerous advantages of caffeine usage, technological limitations (e.g., food processing parameters, exposure to sunlight and oxygen), gastrointestinal digestion and bitter taste, as well as side effects of high levels of caffeine consumption, lead to reduced bioavailability and limited use of caffeine in food products. Different nano/micro-dimensional delivery vehicles (lipid-based formulations, biopolymeric and inorganic nano/micro-structures) have been fabricated to solve the issues mentioned above, by improving caffeine efficacy and bioactivity, masking the bitter taste of caffeine, efficaciously ensuring the caffeine safe journey through the GIT system and its successive sustained/controlled secretion at the desired locus via its protecting inside an appropriate nanocarrier.

The suitability of each method applied for encapsulation of caffeine depends on various factors such as encapsulation efficiency, particle size and distribution, release and bioavailability behaviors, as well as stability and toxicity of obtained nanoformulations. Furthermore, there is no relevant research considering the usage of cubosomes and hexosomal structures as well as micelles in caffeine delivery. Nonetheless, given the superior attributes of these structures in encapsulation and deliverance of other susceptible bioactives/nutraceuticals, they would be considered promising options for caffeine delivery in future nanoencapsulation studies. Also, the progressive research on the health-promoting effects of caffeine and its continuously enhancing utilization in nutraceutical and food products warrants a systematic risk evaluation of this bioactive component and the corresponding NPs in both human clinical trials and animal experiments. All in all, there are many pieces of literature focused on caffeine nanodelivery as reviewed in this study; however, further studies are still needed to investigate the application of nanoencapsulated caffeine in various food products as well as their physicochemical properties, sensory attributes, and their controlled release and even their toxicity and safety to firstly accomplish pilot and clinical settings and secondly to move from the pilot and clinical trials to industrial scale.

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List of abbreviations

AE	Association efficiency
βCD	β-cyclodextrin
BMI	Body mass index
CDs	Cyclodextrins
DSC	Differential scanning calorimetry
EDS	Energy dispersive spectroscopy
GIT	Gastrointestinal tract
HPLC	High-Performance Liquid Chromatography

L	Liposome
LEU	L + eucalyptol
LF-GMP	Lactoferrin-glycomacropeptide
LOA	L + oleic acid
LPS	Lipopolysaccharide
MAE	Microwave-assisted extraction
MCM	Mobil Crystalline Material
MEs	Microemulsions
MLV	Multilamellar vesicles
MPO	Myeloperoxidase
MSNs	Mesoporous silica nanoparticles
MVD	Mean volume diameter
NFs	Nanofibers
N	Niosome
NLCs	Nano-structured lipid carriers
NPs	Nanoparticles
PDI	Polydispersity index
PEG	Polyethylene glycol
PEs	Pickering emulsions
PG	Propylene glycol
PLA	Polylactic acid
PLA-PEG-PLA	Poly(lactic acid)-polyethylene glycol-poly(lactic acid)
P(MAA-co-NVP)	Poly(methacrylic acid-co-N-vinyl pyrrolidone)
PPCs	Protein-polysaccharide complexes/conjugates
PVA	Polyvinyl alcohol
PVP	Polyvinylpyrrolidone
QESD	Quasi-emulsion solvent diffusion method
RH	Relative humidity
SAED	Selected area electron diffraction
SCE	Stratum Corneum Epidermis
SFE	Supercritical fluid extraction
SGF	Simulated gastric fluid
SIF	Simulated intestinal fluid
SLNs	Solid lipid nanoparticles
T	Transferosome
TEM	Transmission electron microscopy
UAE	Ultrasonic-assisted extraction
WGO	Wheat germ oil
WHO IARC	World Health Organization's International Agency for Research on Cancer
XPS	X-ray photoelectron spectroscopy
XRD	X-Ray diffraction

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