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Review article

Curcumin as a bioactive compound: biological properties and encapsulation methods

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ABSTRACT

Curcumin is a bioactive compound from turmeric which has different biological properties and health benefits such as antioxidant, anti-inflammatory, antimicrobial, and anticancer activities. However, the low solubility, poor bioavailability, and rapid degradation under neutral or alkaline pH conditions or when exposed to light, limit the food applications of curcumin. These problems can be solved by different strategies such as encapsulation. Therefore, different methods such as nanocomplexation, gelation, electro-spraying, complex coacervation, and pH-shifting approach have been applied to improve the solubility, stability, and bioavailability of curcumin. Consequently, the pharmacokinetic properties of curcumin including biological half-life and bioavailability/bio-accessibility can be improved resulting in better clinical and functional efficacy *in vivo*. Although the potentials of encapsulated forms of curcumin have been extensively studied in the literature, future studies can help to find better methods for developing encapsulation methods for curcumin for commercial and industrial aims. Accordingly, the present study was prepared to review the biological properties of curcumin. After that, the most common methods for the encapsulation of curcumin were also investigated.

Keywords: Curcumin, Health benefits, Antioxidant activity, Delivery systems, Nanocarrier

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1. Introduction

Curcumin (bis-α,β-unsaturated β-diketone) as a turmeric pigment is the major derivative of the turmeric spice. This bioactive molecule is a hydrophobic natural polyphenolic phyto-constituent extracted from the rhizomes of *Curcuma longa* Linn which is a medicinal plant known to be used for various ailments since ancient times (Tapal & Tiku, 2012; Gilani et al., 2017). Moreover, curcumin is used as a natural antioxidant, flavoring (warm, bitter taste) and natural coloring (a bright yellow color) agent in different food products (Mohammadian et al., 2019a; Rafiee et al., 2019). Chemically, curcumin belongs to diarylheptanoids and consists of two aromatic rings bearing two hydroxyl and two methoxyl groups. The phenolic rings are joined by the aliphatic unsaturated carbon chain with two carbonyl groups placed at C-3 and C-5 (Pan et al., 2014; Rafiee et al., 2019) as shown in Fig. 1. Different studies have been carried out to investigate the bio-functional properties of curcumin. These studies reported various biological and pharmaceutical properties for curcumin including antioxidant activity, antimicrobial activity, ant-cancer properties, anti-tumor activity, antiphlogosis and antilipidemic effects, and anti-inflammatory activity (Liu et al., 2016; Mai et al., 2017; Nelson et al., 2017). It is interesting to be noted that curcumin has been introduced as the third generation of cancer chemo-preventive agent by the National Cancer Institute of America which expands its applications in different fields such as food industry and medicine (Liu et al., 2016). In fact, it was reported that the curcumin blocks the nuclear factor kappa B (NF-kB), a transcriptional factor that regulates inflammation, cell proliferation, apoptosis and resistance in cells (Ravindran et al., 2009; Dwivedi et al., 2018).

Fig. 1. The chemical structure of curcumin (adopted from Rafiee et al., 2019).

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Despite having many proven health-benefits, the application of curcumin in food and drug formulations is still very limited and has many challenges. The most important factor which limits the application of curcumin is its low water solubility which is 11 ng/mL (Tapal & Tiku, 2012). Moreover, curcumin has a rapid metabolism and low gastrointestinal absorption in the body and therefore has a low bioavailability (Chaharband et al., 2018; Mohammadian et al., 2019b). Additionally, curcumin can be degraded under processing and within the gastrointestinal tract conditions which consequently decreases its bioavailability (Pan et al., 2013). Curcumin is stable in the systems with physiological pH values as well as acidic conditions, but under alkaline conditions, it is easily decomposed and also has a low photo-stability (Pan et al., 2013; Xiang et al., 2018; Rafiee et al., 2019). Therefore, different methods have been used to improve the solubility, stability, and bioavailability of curcumin. Encapsulation in different carriers is one of the strategies used to deliver and protect the curcumin (Liu et al., 2016; Mirpoor et al., 2017; Liu et al., 2018). Accordingly, a number of efficient encapsulation techniques and approaches have been proposed for the capsulation of curcumin; these include nanocomplexation, gelation, complex coacervation, electro-spraying, and solvent-free pH-driven encapsulation which are overviewed in this review article. The chemical and biological properties of curcumin were also discussed in this paper. Therefore, this would be useful for readers and researchers to expand their perspective in the applications of curcumin in the production of functional products with health-promoting properties.

Table 1. Some examples for encapsulation methods and carriers which were used to load curcumin as a bioactive molecule.

Encapsulation method	Type of the carrier	Applications	Ref
Nanocomplexation	Soy protein isolate	Enhancing curcumin solubility and stability	Tapal and Tiku (2012)
	Beta-lactoglobulin	Natural antioxidant agents	Li et al. (2013)
	Soy proteins	Improving curcumin stability and bio-accessibility	Chen et al. (2015)
	Glycosylated α-lactalbumin	Improving the curcumin anti-radical activity	Yi et al. (2016)
	Bovine serum albumin	Bioavailability enhancement	Yu et al. (2017)
	Ovalbumin	enhance the aqueous solubility and photo-stability of curcumin	Liu et al. (2018)
	Lactoferrin	Anticancer agent	Chaharband et al. (2018)
	Whey protein nanofibril	Enriching of acidic functional beverages	Mohammadian et al. (2019)
	Egg white protein	Enhancing curcumin solubility	Dabbagh Moghaddam et al. (2019)
	Whey protein aggregates	Targeted delivery of curcumin	Mohammadian et al. (2020)
Gelation	Soy protein isolate and xanthan gum	A potential alternative for a future replacement of artificial colors in gelled systems	Brito-Oliveira et al. (2017)
	Whey protein isolate and xanthan gum	Healthy food production	Geremias-Andrade et al. (2017)
	Whey protein and k-carrageenan	Colon-specific delivery of bioactive compounds	Alavi et al. (2018)
	whey protein and chitosan	Functional foods and drugs	Liu et al. (2020)
Coacervation	Albumin and gum Arabic	Improving the chemical stability of curcumin	Shahgholian and Rajabzadeh (2016)
	Chitosan and gum Arabic	Ideal carrier to deliver hydrophobic bioactive ingredients	Tan et al. (2016)
	Ovalbumin and k-carrageenan	To solubilize and protect sensitive bioactive compounds	Xie et al. (2019)
	Whey protein fibril and gum Arabic	Enhancing the curcumin photo-stability	Mohammadian et al. (2019b)
	Lysozyme and k-carrageenan	Enhance the stability and *in vitro* release of curcumin	Huang et al. (2020)
Electro-spraying	Poly (lactic-co-glycolic acid) (PLGA)	Sustained drug release	Yuan et al. (2015)
	Polylactic acid (PLA)	Drug delivery system with high bioactivity	Mai et al. (2017)
	Zein-chitosan	Improving the solubility and bioavailability of curcumin	Baspinar et al. (2018)
	PLGA	Ovarian cancer therapy	Dwivedi et al. (2018)
pH-shifting approach	Casein	Functional food and pharmaceutical products	Pan et al. (2014)
	Whey proteins	Functional beverages	Taghavi Kevig et al. (2019)
	Walnut proteins	Natural anticancer agent	Moghadam et al. (2020)
	Zein-rhamnolipid	Functional foods and beverages	Dai et al. (2019)
	Porcine plasma protein	Development of new functional polyphenol beverages	Wang et al. (2019)

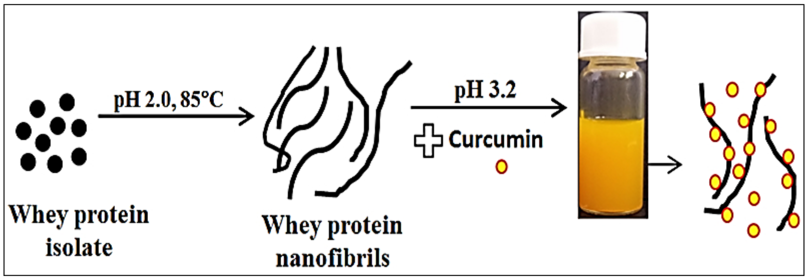

Fig. 2. Nanocomplexation of curcumin with whey protein nanofibrils (designed with respect to Mohammadian et al., 2019a).

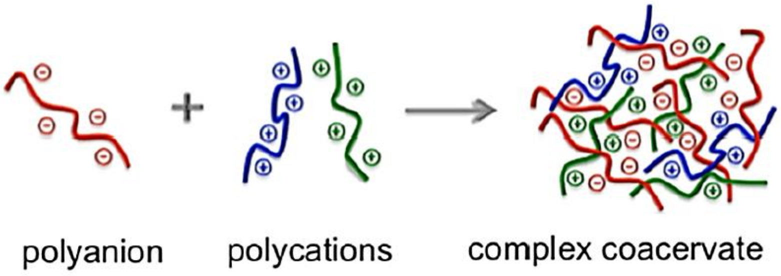

Fig. 3. The complex coacervation process (adopted from Priftis et al., 2014).

2. Biological properties of curcumin

Curcumin has many health benefits, biological functionalities, and therapeutic effects, which the antioxidant and anticancer activities are the most important of these properties (Ali et al., 2006). Antioxidant activity of curcumin is regulated by different enzymes like catalase, superoxide dismutase and glutathione peroxide. Curcumin shows 10 times more antioxidant activity compared to vitamin E as a common antioxidant agent (Wright, 2002). The antioxidant activity of curcumin might be due to the 1.3-diketone system and phenyl ring with methoxyl group. Curcumin has the ability to inhibit diabetes, heavy metals, and hypertension caused by stress with its antioxidant, chelating, and inhibitory effects on the pathways leading to hypertension (Wright, 2002; Gilani et al., 2017). Curcumin and many of its complexes form, have the ability to prompt glutathione-S-transferase and hinder free radical generation, thus acting as a free radical scavengers and antioxidants, preventing lipid peroxidation. The chemical structure of curcuminoids is also accountable for its antioxidant activity (Ak & Gulcin, 2008; Gilani et al., 2017). Several studies reported that curcumin has a strong capacity for scavenging superoxide radicals, hydrogen peroxide, and nitric oxide (NO) from activated macrophages, reducing iron complex and inhibiting lipid peroxidation. These actions may be the major mechanism by which curcumin exhibits its pharmacological/therapeutic activities (Ali et al., 2006). The antioxidant and free radical scavenging properties of curcumin was studied by Ak and Gulcin (2008). They reported that curcumin was able to scavenge different free radicals including DPPH and ABTS. According to this study, curcumin can be used in the pharmacological and food industry as a natural antioxidant agent.

Anticancer activity is another important bio-functionality of curcumin which was investigated by different studies. Among many natural anticancer agents, curcumin is a favorable bioactive molecule that has demonstrated remarkable anticancer activity. Research studies have shown that curcumin efficiently induces apoptosis through a number of different molecular targets and inhibits metastasis, invasion, and angiogenesis (Wilken et al., 2011; Yallapu et al., 2014). Moreover, it was investigated that curcumin is a highly pleiotropic molecule with multiple mechanisms through which it may mediate chemotherapy and chemo-preventive effects on cancer, while remaining safe with little or no side effect (Perrone et al., 2015; Allegra et al., 2016). As an example, Yallapu et al. (2014) studied the anticancer activity of curcumin-loaded poly(lactic-co-glycolic acid) nanoparticles in prostate cancer. They reported that curcumin-loaded nanoparticles efficiently internalized in prostate cancer cells and released curcumin in cytosolic compartment of cells for effective therapeutic activity. Additionally they investigated that the encapsulated curcumin inhibited the proliferation and colony formation ability of prostate cancer cells, whereas the free curcumin was not able to inhibit the proliferation and colony formation ability of the prostate cancer cells. Khazaei Koohpar et al. (2015) also studied the anticancer activity of curcumin on human breast adenocarcinoma. Their findings showed that curcumin significantly inhibited the growth of human breast cancer cell MCF-7 by inducing apoptosis in a dose- and time-dependent manner, accompanied by a decrease in MCF-7 cell viability. Therefore, it seems that curcumin have a high potential to be used as a natural anticancer agent in drug formulations or developing of anticancer functional foods.

3. Encapsulation methods

Despite having many proven biological attributes and bioactivity, curcumin has very limited applications in the food products owing to its extremely low bioavailability which is due to its poor chemical stability, low water solubility, and rapid metabolism (Li et al., 2013; Tsuda, 2018). To overcome these challenges, different methods and approaches have been used. Encapsulation in different carriers was suggested as a promising strategy to improve the aqueous solubility and stability of curcumin (Liu et al., 2016; Rafiee et al., 2019; Moghadam et al., 2020). In this regard different methods and biopolymers have been employed which are summarized in Table 1. In the following sections, some of the most important and widely-used methods for the encapsulation of curcumin are discussed.

3.1. *Nanocomplexation*

The nanocomplexation of curcumin with biopolymers such as proteins is a method to encapsulate curcumin. In fact, nanocomplexation with food biopolymers was introduced as a simple and efficient approach to improve the solubility, stability, adsorption, and bioavailability of hydrophobic bioactive compounds such as curcumin (Mohammadian et al., 2019a). In this method, curcumin can form complexes with carriers especially through the hydrophobic interactions. The hydrogen bonds also can contribute to the formation of these nanocomplexes (Tapal & Tiku, 2012). Between different biopolymers, proteins are the most common carriers for the preparation of nanocomplexes with curcumin due to their amphiphilic nature allowing them to form hydrophobic interactions with curcumin (Dabbagh Moghaddam et al., 2019). Nanocomplexation is a very simple method in which the curcumin is first dissolved in a suitable solvent such as ethanol and then added to the protein solution. The resulting mixture is then stirred to form the nanocomplexes. In some cases, the resulting nanocomplexes are centrifuged to remove the un-loaded and free curcumin. The curcumin-protein nanocomplexes can be used as dispersions or can be converted into powders by freeze drying process for further uses (Mohammadian et al., 2019a).

In a study conducted by Tapal and Tiku (2012), they studied the effect of complexation with soy protein isolate on the solubility of curcumin. They reported that the aqueous solubility of curcumin was increased by 812-fold through the nanocomplexation with soy proteins. Moreover, they observed that the complexation improved the stability and antioxidant activity of curcumin. Li et al. (2013) also reported that the antioxidant activity of curcumin was significantly improved by binding to β-lactoglobulin. Chen et al. (2015) also showed that the nanocomplexation of curcumin with soy protein nanoparticles increased its water solubility by 98000-fold compared to the free curcumin in water. They stated that the formation of the nanocomplexes significantly improved the storage stability of curcumin. *In vitro* simulated digestion experiments also indicated that the nanocomplexation with soy protein-based particles improved the bio-accessibility of curcumin. It was reported for soy proteins that the structural modifications using glutaminase before the complexation with curcumin can improve their ability for loading of curcumin (Xiang et al., 2018). Glycosylated α-lactalbumin-based nanocomplexes were used as nanocarriers for curcumin (Yi et al., 2016). It was investigated that the loading of curcumin into these nanostructures increased its antioxidant activity which can be due to the improvement of curcumin water solubility. Yu et al. (2017) also developed a new bioavailability enhancement strategy of curcumin via self-assembly nanocomplexation of curcumin and bovine serum albumin. The resulting nanocomplexes had suitable solubility, stability, and bioactivity. Nanocomplexation with ovalbumin also increased the solubility of curcumin for 370 times compared to the free curcumin (Liu et al., 2018). Additionally, the photo-stability of curcumin was enhanced significantly by the nanocomplexation with ovalbumin indicating that it is an efficient way to improve the stability of curcumin in contributing to its application in nutritional supplements or functional foods. Improving the water solubility and antioxidant activity of curcumin by binding to egg white proteins was also studied by Dabbagh Moghaddam et al. (2019). They reported that the egg white proteins can be used as efficient systems for increasing the aqueous solubility and antioxidant activity of curcumin expanding its applications in different fields including food, cosmetic, and pharmaceutical industries. As shown in Fig. 2, Mohammadian et al. (2019a) used the whey protein nanofibrils as carriers for curcumin through the nanocomplexation process. They reported that the aqueous solubility of curcumin was significantly increased by binding to nanofibrils. These nanofibrils were prepared by heating of whey protein solution at an acidic condition. The high ability of nanofibrils for loading of curcumin was attributed to their high surface hydrophobicity. The results of antioxidant activity measurements (DPPH radical scavenging activity and reducing power) also indicated that the antioxidant activity of curcumin was improved through the complexation with nanofibrils. The evaluation of *in vitro* curcumin release from nanocomplexes under simulated gastrointestinal conditions also showed that the curcumin was released slowly from the nanocomplexes. This study suggested that the whey protein nanofibril can be used as a nanomaterial to enhance the food applications of curcumin as a water-insoluble bioactive compound.

3.2. *Gelation*

Gels are three-dimensional networks of polymer chains that are cross-linked *via* either physical or chemical bonds and have a high ability to retain water or biological fluids (Farjami et al., 2015; Mohammadian & Madadlou, 2016; Babaei et al., 2019). The gels can be produced by different methods and various gelling agents. There are different gel-based delivery vehicles such as hydrogels, organogels, emulsion gels or emulgels, emulsion-filled gels, aerogels, and bigels (Ahmadi et al., 2015; Abaee et al., 2017, Hashemi et al., 2017). In the gelation method for the encapsulation of curcumin, at first curcumin is added to a protein or protein/polysaccharide solution and then the gelling agent is added. In this case, the curcumin-loaded hydrogels are produced. Moreover, curcumin can be added to an emulsion and after adding the gelling agent, the curcumin-loaded emulsion gels will be fabricated (Alavi et al., 2018; Mohammadian et al., 2018; Liu et al., 2020). Different studies have been done to produce curcumin-loaded hydrogels and emulsion gels.

Brito-Oliveira et al. (2017) studied the stability of curcumin encapsulated in solid lipid microparticles incorporated in cold-set emulsion filled gels of soy protein isolate and xanthan gum. They reported that the stability of curcumin was improved by loading into the gels and the curcumin showed as high stability for 15 days. According to these observations, these authors suggested that the curcumin in solid lipid nanoparticles incorporated in emulsion filled gels can be used as a promising alternative for the replacement of yellow artificial dyes in gelled food products. Geremias-Andrade et al. (2017) also studied the rheological and mechanical properties of curcumin-loaded emulsion-filled gels produced with whey protein isolate and xanthan gum. This study showed that the curcumin-loaded mixed biopolymer gels can be considered as a promising alternative for healthy food production, with reduction of fat total content and maintaining desirable textural properties. Alavi et al. (2018) fabricated the mixed protein/polysaccharide hydrogels using curcumin-loaded whey protein aggregates and k-carrageenan and studied their gastrointestinal fate. They reported that the resulting gel samples not only have a high capacity for loading of curcumin, but also could prevent the loaded curcumin from release and degradation in the upper gastrointestinal tract; so these hydrogels are very suitable for colon-specific delivery of hydrophobic bioactive compounds especially the curcumin. More recently, in a study conducted by Liu et al. (2020), the cold-set hydrogels made of whey protein-chitosan hydrogels were used for the controlled release of curcumin. The curcumin release test showed that the complex hydrogel had huge advantages in continuously releasing curcumin, which finally reached to ~ 7% at 4 h and sustained release. Therefore, they suggested that the whey protein-chitosan complex hydrogel can be considered as an effective delivery system for the application of controlled release of bioactive compounds in functional foods and pharmaceutical products.

3.3. *Complex coacervation*

Complex coacervation is a method which can be used to encapsulate, protect, and deliver the bioactive molecules such as curcumin. This process is considered as the spontaneous liquid/liquid phase separation in colloidal systems given by the electrostatic interaction between two oppositely charged colloids or biopolymers especially proteins and polysaccharides, thus give it ability to be a confidence and efficient encapsulation strategy for the bioactive compounds (Aloys et al., 2016; Santos et al., 2018). The complex coacervation process results in the formation of coacervates which these structures can be used as carriers for curcumin delivery. Different pairs of biopolymers such as protein-protein pairs, protein-polysaccharides pairs, and polysaccharides-polysaccharides pairs can be used to produce coacervates (Shahgholian & Rajabzadeh, 2016). The schematic illustration for the formation of coacervates is shown in Fig. 3.

Different pairs of biopolymers such as chitosan/gum Arabic (Tan et al., 2016), albumin/gum Arabic (Shahgholian & Rajabzadeh, 2016), whey protein nanofibrils/gum Arabic (Mohamamdian et al., 2019b), ovalbumin/k-carrageenan (Xie et al., 2019), and lysozyme/k-carrageenan (Huang et al., 2020) have been employed to fabricate curcumin-loaded coacervates. Shahgholian and Rajabzadeh (2016) used the complex coacervates made of albumin and gum Arabic to load curcumin. They reported that the encapsulation efficiency at the optimum condition was 92% indicating the high capacity of the complexes for loading of curcumin as a hydrophobic bioactive molecule. The curcumin encapsulation efficiency for complexes made of chitosan and gum Arabic was also reported as 90% in a study conducted by Tan et al. (2016). This study also showed that the capsulation of curcumin in the complexes improved its stability and also delayed the release of curcumin in a simulated gastrointestinal environment. The encapsulation was also drastically improved the antioxidant activity of curcumin as measured by ferric reducing antioxidant power assay and DPPH radical scavenging test. Mohammadian et al. (2019b) used complex coacervation process to encapsulate curcumin in the complexes made of whey protein nanofibrils and gum Arabic. The resulting complexes showed a high ability for loading of curcumin which the encapsulation efficiency was about 99%. The fluorescence spectroscopy results indicated that the curcumin was loaded in the hydrophobic cores of the coacervates. The results of this study showed that the reducing power and photo-stability of curcumin were significantly improved by complex coacervation in whey protein nanofibrils/gum Arabic. A sustained-release profile was also observed for curcumin from the complexes in the simulated gastrointestinal conditions. This study suggested that the electrostatic-driven complexes made of gum Arabic and whey protein nanofibrils can be used as promising carriers for the protection and delivery of curcumin. In another study carried out by Xie et al. (2019), the complexes made of ovalbumin and k-carrageenan, were used as carriers for curcumin delivery. The curcumin encapsulation efficiency was between 91.2 to 84.5% for different initial concentrations of curcumin. The curcumin encapsulation efficiency for complexes made of lysozyme and k-carrageenan was also reported as 96.2% by Huang et al. (2020). These results showed that the complex coacervation can be considered as an effective method with high loading efficiency for the encapsulation and protection of curcumin.

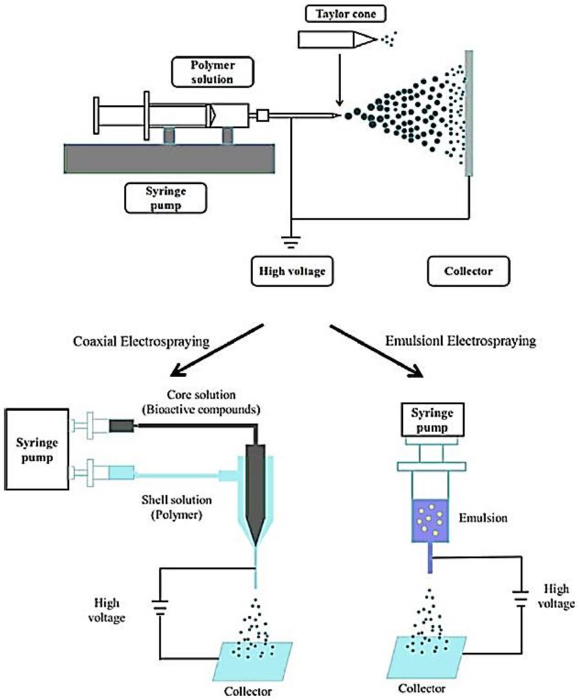

Fig. 4. The schematic illustration for electro-spraying process (adopted from Niu et al., 200).

3.4. *Electro-spraying*

Encapsulation of curcumin can be done using the electro-spray method which produces monodisperse particles with size ranging from sub-micrometers to hundreds of micrometers by applying a high positive voltage between a needle and the ground (Yuan et al., 2015). As shown in Fig. 4, in this method, a liquid droplet at the tip of a capillary nozzle once exposed to a high electric field, undergoes a shape deformation to a cone, due to internal electrostatic repulsions and external attractive Coulombic forces, from which a jet is emitted that subsequently breaks up into fine droplets as a result of varicose instability (Nikoo et al., 2018). The electro-spraying method is a cost-effective and scalable technology for the production of encapsulating structures which make it very interesting for the scientists in the field of food science and drug delivery (Mai et al., 2017). Moreover, many other advantages have been reported for electros-spraying encapsulation such as: improving the bioavailability and solubility of the bioactive compounds, small particle size, having only a single step, high loading efficiency, masking of undesirable, controlling the release profile, high particle deposition rate, narrow particle size distribution, and protecting bioactive molecules (Niu et al., 2020). Therefore this method was used to produce curcumin-loaded microcapsules.

In a study carried out by Yuan et al. (2015), the coaxial electro-spray was used to produce curcumin-loaded poly(lactic-co-glycolic acid) (PLGA) microparticles for sustained drug release. They showed that the electro-spray process yields particles with improved drug release profiles in comparison with traditional microencapsulation methods. Mai et al. (2017) also used the electro-spray process for the fabrication of curcumin-loaded microcapsules based on polylactic acid (PLA). This method showed an entrapment efficiency of 95% for curcumin. The curcumin-loaded microcapsules also showed excellent anti-bacterial activities towards *Escherichia coli* and *Staphylococcus aureus*. These microcapsules were also able to scavenge the free radicals of DPPH showing their high antioxidant activity. This study also revealed that PLA-based microcapsules had significant biocompatibility and low cytotoxicity. This research indicated that the PLA-based electrospray strategy combined with spherical microcapsules has the potential for a broad range of applications in different fields, especially in drug delivery and food industry. Baspinar et al. (2018) also used the electro-spray method for the fabrication of curcumin-loaded zein-chitosan particles. The method showed high encapsulation efficiency for curcumin which was about 90%. Generally, the results of the above-mentioned studies showed that the electro-spraying method can be considered as an effective and promising approach for the encapsulation of bioactive ingredients such as curcumin.

3.5. pH-shifting approach

One of the methods for the encapsulation of curcumin is the pH-shifting approach. In this method, usually proteins are used as a carrier for loading of curcumin in a solvent-free process (Moghadam et al., 2020). This method is based on the high solubility of curcumin the unfolding of protein structure at alkaline conditions. For the encapsulation of curcumin by this method, the pH of a protein solution adjusts to high pH values (more than 11.5). The curcumin crystals will be added at this step and the resulting protein/curcumin mixture will be mixed. After that, the pH value of the mixture returns to neutral pH value (pH 7.0). During this process, unfolding and refolding of proteins make them able to keep such hydrophobic molecules like curcumin entrapped in their structure and carry them easily in an aqueous system which improves their water dispersibility (Pan et al., 2014; Moghadam et al., 2020). Many advantages have been reported for pH-driven encapsulation of curcumin in proteins such as inexpensiveness, high loading capacity and encapsulation efficiency. Moreover, this method does not need any toxic organic solvents such as ethanol for the solubilization of curcumin (Taghavi kevij et al., 2019). Different proteins such as casein (Pan et al., 2014), whey proteins (Taghavi kevij et al., 2019), porcine plasma protein (Wang et al., 2019), zein (Dai et al., 2019), and walnut proteins (Moghadam et al., 2020) have been employed for the pH-driven encapsulation of curcumin. The mechanism of this method is shown in Fig. 5.

As shown in Fig. 5, Pan et al. (2014) used the self-assembled casein nanoparticles for the pH-driven encapsulation of curcumin. They reported encapsulation efficiencies between 70 to 100% for this method which was dependent on the incubation time at the alkaline conditions as well as the initial curcumin concentration. The encapsulation efficiency of curcumin was decreased by increasing the initial curcumin concentration in the casein solution. Wang et al. (2019) also reported that the antioxidant activity and aqueous solubility of curcumin was significantly enhanced loading into porcine plasma protein through the solvent-free pH-shifting method. In a study by Taghavi Kevij et al. (2019), the pH-shifting method was used to prepare curcumin-loaded whey protein isolate with pH values of 3.0 and 7.0. They reported that the curcumin solubility was significantly improved by loading into the whey proteins. These scholars suggested that the curcumin-loaded whey proteins formed by pH-shifting method could be used in the aqueous formulation of functional foods and beverages owing to their high water solubility, excellent antioxidant activity, and chemical stability. Moghadam et al. (2020) used the pH-shifting method to load curcumin in walnut proteins. They also compared the efficiency of this method with the conventional encapsulation. They reported that the encapsulation efficiency for the pH-shifting method was about 60%, whereas the sample which was prepared without pH-shifting method showed an encapsulation efficiency of 2.53%. Therefore, they suggested that the pH-shifting method can form more binding sites for complexation of curcumin with walnut proteins. Moreover, they reported good anti-radical and anticancer activities for the curcumin-loaded walnut proteins prepared by pH-shifting approach.

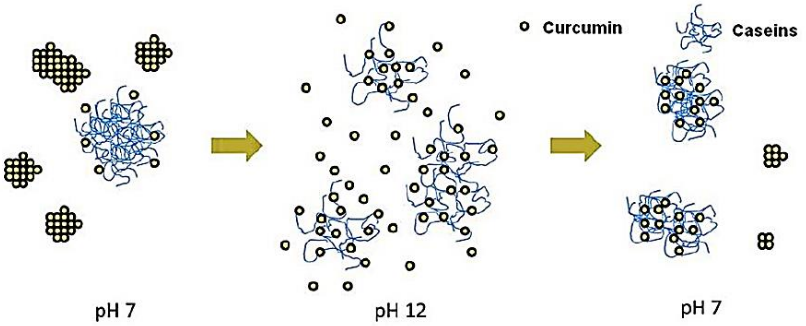

Fig. 5. The proposed mechanism for the pH-driven encapsulation of curcumin in casein (adopted from Pan et al., 2014).

4. Conclusion

Curcumin is a natural polyphenolic compound. This biologically active molecule has been proved to have a wide range of functional and biological properties such as antioxidant and anticancer activities. In addition to uses as food additives such as colorant and antioxidant, curcumin is used in remedies purposes. However, the applications of curcumin in the food formulations are very limited due to the low aqueous solubility and poor chemical stability of curcumin. Therefore different methods such as nanocomplexation, gelation, electro-spraying, coacervation, and pH-shift approaches and various carriers have been used to improve the solubility, stability, and bioavailability of curcumin. This review showed that the encapsulated forms of curcumin are potentially useful in the near future for the different bio-products with health-promoting attributes. Therefore, it seems that more studies are required in the future to investigate the applications and characteristics of curcumin-loaded structures in the real food systems to establish their function under the harsh conditions present in many food products. Moreover, it seems that the lack of *in vivo* studies is a limitation of many included reports and more detailed studies are needed in this research area. Additionally, there is still a pressing need to assess the toxicological safety of the curcumin application as a medicine for the prevention and treatment of various diseases or/and as an additive in the food products.

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