Encapsulation and Delivery of Ascorbic Acid

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Contributor: Li Liang ,

The L-enantiomer of ascorbic acid is commonly known as vitamin C. It is an indispensable nutrient and plays a key role in retaining the physiological process of humans and animals. L-gulonolactone oxidase, the key enzyme for the de novo synthesis of ascorbic acid, is lacking in some mammals including humans. The functionality of ascorbic acid has prompted the development of foods fortified with this vitamin. As a natural antioxidant, it is expected to protect the sensory and nutritional characteristics of the food. It is thus important to know the degradation of ascorbic acid in the food matrix and its interaction with coexisting components. The biggest challenge in the utilization of ascorbic acid is maintaining its stability and improving its delivery to the active site.

Ascorbic Acid Stabilizer Encapsulation Delivery

1. Low-Molecular-Weight Stabilizer and Derivatives

Ascorbic acid can be protected by adding other antioxidants. Food is a system in which multiple ingredients coexist, and there may be preservation effects of certain antioxidants, which involve regeneration mechanisms [1]. Ascorbic acid and flavonoids can regenerate α-tocopherol by reacting with α-tocopheroxyl radical. The bond dissociation energy of coexisting antioxidants that play a regenerative effect is lower than or close to the O-H bond [2]. It is well known that the conversion between ascorbic acid and its degradation product dehydroascorbic acid is reversible. Tert-butyl hydroquinone (TBHQ), which is often used as an antioxidant in high-fat foods, has been found to accelerate the conversion of dehydroascorbic acid to ascorbic acid, thereby stabilizing ascorbic acid. This reaction follows the first-order kinetic model, and the regeneration efficiency is proportional to the reaction time [3]. Moreover, glutathione with the free sulfhydryl group acts as a nucleophile and reducing agent. In the ascorbic acid solution, glutathione reduces dehydroascorbic acid and inhibits the degradation of ascorbic acid. The degradation kinetic model of ascorbic acid gradually changes from first-order to zero-order with the increase in glutathione concentration [4]. Meanwhile, as an effective antioxidant, ferulic acid has a synergistic effect with ascorbic acid. The oxidation–reduction potential of ferulic acid (0.595) is significantly higher than that of ascorbic acid (0.282), thus the former protect effect on ascorbic acid is indirect. There is a hypothesis that ferulic acid preferentially reacts with pro-oxidant intermediates or acts as a sacrificial substrate [5]. As mentioned above, low-molecular-weight stabilizers can inhibit the degradation of ascorbic acid to a certain extent, but it is hard to mask the acidic taste of ascorbic acid.

Considering the long-term mechanism of antioxidation and the high stability requirements of commercial products, ascorbic acid derivatives are also widely used, in addition to adding antioxidants or preservatives to stabilize ascorbic acid. For example, 2-O-D-glucopyranosyl-L-ascorbic acid, the glycosylated ascorbic acid in which the

hydroxyl group on the C_2 position is substituted by glucose residue, has excellent thermal stability and antioxidant properties [6]. Its application in anthocyanin-containing beverages can avoid the degradation of anthocyanins and maintain a high level of vitamin C content [7]. Ascorbate derivatives are also formed by introducing a phosphate group or combining sodium and magnesium salts at the C_2 position of ascorbic acid, showing better stability than ascorbic acid [8]. In addition to hydrophilic ascorbic acid derivatives, there are lipophilic-derivatives such as ascorbic acid 6-palmitate and tetra-isopalmitoyl ascorbic acid. However, these derivatives need to undergo some reactions in vivo to be converted into ascorbic acid and exert their physiological activities, and the high-cost is a limitation of their application into large-scale commercial products.

2. Construction of Carriers Based on Bio-Macromolecules

2.1. Chemical Interaction

Several technologies have been widely used to construct biomacromolecule-based carriers for ascorbic acid, in order to shield the unfavorable environmental factors and improve the taste of the product. These processes involve physical and chemical interactions between carriers and ascorbic acid; chemical interactions mainly refer to covalent and non-covalent bonds.

Proteins are generally recognized as safe (GRAS) and have high nutritional value. The delivery systems based on proteins have received widespread attention in food field due to their biocompatibility, biodegradability and tunability. Ascorbic acid binds to β-lactoglobulin (β-LG) through ion contact to form a more stable conjugate than human serum albumin (HSA) and bovine serum albumin (BSA). β-LG, HSA and BSA can, respectively, bind about 50–60%, 40–55% and 35–50% of ascorbic acid, and the proteins can be used to deliver vitamin C in vitro [9]. Through a cationization reaction, the quaternary ammonium salt cationic group was attached to the soybean protein isolate (SPI) chain, which increases the solubility of the protein and favors the encapsulation of ascorbic acid [10]. However, the low loading capacity and carrier instability in the stomach and intestines are the main challenges that restrict proteins from being ideal delivery vehicles for ascorbic acid. Since the excellent hydrophilicity of ascorbic acid and its same charge as most proteins (isoelectric point, pI < 7) at physiological pH, their interactions such as hydrophobic interaction, electrostatic interaction, hydrogen bonds and van der Waals forces are usually weak or absent. This results in a low encapsulation efficiency and rapid release of ascorbic acid from protein nanoparticles in the aqueous solutions.

Chitosan is a cationic polysaccharide with excellent chelating and cross-linking properties and is widely used as a delivery vehicle in the food field. The formation of chitosan nanoparticles requires cross-linking with polyanions, such as tripolyphosphate (TPP). The amino groups of chitosan in the polymer backbone can interact with ascorbic acid to form a strong hydrogen bond, which captures and retains ascorbic acid on the polysaccharide [11][12]. The formed chitosan-ascorbic acid complexes have high singlet oxygen scavenging ability and then maintain the high antioxidant capacity of ascorbic acid. The nanoscale size and positive charge of the particles are very important for their adsorption on the mucosa, which is conducive to achieving a high uptake rate of the loaded ascorbic acid by the intestinal cells. Chitosan-ascorbic acid complex nanoparticles increase the residence time of ascorbic acid in

the digestive tract of trout. Compared with protein nanoparticles, chitosan nanoparticles strengthen the interaction with ascorbic acid through electrostatic interaction, but the encapsulation efficiency is still relatively low [13]. This is related to the molecular weight and concentration of chitosan, the addition of ascorbic acid and the measurement method of the encapsulation. There are two views about the influence of chitosan molecular weight on the encapsulation efficiency of ascorbic acid. One is that high-molecular-weight chitosan has more surface charges to bind with more ascorbic acid molecules, thus the long backbone can capture more ascorbic acid. As the molecular weight of chitosan increased from 65 kDa to 110 kDa, the content of ascorbic acid loaded increased from 30% to 70%, respectively. With the further increase in chitosan molecular weight, the particle size increases but the overall surface area decreases, resulting in a decrease in the encapsulation efficiency of ascorbic acid [14]. Short fragments of low-molecular-weight chitosan are easier to protonate free amino groups, thereby complexing with ascorbic acid through electrostatic interactions. The average diameter of 55-kDa chitosan complex particles is 70.6 nm, and the loading efficiency of ascorbic acidic is about 66% [15].

2.2. Physical Barrier

In order to maintain the stability of ascorbic acid in food applications, ascorbic acid can be loaded into biomacromolecule-based delivery vehicles through physical encapsulation and adsorption. Compared with ascorbic acid nanoparticles chelated with protein and chitosan, the construction of physical barriers such as microcapsules based on protein and polysaccharide, solid lipids and liquid state multiple emulsions have a better loading capacity of ascorbic acid in the core and hence, this improves stability.

The process of encapsulating ascorbic acid in a core walled by polymers coating to isolate it from the external adverse factors is microencapsulation. The current preparation methods of microcapsules mainly include spray chilling, spray drying and complex coacervation. Among them, spray drying is one of the most common techniques due to its low cost, continuity and easy industrial scale production [16]. The selection of wall materials includes various proteins and polysaccharides, such as gum Arabic, maltodextrin, pectin, xyloglucan, sodium alginate. Gum Arabic and sodium alginate are low-cost and GRAS category polysaccharides, which are often used as food additives. The sodium alginate/gum Arabic microcapsules prepared by spray drying have an excellent loading capacity of ascorbic acid, which can reach more than 90%. Meanwhile, the thermal stability temperature of ascorbic acid is increased to 188 °C, which is higher than the temperature required for product preparation [17]. The xyloglucan extracted from *Hymenaea courbaril var. courbaril* seeds is a water-soluble polysaccharide containing gum Arabic, which is used as a thickener, stabilizer and crystallization inhibitor in the food industry. The spray-dried microcapsules can encapsulate around 96% of ascorbic acid. The system shows strong antioxidant activity and inhibits the formation of furan, an ascorbic acid degradation product, during the preheated process of products. After 60 days of storage at room temperature, the retention of ascorbic acid in the system is still around 90% [18]. However, the high viscosity of high-concentration polymers limits the granulation by spray-drying. To a certain extent, the loading capacity is related to the wall-to-core ratio and increases with the increase in the coating of wall materials [19]. Complex coacervation is the phase separation of at least two hydrocolloids from the initial solution, and then the coacervate phase is deposited around the suspended or emulsified bioactive compounds. One of the hydrocolloids is in the colloidal state. On the contrary to hydrophobic bioactive compounds, hydrophilic ascorbic

acid needs to be emulsified before it is prepared [20]. Compared with spray drying, this method does not involve a heat treatment process and is more suitable for encapsulating thermally unstable ascorbic acid [21]. The microcapsules prepared with gelatin and pectin as wall materials improve the thermal stability of ascorbic acid, although the solubility of the microcapsules is relatively low [19]. The encapsulation efficiency of ascorbic acid using gelatin and acacia as wall materials is about 97% [20].

The systems based on lipids, such as solid lipid microcapsules and emulsions, can be obtained by high-pressure homogenization, microfluidics, and solvent evaporation. The solid lipid microcapsules prepared by polyglyceryl monostearate (PGMS) have the encapsulation capacity of ascorbic acid up to about 94%. The system can be added in to fortify milk, significantly inhibiting the Maillard reaction between milk proteins and ascorbic acid. Sensory analysis showed that there was no significant difference in most aspects between the control sample and the fortified sample encapsulated with ascorbic acid after 5 days of storage [22]. As reported, palm fat was used as wall material to fabricate the solid lipid microcapsules to encapsulate and protect ascorbic acid using a microfluidic technique. The internal phase was added with salt or chitosan to further improve the encapsulation efficiency of ascorbic acid. The two different mechanisms involve pore blockage and ascorbic acid chelation [23]. This system has better physical isolation performance than protein and/or polysaccharide solid microcapsules. However, the operation process includes thermal melting and ice bath cooling of liposomes. This method is limited to the laboratory scale and is difficult to industrialize. On the other hand, the storage stability of ascorbic acid in oil-containing systems may be affected by lipid oxidation and thermodynamic instability of emulsions, which is lower than that of carrier-stable protein and polysaccharide microcapsule systems [24][25].

The microcapsule system based on the physical barrier has a better loading capacity of ascorbic acid than complex nanoparticles. In addition to the properties of the delivery carriers, it may also be related to the different measurement method of encapsulation efficiency. For delivery systems in micro-scale, the measurement conditions for encapsulation efficiency of ascorbic acid are gentler than those of protein and/or polysaccharide nanoparticles. The determination method includes separation by standing, ultrasonic and filter paper filtration [3][6][7][8][9]. Compared with the ultra-isolation method [26][1] used in the nanoparticle system, these methods reduce the release and diffusion of ascorbic acid during the measurement process.

2.3. Controlled Release of Ascorbic Acid

The challenge of ascorbic acid in food applications is not only to maintain its stability, but also to improve the effectiveness of delivery it to the active site. The release of bioactive compounds in the body is expected to occur in the intestine rather than the stomach, because the absorption mainly occurs in the small intestine. It was found that ascorbic acid in pomegranate juice was approximately 29% degraded during gastric digestion, which severely reduced the bioavailability of ascorbic acid. Additionally, the compounds that are transported by specialized processes are usually only absorbed in certain parts of the gastrointestinal tract. The absorption of riboflavin begins in the upper region of the small intestine, as does ascorbic acid [27]. Therefore, the changes in gastric and intestinal transit rates may affect the absorption efficiency of orally administered bioactive compounds. Additionally, the bioavailability of oral ascorbic acid is related to the following key steps: (1) Release of ascorbic acid in the

gastrointestinal tract, and its solubility in gastrointestinal fluids. (2) Intestinal epithelial cells absorb ascorbic acid and undergo biochemical transformation. Studies have shown that a single high dose of ascorbic acid causes a temporary increase in plasma that is rapidly absorbed by the gastrointestinal tract and then quickly excreted in the urine [28]. A form of ascorbic acid that can be slowly released in the intestine is desired to maintain a constant level of ascorbic acid in plasma.

The release process of encapsulated ascorbic acid is as follows: absorption of solvent by the carrier, dissolution of the wall-coating, and the diffusion of inner core. The release of bioactive compounds in carriers depends on many factors, such as the selection of the wall material, the ratio of wall/core, the size of the carrier, the solubility of the bioactive compound, and the release conditions [19][25]. Ascorbic acid releases kinetics from ascorbate gummies, which were investigated using an in vitro simulated digestion model. The results show that the disintegration time of ascorbic acid candy was about 22 min, after which the functional ingredient ascorbic acid was gradually released, reaching 93.6% within 2 h. Notably, the components in gastric juice may have an effect on the release of ascorbic acid, with gastric juice containing 5% starch slowing the release of bioactive ascorbic acid in the gummies, but other dietary components had no significant effect on its release [29]. This may be related to the encapsulation of ascorbic acid in starch in the stomach. Compared with the afore-mentioned delivery vehicles based on polysaccharide and lipid, the protein carrier has poor stability in the stomach. The low pH of the gastric environment and the presence of pepsin cause the denaturation and degradation of the protein carrier, leading to the leakage of loaded bioactive compounds in the stomach before reaching the small intestine [30]. Gelatin/pectin microcapsules show a high loading capacity of ascorbic acid. However, due to the dissolution of gelatin coating in the gastric environment, the release of ascorbic acid in the gastric environment is faster than in the intestine [19]. Therefore, it is necessary to design a carrier that is relatively stable in the stomach and which can provide a sustained release of ascorbic acid in the intestine.

The small size and positive charge of the particles contribute to the high uptake rate by intestinal cells. The loading in chitosan nanoparticles effectively prolong the residence time of ascorbic acid in the intestine of rainbow trout [14]. Nanoparticles based on chitosan with low molecular weight have a higher delivery rate of ascorbic acid. The mechanism of ascorbic acid released from nanoparticles in the gastric environment and the intestinal environment are diffusion and erosion, respectively. Under the neutral conditions of the intestine, the ion exchange between chitosan and the release medium leads to the erosion of nanoparticles. The release rate of ascorbic acid increased from 30% in the stomach to more than 75% in the intestine [14]. As reported, the water-soluble derivative N,N,N-trimethylchitosan (TMC) as a carrier can efficiently transport hydrophilic molecules through mucosal epithelial tissues such as the oral cavity, nasal cavity, lungs and intestines [12]. Thus, the carriers based on chitosan coatings may be an effective strategy to achieve intestinal release of ascorbic acid. Based on the continuous deposition of positively charged chitosan and negatively charged sodium alginate on the surface of anionic nano-liposomes, a liposomal polyelectrolyte delivery system of ascorbic acid was prepared. The clinical results showed that the bioavailability of orally administered liposomal ascorbic acid was 1.77 times higher than that of non-liposomal ascorbic acid, with higher bioavailability [31]. The ability of the outer layer of chitosan to withstand the gastric environment is beneficial for maintaining the stability of the carrier structure. The excellent sealing properties of

liposomes and better penetration with enterocyte phospholipid bilayers also contributed to the improved bioavailability of released ascorbic acid.

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