

Review

Research Progress in the Industrial Crystallization of Citrate—A Review

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Abstract: The citrate industry has a wide range of applications in food, pharmaceutical, and other fields. As a common class of food additives and functional supplements with tremendous development potential and strong core competitiveness, particles with good powder characteristics and functionalization are becoming one of the primary directions in the evolution of citrate into the high-end market. This article reviews the primary citrate crystallization techniques and examines the fundamental citrate crystallization mechanisms by describing citrate nucleation and growth during the industrial crystallization process. A variety of citrate hydrates are also summarized. The primary control conditions of the three essential product indices of purity, particle size, and grain shape are established. The need to take into account the density, fluidity, caking resistance, dissolution rate, suspension, bioavailability, and other indices of products is highlighted, along with applications for products that meet the purity and particle size requirements. While summarizing industrial citrate crystallization equipment, this paper also discusses the beneficial effect of continuous crystallization in achieving industrialization. Finally, the future development of citrate crystals is anticipated, and it is suggested that the combination of basic research and application research should be strengthened to explore the new application field of citrate crystals, and the automation and intelligence of the crystal preparation process should be realized as far as possible.

Keywords: citrates; crystallization method; product indicators; crystallizer



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1. Introduction

As a common class of food additives and functional supplements [1] in pharmaceuticals [2–4], medicine [5–11], healthcare [12,13], and daily chemicals [14], the market for citrate products has expanded to include North America, South America, Asia Pacific, Europe, Africa, and other regions. Compared with other inorganic salts, citrate shows superior biological compatibility for ionic supplements for human consumption, including sodium [15–17], potassium [18–20], calcium [21–23], magnesium [24–26], and zinc [27,28]. In addition, the lead citrate precursor route, which is very famous and important for synthesizing nanostructural lead oxide from spent lead-acid battery paste, is of great significance in the recovery of waste lead-acid batteries [29,30]. Therefore, citrate has tremendously desirable development potential and strong core competitiveness over time [31–34]. Citrate research and commercial trends have steadily shifted toward enhancing the numerous functional requirements of substances, including those for food, materials, reagents, etc. In terms of product quality, particles with good powder properties and functionalization are becoming one of the primary directions in the evolution of citrate into a high-end

supplement [35]. For the purpose of assuring the security and efficacy of direct action on the human body, the market is growing more demanding in terms of quality indicators such as purity, particle size, grain shape, and other factors of citrate products. On the other hand, higher requirements are also presented by adsorption, crystallization, granulation, process efficiency, and other post-treatment operations [36].

Citrate is commonly used in the form of multiple citrate hydrates. The majority of citrate prepared currently by reactive crystallization or crystallization methods that combine reaction with cooling or evaporation is needle-like powder of low stack density, poor flowability, and poor suspension stability. Therefore, there is a pressing need to develop an effective regulatory mechanism for the preparation of form-controlled and shape-controlled citrate crystals [37–39]. However, precise product quality control through quantifying variables is challenging. Essentially, the difficulty is a result of the complexity of the crystallization, which often entails a number of steps including mixing of the raw materials, reactions, crystal nucleation, growth, agglomeration, and fragmentation. In particular, the pressure of effective control of the entire process has been substantially expanded owing to the setting needs of the cooling procedure and the requirement for modification of the evaporation temperature [35]. In general, the sensible and correct control process of crystallization and purification is an urgent issue that needs to be addressed and is key to the significant improvement of the properties of products.

This paper is the first review so far in the field of industrial crystallization of citrate. To explore the research progress of the industrial crystallization of citrate and provide references for the development of the citrate industry, we investigated the research on citrate in the past 20 years, from 2003 to 2023. Scholars at home and abroad are currently studying the industrial crystallization of citrate through theoretical simulation, experimental research, industrial application, and other methods, and some research results have been obtained. However, particle properties such as shape, size, flowability, anti-caking property, dissolving rate, etc., are some of the important factors affecting the industrial production of citrate. Therefore, how to control the particle properties is a hot topic and a difficult problem in the research into industrial crystallization of citrate. Future research directions should focus on controlling the crystallization process more precisely and optimizing the crystallization conditions so as to obtain better application in industrial practice.

2. Mechanism of Crystallization of Citrate

2.1. Main Methods for Citrate Crystallization

Crystallization is one of the critical processes for purifying solid compounds. The primary method of crystallization for creating premium citrate products has gained increasing attention with the global trend toward high-end fine chemicals. To ensure the stability of the crystallization process, the choice of crystallization methods is crucial. According to the properties of crystal phase transition, solution crystallization and reactive crystallization, including evaporation crystallization, cooling crystallization, and reactive crystallization, are the main crystallization techniques employed in the manufacturing of citrate. The chemical reaction is the driving force in the reactive crystallization process. To achieve separation and purification, the differences in solubility between the constituents are key factors. Cooling crystallization produces the driving force of crystallization by lowering the temperature, whereas evaporative crystallization produces it by removing solvent. A vacuum level was created by decompression techniques to strengthen the driving power of the processes and encourage the initiation and growth of crystals during the crystallization process [40–43]. In general, the solubility of the substance can be used to select rapidly and conveniently the appropriate crystallization form.

The recombination reaction-coupled crystallization process is regarded as one of the crystallization methods with great potential because of the substantial solubility differences between zinc citrate, magnesium citrate, and calcium citrate products and reactants. While potassium and sodium citrate have substantial solubilities and their solubilities fluctuate greatly with temperature; the simple reaction crystallization procedure cannot provide

enough driving power to encourage the formation of crystals. Therefore, the combination of reactive crystallization with cooling crystallization or evaporative crystallization is a common choice. Researchers have paid considerable attention to the reaction materials in the citrate crystallization system due to their high potential for biocompatibility and environmental friendliness. Especially recently, researchers have become more and more interested in biological calcium sources, because their utilization is expected to lessen environmental stress and address the issue of low use of biological waste shells and bones [44–49].

In addition, the temperature has an important effect on the crystal shape because the citrate product contains a large amount of hydrates, which directly affects the amount of water present in it. Seham A.A.Mansour [50,51] and A.Srivastava [52] researched the thermal analysis of citrate products to assess the decomposition of the product at various temperatures. The optimal temperature range for the reaction crystallization process of citrate was defined, and is listed in Table 1, according to the requirements for yield, quality, and the actual production scale [53].

Table 1. Crystallization conditions for citrate products.

Name	Crystallization Method	Raw Materials	Temperature	pH
Sodium citrate	Evaporation crystallization, cooling crystallization	Citric acid, sodium source (sodium hydroxide and sodium carbonate)	Approx 85 °C	7–9
Potassium citrate	Evaporation crystallization, cooling crystallization	Citric acid, potassium source (potassium bicarbonate and potassium hydroxide)	70–80 °C	5.5–9.5
Calcium citrate	Reaction crystallization	Citric acid, calcium sources (chemical calcium sources such as calcium carbonate, calcium hydroxide, calcium chloride, calcium nitrate, and natural biological calcium sources such as shells, egg shells, shrimp head shells, cow bone, etc.)	No more than 110 °C	3–5
Magnesium citrate	Reaction crystallization	Citric acid, magnesium source (magnesium oxide, magnesium hydroxide, magnesium carbonate, and magnesium bicarbonate)	60–90 °C	5–8
Zinc citrate	Reaction crystallization	Citric acid, zinc source (zinc oxide, zinc carbonate, zinc nitrate)	40–80 °C	4–7
Lead citrate	Cooling crystallization	Citric acid, sodium citrate, lead source (spent lead paste, lead sulfate)	35–95 °C	<6

Reaction crystallization is a process that couples reaction and crystallization, and the study of kinetics encompasses both reaction kinetics and crystallization kinetics. The complexity of the study of the coupling process is therefore considerably enhanced. Meanwhile, the multiple processes included in a reaction also make it more challenging to precisely regulate the ensuing crystallization process [35]. The use of computer simulation and machine learning methods could significantly improve the predictability and controllability of crystal growth through online, real-time observation and evaluation of the reactive crystallization process. Furthermore, the effective and precise control of the reactive crystallization process is increasingly anticipated [54,55]. To provide the driving force for crystallization, cooling crystallization necessitates heat exchange with the cooling medium, which lowers the temperature of the solution, and evaporative crystallization needs heat to speed up the evaporation of water molecules. However, these operations use a lot of energy, which remarkably raises the cost of the process. To meet market demand, the development of eco-friendly and effective crystallization purification technology and the renewal of crystallization machinery will raise increasing concerns, with the intention of decreasing energy

consumption, shortening the crystallization cycle, and boosting crystallization efficiency during the production of citric acid and citrate [56–59].

2.2. Formation of Citrate Hydrate

Citrate contains a large number of hydrates, and this is one of the most notable properties of citrate crystallization. Hydrates with different water contents exhibit considerable changes in solubility, dissolution rate, appearance, and bioavailability, affecting crystal stability, bioavailability, and efficacy. In particular, anhydrous citrate is a scarce and highly profitable product around the world. In general, the ability of the procedure to produce a single stable form of crystal is an inevitable requirement for product purity. On the other hand, it also has an indirect impact on the international competitiveness of products.

The two most common hydrates of sodium citrate are dihydrate and pentahydrate. Potassium citrate is mainly monohydrate [60]. In the fields of food processing, daily chemical, and pharmaceuticals, raw materials such as sodium citrate and potassium citrate products are required to be water-free. The transition from hydrate to anhydrous geocrystalline form can be achieved simply by adjusting the drying temperature [61–63].

Dihydrate and trihydrate are two forms of zinc citrate hydrates. Since 2015, the production process of dihydrate has been continuously developed in order to increase the content of zinc citrate in the product [64]. Moreover, for the purpose of enhancing particle uniformity and the purity of zinc citrate dihydrate crystal products, good control of the reaction system conditions, especially pH, is critical. Some studies report that when the pH of the reaction end point is kept within the range of 4.5–5.5, the content of zinc citrate in the manufactured products can reach 97.0–99.8% by weight [64,65].

The forms of calcium citrate hydrate consist of monohydrate, dihydrate, trihydrate, tetrahydrate, and hexahydrate. The characteristics between different calcium citrate forms are varied, and are usually impacted significantly by temperature. For example, hexahydrate crystallizes at low temperatures, and tetrahydrate crystallizes at higher temperatures. The conversion point between these is 51.6 °C [66,67]. Furthermore, anhydrous matter and dihydrate crystallize to tetrahydrate via solvo-mediated transformation, and the tetrahydrate dehydrates into protocrystalline form via one-step dehydration at 80 °C and two-step dehydration at 130 °C [68,69].

Magnesium citrate is mainly nonahydrate. According to extensive research on the pyrolysis mechanism and microstructure evolution throughout the pyrolysis process, anhydrous products can be obtained with a drying temperature of 150 °C and a breakdown point of about 300 °C. However, the drying temperature of magnesium nonahydrate is only around 70–80 °C [70,71]. Terahertz (THz) time-domain spectroscopy can be used as an effective means to detect and analyze various citrates and distinguish their crystalline hydrates. Researchers discovered that the distinctive terahertz absorption peaks were significantly affected by water content and crystalline state of the metal cation species of a citrate sample [72]. Additionally, variations in temperature, pressure, and solvent may cause the adsorption and removal of solvent water in hydrates, resulting in the crystalline transition of hydrates and subsequent loss of product purity. Further study is needed in the field of stabilizing the production process to create products with a particular water content.

Trihydrate is the common hydrate form of lead citrate. Research has shown that the thermal decomposition process can be divided into three stages: dewatering at 100–200 °C, organic constituent decomposition, and, subsequently, burning. Furthermore, the decomposition of lead citrate in air is significantly affected by roasting temperature. The main components of the product with low-temperature roasting are α -PbO, β -PbO and metallic lead, while the main components of the product with high-temperature roasting are β -PbO [73].

2.3. Nucleation and Growth of Citrate

The fundamental process of crystallization involves crystal nucleation and growth, which determine the structure, form, and characteristics of the crystal, and the improvement

of mechanisms for crystal nucleation and growth has been the driving force behind the development of the crystallization industry for decades [74,75]. Numerous elements influence the formation and growth of the citrate crystal. Therefore, comprehension of citrate nucleation and growth mechanisms is essential to targeting a method for controlling crystal quality and improving the poor crystal shape (e.g., needle-like shape, sheet-like shape, etc.) of citrate products in the current industry. However, systematic research on the mechanism of nucleation and growth of citrate is rare at present. The primary research direction has been toward understanding the effects of solvent ratio, temperature, supersaturation, and other external strengthening methods on crystal nucleation and growth, generally focusing on research at a phenomenal level and essentially boosting nucleation and growth rates.

The usual crystallization methods of citrate involve the interaction of evaporation, cooling, chemical reactions, and crystallization. This synergistic impact gives the nucleation and growth of crystals corresponding properties [76,77]. The supersaturation of evaporative crystallization is the result of solvent removal and forms a gradient of concentration within the droplet, which is a quantitative representation of the driving force during the crystallization process and a crucial reference for determining the timing of crystal seed addition. The effect of supersaturation on the rate of nucleation growth during potassium citrate production was investigated by Luo Hu et al., who discovered that nucleation and crystal growth rates were optimal when crystalline seeds were added and crystallized by evaporation at a degree of supersaturation in the range 1.05–1.15 (the ratio of the weight of solute actually dissolved in the solvent at a given temperature to the weight of solute theoretically dissolved in the solvent when the solution is saturated at that temperature) [78]. Compared with other crystallization methods, reactive crystallization is unique in that the reaction rate affects the time required for the crystallization process, which is a qualitative expression of the costs and benefits in engineering practice. Strengthening the reaction process naturally increases the crystallization rate [79]. Figure 1 illustrates the common nucleation growth pathway of a crystal, standard designs of ultrasound reactors, and representations of different designs for microwave reactors. Over the years, the use of external force fields such as ultrasonic and microwave has become an extremely effective strengthening method that can significantly affect the nucleation growth process. Shi Zhiyong et al. found that the ultrasonic microwave technique is advantageous as it can be used to speed up the crystallization of magnesium citrate. Essentially, an ultrasonic wave can speed up the pace at which the magnesium source dissolves and, in the meantime, encourage the reaction between magnesium source and citric acid through the cavitation effect, and microwaves can hasten the nucleation of crystals while simultaneously speeding up the collision of citric acid and magnesium source molecules in aqueous solution by causing molecular motion through vibration [79,80]. On the other hand, microwave irradiation can also heat the solution uniformly while at the same time supplying the necessary energy to facilitate the quick nucleation and development of crystals. Compared with no ultrasonic microwave process, ultrasonic microwave technology showed significant enhancements in shortening the reaction time and accelerating crystallization. Finally, the nucleation induction time was reduced from 3–4 h to 6–10 min [81]. Furthermore, Li Junfeng et al. discovered that calcium citrate crystal nuclei could form quickly and uniformly under homogeneous water and alcohol mixing conditions because calcium citrate has poor solubility; it is barely soluble in water and insoluble in alcohol, and further growth of crystal nuclei could be inhibited. Direct preparation of nano-sized calcium citrate crystals with a width of about 60 to 700 nm and a thickness of about 20 to 50 nm without the need of crushing or further procedures is possible under these conditions [82].

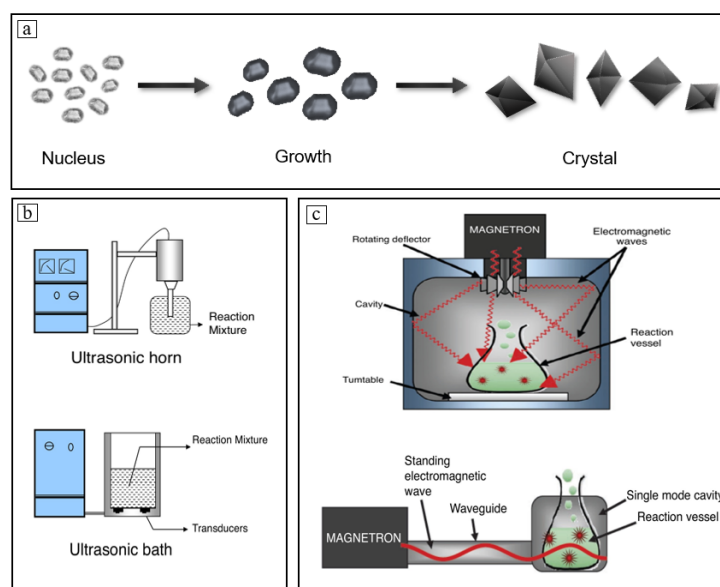


Figure 1. (a) Common nucleation growth pathway of a crystal; (b) standard designs of the ultrasound reactors; (c) representations of different designs for microwave reactors.

In addition to the aforementioned customary investigations on nucleation and growth that concentrated on increasing production efficiency, Yan hypothesized a unique mechanism of noncrystallographic branching during reactive crystallization of calcium citrate, as shown in Figure 2a. The morphological evolution of calcium citrate spherulite can be synoptically divided into three phases according to images of optical microscopy displayed in Figure 2b. In the first phase, the early precursor materials gather to form rod-like crystals that grow from the center to the ends. The beginning of the second phase consists of the front of both sides of the crystal gradually developing small angular branching without clear direction due to the various growth angles. The third phase involves the formation of spherical crystals through the complete filling of the crystal from the center outward in all directions. Additionally, the image shown in Figure 2c indicates that supersaturation and spherulite development are tightly connected [35].

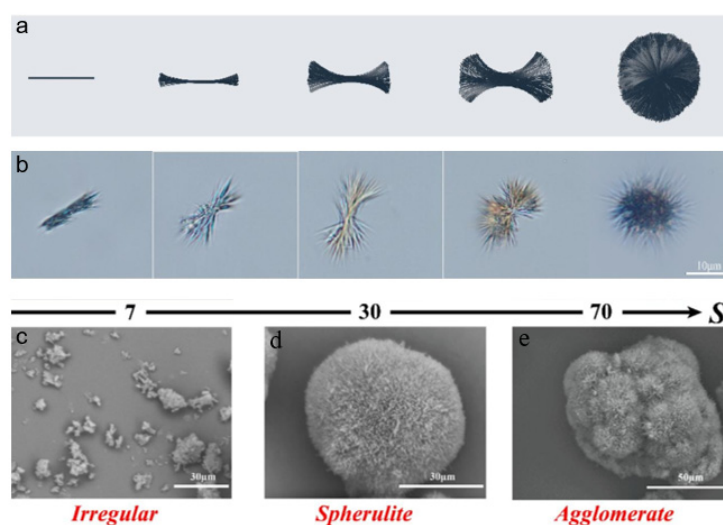


Figure 2. (a) Schematic diagram of the spherulitic growth mechanism; (b) optical microscopy images at different growth stages under the experimental conditions ($S = 20$, temperature = $40\text{ }^{\circ}\text{C}$); SEM images at different supersaturation levels: (c) $S = 7$; (d) $S = 30$; (e) $S = 70$.

The work of Yan examines the calcium citrate spherulite mechanism, which is generated by tiny corner branches on both sides of linear precursor fibers and offers a potential method for the nucleation and growth of organic acids like zinc citrate and magnesium citrate. Overall, there has been a significant absence of research on the classical and non-classical nucleation development of citrate, as well as research on kinetics and unusual growth phenomena. Furthermore, the citrate development process is plagued by the problem of tiny particle size and excessive fine crystals induced by crystal nucleation. Hence, continued studies about the effects of additives on crystal nucleation growth will attract wide interest [60,83,84]. Meanwhile, to further comprehend and optimize the crystallization process, knowledge of nucleation growth mechanisms must also be developed.

3. Key Product Indicators and Crystallization Control Measures for Citrate Crystals

3.1. Crystal Purity

As shown in Figure 3, product purity, along with crystal size and grain form, makes up the fundamental quality metrics for citrate products, which have a direct impact on their functionality and potential applications. An effective control approach to address the issue of product purity is to adopt crystal growth condition control, impurity control, post-treatment technology, crystal growth control, crystal structure optimization, etc., based on the specific causes of such difficulties [85–89]. Specifically, the crystal transformation that results in the product becoming a mixture of various crystal forms is primarily responsible for the purity of citrate products. For the purpose of preventing crystal change and increasing product purity, there is an urgent need to ensure a precise operation point and stable operation procedure. On the other hand, in the citrate industry chain, the upstream raw material citric acid is mainly prepared by microbial fermentation; therefore, impurities like mycelium, mineral salts, proteins, and other organic acids will undoubtedly be introduced as a result of the fermentation process, and impurity retention may occur during the growth of citrate crystals, which poses significant challenges relating to the demand for high-purity citrate products [90].

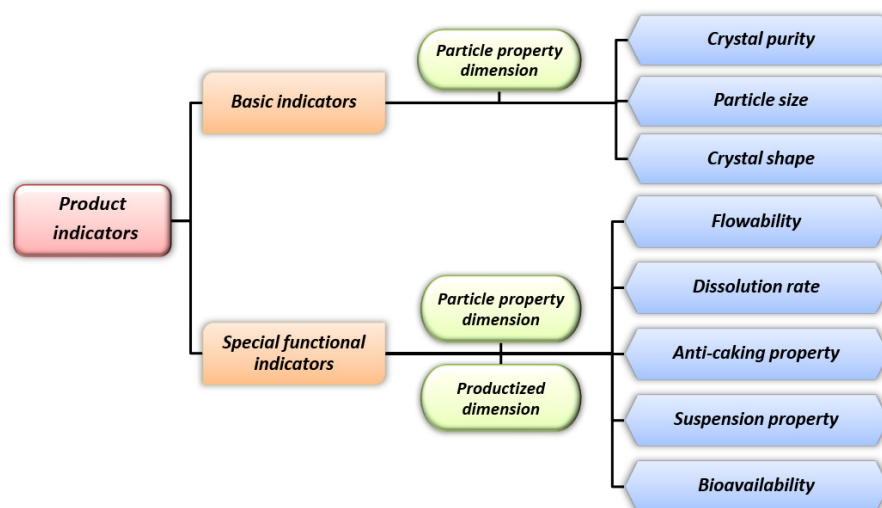


Figure 3. Key product indicators of citrate crystal.

The quality of the raw materials differs significantly between the fermentation process and the chemical method. Recently, the close attention paid to maintaining the purity of raw materials has prompted researchers to respond by improving and developing citric acid purification technology. Some reports have demonstrated that bipolar membrane bioelectrodialysis and two-phase electro-dialysis technologies have a wide range of potential applications because of their advantages preventing reverse diffusion brought on by concentration differences and can recover citric acid at higher rates [91–94]. In addition, another simple and efficient option is to directly buy high-purity raw materials. For ex-

ample, Wu Jian et al. used high-purity sodium citrate and zinc sulfate heptahydrate as raw materials to prepare zinc citrate, which successfully achieved the goal of effectively controlling the heavy metal content of the product from the reaction source. Furthermore, another primary cause of the decrease in product purity is the inclusion of excessive reactants in the final product [78]. Calcium citrate can be prepared through two-step reactive crystallization, in which calcium sources usually use calcium carbonate and calcium citrate. In a one-step reaction, calcium carbonate reacts with citric acid to form calcium hydrogen citrate, with a reaction endpoint pH of 2.7–3.5. In the second step, calcium hydroxide reacts with calcium citrate to form calcium citrate, and the pH range is 3.8 to 4.5. The excessively high pH means that more alkali sources exist in a reactive system, which may result in the occurrence of raw material encapsulation and thus decrease the purity of the product. Conversely, dissolving loss of the product may increase as a result of too low pH and ultimately lead to a lower yield. Therefore, the aforementioned issues can be greatly reduced by monitoring the pH value of the combination to help establish the ideal ratio of materials and keeping the two-step reaction within the most favorable pH intervals for making calcium citrate [95–98]. Additionally, the uniformity and stability of the reaction process are crucial for increasing product purity [99,100]. Ultrasonic, microwave, and other applied force fields were used as some of the earliest efficient methods. Yao used alkenyl imidazole salt as the catalytic agent, which generated a microwave reaction environment and ensured that the reaction components made full contact with one another. Finally, this method successfully ensured the uniformity of the reaction, so as to realize the specificity of the product [64,101–103].

3.2. Particle Size

Particle size is a crucial aspect of powder characteristics that directly affects the solubility, suspension stability, bioavailability, flowability, and compressibility of the product. Therefore, it has become a necessary indicator to characterize product quality. Product granularity needs vary depending on the functions of products. To achieve precise preparation of products with a specific size distribution, adjusting the crystallization process has become a research target and hotspot [35].

An appropriate degree of supersaturation could regulate the nucleation rate and growth rate of crystals and thus influence the particle size and distribution of products. Hence, it is crucial to adjudicate suitable supersaturation by designing the optimum cooling, cooling rate, and evaporation and concentration temperatures [104]. Based on reported studies, it was discovered that the crystal nucleation and growth rate of sodium citrate were best suited when the cooling rate was adjusted from 5 °C to 12 °C/h, which could then effectively control the particle size of sodium citrate in the range of 0.38–0.83 mm. Furthermore, a common control strategy is to make sure the ion concentration or pH of the reaction material is within the proper range. For example, the particle size distribution of calcium citrate products was best when the concentration of calcium ions was adjusted between 0.001 and 1 mol/L, and the range of pH between 4.1 and 4.5 is superior to others because the zinc citrate crystal particles are more homogeneous within this control zone [100]. Additionally, adding crystal seed is the most effective way to control primary nucleation and induce crystallization. As such, timing and amount of seed addition are crucial factors in determining the final product size [105]. Tang proved that the optimal moment to add the crystal seed during the production process of sodium citrate is when the material and liquid ratio reaches 1.34 g/mL. Meanwhile, maintaining a cooling rate within 5–12 °C/h could finally result in the creation of crystal particles with uniform particle size [104]. In conclusion, based on the research of many scholars, it is apparent that crystal seed plays an absolutely crucial role in optimizing the quality of the final product and controlling the crystallization process. In light of this, it is anticipated that crystal seed addition technology research and development will lead to more effective control of product particle size distribution and improved product quality [106].

3.3. Crystal Shape

Crystal characteristics and product applications are commonly influenced by crystal shape [107]. The citrate products currently prepared are mostly irregular particle shapes such as needle-like, rod-like, and flake-like and easily formed paste suspensions, which result in poor powder properties and limited high-end development. However, the current citrate industry is mainly oriented toward commercial production to maximize economic benefit, and the attention paid to the control of product shape is insufficient. Therefore, much is yet to be explored in terms of shape-controlled citrate for product quality enhancement and expansion of application range.

Studies have reported that ultrasonic treatment can effectively regulate the crystal morphology of lead citrate crystals. Xiaojuan Sun et al. found that after ultrasonic treatment, flakes of lead citrate crystal were successfully transformed into a column with a length-to-diameter ratio of about 8:1, and the length of the crystal ranged from 20 μm to 50 μm , resulting in an improvement in the filter performance of the lead citrate precursor [29]. Furthermore, Dongsheng He et al. found that under synthetic conditions of 35 °C, the crystal was sheet-like, while at 95 °C, the crystal was rod-like, which suggested that the morphology was affected by the temperature variation [108]. In 2014, a study conducted by Li Junfeng et al. made a breakthrough in improving the shape of calcium citrate products. The most important achievement was the successful preparation of a fiber-like crystal with a length–diameter ratio greater than 100 [109], a strip-like crystal with dimensions of 5–100 μm , 0.5–3 μm , and 5–30 nm [110], and a sphere produced by the self-assembly of flake-like calcium citrate [111] by adjusting the solvent ratio, ion concentration, crystallization temperature, and other parameters, which greatly broadened the characteristics of calcium citrate products. In comparison, spherical particles are superior to other shapes for the creation of high-end products and have a wider range of applications because of their better flow properties, stronger compressive qualities, higher drug solubility, and biological compatibility [112–114]. According to Yan, factors affecting the shape of calcium citrate during reactive crystallization include supersaturation and shear stress. They therefore pioneered the exploration of reactant concentration for the formation of calcium citrate spherules based on the strong dependence of the crystal shape on solution supersaturation and initial concentration, and the key control parameters for the morphology were determined to be the stirring rate and residence time, based on the investigation of shear stress. Finally, they successfully scaled up the study in semi-batch mode and further verified the guiding significance of the research to improve the possibility of industrializing spherical calcium citrate [35]. Therefore, spherical morphology will essentially be the predominant shape of citrate products in comparison to needle-like, rod-like, flake-like, etc., due to the excellent particle characteristics it possesses, which will assist in its standing in the ranks of high-end food additives and nutritional agents.

In conclusion, the major progress made in the study of calcium citrate and lead citrate breaks the status quo of the paucity of in-depth research on the morphological control mechanism of citrate and provides direction for the exploration of the particle shapes of other citrates, which will inspire the development and completion of the particle shape control mechanism of the product.

3.4. Special Functional Indicators

As a univariate, multi-objective control process, other special functional indicators in addition to the above-mentioned, such as product stacking density, flowability, anti-caking property, dissolving rate, suspension property, and bioavailability, should be investigated in the crystallization process. As such, these special functional indicators are influenced by the fundamental characteristics of the particles, and they simultaneously advance higher standards for fundamental characteristics, further promoting the advancement of particle micro- and nanotechnology [115,116].

Nutritional products and pharmaceuticals are common applications of citrate products; hence, bulk handling characteristics such as particle flowability and bulk density, which are

greatly influenced by the particle size distribution and shape of the crystals, are considered critical [117]. In general, smaller particle sizes, together with needle-like and flake-like shapes, are extremely likely to result in decreased powder fluidity and decreased bulk density, which in turn affect compaction and consolidation during product handling [118].

For the purpose of maintaining flowability, the resistance to caking of crystal products is expected to be improved [119,120]. Crystal caking is commonly the result of multiple factors that correlate [121,122]. Optimized crystals with higher fluidity in terms of shape and form are the most direct strategy to improve product properties. Additionally, the improvement of particle dispersion through grinding and other techniques is also worthy of close attention [111,123]. In recent years, a great variety of evaluation and prediction models of the critical caking period have been studied to assist in the search for the best crystallization operating curve. The application of these models could improve design efficiency by an order of magnitude on the premise of ensuring product performance and quality [124–126].

The dissolution rate is a key indicator of product quality for powdered products with dissolution requirements, such as pharmaceutical powders and milk powders, and can be greatly increased under micropulverization circumstances. In addition, to achieve rapid dissolution of products, preparing amorphous products is desirable due to the elimination of the energy barrier at dissolution [127,128].

Improving the suspension properties of slurries is effective in reducing particle agglomeration [129–131]. Commonly, micropulverization of particles could be considered an effective method to produce a product with good suspension stability and avoid the incidental tendency of rod-like and flake-like crystals to cause suspension formation. Particles with a homogeneous particle size distribution exhibit stronger affinity and are more successful in enhancing the suspension stability of the product when added as a formulation agent to diverse complicated systems [132].

Previous studies have indicated that organic salt supplements of various trace elements are more bioavailable than oxides or inorganic salts. Essentially, citric acid is naturally present in blood, muscle, and bone and is one of the main intermediate metabolites of the tricarboxylic acid cycle in the human body; therefore, citrate has a natural advantage as a supplement for improving the bioavailability of nutrients such as calcium, magnesium, zinc, sodium, and potassium. There have been increasing concerns over the concentration of ions in fortified nutritional products, which is challenging in the industrial production of citrate.

4. Industrial Crystallization Equipment for Citrate

4.1. Crystallizer Device Forms

Citrate manufacturing has steadily become an industry trend owing to the rising demand for the substance. The form, size, production rate (g/h), surface properties, and fluid dynamics conditions of the crystallizing devices have an important effect on the shape, size, distribution, and purity of the crystals during the crystallization process. Therefore, reasonable selection and design of crystallizing apparatus is one of the important measures to improve the crystallization efficiency and quality of citrate, attendant to higher requirements for crystallization devices used in citrate production machinery. Batch crystallizers made up the majority of the first generation of crystallization equipment employed in the chemical sector, and subsequently faced elimination due to significant encrustation deposits, small crystallization capacity, and high labor requirements. Modern crystallization equipment is increasingly evolving toward larger, automatic, and continuous development [133]. Figure 4 depicts typical citrate crystallizers used in industry, including a forced-circulation crystallizer, draft-tube baffled crystallizer, and Oslo crystallizer. The citrate crystallization process involves cooling, evaporation, adiabatic flash evaporation, and other operations. Hence, the crystallizer is required to be equipped with the necessary components. However, one of the major difficulties facing citrate crystallizers today is encrustation, which adversely affects the mixing and heat transfer in the crystallizer and

ultimately renders the operation inefficient and unprofitable [134,135]. In addition, in order to ensure constant product uniformity throughout the production of citrate products, premixing of the raw materials is required. However, direct stirring has a lengthy mixing cycle, which may cause a significant decrease in production efficiency, but shortening the mixing cycle also leads to poor mixing of the raw materials and consequently poor crystal size [136]. Therefore, how to prevent encrustation and strengthen the mixing of materials including liquids become key issues to take into account when designing crystallization equipment.

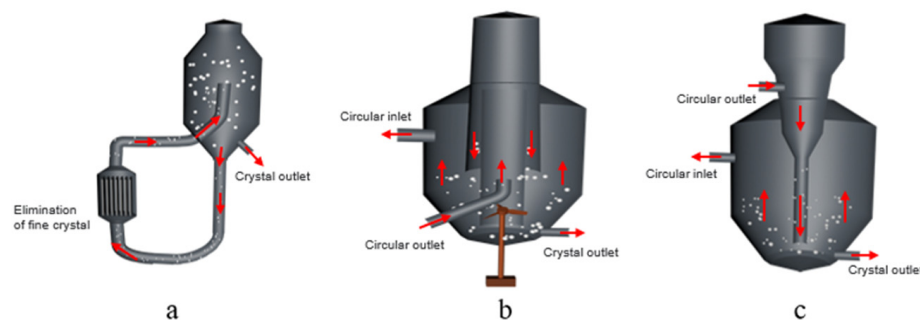


Figure 4. (a) Forced-circulation crystallizer; (b) Draft-tube baffled crystallizer; (c) Oslo crystallizer.

A vacuum crystallizer generally has no heater or cooler, and the preheating or precooling of the solution is carried out in the unsaturated state, which avoids the precipitation of crystals on the complex surfaces of heat exchangers. Therefore, subsequent issues, like lower heat-transfer capacity due to encrustation, can be avoided fairly easily. Based on this, Gong conducted research and developed a multi-stage vacuum adiabatic flash continuous crystallization apparatus, consisting of numerous crystallizers connected in series. The overall structure of the crystallizer is divided into three parts, namely the upper straight cylinder section, the reducer cylinder section, and the lower straight cylinder section. Meanwhile, the lower straight section of the devices has a guide tube, the bottom of the crystallizer is W-shaped, and the top of the devices is provided with a double-layer stirring paddle. The solid content of the crystallizer needs to be kept under control at all levels during use. Commonly, in the first crystallizer stage, the solid content is typically controlled between 3% and 10%, in the second crystallizer stage between 10% and 20%, in the third crystallizer stage between 20% and 30%, and in the fourth crystallizer stage it does not exceed 50%. Currently, the production experience has demonstrated that this crystallizer is very production-efficient, and the product has the qualities of good shape, large particle size, and uniform particle size distribution. Hence, the vacuum crystallizer has nearly completely replaced the cooling crystallizer in recent years [137].

On the basis of solving the fouling problem, experts started considering ways to boost production effectiveness and product quality even more. Generally, in an evaporative crystallizer, the crystallizer itself is attached to the evaporator. To enhance the heat transfer capacity of the evaporation heater, many contemporary evaporators also come with circulation pumps or built-in circulation propellers. This section focuses on introducing the DTB (draft-tube baffled) evaporative crystallizer, referred to as the “masked” crystallizer, which has been widely used in industry [133]. It is a kind of device with low supersaturation and is distinguished by an internal crystallization circulation pump, low resistance, and high circulation capacity. The DTB crystallizers commonly used in industry have diameters ranging from 0.5 to 10 m. They can produce crystals as thin as 0.5 to 1.5 mm, with residence times of 3 to 4 h and slurry densities as high as 25. This form of evaporative crystallizer equipment has achieved efficient internal circulation and greatly reduced the probability of secondary nucleation owing to the utilization of specialized stirring paddles. It has a high heat-exchange surface, which eliminates the need for a separate heater or chiller. Furthermore, it can realize continuous production operations [138]. In addition, other effective, cutting-edge devices have been reported. For example, to address the problem that the

current equipment is not perfect for filtering small particles of contaminants, Feng Kuanyu et al. developed a potassium citrate processing apparatus that includes a pH sampling tube, a stirring mechanism to speed up the neutralization reaction, and an adsorption mechanism that uses active adsorption to remove impurities in the mixture, which has obtained satisfactory results in the field of efficient impurity removal [139]. Another potassium citrate production system with a supermembrane filter, evaporator, and centrifuge was created by Zhao Shizhe et al. This invention preheats the potassium citrate solution entering the evaporator and allows the potassium citrate solution to flow inside the evaporator. Overall, it achieves heat recovery and utilization, improves evaporation efficiency, and significantly increases the quality of the manufactured potassium citrate [140].

4.2. Continuous Crystallization

Continuous crystallization refers to the crystallization process in which the reactants are continuously added into the crystallizer and the products are continuously produced to reach a stable state. Compared with batch crystallization, which is more prone to quality differences between different batches of products and has the shortcomings of low productivity, continuous crystallization has attracted more and more attention because of its advantages of high safety, easy control, stable operating parameters, and more uniform, high-quality products [141,142].

The use of each level of the reaction tank must be specified in the continuous crystallization process in order to facilitate a flexible design in accordance with reaction requirements. In the process of continuous crystallization, how to achieve effective control of the process and enhance crystal nucleation and growth should be considered. Meanwhile, efforts should be made to reduce the generation of encrustation [143].

Continuous crystallization of citrates is often carried out using a multi-stage process with multiple tanks in series. Normally, the first-stage reaction often takes place in the first-stage reaction tank, which is also used for continuous feeding, while the last-stage reaction tank controls removal of the finished product and return of the impurities. Finally, the task of advancing the reaction or separating the reaction product is carried out in the intermediate reaction tank. During the design process, the reaction conditions for each stage of the tank need to be clarified, including crystallization temperature, crystallization time, pH, stirring rate, etc. The flow rates at the inlet and outlet of each tank also need to be determined so that the process remains continuous and stable. In addition, the reactor volume design relies heavily on the residence time of the reaction material, which likewise calls for specific consideration [143].

The citrate salts that have been continuously crystallized include potassium citrate, sodium citrate, and calcium citrate. The application of continuous crystallization technology has achieved remarkable results in improving these products' purity, saving production costs, and reducing energy consumption during the process. Over time, continuous crystallization processes have been reported in increasing numbers. For example, Cai ZaiHua et al. achieved a mother liquor turn-back rate as low as 6% in the continuous potassium citrate production process [144]. Li Changtao et al. designed a continuous sodium citrate crystallization technique with three stages of neutralization crystallization, which was proved to obtain sodium citrate crystals of higher purity than those prepared by the conventional one-step process [145]. In addition, Jian Li et al. developed a four-stage continuous calcium citrate online production process, which effectively addressed the issue of rational design of the solid–liquid separation process in the calcium citrate production process, reduced production costs, and improved the efficiency of large-scale industrial production [146].

Despite the fact that numerous high-efficiency crystallizers are being developed and significant progress has been made in addressing the drawbacks of continuous crystallization like clogging and encrustation, it is undeniable that continuous crystallization is more challenging to operate and requires high-level operators with extensive experience. Furthermore, unlike well-controlled batch crystallization processes, it could be tricky to completely avoid fluctuations in the particle size distribution of the crystals in the de-

vice even when the operating conditions remain stable. Nevertheless, it is reasonable to anticipate a trend toward large-scale, continuous industrial crystallization operations in the future. With the continuous improvement of the theoretical model of continuous crystallization and the application of new auxiliary technologies and applications, a more repeatable and controllable continuous crystallization method will be developed on the premise of ensuring the consistency of crystal quality and performance. Meanwhile, researchers should try to develop online process analysis technology, which will realize a more efficient crystallization process and eventually achieve the universal application of continuous crystallization operations [147].

5. Conclusions

In conclusion, the industrialization process and the crystallization of citrate have received a great deal of attention. With the increasing application of citrate in food additives and functional nutritional ion supplements, it can be predicted that high-purity anhydrous citrate with high dissolution performance, high bioavailability, and good caking resistance will become a mainstream product. The citrate market is currently expanding and is anticipated to reach USD 1101 million by 2025. One of the most contentious topics in the manufacture of citrate will be environmental preservation, and the future tendency will be toward adaptability. In addition to its conventional applications in food, pharmaceuticals, and cosmetics, citrate will be extensively employed in new fields such as clean energy and materials. As the emphasis on health and food safety continues to increase, the quality and purity of food additives are becoming more and more demanding. This will also prompt manufacturers to improve the purity and quality of their products through crystallization production processes and technologies. In the future, the citrate industry will focus on technological innovation and product development to develop high-value-added products and improve market competitiveness.

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