Investigation on The Effect of Low Frequency Ultrasound on The Crystallization of a Pharmaceutical Compound L+ Ascorbic Acid

Sarra Guilane*
Manel Nedjoua

Laboratory of Environmental Engineering, Process Engineering Department, Faculty of Technology, Badji Mokhtar - Annaba University, P.O. Box 12, Annaba 23000, Algeria
*e-mail: sarah.guilane@yahoo.fr

Abstract. One of the most crucial processes in the chemical processing industry is crystallization, which has the major challenge of producing solid products with the required purity and properties. The standard crystallization methods have various processing limitations; hence, research into alternative methods like ultrasonic-assisted crystallization has been at the forefront. The present work investigates the application of low-frequency ultrasound irradiation (40 kHz) for improving the cooling crystallization of ascorbic acid. The impact of ultrasonic irradiation on crystal size, shape, and induction time has been studied, and a comparison with the conventional method has been made. The standing time had a minor effect on particle size on average, while the initial temperature had a far more significant impact. Photographic analysis using image-analysis software indicated that when ultrasound was applied to the saturated solutions, the resulting crystals were smaller and more uniform in size and shape. The resultant crystal grows predominantly in a single direction, resembling thin prisms. The use of ultrasound was also shown to reduce the induction time significantly. This ultrasonic impact is stronger at lower initial temperatures. Indeed, the smallest induction time of 300 s was obtained for sonicated solutions at an initial temperature of 65°C and ultrasonic power of 250 w. When different levels of ultrasonic power dissipation were tested, it was established that the time required for the first nuclei to appear decreased as the power increased. There was, nevertheless, a marginal impact on average crystal size.

Keywords: Ascorbic Acid, Crystal Morphology, Low Frequency Ultrasound, Sonocrystallization, Ultrasonic Bath

INTRODUCTION

Crystallization is one of the most important separation and purification unit processes. It is applied in many chemical, agrochemical, and pharmaceutical fields, where it plays a key role in determining the final product quality in terms of purity, size, and morphology (Giulietti et al., 2001). This unit operation involves the change of state that leads from a gaseous or liquid phase to a solid phase called a crystal. Generally, based on the mode used for applying supersaturation, three types of crystallization
are distinguished: evaporative, antisolvent, and cooling crystallization. Crystallization methods are selected based on the compound thermodynamic characteristics. Antisolvent crystallization is often preferred for substances with low solubility or those with a minimal effect of temperature on solubility. In contrast, evaporative or cooling crystallization is preferred for compounds with temperature-dependent solubility fluctuations. Cooling crystallization is typically indicated if solubility is strongly temperature dependent (Pritula et al., 2015; Ashish et al., 2022). However, the fundamental mechanisms of these crystallization methods are similar. Indeed, there are two critical steps in the appearance of the solid. The crystals will first appear during the first step, known as nucleation, and then grow during the second stage. Since the relative dominance of nucleation and growth can change depending on the experimental condition (Haan, 2013), it isn’t easy to achieve uniformity in crystal size and shape, crucially significant when discussing pharmaceuticals. The difficulty is to control the primary nucleation so that specific product characteristics are obtained without the need for additional complicated mechanical particle techniques. To fill in the gaps in the crystallization processes that are currently used, researchers are interested in using process intensification techniques, such as microwave-assisted (Bonacorsi, 2003) and ultrasound-assisted crystallization.

Acoustic cavitation is induced by ultrasonic irradiation of a liquid media under controlled experimental conditions. Cavitation is the formation of unique reaction environments within and around bubbles as a result of their fast growth and implosive collapse in a liquid (Guilane et al., 2015; Adewuyi et al., 2001; Muthupandian et al., 2004; Pétier et al., 2007; Thompson et al., 1999; Son et al., 2012). Both cavitation effects, namely sonophysical, which promotes mixing and homogenization, and sonochemical, resulting from radical production, affect crystallization by changing the induction period, supersaturation, concentration, and metastable zone width, which are the primary variables in this physical process, as well as controlling crystal size and morphology (Sharma et al., 2020) giving greater control over the final product’s characteristics. Amara et al. (2001) detailed the impact of ultrasound on crystal yield, morphology, and size of potash alum. They found that introducing ultrasonic irradiation significantly improved crystal recovery and characteristics. Moreover, Lyczko et al. (2002) reported that ultrasound application reduced the apparent order of nucleation during the cooling crystallization of potassium sulfate in a batch reactor. Despite reports indicating the predicted advantages of using ultrasound, it is crucial to understand that these advantages frequently depend on the particular substance and thus cannot be generalized. The current work focuses on improving the crystallization process of a pharmaceutical compound, L+ ascorbic acid, using low frequency ultrasound. L+ ascorbic acid, known as vitamin C, was the first chemically synthesized vitamin (Squires, 2011) and is one of the most important vitamins for human health (World Health Organization Model List of Essential Medicines, 2019). Vitamin C antioxidant properties are widely known for avoiding inflammatory disorders and enhancing immunity. Ascorbic acid is created from glucose by the industrial Reichstein-Grüssner method (Yadav 2022), followed by a crystallization procedure. The success of the crystallization process as a post-treatment
step is crucial to the cost-effective synthesis of the ascorbic acid of high purity and enhanced yield. Ascorbic acid has been selected as the model compound as there have not been many studies related to the crystallization of this compound using the conventional or ultrasound-assisted approaches. Hassan et al. (2019) have studied the influence of several solvents on the crystallization of ascorbic acid by the evaporation method. They observed a systematic change in crystal habits with the change in the solvent’s polarity. Wierzbowska et al. (2008) investigated the Growth kinetics of vitamin C crystals during the batch mass crystallization process in L(+)-ascorbic acid–methanol – ethanol–water systems. They indicated that a precise kinetic model, directly predicting the population density, is required to control the process yield and the product quality. The variability in crystal’s size and morphology can affect the properties and performance of the final pharmaceutical product. Using conventional approaches, achieving precise control over crystal size and morphology can be challenging, leading to reproducibility and formulation consistency difficulties. Consequently, the need for using the ultrasound-assisted approach, particularly for crystallizing pharmaceutical compounds, is justified. Susan Halász et al. (1993) in a study on the morphological and chemical stability of vitamin C crystals, reported that larger crystals tend to have more impurities and briefly indicated that low-frequency ultrasound produces smaller and high-purity homogeneous ascorbic acid crystals. Except for the discussed work, to the best of our knowledge, there is no detailed publication on the sonocrystallization of ascorbic acid.

This study presents a comprehensive analysis of the ultrasound-assisted method compared to the traditional stirring-based method. It elucidates the influence of ultrasound on the formed crystal habit and the primary nucleation. The primary aim of the current work is to employ ultrasonic irradiation to enhance the L+ ascorbic acid crystallization process. Firstly, it has been demonstrated that ascorbic acid’s solubility depends on temperature. Then, the effects of the operating parameters, such as the initial temperature, crystallization time, and intensity of ultrasound irradiation, were investigated.

**MATERIALS AND METHODS**

**Materials**

The ascorbic acid used in this study was purchased from PROLABO with a purity of 99.0 % and was used as obtained without any additional purification. Distilled water prepared in the laboratory was employed as a solvent.

**Experimental setup**

The experimental setup used for crystallizing ascorbic acid in the presence of ultrasound and under silent conditions is shown schematically in Fig. 1. A constant temperature bath maintained the temperature at the chosen value for conventional cooling crystallization. The agitation was provided using a magnetic stirrer procured by IKA (Germany) and placed below the bath at a constant stirring speed of 300 rpm (Fig. 1a). FUNGILAB procured the ultrasonic bath with a frequency of 40 kHz and variable power dissipation of 125 and 250 W (Fig. 1b). The sonication lasted one hour. Temperatures of the solutions can be controlled and range between 15 and 90°C. The glass reactor was placed at the center of the ultrasonic bath and an indirect irradiation mode was used.
**Methods**

The ascorbic acid solutions were prepared at different temperatures based on the solubility data (Fig. 2). In the conventional approach, a magnetic stirrer was used to ensure uniform bulk mixing. At the chosen working scales, ultrasound alone provided sufficient mixing to initiate crystallization; therefore, no external agitation was used in the sonocrystallization experiments.

![Diagram of experimental setup](image)

**Fig. 1:** Scheme of experimental setup. (a) Conventional approach (b) Ultrasound-assisted approach

The reactors were exposed to ambient conditions. The solution temperature decreased, and a natural air cooling mode was employed. The collected crystals were then transferred to a microscope slide. The obtained samples were recorded using an optical microscope (OPTIKA) equipped with a digital camera. Image analysis software (ImageJ) examined the crystal's size and habits.

**RESULTS AND DISCUSSION**

**Solubility of Ascorbic Acid**

The solubility data of ascorbic acid in water was determined using the successive additions method described in (Detoisien, 2009; Benmessaoud, 2016) at a temperature range of 25°C to 65°C. A definite amount of solute was gradually added to a known solvent volume at a constant temperature. This addition continues until the solute no longer dissolves, at which point equilibrium is reached. The experimental solubility of ascorbic acid in water was compared with the literature data shown in Fig. 2. The obtained results confirm a satisfactory agreement between the results of the current work and those reported in the literature (Nemdili et al., 2022; Shalmashi 2008). Ascorbic acid is a cyclic polar molecule, and solvents with higher polarities increase solubility.

Previous research has shown that L-(+)-ascorbic acid is more soluble in water than in other solvents (Hassan et al., 2019). The solubility of ascorbic acid increases as the temperature rises; this tendency might be explained by the fact that high temperatures, due to their high kinetic energies, promote more efficient collisions and intermolecular interactions between solute and solvent molecules (Nemdili et al., 2022). The current work's usage of cooling crystallization is supported since solubility showed excellent temperature dependence.
Investigation on the effect of low frequency ultrasound on the crystallization of a pharmaceutical compound L+ ascorbic acid

Fig. 2: Comparison of the obtained experimental results for L+ ascorbic acid. Solubility in water with those of Nemdili et al., 2022 and Shalmashi Eliassi, 2008

Effect of Crystallization Time

The impact of total crystallization time, defined as the period during which the solution is maintained for crystal growth, was investigated. The study was conducted over three-time intervals of 1h, 3h, and 12h, with an operating frequency of 40 kHz, a power consumption of 250 W, and two initial temperatures of 25 °C and 65 °C. From the data in Table 1, it was established that allowing the solution to stand for an extended period did not significantly impact the particle size. Over the three chosen stand-up times, the final crystal sizes were found to be nearly stable. Hatkar and Gogate (2012) also studied the influence of crystallization time. They found that after allowing the solution to remain undisturbed for 1, 2, 4, 8, and 12 hours, a minor change in crystal characteristics was observed after an optimal standing time. This tendency is explained by the fact that after 1 hour, the supersaturation generated in the solution decreases, and equilibrium is reached. At this point, no further crystal growth or nucleus formation occurs. Thus, 1 hour of effective crystallization time was determined to be sufficient for full crystal development. This period was consequently employed in subsequent experimental series.

Estimation of Induction Time with a Comparison between Conventional and Ultrasound-Assisted Approach

The effect of the initial temperature on the induction time was investigated to examine the advantages of ultrasound-assisted crystallization to the conventional method of cooling crystallization. The induction time ($t_{\text{ind}}$) is an important parameter that can provide information on the nucleation kinetics. This time presents the system’s capacity to maintain metastable equilibrium and can, therefore, be used to estimate the metastability limit of the parent phase (Kashchiev et al., 1991). From a practical perspective, the induction time is the interval between the onset of supersaturation and the formation of crystals. The techniques used for establishing the onset of crystallization vary from visual observation to analytical techniques. In this study, visual observation method determined the induction time. To confirm measurement results, all experiments were carried out in triplicate. The maximum standard deviation was ± 2%. For both approaches, crystallization experiments were conducted at five different initial temperatures: 25, 35, 45, 55, and 65 °C. The solutions were prepared based on the solubility data depicted in Fig. 2. For ultrasound-assisted crystallization, the operating conditions were an operating frequency of 40 kHz, an electrical power of 250 W, and an irradiation time of 1 h.
Table 1. Effect of standing time on crystallization of L+ascorbic acid using ultrasound-assisted approach

<table>
<thead>
<tr>
<th>Initial Temperature [°C]</th>
<th>Standing time: 1 h</th>
<th>Standing time: 3 h</th>
<th>Standing time: 12 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Length (µm)</td>
<td>Width (µm)</td>
<td>Length (µm)</td>
</tr>
<tr>
<td>25</td>
<td>152.13</td>
<td>56.12</td>
<td>154.6</td>
</tr>
<tr>
<td>65</td>
<td>376.03</td>
<td>106.22</td>
<td>377.13</td>
</tr>
</tbody>
</table>

Fig. 3: Effect of initial temperature on induction time using conventional and ultrasound-based crystallization methods. Conventional- stirring speed: 300 rpm; US bath- power: 250 W; Sonication time: 1h; Crystallization time: 1 h

Figure 3 presents the results of induction time measurements in the presence of ultrasound and under silent conditions. It was observed that the highest induction time of 5700 s was obtained at an initial temperature of 25 °C. These results are in accordance with reports from the literature (Prasad et al., 2020, Hatkar et al., 2012, Mohod et al., 2018). In a study related to the crystallization of copper sulfate, Ashish et al., 2022 reported that the required induction times were 175 s and 80 s at saturation temperatures of 40°C and 70°C, respectively. According to nucleation theory, the nucleation rate depends on the temperature. Longer periods for the onset of crystallization under the air cooling mode are caused by the fact that the nucleation rate reduces as temperature increases and fewer nuclei are produced at higher temperatures (Luque de Castro et al., 2007). The reduction in induction time was significant in the presence of ultrasound. Indeed, the influence of cavitational activity on crystallization, in particular on primary nucleation, has been the subject of numerous studies (Prasad et al., 2020; Hatkar et al., 2012; Mohod et al., 2018). The ability of ultrasound to induce primary nucleation was investigated. These studies have thus shown that applying ultrasound reduces the induction time. Luque de Castro and Priego-Capote (2007) reported that this effect depends on the particular medium and operating parameters. The main action of ultrasound is the consecutive formation and implosion of cavitation bubbles that cause severe disturbance inside the solution (Prasad et al., 2020). In opposition to the conventional approach, ultrasonic waves induce the solution to instantly become highly supersaturated due to local solvent vaporization caused by the release of an important amount of energy and high temperature. This leads to the rapid production of nuclei (Ramisetty et al., 2013). Consequently, the appearance of crystal formation occurs more quickly, and induction time is reduced. Furthermore, the cavitational
Investigation on the effect of low frequency ultrasound on the crystallization of a pharmaceutical compound L+ ascorbic acid

effect was more important at lower initial temperatures. Higher intensification benefits in terms of induction time are attained at an initial temperature of 25 °C compared to the usage of 65 °C. Similar to that observed in the present study, Guo et al., 2005 reported that the cavitation effect on nucleation is more pronounced at low supersaturation levels.

**Effect of the Ultrasound Activity on The Crystal Shape and Habit**

The effect of Ultrasound on the external shape and size of L+ Ascorbic Acid crystals obtained by cooling crystallization has been examined. An optical microscope of type OPTIKA equipped with a digital camera was used to observe and record the ascorbic acid crystals’ habits. The obtained photographic images are presented in Fig. 4. For both approaches, the formation of stable prismatic crystals was observed. These findings are in accordance with reports from previous works (Hassan et al., 2019; Hvoslef 1968; Srinivasan 2010; Wierzbowska 2008). A thermodynamic study of the properties of ascorbic acid-saturated solutions also revealed that the crystal formed from water is the most stable of the solvents (Hvolsef, 1968).

The average crystal size of ascorbic acid was quantified at different initial temperatures. Image analysis software ImageJ was used to evaluate the crystal size in length and width (Ashish et al., 2022; Sharma et al., 2020). The results are shown in Table 2.

![Fig. 4: Microscopic photographs of L+ Ascorbic Acid crystals obtained using conventional (a,b) and Ultrasound (c,d) assisted approach. Conventional- stirring speed: 300 rpm; US bath-power: 250 W; Sonication time: 1h; Crystallization time: 1h](image-url)
As the initial temperature increased from 25 to 65 °C, the conventionally crystallized sample increased the crystal's average size. A similar tendency was obtained with the ultrasound-assisted crystallized sample. These results agree with other studies (Patil et al., 2008; Chow et al., 2003; Rakhi et al., 2017). Vishwakarma et al., 2017 determined in their study on the crystallization of oxalic acid that the average crystal size increased with the increase in initial temperature. The increase in solubility at high temperatures delays the substance's precipitation from the solution. Therefore, a limited number of nuclei are formed under air-cooling crystallization mode, resulting in larger particles at higher initial temperatures.

<table>
<thead>
<tr>
<th>Initial temp (°C)</th>
<th>Conventional approach</th>
<th>Ultrasound-assisted approach</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Length (µm)</td>
<td>Width (µm)</td>
</tr>
<tr>
<td></td>
<td>Length (µm)</td>
<td>Width (µm)</td>
</tr>
<tr>
<td>25</td>
<td>186.17</td>
<td>113.24</td>
</tr>
<tr>
<td></td>
<td>152.13</td>
<td>56.12</td>
</tr>
<tr>
<td>35</td>
<td>342.25</td>
<td>226.79</td>
</tr>
<tr>
<td></td>
<td>252.17</td>
<td>66.47</td>
</tr>
<tr>
<td>45</td>
<td>386.5</td>
<td>248.94</td>
</tr>
<tr>
<td></td>
<td>235.66</td>
<td>107.87</td>
</tr>
<tr>
<td>55</td>
<td>439.75</td>
<td>205.28</td>
</tr>
<tr>
<td></td>
<td>340.66</td>
<td>110.77</td>
</tr>
<tr>
<td>65</td>
<td>472.09</td>
<td>203.52</td>
</tr>
<tr>
<td></td>
<td>376.03</td>
<td>106.22</td>
</tr>
</tbody>
</table>

The comparison based on the optical microscope images indicates that the crystals formed by the conventional approach present a non-uniform shape and a noticeable size diversity; however, the crystals produced by the ultrasound method were more uniform. In a study related to optimizing the sonocrystallization of sulfathiazole, Kuo et al. (2017) indicated that contrary to the conventional method, a pure and stable form III polymorph was produced using sonocrystallization processing. These results confirm that ultrasound ensures better control over the crystallization process. Ultrasonic reactors produce a high degree of mixing, primarily at the micro-level, accompanied by a significant degree of turbulence. These results in uniform nucleation across the whole reactor, which facilitates the creation and growth of crystals in a more consistent manner than the results obtained with conventional stirring. (Ashish et al. 2022; Vishwakarma et al. 2017; Zhong et al., 2022)

In addition, from Table 2, it is seen that the application of ultrasound to saturated solutions decreased the average particle size. A slight reduction in crystal mean length was observed. The crystal mean width, on the other hand, was significantly reduced. It has also been noticed that the obtained crystal tends to grow in one direction, forming long needle-like crystals that are classically described as thin prisms. These findings show that ultrasound irradiation alters particle morphology significantly. Manish et al., 2005, in their study on the crystallization of adipic acid, reported the formation of plate-like structures of adipic acid in ultrasonic conditions and needles in silent conditions. Crystallization is a complicated process involving numerous interacting processes, which may be difficult to manage, particularly for organic molecules (Mohod et al., 2018; Prasad et al., 2020; Ramisetty et al., 2013; Su et al., 2015; Zhong et al., 2022). Several studies have investigated the effect of solvent systems on the crystal's habit (Benmessaoud et al., 2016; Hassan et al., 2019; Halász et al., 1993; Kim et al., 2003; Nemdili et al., 2022). It has been established that the change in crystal morphologies is caused by hydrogen bonds between solvents and crystal faces. Recently, there has been an increasing...
Investigation on the effect of low frequency ultrasound on the crystallization of a pharmaceutical compound L+ ascorbic acid

interest in studying the effect of ultrasound irradiation on crystal morphologies. Ultrasound is mainly employed to affect the nucleation process. It has been reported that, for the same solvent, the crystals obtained from sonicated solutions revealed shape and size alterations compared to those obtained by the conventional crystallization method. To improve flowability, Su et al. (2015) employed the ultrasound-assisted approach to change the phenacetin crystal habit from irregularly shaped to elliptical particles. Dhumal et al. (2009) also applied the sonocrystallization process to produce finely elongated needle-shaped salbutamol sulfate particles that were more suitable for inhalation. Lee et al. (2014) indicated that the shearing action of ultrasound is responsible for inducing an alteration in the crystal's morphology. Besides, the ultrasound treatment of the saturated solutions modifies the crystal formation kinetics regarding nucleation and growth rates, resulting in a considerable effect on the final particle morphology. Kim et al. (2003), in a study related to the sonocrystallization of an active pharmaceutical ingredient, reported that in the presence of ultrasound irradiation particle size decreased from 100–200 µm to 20 µm. These positive results are due to the sonophysical effects attributed to symmetric and asymmetric cavitation (Thompson, 1999).

The motion of bubbles during oscillation and collapse considerably impacts fluid flow, including microstreaming and microturbulence, shock waves and microjets (Ashokkumar, 2009). Dalvi et al. (2009) reported that ultrasound significantly reduced the mixing time from 8413 ms to 0.8 ms during the liquid antisolvent precipitation of an active pharmaceutical compound griseofulvin. Similar observations were also reported by Narducci et al. (2012) during a study on the cooling crystallization of adipic acid in the presence of ultrasound. This significant decrease in mixing times leads to more efficient mixing that provides uniform supersaturation and a greater possibility of solute molecule collisions. Higher nucleation rates then decrease the amount of supersaturation available for particle growth, which in turn causes a reduction in particle size (Prasad et al., 2020). Furthermore, it was reported that these phenomena increase mass transfer, which promotes crystal development with a regulated size based on preventing agglomeration (Ashish et al., 2022; Rakhi et al., 2017). In fact, the crystal's size and morphology can directly impact the performance and efficacy of drug delivery systems. The ability to produce smaller and more uniformly sized crystals through sonocrystallization is particularly significant for enhancing the dissolution and bioavailability of drugs and offering more opportunities for improved therapeutic outcomes. (Sharma et al., 2020).

Effect of Ultrasound Intensity of Irradiation

The effect of the intensity of ultrasound irradiation on the sonocrystallization of ascorbic acid was examined. Two electrical powers 125 and 250 W were tested. Figure 5 illustrates the results of varying power dissipation on the nucleation process, quantified in terms of induction times. It was observed that for the five initial temperatures examined, the time required for the appearance of the first nuclei decreased with the increase in power. A minimum induction time of 300 s was obtained at the higher power of 250 W. It is seen that the induction time is intensely reduced in ultrasound-assisted experiments; however, the influence depends on the specific medium and the
operating conditions. The same findings have been reported by Sharma and Gogate (2020) in a study related to the ultrasound-assisted crystallization of memphenic acid.

Fig. 5: Variation in induction time with Irradiation Power Intensity. US bath- power: 125–250 W; Sonication time: 1h; Crystallization time: 1h.

As per the data depicted in Figure 6, it was observed that the crystal's mean Length and width decreased when the ascorbic acid-saturated solution was subjected to increased power dissipation. The acoustic power can affect the cavitation activity by influencing the active bubble population, cavitation intensity, and cavitation threshold (Sharma et al., 2020). Gracin et al. (2005) indicated that the application of ultrasound may accelerate nucleation phenomena and enable the excitation of energy barriers associated with nucleation. Furthermore, it was reported that these effects are more favorable at higher power dissipation, which explains the continuous decrease in induction time (Guo et al., 2005) and average particle size (Ashish et al., 2022; Sharma et al., 2020).

Fig. 6: Effect of Irradiation Power Intensity on Ascorbic Acid Crystals-(a) Crystal's length; (b) Crystal's width- US bath-power: 125–250 W; sonication time: 1h; crystallization time: 1h
CONCLUSION

The beneficial effects of employing an ultrasound-assisted approach for the crystallization of ascorbic acid have been demonstrated through the significant reduction in induction time and the achievement of more uniform, smaller average-size crystals compared to conventional cooling crystallization. The application of ultrasound has enhanced nucleation, leading to a shorter induction time. This effect is more pronounced at lower initial temperatures. In experiments using various ultrasound power dissipation methods, it was found that the time required for the appearance of the first nuclei decreased with the increase in power and promoted the formation of finer and more uniform particles, thereby influencing the quality and properties of the crystallized product. Overall, the findings indicate that the ultrasound-assisted approach presents a promising method for improving the crystallization of ascorbic acid, offering opportunities for further exploration and application in the pharmaceutical and food industries.

REFERENCES


Investigation on the effect of low frequency ultrasound on the crystallization of a pharmaceutical compound L+ ascorbic acid


thermodynamics, metastable zone width (MSZW) and crystal habit of L-ascorbic acid." Crystals 12, 1798.