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Application of Magnetic Field to Accelerate the Crystallization of Scopolamine Hydrobromide

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Abstract: In this paper, a rapid and efficient method for the preparation of scopolamine hydrobromide with high purity was established, named as magnetic field-induced crystallization. Based on the difference in solubility between scopolamine and scopolamine hydrobromide, salifying crystallization was selected and then treated with the synergistic effect of magnetic field to achieve the goal of purifying scopolamine. The influence of crystallization solvents and magnetic field intensity on the crystallization process of scopolamine hydrobromide, as well as the impact of magnetic field on the crystal growth direction, were investigated. The results revealed that treatment under magnetic field led to a shortened induction time (25.64–75.46%), an increased purity of crystals (0.95–2.92%), and an enhanced recovery rate (4.51–10.78%). Furthermore, it was also discovered that magnetic field could destroy hydrogen bonds within the solution, and change the physical properties of the mother liquid, so as to promote the nucleation formation and crystal growth. These findings suggested that external magnetic field could be a promising method for scopolamine preparation.

Keywords: scopolamine; crystallization; magnetic field; physical properties; hydrogen bond

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1. Introduction

Flos daturae, a well-known medicinal herb, is widely distributed across East India, North America, and China [1]. It has traditionally been utilized as an anti-cholinergic, anti-spasmodic, mydriatic, and preanesthetic agent [2]. Recent studies have revealed the presence of tropane alkaloids in *Flos daturae*, including scopolamine, hyoscyamine, anisodamine, and anisodine [3]. Among these compounds, scopolamine exhibits diverse bioactivities, such as mydriatic, antispasmodic, anticholinergic, anesthesia, analgesic, and sedative properties. Consequently, it has received increasing attention during the past few decades [4]. Compared to hyoscyamine or atropine (the racemic form of hyoscyamine), scopolamine possesses fewer adverse reactions and stronger efficacy. Based on preliminary statistics, the market demand for scopolamine is ten times higher than that for the total of hyoscyamine and atropine [5]. Therefore, significant efforts have been devoted to the production of scopolamine.

Currently, scopolamine is primarily obtained through chemical synthesis [6], biosynthesis [7,8], and extraction from plants [9]. However, the scale-up of chemical and biosynthetic methods for industrial production remains a challenge because of technical difficulties and complex processes. On the other hand, the extraction method of scopolamine from plants has gained more and more attention due to abundant species, low toxicity, and high efficiency. The common preparation process includes alkalization, extraction with non-polar solvents [10–15], polar solvents or acid water [16–21], and purification via multiple liquid–liquid extraction (LLE). Unfortunately, the use of large amounts of toxic organic

solvents in multiple LLE poses safety concerns, environmental pollution, and low efficiency issues. Recently, new separation methods have been adopted as clean-up steps, like Extrelut (Merck) cartridges, solid phase extraction (SPE) [13,21,22], dispersive solid phase extraction (d-SPE) [23], supercritical extraction [24], capillary electrophoresis [25], and molecularly imprinted polymers (MIPs) [26]. Although these methods have been successfully applied in the pretreatment of chromatographic analysis or small-scale preparations, further research, including bio-activity tests and clinical research, is still seriously limited by the lack of adequate supply of raw materials. Therefore, it is urgent to develop a fast, reliable, and effective preparation method for scopolamine with high purity and considerable quantity.

Crystallization is a commonly used method for the separation and enrichment of natural products [27,28]. However, traditional crystallization methods have some limitations, such as long induction time, low product yield, various influencing factors, and difficulty in controlling crystal forms. To address these issues, external fields have been applied to control or improve the crystallization process. Electric field [29], sound field [30–32], microwave [33], light field [34], pressure field [35], and magnetic field [29,36–38] have been introduced to shorten the induction time, control crystal growth, and improve the crystal quality. Among them, the application of magnetic field has gained increasing attention. However, previous reports show that magnetic field was mainly employed in the crystallization of protein or inorganic small molecules. Few studies have been carried out for the preparation of natural products, especially for alkaloids. In our previous studies, we investigated the effect of magnetic field on the crystallization process of puerarin and menthol [39,40]. The experimental results suggested that the induction time was shortened and regular crystals were obtained after magnetic field treatment. Therefore, magnetic field is potentially useful for promoting scopolamine preparation.

The aim of this study was to establish a fast and efficient method for the preparation of high-purity scopolamine hydrobromide using magnetic field-induced crystallization. After successfully transforming scopolamine to its slat form (scopolamine hydrobromide), the effect of crystallization solvent and magnetic field intensity on the crystallization process of scopolamine hydrobromide, as well as the effect of magnetic field on the crystal growth direction were investigated. Additionally, we evaluated the influence of magnetic field on the physical properties of the solution and clarified the mechanism of magnetic field-induced crystallization.

2. Materials and Methods

2.1. Materials and Reagents

The dried flowers of *Flos daturae* were supplied by Anhui Dexinjia Biopharm Co., Ltd. (Anhui, China). Standards of scopolamine and scopolamine hydrobromide (purity $\geq$ 99.8%) were bought from Yihe Biotechnology Co., Ltd. (Shanghai, China). The extracts of scopolamine (purity $\geq$ 83%) were provided by Shanxi Yuning Biological Science and Technology Co., Ltd. (Shanxi, China). High performance liquid chromatography (HPLC)-grade methanol was purchased from Sigma-Aldrich (St. Louis, MO, USA). Other reagents, including methanol, ethanol, isopropanol, n-butyl alcohol, ethyl acetate, sodium acetate, hydrobromic acid, acetic acid, and triethylamine, were of analytical grade and obtained from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Watson's distilled water (Guangzhou, China) was used throughout the experiment as deionized water.

2.2. HPLC Analysis

A standard stock solution of scopolamine was prepared in methanol (4.0 mg/mL) and serially diluted with methanol to produce working solutions (0.125, 0.25, 0.5, 1.0, and 2.0 mg/mL). The standard curve was plotted with the concentration of scopolamine standard as the abscissa (X) and the peak area determined via HPLC as the ordinate (Y). HPLC analysis was performed on an Agilent 1260 chromatographic system (Agilent Technologies Inc., Santa Clara, CA, USA) equipped with a G1311A quaternary pump, an online G1322A degasser, and a G1315A diode array detector (DAD). The separation was achieved on an SGE protecol

C_{18} column (4.6 × 250 mm i.d., 5.0 μm) at 35 °C. The mobile phase consisted of methanol and 0.02 mol/L sodium acetate solution containing 0.02% triethylamine (40:60, *v*/*v*) and was eluted at a flow rate of 1.0 mL/min. After injecting 20 μL of samples into the system, the DAD detector was set at 215 nm to acquire chromatograms.

2.3. Device Used for Magnetic Field Generation

Figure 1 illustrates the device used to generate a magnetic field, which consisted of two cylindrical electromagnets positioned in opposite directions. Each magnet had a flat-type electromagnetic pole face with a diameter of 14.5 cm and equipped with a hand-wheel for adjustable air gap between the poles, ranging from 0 to 18 cm. A water cooling system was installed outside the magnetic poles to dissipate heat generated during the experiment. The rated excitation voltage and current were 0–340 V and 0–28 A, respectively. The intensity and direction of the magnetic field were measured using a Tesla meter (HT-20, Shanghai Hengtong Magnetoelectric Science and Technology Co., Ltd., Shanghai, China). This device is similar to the one described in a previous article [41], so we can assume that the magnetic field gradient is also similar. In our experiment, the gap between two poles was 15 cm and the magnetic field intensity was controlled by adjusting the magnitude of the voltage and current. When the device was turned on, the magnetic field intensity increased from the center of the surface of magnetic pole to the boundary. Furthermore, the magnetic field intensity was the highest when closest to the magnet and stronger at both ends of the magnet than that at the center. The crystallizer was placed at the center position between two poles, and then the strength and direction of magnetic field were measured. Although the magnetic field intensity increased along the center toward the electromagnet, the influence of magnetic force-induced by magnetic field gradient on the results of our experiment was relatively small, due to the small size of the crystallizer (r = 5 mm).

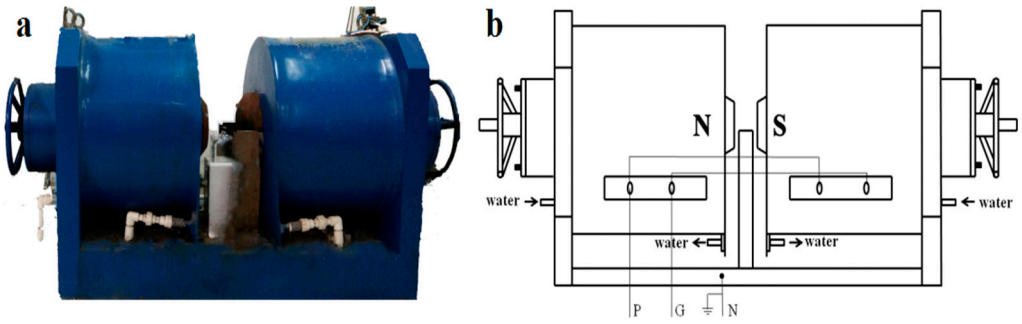

Figure 1. (**a**) Prototype of the device used for magnetic field generation; (**b**) schematic diagram of the device.

2.4. Effect of Different Solvents on the Crystallization

Five solvents, including methanol, ethanol, isopropanol, n-butanol, and a mixed solution of ethyl acetate and water (*v*/*v* = 9:1), were selected for crystallization. Scopolamine solutions with a concentration of 100 mg/mL were prepared with each solvent. Excessive hydrobromic acid was added to each solution at a molar ratio of 1.2:1. Each solution was then divided into two equal portions, one portion was subjected to a magnetic field with an intensity of 0.4 T for 3 h, while the other portion served as a blank control and crystallized at 20 ± 2 °C without a magnetic field. The samples were observed for crystal growth in different crystallization bottles after removal from the magnetic field. The effect of magnetic field on the crystal growth direction was compared. Additionally, after being removed from the magnetic field for 24 h, the solution was filtered using suction filtration. The crystals were washed three times with ice ethanol and then placed in a vacuum oven at 40 °C for 24 h to remove the solvent and water. The dried crystals were accurately weighed and their purity was determined via HPLC.

2.5. Effect of Magnetic Field Intensity on the Crystallization

The effect of magnetic field intensity on crystallization was investigated from the following aspects, including induction time, crystal purity, and recovery rate of crystals. Five portions of scopolamine solution with a concentration of 100 mg/mL were prepared with ethanol, and added with excessive hydrobromic acid at a molar ratio of 1.2:1. These solutions were then subjected to magnetic field with intensities of 0, 0.2, 0.4, 0.6, 0.8 T for 3 h, respectively (20 ± 2 °C). After being removed from the magnetic field for 24 h, 20 μL of crystallization solution was taken, dried under vacuum, dissolved in a mixed solution composed of methanol and water (v/v = 40:60) under ultrasound treatment, and used for HPLC determination. The remaining solution was filtered using suction filtration, and the crystals were washed three times with ice ethanol, and then placed in a vacuum oven at 40 °C for 24 h to remove solvent and water. The dried crystals were accurately weighed and their purity was determined via HPLC. The recovery rate (R) was calculated according to the following formula:

$$R = \frac{m_{crystal} \times P}{1.445 \times m_{raw} \times 0.83}$$

where R is the recovery rate, %; $m_{crystal}$ is the weight of crystals, g; P is the purity of sample, %; m_{raw} is the weight of raw materials, g; 1.445 is the molar mass ratio of scopolamine hydrobromide to scopolamine; and 0.83 is the purity of scopolamine in raw materials.

2.6. Effect of Magnetic Field on the Absorbance of the Solution

With pure water as the reference, the UV absorbance of five solvents, including methanol, ethanol, isopropanol, n-butanol, and ethyl acetate, was measured at wavelengths of 220, 230, 240, 250, and 260 nm, respectively, at 20 ± 2 °C. Then, all the solvents were placed under a magnetic field with an intensity of 0.4 T for 0.5, 1, 2, 3, 4, 5, and 6 h, respectively. The UV absorbance of each solvent was then measured at the corresponding wavelength after each interval.

Scopolamine solutions with a concentration of 0.125 mg/mL were prepared using methanol, ethanol, isopropanol, n-butanol, and ethyl acetate as solvents at 20 ± 2 °C, respectively. The UV absorbance of five solutions was then measured at the corresponding wavelength. Finally, all the solutions were subjected to magnetic field with an intensity of 0.4 T for 0.5, 1, 2, 3, 4, 5, and 6 h, respectively. The UV absorbance of five solutions was subsequently measured after each interval.

2.7. Effect of Magnetic Field on the Interfacial Tension of the Solution

Scopolamine solutions were prepared with a concentration of 2 mg/mL using methanol, ethanol, isopropanol, n-butanol, and ethyl acetate as solvents, respectively, at 20 ± 2 °C. Then, excessive hydrobromic acid was added to each solution at a molar ratio of 1.2:1. Each solution was then divided into two equal portions, one portion subjected to a magnetic field with an intensity of 0.4 T for 3 h, while the other portion served as a blank control in the absence of a magnetic field. The interfacial tension of each solution was measured using an interfacial tension meter (BZY-3B, Shanghai Hengping Instrument and Meter Factory, Shanghai, China).

2.8. Effect of Magnetic Field on Viscosity and Density

Scopolamine solutions were prepared with a concentration of 1 mg/mL using methanol, ethanol, isopropanol, n-butanol, and ethyl acetate as solvents, respectively, at 20 ± 2 °C. Excessive hydrobromic acid was added to each solution at a molar ratio of 1.2:1. Each solution was then divided into two equal portions, one portion subjected to a magnetic field with an intensity of 0.4 T for 3 h, while the other portion served as a control without a magnetic field. The viscosity of different solutions was measured with a kinematic viscometer (PXSYD-265B, Shanghai Pingxuan Scientific Instrument Co., LTD., Shanghai, China), and the density was calculated by measuring the volume and quantity of the solvent.

3. Results and Discussion

3.1. Effect of Magnetic Field on the Crystal Growth Direction

In comparison to control samples, more crystals grew against the wall on the S-pole side under a magnetic field of 0.4T (Figure 2). A similar phenomenon was also reported by Yin [37] and Pareja-Rivera [29] in their respective studies on lysozyme crystals and protein crystal growth, highlighting the directing effect of the magnetic field. The crystallization process can be affected by the wall effect of the container, as the solution surface tension at the wall of a container is lower than that in the center of the solution. Based on classical nucleation formulae, positions with low surface tension are beneficial for crystal precipitation. Furthermore, by comparing the crystal growth on the S-pole and N-pole sides, it was confirmed that crystals preferentially grew on the S-pole side, indicating that the movement of molecules in the solution was influenced by the magnetic field, leading to the gathering of scopolamine hydrobromide molecules at the S-pole side. As the concentration of scopolamine hydrobromide increased at the S-pole side, the supersaturation of the solution increased, subsequently accelerating crystal nucleus formation and crystal growth.

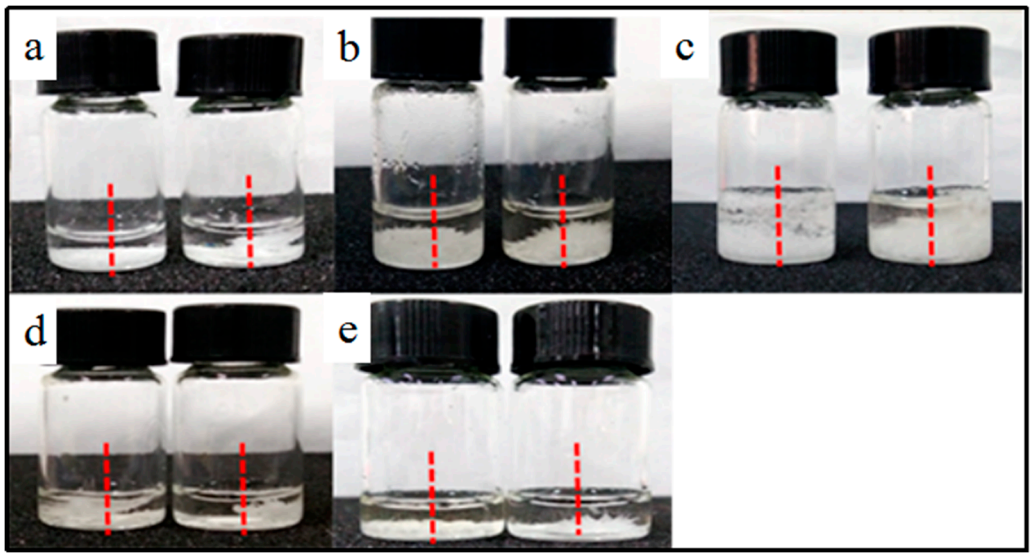

Figure 2. Effect of magnetic field on the crystal growth direction. (**a**–**e**) Crystal samples obtained by using different solvents, in which the right and left sides represent crystallization with and without magnetic fields, respectively. (**a**) Methanol, (**b**) ethanol, (**c**) isopropanol, (**d**) n-butanol, and (**e**) ethyl acetate/water (v/v = 9:1).

3.2. Effect of Different Solvents on Crystallization

In this study, the induction time was defined as the period from the moment when a well-prepared crystalline solution was quickly placed into the magnetic field until the first appearance of crystals. The effect of five different solvents on the crystallization process is shown in Figure 3. All the induction time of scopolamine hydrobromide was shortened after magnetic field treatment at 0.4 T (Figure 3a). The order of shortening was listed as follows: ethanol (75.5%) > methanol (38.6%) > n-butanol (35.6%) > ethyl acetate/water (27.1%) > isopropanol (25.6%). These findings indicated that magnetic field accelerated the formation of nuclei and promoted the crystallization process. According to our results described in Section 3.1, the directed effect of magnetic field caused molecules to move in a specific direction and orderly manner, leading to an increase in concentration in some regions of the solution, thereby enhancing the supersaturation of solution here. A certain degree of supersaturation can stimulate the nuclei formation and crystal growth.

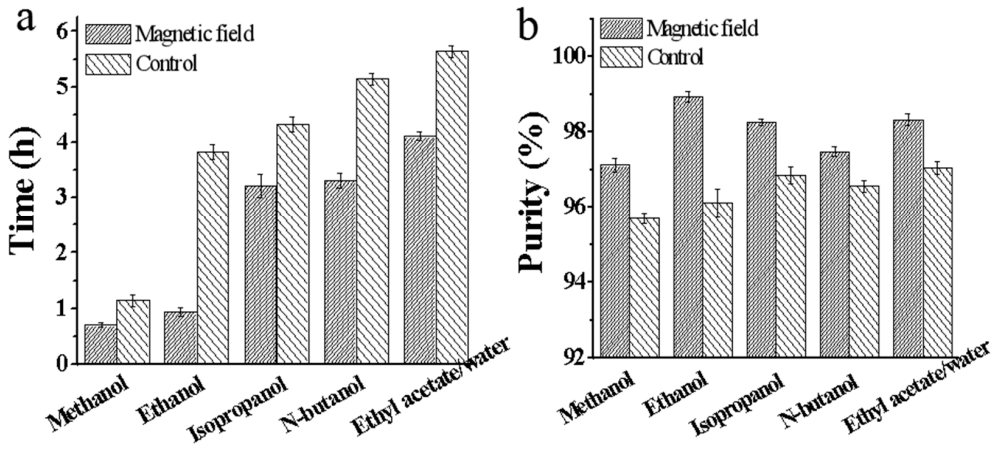

Figure 3. Effect of five different solvents on the crystallization. (**a**) Effect of five different solvents on the induction time. (**b**) Effect of five different solvents on the purity of crystals.

Molecular structure analysis revealed that scopolamine contains a seven-membered ring, an ester group, a hydroxyl group, and a nitrogen atom. Within the seven-membered ring, there is an epoxy group. The oxygen atoms in the ester group, hydroxyl group, and epoxy group possess negative charges that can form hydrogen bonds with the hydrogen atoms having positive charge. For crystalline solvents except for ethyl acetate, the hydrogen atoms in the hydroxyl group of methanol, ethanol, isopropanol, and n-butanol can also form intermolecular hydrogen bonds with the oxygen atoms. Additionally, the oxygen atoms in the hydroxyl groups of different solvents can form hydrogen bonds with the hydrogen atoms in the hydroxy of scopolamine. Moreover, hydrogen atoms in water molecules can also form intermolecular hydrogen bonds with oxygen atoms in scopolamine molecules. Thus, extensive hydrogen bonds exist between the solute and solvent in the crystalline mother liquor. Meanwhile, as energy, the magnetic field also promoted the vibration of scopolamine hydrobromide molecules themselves and destroyed the association between solute and solvent molecules [42]. Therefore, it was hypothesized that the magnetic field destroyed hydrogen bonds between solute and solvent, reducing their binding force, and then accelerated the crystallization process.

Moreover, crystals obtained under a magnetic field exhibited a higher purity compared to those without a magnetic field. As depicted in Figure 3b, the crystalline purity was improved in various solvents, such as methanol (95.7% to 97.12%), ethanol (96.12% to 98.93%), isopropanol (96.85% to 98.25%), n-butanol (95.56% to 97.48%), and ethyl acetate/water (97.05% to 98.32%). The increase in purity suggested that fewer impurities were present in the crystals. Generally, the main sources of impurities in the crystals can be divided into two aspects. Firstly, lattice defects cause impurities wrapped in the crystals during the crystallization process. Secondly, impurities exist in the mother liquor, and residuals on the crystal surface have not been completely washed away. Due to the directional effect of magnetic field on crystallization, more regular crystals were obtained, which facilitated removing residual impurities in the mother liquor during the washing process. Furthermore, treatment under a magnetic field also reduced the impurities wrapped in the crystals and improved their quality.

3.3. Effect of Magnetic Field Intensity on Crystallization

In the absence of a magnetic field, crystals began to appear after approximately 230 min (Figure 4a). However, when subjected to a magnetic field with an intensity of 0.2 T, crystallization could be observed only after about 116.7 min. As the magnetic field intensity increased from 0 to 0.8 T, the induction time gradually shortened from 230 to 40 min, indicating a 82.6% reduction in the duration. Additionally, the shortening effect slowed down as the magnetic field intensity was adjusted to 0.4 T, possibly due to the saturation effect of the magnetic field on the solution. In other words, when the magnetic

field intensity was higher than 0.4 T, the reduced influence of the magnetic field on the induction time was not obvious, i.e., the influence was saturated [43,44]. Magnetic field accelerated the formation of crystal nuclei and shortened the induction time by affecting molecular movement and the intermolecular hydrogen bonds. However, this effect is limited due to the limited number of molecules in the solution. That is to say, to some extent, the influence of the magnetic field on crystallization is effective. But if the magnetic field intensity increases beyond this range, the influence of the magnetic field on the crystallization process does not significantly increase and reaches saturation.

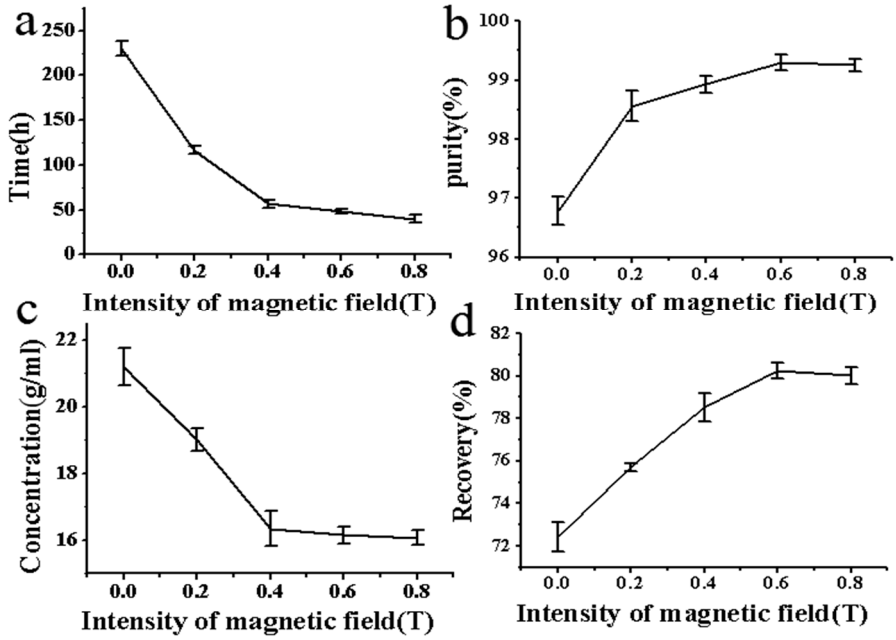

Figure 4. Effect of magnetic field intensity on crystallization. (**a**) Effect of magnetic field intensity on induction time. (**b**) Effect of magnetic field intensity on the purity of crystals. (**c**) Concentration of scopolamine hydrobromide in crystallization mother liquor at 24 h. (**d**) Effect of magnetic field intensity on the recovery rate of crystals.

As illustrated in Figure 4b, the purity of crystals obtained in the absence of magnetic field was determined to be 96.78%. All the purities of crystals treated under magnetic field were more than 98%, and even more than 99% when intensity was 0.6 and 0.8 T. However, the crystal size decreased with the increase in magnetic field intensity. The above results could be attributed to the fact that the increase in magnetic field intensity promoted the nucleation of solution, and too many nuclei could not fully grow, resulting in relatively small crystal sizes.

Another interesting finding was that the concentration of scopolamine hydrobromide in the solution decreased with the increase in magnetic field intensity (Figure 4c). After crystallization without a magnetic field, the concentration of scopolamine hydrobromide in the solution was determined to be about 21.19 mg/mL. However, after treated under a magnetic field with an intensity of 0.8 T, the concentration of scopolamine hydrobromide reduced to 16.08 mg/mL, which was consistent with the theory that magnetic field could accelerate crystal growth and promote crystallization to reach equilibrium more quickly. At the same time, the magnetic field could affect the solubility, destroy hydrogen bonds formed between the substance and the solution, and decrease the solubility. According to mass balance theory, the concentration of scopolamine hydrobromide in the solution decreased after magnetic field treatment, which would also cause an increase in recovery rate.

In the absence of a magnetic field, the recovery rate of crystals was approximately 72.43%. However, after treatment with a magnetic field, the recovery rate gradually increased, and reached its maximum value of 80.24% when the magnetic field intensity was

0.6 T (Figure 4d). Nevertheless, the recovery rate slightly decreased from 0.6 T (80.24%) to 0.8T (80.02%). On one hand, as the magnetic field intensity increased, many crystal nuclei in the solution could not fully grow, resulting in the formation of smaller crystal particles and loss during the filtering and washing process. On the other hand, the saturated effect of the magnetic field on solubility would also lead to the stabilization of the recovery rate increase. Therefore, the recovery rate decreased during the process of magnetic field strength from 0.6T to 0.8T.

According to the theory of mass balance, the mass lost during the filtration and drying process is equal to the theoretically obtained mass minus the actually obtained mass. Meanwhile, the theoretically obtained mass is equal to the total amount of scopolamine minus the residual amount in the solution. Therefore, the loss rate during the filtration process was calculated and listed in order: 8.97% (0 T) > 7.60% (0.2 T) > 7.13% (0.4 T) > 5.86% (0.8 T) > 5.58% (0.6 T), where it can be found that the loss rate during the filtration and drying process decreased with the increase in magnetic field intensity. The results could be explained by the fact that crystals obtained under a strong magnetic field were more regular and tightly arranged, causing fewer crystals to be lost during the washing process.

3.4. Effect of Magnetic Field on Absorbance of Solution

As shown in Figure 5, after being subjected to a magnetic field for 6 h, the UV absorbance of five solvents increased. Ethanol (0.108) had the highest increase, followed by isopropanol (0.101), n-butanol (0.023), methanol (0.019), and ethyl acetate (0.018). Similarly, the UV absorbance of five scopolamine solutions also increased after being placed under a magnetic field. Methanol (0.067) had the highest increase, followed by isopropanol (0.058), ethanol (0.051), ethyl acetate (0.018), and n-butanol (0.009). These results suggested that the adsorbed energy of hydrogen under magnetic field reached the energy barrier required for the hydrogen bond cleavage, leading to more broken hydrogen bonds in the solvent. Consequently, the UV absorption clearly increased. Additionally, with the prolongation of magnetic field treatment time, the UV absorption of five solvents and solutions also gradually increased.

Generally, the absorption spectrum in the UV region is influenced by several factors, such as the excitation level of the electron layer outside the nucleus, the structure of the material bond, and temperature. The UV absorbance of solvent increased with the increase in temperature. This is because heating can accelerate the thermal motion of solvent molecules and gradually destroy hydrogen bonds in the molecules, leading to smaller molecular clusters or individual solvent molecules. However, when the temperature is constant, magnetic treatment does not cause a change in the key structure, thus it might be due to changes in the structure of the molecular state. Our experimental results suggested that intermolecular interaction in the solution was found to be hydrogen bonds. Based on these findings, we hypothesize that hydrogen bonds between solvent molecules are destroyed during magnetic field treatment. This is because only when the hydrogen bond is destroyed will changes occur in the internal structure of the solvent and achieve a series of physical and chemical properties changes.

3.5. Effect of Magnetic Field on Interfacial Tension of Solution

According to a previous study [34], the classical nucleation equation can be expressed as follows:

$$J = A * \exp\left[-\left(\frac{16\pi}{3}\right)\left(\frac{\gamma^3 V_m^2}{\Delta\mu^2 k_B}\right)\right]$$

where A is the pre-exponential factor; γ is the interfacial tension between the solid and the solution phases; V_m is the molar volume of the solid phase; $\Delta\mu$ is the difference in the solute chemical potential between the solution and the solid phase; and K_B is Boltzmann constant.

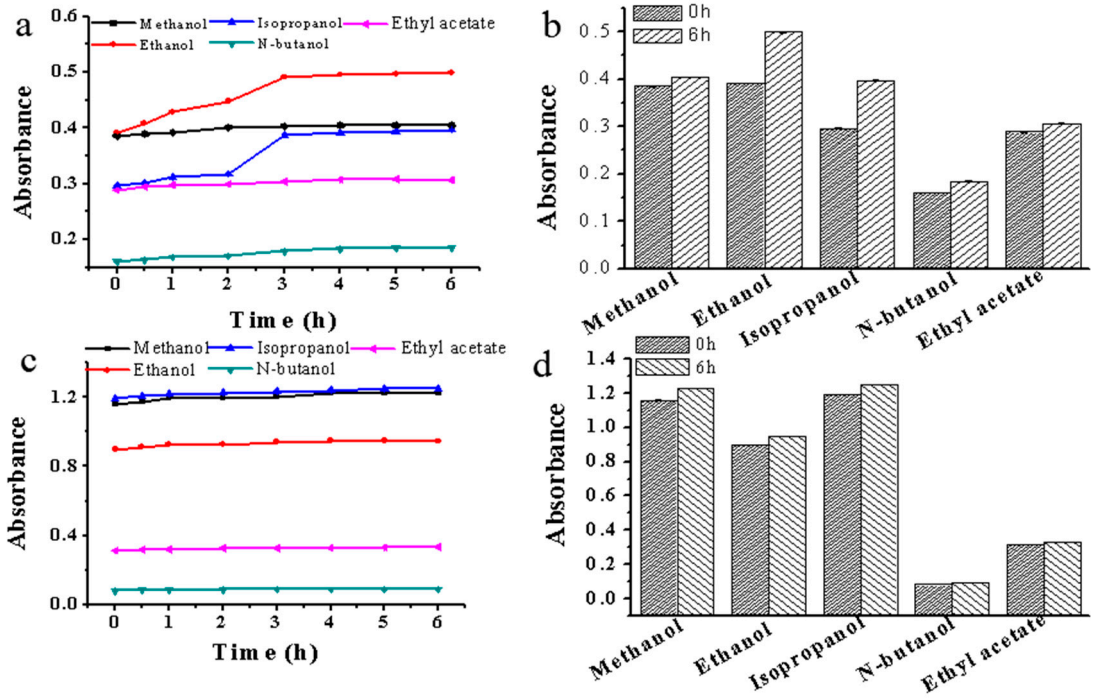

Figure 5. Effect of magnetic field on the absorbance of solution. (**a**) Effect of magnetic field on the absorbance of five pure crystallization solvents. (**b**) The absorbance of five pure crystallization solvents without and with magnetic field treatment for 6 h. (**c**) Effect of magnetic field on the absorbance of five scopolamine solutions. (**d**) The absorbance of five scopolamine solutions without and with magnetic field treatment for 6 h.

Through several mathematical transformations and formula derivations, the equation can be re-written as follows:

$$J = A * \exp\left[-\left(\frac{16\pi}{3}\right)\left(\frac{\gamma^3 v^2}{k_B^3 T^3 \{\ln S\}^2}\right)\right]$$

where A is the pre-exponential factor; γ is the interfacial tension between the solid and the solution phases; V is the molecular volume; K_B is Boltzmann constant; T is the temperature; and S is the supersaturation.

Based on the newly developed equation, the rate of nucleation is related to temperature, the degree of supersaturation, and interfacial tension. Therefore, increasing temperature and supersaturation, as well as reducing interfacial tension are conducive to nucleation. As illustrated in Figure 6a, all five solutions showed a decrease in interfacial tension, with isopropanol (0.8 mN/m) having the greatest decrease, followed by n-butanol (0.7 mN/m), ethanol (0.5 mN/m), ethyl acetate (0.37 mN/m), and methanol (0.36 mN/m). This decrease in interfacial tension suggested that treatment with magnetic field is favorable for crystal nuclei formation. The above findings that the crystals were preferentially precipitated at the inner wall of the container were also verified, as a decrease in surface tension promoted nuclei formation.

As surface tension is a fundamental property of the solution, a decrease in surface tension indicates a change in the physical properties of the solution, without the addition of new substances. Hydrogen bonding is an intermolecular force commonly found in solutions. The reduction in surface tension in the solution demonstrates that hydrogen bonds are broken under the magnetic field, reducing intermolecular interaction and the surface tension of the mixed solution. This implies that the magnetic field reduces the surface tension of the mixed solution by breaking the intermolecular hydrogen bonds,

promoting crystal nuclei formation, accelerating crystals formation, and shortening the induction time.

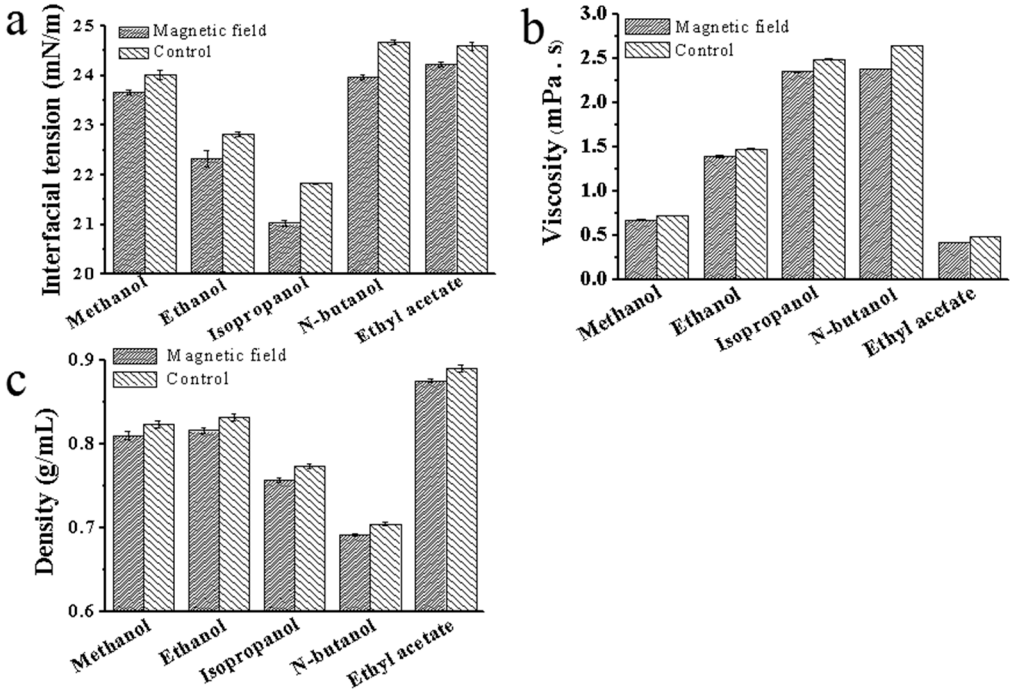

Figure 6. Effect of magnetic field on the properties of solution. (**a**) Effect of magnetic field on interfacial tension. (**b**) Effect of magnetic field on viscosity. (**c**) Effect of magnetic field on density.

3.6. Effect of Magnetic Field on the Viscosity and Density of Solution

As depicted in Figure 6b,c the solutions treated under magnetic field showed reduced viscosity and density to varying degrees. The greater the viscosity of a solution, the more obviously the degree reduced. This reduction in viscosity is favorable for crystal precipitation from the solution. Viscosity and density are considered as fundamental properties of the solution and are closely related to hydrogen bonds in the solution. When intermolecular hydrogen bonds form, molecular association may occur, leading to an increase in viscosity and density of the solution. However, the formation of intramolecular hydrogen bonds does not cause an increase in viscosity and density. Therefore, the destructive effect of magnetic field on hydrogen bonding can be demonstrated by measuring viscosity and density. After treatment under magnetic field, the density and viscosity of the solution decreased, indicating that the intermolecular hydrogen bonds were destroyed by the magnetic field. Consequently, the magnetic field destroyed the intermolecular hydrogen bonds in the solution and weakened the interaction between the solute and the solvent, making it easier for the solute to crystallize.

4. Conclusions

Our research aimed to develop an efficient and fast preparation method for high-purity scopolamine hydrobromide, based on external magnetic field-induced crystallization. Through a comparison between five different solvents, a directional effect of magnetic field on scopolamine hydrobromide was identified. A better performance of purity, recovery rate, and shortened induction time were confirmed when ethanol was used as solvent with a magnetic field intensity of 0.6 T. Furthermore, the destruction effect of a magnetic field on hydrogen bonds was considered as the main reason of the promotion of nuclei formation and crystal growth. This conclusion was supported by our observations that magnetic field increased the absorbance, as well as reduced the interfacial tension, density, and viscosity of the solution. In conclusion, our study provides a valuable insight into the use of external magnetic fields in the preparation of highly purified scopolamine hydrobromide.

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