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Methods for Crystal Production of natural compounds; a review of recent advancements

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Abstract

The current study aimed to determine the advanced techniques for the crystallization of natural compounds. Crystallization is an effective purification and separation process utilized in industries due to its ability to provide superior purity. There are three main methods of crystallization used for natural compounds, namely, conventional methods, chemical methods, and improved methods. Fractional distillation and chromatographic methods are the two conventional methods that were initially used and remain effective for natural compound crystallization. Chemical methods involve using a suitable solvent, such as acetonitrile, acetone, propyl, or ethanol, to carry out crystallization and provide high selectivity. Striping crystallization is an advanced and improved method that is also used for natural compound crystallization and in the pharmaceutical sector. The crystal size and morphology affect the ease of separation, washing, handling, dehydrating, packaging, and storage. Product crystal size and morphology are typically determined by considering factors like temperature, blending intensity, solvents, supersaturation, or the addition of seed crystals.

Keywords: Crystallization, fractional distillation, solvent method, stripping crystallization, natural compounds

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1. Introduction

Crystallization has been extensively applied in the industrial sector for purification and separation processes. It is very important to control crystal size and shape distribution to achieve effective downstream processing and product efficiency [1-2]. Crystallization plays a vital role in the pharmaceutical industry in purifying and separating chemical compounds. This process involves dissolving the compound in a solvent and allowing it to form crystals through evaporation or cooling. The isolated crystals can then be further purified and used for drug formulation. The purity of the compound is essential for ensuring the safety and effectiveness of the final drug product. Additionally, the properties of the crystals formed, such as size and shape, can have a significant impact on the drug's properties [3].

The production of more than 90% of currently marketed APIs (Active Pharmaceutical Ingredient) involves at least one crystallization step [4]. The size and shape of crystals not only affect downstream operations, such as bulk density and flowability but also impact the dissolution rate and bioavailability of the final drug product. The significance of this process has led to an increased focus on continuous crystallization in recent years [5-8]. In the production process, after crystallization, filtration is employed to isolate the solid product [9].

This applies especially to crystals manufactured in the pharmaceutical sector. The ease of separation, cleaning, drying, packaging, transportation, and preservation can be influenced by crystal size and shape. They may also affect the pharmaceutical industry's compression into pills bioavailability, and dissolving characteristics. Temperature, solvent, mixing speed, supersaturation, and seed crystal addition are routinely utilized to alter crystal size and morphology [10]. Menthol ($C_{10}H_2O$) is a natural cyclic terpene alcohol of plant origin that imparts a characteristic odor and flavor to plants of the genus Mentha [11-12]. It was first isolated in 1771 by Dutch botanist Gambius as the principle of crystallization. Peppermint is the primary source of menthol and has been harvested in Japan for over 2,000 years for medicinal purposes. Today, menthol is consumed in staggering quantities, over 7,000 tons per year, and the value of the raw product is around $300 million. The consumption of menthol is estimated to be 30 to 32,000 tonnes per year. As with vanilla and citrus fruit, menthol has become one of the major flavoring agents in a wide range of tobacco products where it was originally used as an additive in 1920 [13-14]. Menthol's local anesthetic effect makes it useful in treating minor conditions such as sore throat and muscle aches [15-16]. Menthol can be produced commercially through various synthetic routes, and it can

also be obtained in its pure crystalline form by steam-distilling the essential oil of corn mint [17-18].

Menthol has various applications in industries such as fragrance, medicinal products, and flavorings. The peppermint plant is the major natural source of menthol, which is extracted from its leaves through a process called steam distillation. The recovered oil is then subjected to low-temperature crystallization to obtain menthol. The process of obtaining "decentralized peppermint oil" involves centrifuging the product to remove the liquid fraction that does not crystallize. The remaining crystalline proportion is air-dried at low temperatures in a refrigerated chamber for approximately 25-30 days. Although not all of the menthol in peppermint essential oil forms crystals during this procedure, an oily product is formed in addition to the solid portion. This leftover liquid is known as "Dementholized peppermint oil. Despite containing significant amounts of menthone (25-30%), menthol (35-45%), iso menthone (12-18%), and neomenthol (11-15%), this product has low commercial value due to (-)-menthol's low melting point of 42-44°C, which means it is usually solid at room temperature. This property makes transportation and storage difficult as it must be kept in closed vessels and is prone to sublimation during packing. Moreover, the low density of menthol crystals increases transportation costs. As a result, companies that produce (-)-menthol are distributing liquid menthol instead of crystals [19-20].

The quality of the crystalline product is determined by various factors, such as crystal shape, size, distribution, agglomeration, and purity. These factors are primarily influenced by the crystallization process, and they play a crucial role in determining the product's filterability, formulation behavior, drying behavior, flowability, f, and bioavailability [21-23].

2. Conventional Methods of Crystallization

The following methods are used for the crystallization of menthol.

2.1. Fractionation method

Fractional distillation is a separation method that separates components in a mixture based on their differences in volatility. The process involves heating the mixture and then condensing the vapors back into a liquid state, with the more volatile components condensing at lower temperatures. The effectiveness of the separation depends on various factors, such as the physical and chemical properties of the components and the conditions during the distillation process. The efficiency of fractional distillation also depends on the transfer of mass and energy between the liquid and vapor phases. The column used in fractional distillation is packed with materials that provide a large surface area for mass transfer, such as ceramic or metal beads. The height and diameter of the column are chosen based on the desired separation efficiency. The choice of column packing and dimensions can affect separation selectivity and productivity, so it's essential to choose the appropriate configuration based on the mixture being separated. Successful fractional distillation requires careful control of the operating conditions and appropriate selection and design of the column to achieve the desired separation outcome [24].

Fractional distillation is a method that separates a mixture of liquids into their components based on their boiling points. The process involves heating the mixture and separating the component with the lowest boiling point first, followed by progressively separating the components with higher boiling points. To reduce the boiling points of the components, the process is often carried out under a vacuum. As the vapor phase reaches the top of the column, it becomes enriched with the most volatile component. Fractional distillation is commonly used to separate essential oils and other liquid mixtures [25-27]. The essential oil of *Mentha* arvensis typically contains a high percentage of menthol (60-85%) and menthone (12-20%). However, the co-presence of these compounds presents a challenge for isolating menthol from the essential oil as they have similar physical characteristics. Menthol has a boiling point of 212°C, and menthone has a boiling point of 209°C at 760 mmHg pressure, with only a 3°C difference in boiling point, making it difficult to separate these two compounds initially using fractional distillation. Some sources indicate that the boiling point of menthol at 760 mmHg is 216°C. However, at reduced pressures, the boiling point difference becomes more significant, with a difference of 15 degrees at 20 mmHg absolute pressure and 18 degrees at 5 mmHg absolute pressure.

The process consists of three main steps. Firstly, the menthone and other fractions are separated using a vacuum distillation column. Secondly, the menthol is separated from the non-volatile components through hydro-distillation. Lastly, the menthol is purified through water-based digestion, leading to the production of crystals. In an experiment, mint oil was fractionally distilled in a batch column with approximately 50 theoretical plates and a reflux ratio of about 50 at a pressure of 20 mmHg. After distillation, the recovered fraction contained menthol (65.2%), menthol esters (1.8%), and menthone (12.5%). The distillation was then stopped, and the resulting product, known as menthone-free oil, began to solidify at room temperature, accounting for around 70% of the total weight. This menthone-free oil contained approximately 89% menthol and 6.5% unstable components. The menthone-free oil was then steam distilled at atmospheric pressure until all unstable constituents were removed. The resulting condensate was separated into two layers, and upon cooling, the layer containing menthol crystallized into a solid substance. The resulting menthol had a melting point of 29-35°C, which did not meet U.S. standards.

The crude menthol produced had a yield of about 88% compared to the menthone-free oil. To remove impurities, the unrefined menthol was cleaned using water absorption. Approximately 10 grams of crude menthol were heated with 100 milliliters of water in a flask for around 10 minutes while continuously mixing and shaking. The layer of menthol solidified upon cooling and was then separated from the solution. The process was repeated with another 100 ml of water, resulting in a product with a melting point within the U.S. Pharmacopeia specifications of 41.6°C to 42.7°C. The pure product yielded almost 9.5 grams of long needle-like crystals, which contained approximately 92% of the USP standard menthol obtained from the crude menthol. It is now possible to isolate the total menthol, which is 85% present in the EO. However, there was a small loss of menthol due to impurities in the aqueous solution, as

menthol solubility at room temperature is only 0.42 g/liter of solution.

Fractional distillation is a separation method that relies on the varying volatility of different chemical compounds. The effectiveness of this method is influenced by factors such as the chemical and physical properties of the components being separated and the pressure and temperature conditions during the distillation process. The efficiency of separation is also affected by the mass-energy shift that happens between the mixture's liquid and vapor phases. That's why, the design of the packed column used in the distillation process, including factors such as the type of packing material, column diameter, and height, can have a significant impact on the success of the separation [24]. Fig 1 indicates the percentage yield of menthol obtained by fractional distillation at different temperatures. In the process of fractional distillation at 42.7ºC highest yield of menthol was obtained.

2.2. Advantages of fractional distillation

Fractional distillation is a widely used and inexpensive technique for separating essential oils due to its simplicity. Batch vacuum distillation, which operates at low temperatures, is commonly used to separate various oils. The main benefits of the batch method are its versatility and ability to work on a small scale, which allows for the testing of raw materials before large-scale processing [26].

2.3. Chromatographic Method

The major constituents of mint oils are menthol, menthone, terpene hydrocarbons, and menthyl esters, although the composition may vary. *Mentha* arvensis typically contains 60% to 85% menthol. Among the components of mint oil, menthol, and menthone are the most abundant. A commercial-scale process using adsorbents and specific eluents can be used to obtain quantitative yields of menthol and menthone. In a technique, corn mint oil is dissolved in a non-polar solvent, and then passed through adsorbent material. The adsorbent material selectively adsorbs the desired components, which are then separated using eluants. The fractions obtained in this process are menthone and menthol. This technique is often used for the purification and separation of various organic compounds, including those found in essential oils.

Menthone and menthol can be separated from solvents by an appropriate method such as solvent evaporation. Chromatographic adsorption is a process that involves the use of adsorbent materials such as activated magnesia, activated charcoal, alumina in its activated form, and Fuller's earth. These materials have large surface areas and can selectively adsorb specific components from a mixture. The selection of adsorbent material relies on the composition of the mixture and the components that are to be separated. This technique is widely employed in the purification and separation of organic compounds, including those present in essential oils, as well as in the chemical and pharmaceutical industries. The eluents are chosen in a way that allows one adsorbent to be completely and immediately removed from the mixture at a time. To isolate different components of mint oil, the oil is initially adsorbed onto the top of a column containing activated carbon adsorbent and then washed with appropriate solvents to release the adsorbed solutes through the column. Components that were weakly adsorbed moved faster, while those that were strongly adsorbed moved slowly, resulting in an increasing separation of the adsorbed components. The mint oil used in the study had the highest adsorption affinities for menthol, menthone, menthyl esters, and terpene hydrocarbons, with terpene hydrocarbons exhibiting the lowest affinity. The raw material used for the study was corn mint oil with approximately menthol (65.2%), menthone (12.5%), and methyl esters (1.8%). The activated carbon adsorbent was crushed and passed through a sieve with a mesh size (100 or 200) before being packed into a 6.5 cm glass column to a height (50 cm). This process is widely used in the purification and separation of various organic compounds, including those found in essential oils, in the pharmaceutical and chemical industries.

The process for refining the mint oil began with steam distilling and obtaining 25 g of the oil, which was then dissolved in a hydrocarbon solvent with a boiling point range of 77-115°C to create a 150 ml solution. This solution was adsorbed onto the peak portion of a 50 cm tall, 6.5 cm wide glass column that contained 1200 g of activated carbon that had been crushed and sieved through a 100 or 200 mesh sieve. The column was developed gradually with a 1000 ml mixture of hydrocarbon solvent, and the eluant stream was maintained at a direct rate of 10 mm/min with an adsorbent proportion of 1:50. After collecting the percolated fractions, the solvents were removed, resulting in three distinct fractions: terpenes and menthyl esters, menthone, and menthol. The Menthyl esters and terpenes were first washed by water, followed by the immediate collection of the menthone fraction, and finally, the menthol fraction was collected, which melted at a temperature range of 41–43°C. The yield for both menthol and menthone was 95%-90% individually [28]. Table 1 shows the percentage purity of menthol which is obtained by different crystallization techniques.

3. Chemical Methods of Crystallization

3.1. Crystallization using suitable solvents

Crystallization solvents from the nitrile series were employed, with the formula RCN, where R is an alkyl group. Nitrile (solvents) with lower alkyl groups like acetonitrile, butyric nitrile, propionitrile, and iso-butyric nitrile were found to be more favorable. Acetonitrile was the preferred solvent due to its low cost and ease of removal. Nitrile solvents could be used alone or in conjunction with other solvents, though it was recommended to use only a nitrile series of solvents. Examples of other solvents that could be combined with nitrile solvents include acetone and methyl acetate. In the experiment, crude menthol was first dissolved in a nitrile-series solvent, and the resulting solution was cooled to allow crystals to form. These crystals were collected via filtration to obtain optically pure menthol.

The amount of solvent required to dissolve menthol should be between 0.5 and 10 times the amount of menthol, with the preferred range being between 1 and 5 times the amount of menthol. The recommended dissolution temperature is between 20 and 40 °C, while the cooling T should be between (0 and 20 °C). Although the cooling rate is not strict It is preferable to cool slowly and gradually such as allowing the mixture to cool down to room temperature at a rate of approximately 1 to 5 °C/min. Proper cooling

methods should be employed to achieve a temperature that is the same as or less than room T. The rate of temperature decrease can be the same in this case.

3.2. Use of Acetonitrile as a Solvent

Acetonitrile is commonly used as a solvent in the pharmaceutical industry due to its high solvency power, low toxicity, low viscosity, and high boiling point. It is often used to produce active pharmaceutical ingredients (APIs) and other pharmaceutical products. Acetonitrile is also a preferred solvent for chromatography in pharmaceutical analysis due to its low UV absorbance and compatibility with many detectors. However, it is important to handle acetonitrile with caution, as it can be flammable and irritating to the skin and eyes. Proper safety precautions should always be taken when working with acetonitrile[29]. To crystallize menthol, 50 ml acetonitrile was mixed with 16.3 g of menthol (crude) with a chemical purity of 95% (L)-menthol and optical purity of 97.3% and warmed to 30°C for dissolution. After cooling the solution to 5°C, the resulting crystals were filtered and subsequently distilled to obtain purified (L)-menthol.

3.3. Use of Acetone as Solvent

Acetone, also known as dimethyl formaldehyde, dimethyl ketone, ketone propane, and pyro acetic ether, is a transparent, colorless volatile liquid that has a pleasant scent. Acetone is a highly combustible substance with a high vapor pressure, which makes it a fire hazard. It can dissolve in water at a temperature of 208°C and is soluble in benzene, most oils, and ethanol. Due to its ability to dissolve a variety of substances, acetone is widely used as a solvent in various industries. Additionally, it is used as a chemical intermediate in oil production, coatings, and varnish. The photography, leather, and, rubber industries also use acetone as a cement in their products [30]. The attempted crystallization of menthol using 20 ml acetone and 80 g crude menthol at room temperature did not result in the formation of crystals. The chemical purity of the crude menthol used was 95%, and the optical purity was 97.3%. The solution was then cooled to 0°C, but crystals were not obtained.

3.4. Use of Iso Propyl as a Solvent

Isopropyl alcohol, also known as rubbing alcohol or isopropanol, is a colorless, flammable liquid with a mild odor and low toxicity. It is commonly used as a solvent in the pharmaceutical and industrial fields due to its ability to dissolve a wide range of substances, including oils, resins, and gums. Additionally, it is used as a chemical intermediate in the production of other chemicals. In the medical field, isopropyl alcohol is commonly used as a disinfectant to clean and sanitize surfaces, instruments, and skin. It is also used as a rubbing alcohol for topical applications, such as cleaning wounds, or as a cooling agent for fevers. Isopropyl alcohol is often used in hand sanitizers and other personal care products.

It's worth noting that isopropyl alcohol is flammable and should be handled with care. It can also cause skin irritation if not used properly. However, it is generally considered to be a safe and effective solvent and disinfectant when used appropriately[31]. The given method describes the crystallization of menthol using isopropyl ether as the solvent. 10 ml isopropyl ether was mixed with 10 g of crude menthol (with a chemical purity of 95% and an optical purity of 97%) and dissolved. The solution was then cooled to -25°C to facilitate crystallization. The obtained crystals were analyzed, and their chemical and optical purities were found to be the same as the crude menthol, i.e., 95% and 97%, respectively, with no change.

3.5. Use of Ethanol as a Solvent

To crystallize menthol using ethanol as the solvent, a mixture of 100 ml of ethanol and 100 g of crude menthol was mixed. The chemical purity of (L)-menthol in the crude mixture was 95%, with an optical purity of 97%. The mixture was dissolved at room temperature and then cooled to -20°C, however, no crystals were observed [32]. Fig 2 shows the step-wise process of crystallization through the solvent.

Several factors affect the performance of crystallization. Some of the most important ones include:

I. Solubility

The solubility of the compound in the chosen solvent can greatly impact the efficiency of crystallization. If the compound is too soluble, it may not form crystals at all. If it is not soluble enough, the yield may be very low.

II. Cooling rate

The rate at which the solution is cooled can affect the size and quality of the crystals that are formed. If the solution is cooled too quickly, the crystals may be small and poorly formed.

III. Seed crystals

The addition of seed crystals can help to initiate the crystallization process and promote the growth of larger, well-formed crystals.

IV. Impurities

The presence of impurities in the solution can interfere with the crystallization process, leading to a lower yield or poorly formed crystals.

V. Agitation

The degree of agitation during the crystallization process can also affect the efficiency of the process. Too much agitation can break up the crystals and lead to a lower yield, while too little agitation can result in poorly formed crystals [33-35].

3.6. Limitations of Using Solvent Methods

Solvent methods have certain limitations, such as their high cost due to the use of synthetic materials. Additionally, the solvent method requires the drying of biomass, which can also lead to environmental issues [36].

3.7. Purification of menthol by using the Solvent Method

The process of obtaining menthol crystals through crystallization involves dissolving the crude menthol in a solvent from the nitrile series. The T of this solution is then gradually lowered to allow for the formation of crystals, which are then collected by filtration. The resulting menthol crystals are optically pure. In case further purification is

required, additional methods such as distillation or sublimation can be applied to the filtered crystals. It should be noted that the temperature at which the crude menthol is dissolved in the solvent is equal to or below the M.P of menthol, which is 42°C.

The fractional distillation method employs differences in compound volatility, which can be influenced by the physical and chemical properties of the components, as well as the pressure and temperature during the process. The energy as well as mass transfer between the mixture's aqueous and vapor phases also affects separation efficiency. As a result, the packed column's packaging type, width, and length play an important role in getting the required outcomes. For instance, to obtain menthol crystals, the T for dissolving the menthol (crude) should be set (between 25 and 40 °C), while the crystallization temperature can range from room T (around 10-20 °C) to slightly below (around 0-10 °C). Thus, its recommended to dissolve the menthol (crude) in a solvent (hot) at the aforementioned T [32].

4. Improved Methods

4.1. Stripping Crystallization

Stripping crystallization (SC), also known as distillation freezing (DF), has been used to separate the mixtures with boiling points that are very close to each other. This process involves the removal of the more volatile component by distillation while simultaneously cooling the mixture to a temperature below the melting point of the less volatile component, causing it to crystallize and separate from the liquid phase[37]. The SC method operates under triple-point conditions, which allows for simultaneous vaporization and crystallization of the liquid mixture due to the three-phase equilibrium. This method employs a combination of distillation and crystallization to produce pure crystals. By lowering the temperature and pressure during operation, the SC method results in the formation of pure crystals, as well as liquid and vapor phases of mixtures. The process is continued until the liquid phase is completely removed from the feed, leaving only pure crystals. Unlike traditional crystallization, the SC method does not require filtration or centrifugation to separate the solid crystals from the mother liquor, as pure crystals contain no mother liquor. Additionally, there is no need for crystal washing because no impurities are adhered to the crystal surfaces at the end of the process [38]. Stripping crystallization method can be used effectively for the crystallization and purification of menthol from rest of the components.

5. Crystallization of Borneol

The rectification process involves heating the mixture of volatile oil and water in the round-bottom flask to its boiling point. As the mixture vaporizes, it enters the distillation column, where it comes into contact with the packing material. The packing material offers an extensive surface area for the vapor to undergo condensation and recondensation, improving the separation of the volatile oil and water. The reflux condenser is placed at the top of the column, where it cools and condenses the volatile oil vapors that rise to the top of the column. The condensed volatile oil flows back down the column as reflux, while the remaining water and volatile oil mixture flow into the receiving flask.

The reflux ratio is controlled by adjusting the flow rate of the reflux, which affects the composition of the distillate. When the reflux ratio is increased, the more volatile components are concentrated in the reflux, whereas decreasing the reflux ratio results in a higher concentration of less volatile components in the distillate. The intelligent thermostat is used to maintain a constant temperature throughout the process, which helps to ensure consistent results. Quality control tests are performed on the resulting distillate to ensure that it meets the desired specifications. The purpose of this process was to separate different components of the oil residue based on their boiling points. By heating the mixture and allowing it to vaporize, the more volatile components will rise in the column and condense on the cooler surface of the reflux condenser before falling back into the column as reflux. This continuous refluxing helps to establish a steady-state vapor-liquid equilibrium in the column. By controlling the reflux ratio, different fractions can be recovered at different B.P. Increasing the reflux ratio can help to increase the purity of the desired fraction by trapping more of the volatile components and returning them to the column, while decreasing the reflux ratio can help to collect more of the desired fraction.

This process describes a method of fractionation for separating different components of an oil residue. Under normal atmospheric pressure, the oil residue (300 g) is heated in the round-bottomed flask of a fractionating column. When the oil residue approaches 170°C, it begins to reflux, and the system is kept at total reflux for 1 hour to achieve vapor-liquid equilibrium. The degree of heat in the fractionating column is monitored, and fractions at various boiling temperatures are obtained. The reflux ratio is then raised to 3 for 2 hours before it is decreased to 1. The purpose of changing the reflux ratio is to improve the separation efficiency of the process by adjusting the ratio of condensed vapors that return to the fractionating column to that which is removed as a product. This method allows for the separation and collection of different components of the oil residue based on their boiling points.

The experiment required obtaining oil residue fractions at 20-minute intervals until the T at the bottom of the tower raise to 210.0°C. Subsequently, the fractions gathered were measured and examined using GC (FID) and GC (MS) techniques. The distillation resulted in three fractions based on the temperature of distillation: fraction A, fraction B, and raffinate. Raffinate was stored and recrystallized to obtain natural borneol crystals. Parameters such as solvent, reflux ratio, and solvent amount were optimized for fractional distillation and recrystallization. Figure 3 shows the flow diagram for the fractionation and recrystallization of natural borneol from oil residue.

5.1. Recrystallization yield and recovery of natural borneol

Selecting a suitable solvent is crucial in the recrystallization of natural borneol. To determine the most suitable solvent, n-hexane, and ethyl acetate were evaluated. The experiment involved dissolving 1 gram of crude natural borneol in 3 mL of n-hexane and 2 ml of ethyl acetate separately to obtain natural borneol of high purity via recrystallization. The purity, yield, and recovery of the product were measured.

Table 1. The % age purity of menthol obtained by different crystallization techniques [28].

Crystallization technique	%age Purity of Menthol
Fractionation Method	92%
Chromatographic Method	95%
Solvent Method	95%

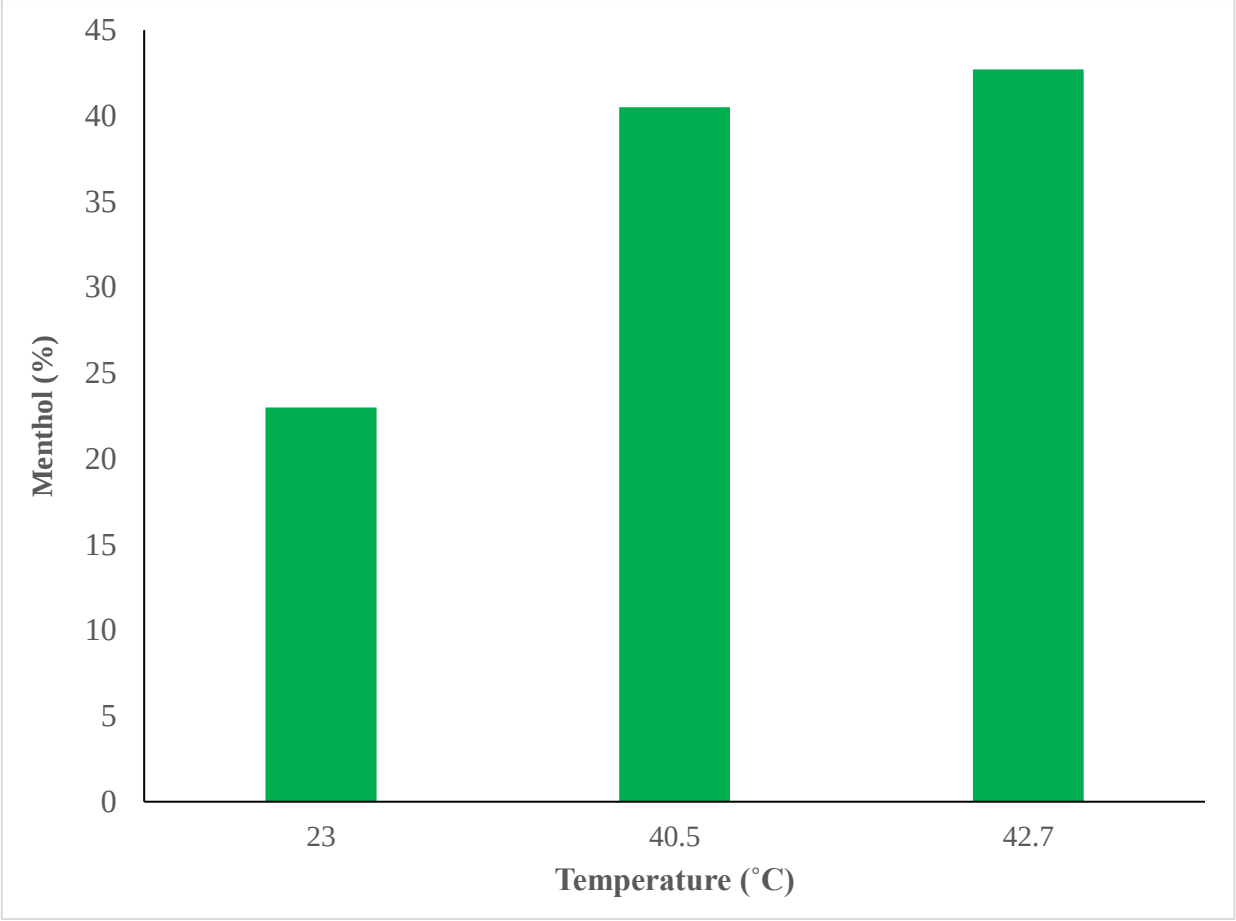

Fig 1. The yield of menthol obtained by Fractional distillation at different temperatures.

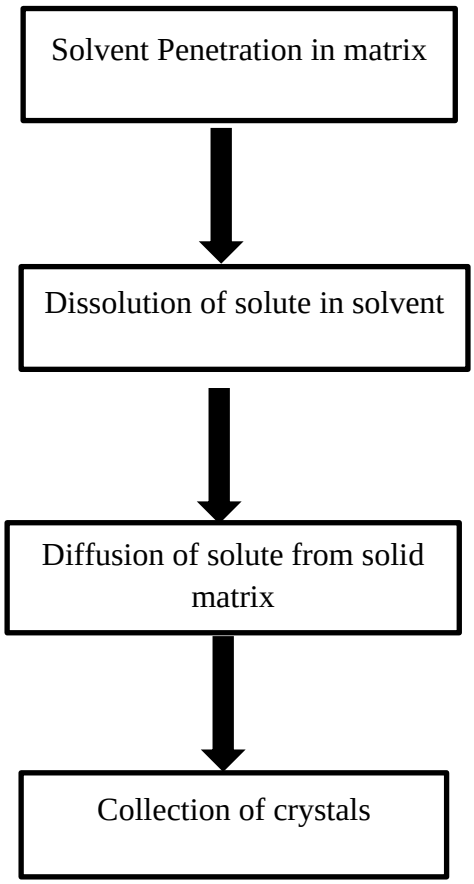

Fig. 2. Stepwise process of crystallization process using suitable solvent

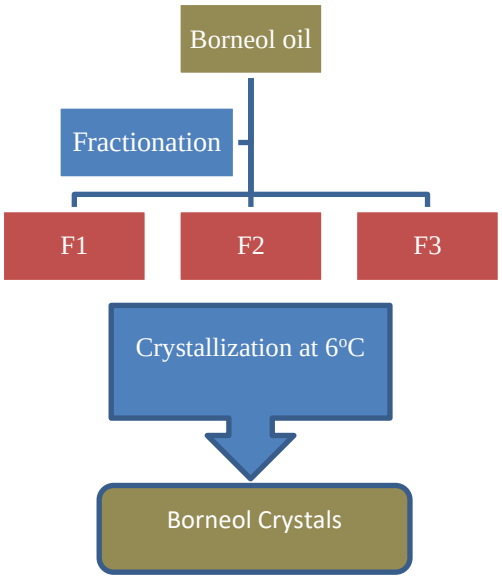

Fig. 3. Flow sheet of Borneol Oil Crystallization

The results showed that the amount of borneol crystallized from n-hexane was significantly greater than that obtained from ethyl acetate (with a p-value of less than 0.05). Therefore, n-hexane is considered to be a better solvent than ethyl acetate for recrystallization in the purification of natural borneol.

5.2. Solvent effect on natural borneol crystallizing

To identify the optimal n-hexane ratio for natural borneol crystallization, five different ratios (1:1.2, 1:1.5, 1:1.8, 1:2.0, and 1:2.2) were investigated and the results are s presented in Table 3. The findings revealed that as the n-hexane ratio increased (1:1.2 to 1:2.2), the natural borneol content increased, while the yield and recovery decreased. The yield and recovery significantly decreased (with a p-value of less than 0.05) as the n-hexane ratio (from 1:1.8 to 1:2.2). However, the natural borneol purity increased slightly by 0.5% (with a p-value of greater than 0.05) Based on the effectiveness of the treatment and the amount of solvent used, the ratio (n-hexane) 1:1.8 was determined to be optimal solvent for the natural borneol recrystallization [39]. The combination of fractional distillation and recrystallization was successful in producing natural borneol from the oil residue with a yield of 7.6% and a purity of 99%. Additionally, the resulting natural borneol product met the quality standard outlined in the Chinese Pharmacopoeia [40]. Choosing an appropriate solvent is a crucial aspect of the recrystallization process [41].

Natural borneol is a lipophilic compound with a small molecular size that can dissolve readily in chloroform, ethanol, and ethyl acetate. Typically, gasoline is the solvent of choice for purifying natural borneol with a recovery of 68%. In this study, gasoline and ethyl acetate were tested for their ability to refine natural borneol with recovery (70% and 57%). n-Hexane, which is a main component of gasoline and is often utilized as a relatively safe and inexpensive solvent in the refining as well as extraction processes, has not been previously studied for the purification of natural borneol. Therefore, in this study, n-hexane and ethyl acetate were used as solvents. The crude crystals were found to be strongly soluble in the boiling n-hexane but barely soluble at room T in n-hexane. Any contaminants present, however, be soluble in the solvent at room T. As a result, after cooling the solvent and forming natural borneol crystals, any remaining contaminants have been removed by filtration. According to the results of this study, n-hexane appears to be a better solvent for crystallizing natural borneol from *C. canephore* var [39].

6. Conclusions

The use of natural essential oil compounds, which are vital aroma molecules, is constantly growing worldwide. However, conventional methods of crystallization may not be sufficient to meet future demands. The combination of fractional distillation and recrystallization is a practical and effective approach for producing natural compounds with high purity. This approach is economical and optimizes resources, providing a relatively high yield and recovery. Nonetheless, transitioning to advanced crystallization methods poses challenges, such as cost and availability. Therefore, research into crystallization methods remains crucial, particularly to develop cheaper approaches that can make natural compounds commercially viable for industrial-scale production.

7. Future Perspectives

In the future, advanced methods of crystallization could be developed to produce highly pure I-menthol and other natural products. This could be achieved by gradually cooling the substance under controlled temperature conditions, which can be adjusted in a stepwise or continuous manner over some time. By following such a method, the crystallization and purification of I-menthol can be completed in less than two weeks, which is significantly faster than previous methods that took almost a month. To obtain better results, it is recommended to reduce the temperature gradually over a period of at least ``24, 36, or 48 hours from the starting temperature down to the crystallization temperature. The temperature can then be maintained at the final crystallization temperature or further reduced gradually until the desired degree of crystallization is achieved.

The total cooling time for the crystallization process is not fixed and depends on various factors, such as the cooling rate and compound concentration. Additionally, it is feasible to heat l-menthol while simultaneously applying reduced or increased pressure to assist in the removal of Dementholized oil. For instance, a pressurized gas system can direct gas through the crystallizer during a gradual temperature increase to aid in removing melted impurities. Alternatively, an aspirator can apply a vacuum to eliminate melted impurities from the crystallizer**.**

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