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REVIEW ARTICLE

A Comprehensive Review of Distillation in the Pharmaceutical Industry

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Abstract: Distillation processes play a pivotal role in the pharmaceutical industry for the purification of active pharmaceutical ingredients (APIs), intermediates, and solvent recovery. This summary explores the fundamental principles governing distillation, including mass transfer and phase equilibrium concepts. It delves into various distillation methods employed in pharmaceutical engineering, encompassing fractional distillation, azeotropic/extractive distillation, steam distillation, vacuum distillation, membrane distillation, and molecular distillation. Recent advancements in distillation technology, such as process intensification, miniaturization, and integration with other separation processes, are highlighted. The current state of distillation in pharmaceutical engineering is discussed, addressing regulatory considerations, solvent selection, and recovery challenges. Future prospects emphasize the need for energy-efficient and sustainable processes, advanced distillation technologies, process modeling and optimization, continuous manufacturing integration, and interdisciplinary collaboration. These efforts aim to drive innovation and address the evolving needs of the pharmaceutical industry, ensuring the continued importance of distillation in the purification and separation of pharmaceutical compounds.

Keywords: Distillation; Pharmaceutical Engineering; Purification; Solvent Recovery; Process Intensification.

1. Introduction

Distillation is a widely used separation technique in the pharmaceutical industry for the effective removal or exchange of solvents during the isolation of active pharmaceutical ingredients (APIs) or intermediates. Modeling distillation processes can aid in solvent selection and significantly reduce the number of laboratory experiments required to optimize distillation parameters [1]. While distillation is a technically mature process, it faces challenges such as high capital investment and excessive energy consumption. Therefore, investigating and developing new, highly efficient mass transfer units and energy-saving distillation methods is of substantial socio-economic importance [2]. The term "distillation" refers to a general class of techniques used to separate components from a mixture based on their differences in volatility. In general, a distillation system involves heating the liquid mixture to the vapor state, allowing the selective condensation and withdrawal of the desired component(s). When the vapor and liquid phases flow in a concurrent direction, the separation efficiency is limited to a single stage. If higher separation efficiency is required, the liquid and vapor are brought into counter-current contact, a process known as fractional distillation, which is one of the most widely used separation techniques in the chemical process industry [3]. This review will discuss the basic principles of distillation, different types of distillation processes, recent advancements in distillation technology, and future prospects for distillation in pharmaceutical engineering.[6].

2. Overview of distillation

2.1. Principle

The rate of separation in distillation processes is governed by mass transfer, while the extent of separation is controlled by thermodynamic equilibrium. Miniaturizing the separation process offers the advantage of producing wide gradients and high surface-to-volume ratios, which enhance mass transfer performance. However, establishing such an interface in microchannels is a significant challenge, as many conventional chemical separation processes, including distillation, absorption, and stripping, rely on mass transfer across a gas-liquid interface [3]

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2.1.1. Mass transfer and phase equilibrium

Distillation operates on the fundamental principle of separation: close contact between the initial mixture and a second phase facilitates effective mass transfer. The thermodynamic conditions are selected such that the component to be separated from the feed mixture can enter the second phase. This process results in the formation of two distinct phases, each with a unique composition.

The distillation process typically involves the following steps:

- Generation of a two-phase system
- Mass transfer across the interface
- Separation of the phases

In distillation, the second phase is generated by the partial vaporization of the liquid feed. This approach avoids the need for an auxiliary substance, often referred to as a mass separating agent, which would require expensive recovery. The only energy required for distillation is heat, which can be easily dissipated from the system, making it one of the key advantages of distillation [4].

Mass transfer effects are considered in the design of distillation columns. The column design equations incorporating mass transfer effects are similar to the traditional design equations and are equally straightforward to calculate numerically. Mass transfer effects do not alter the pinch-point curves or the pitchfork distillation boundaries. However, mass transfer can influence the composition trajectories, potentially causing them to cross the pinch-point curves. By incorporating mass transfer into the design equations, the actual number of stages (or column height) can be approximated. The curvature of the composition trajectory may significantly impact the location of the feed stage and the overall number of stages. For columns with a very sharp split, mass transfer effects have no impact on the minimum reflux [5].

In practice, distillation requires intimate contact between vapor and liquid under conditions that facilitate the desired components of the liquid entering the vapor phase. This process is governed by vapor-liquid equilibrium. Many distillation techniques aim to determine how closely the vapor-liquid equilibrium can be approached. Regardless, it is necessary to separate the liquid and vapor phases afterward. The vapor and liquid are brought into intimate contact through counter-current or cross-current flow, and mass exchange occurs due to the thermodynamic non-equilibrium between the two phases. The phases produced during distillation are formed by evaporation and condensation of the initial mixture. The separation process can only be controlled by the heat supply [4]

2.1.2. Difference in Boiling Point

Different liquids have different boiling points. In a mixture, the substance with the lower boiling point starts to boil first and eventually converts into vapors that can be separated once the mixture is heated. Distillation occurs when the solvents reach their boiling temperatures, which happens when the vapor pressure and air pressure are equal. A liquid with a higher relative volatility allows for improved component separation in the mixture. The liquid is heated, causing the vapors to boil and condense.

3. Types of Distillation Processes

Pharmaceutical engineering employs various distillation processes to separate and purify compounds based on their volatility differences. Some of the commonly used distillation techniques in the pharmaceutical industry are:

3.1. Flash distillation

Flash distillation is a widely used continuous distillation technique. The feed enters the still, where the liquid is vaporized. For the vapor to be in equilibrium with the liquid, it must remain in contact with the liquid at the point where the liquid-vapor mixture exits the still and is separated (Figure 1a). Unlike other processes that either remove all the vapor or condense it as products, flash distillation involves condensing a portion of the vapor and returning it as liquid to the still [6].

3.2. Azeotropic and Extractive Distillation

Azeotropic distillation is an efficient and well-researched method for separating azeotropic mixtures, which can be more energy-efficient than extractive distillation (ED) and pressure-swing distillation (PSD) in certain cases involving water azeotropes [7]. Batch extractive distillation (BED) is an effective technique for separating azeotropic and low relative volatility (low α) mixtures.

Azeotropes are mixtures where the boiling point of the mixture may be higher or lower than both of its components, resulting from intermolecular interactions between the species in the mixture. When the liquids in an azeotrope evaporate, the vapor has an identical composition to the mixture, making separation by conventional distillation techniques challenging [6]. To remove the azeotropic point and achieve separation, a heavy entrainer can be introduced to improve the relative volatility of the original components in counter-current contact [8]. Although azeotropic distillation can be improved in certain situations using various methods, such as adding a solvent that freely mixes with one component but not the other (extractive distillation), a chemical that reacts with one component but not the other (reactive distillation), or ionic salts that alter the volatilities of the mixtures. Collectively, these techniques are known as azeotropic distillation [6].

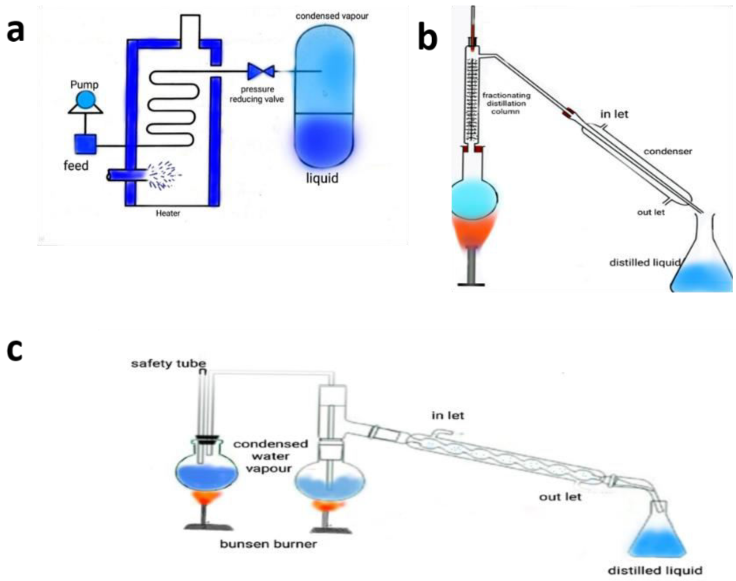

Figure 1. a. Flash distillation b. Fractional distillation c. Steam distillation

Industrial applications of azeotropic distillation include:

- Manufacture of nanometer-sized ZrO2/Al2O3 powders
- Combining fungal dehydration and lipid extraction
- Removing by-products from lipase-catalyzed solid-phase synthesis of sugar fatty acid esters
- Synthesizing nanoscale powders of yttrium-doped ceria electrolyte
- Wastewater treatment
- Dehydration of propanol
- Separation of propylene glycol methyl ether and water [9]

3.3. Steam Distillation

In steam distillation, the plant material is placed in a glass vessel with the lower and upper portions connected to a water flask and a condenser, respectively. The water vapor supplied from the flask passes through the plant material, carrying the essential oil before reaching the condenser, where it is condensed (Figure 1c). The oil is then separated from the water by decantation. A similar process, known as hydro-distillation, involves immersing the plant material in water-filled flasks and heating until it boils. The resulting water-oil vapor mixture is then condensed, and the oil is recovered by decantation [6]. Historically, there have been three main types of distillation: steam, water, and water-steam distillation. Water distillation is sometimes referred to as "indirect" steam distillation, where the plant material is immersed in water and heated to boiling. The volatile oils are carried by the steam produced when the water boils, and the oil and water are then separated by cooling and condensation [10].

3.4. Vacuum Distillation

The fundamental principle behind vacuum distillation is that it allows the separation of mixtures that are air-sensitive and susceptible to degradation at high boiling points. There are two common types of vacuum distillation:

- Simple Vacuum Distillation: Employed when higher vacuum levels are not required. Examples include the Perkin Triangle and rotating evaporators.
- High Vacuum Distillation: Used when the separation requires higher vacuum levels. Distillate purity is higher compared to other distillation methods, and this approach is used to separate and purify thermally unstable mixtures [6].

Vacuum distillation (VD) is a widely employed separation technique that takes advantage of the behavior of certain thermosensitive compounds under vacuum conditions. The lower pressure at which VD operates reduces the boiling temperatures of the compounds to be separated and increases their relative volatility. This preservation of the desirable features of thermally sensitive compounds is a significant advantage of VD [15].

3.4.1. Vacuum Membrane Distillation (VMD)

Polymers with low thermal conductivity, high hydrophobicity, and chemical inertness, such as polypropylene, polytetrafluoroethylene, and poly(vinylidene fluoride) (PVDF), are required for the vacuum membrane distillation (VMD) process [24], [25]. Additionally, PVDF copolymers like tetrafluoroethylene and hexafluoropropylene exhibit a higher degree of hydrophobicity and a larger free volume compared to PVDF [26], [27]. Recently, there has been significant interest in using poly(vinylidene fluoride-co-hexafluoropropylene) (PVDF-co-HFP) to fabricate VMD membranes [28], [29]. PVDF-co-HFP has a higher fluorine concentration than PVDF due to the hexafluoropropylene group, making it more hydrophobic [30]. Therefore, PVDF-co-HFP is a suitable choice for VMD applications that require highly hydrophobic membranes [11].

3.5. Fractional Distillation

Fractional distillation is based on differences in the volatility of compounds, which are influenced by their physical and chemical properties, as well as the pressure and temperature during the distillation process. The efficiency of the separation is affected by the mass and energy transfer between the liquid and vapor phases of the mixture. Consequently, the results are directly influenced by the height, diameter, and packing style of the packed column [12].

Processes involved in fractional distillation include extractive distillation, vacuum distillation, stabilization, topping, rectification, exhausting, and stripping. In general, the separation process of distillation is used to separate a liquid mixture of two (binary) or more (multi-component) substances into their component parts. The components that need to be separated are typically miscible liquids with different boiling points and volatilities (Figure 1b). The separation is achieved through this thermal unit operation, which utilizes differences in vapor pressure. The process involves heating the vapor or liquid mixture, causing the more volatile components to evaporate, condense, and be allowed to drip or separate, also known as distillation or destillare [14].

The main difference between fractional and simple distillation is that the former involves repeating a similar process in successive cycles. Each cycle produces a mixture enriched in the more volatile component compared to the previous one. Fractional distillation becomes crucial when the liquids in the initial mixture have boiling points so close that simple distillation is insufficient to purify either component. In fractional distillation, the vapor emerging from the distillation pot is repeatedly condensed and re-evaporated in a fractionating column. After a few of these re-condensation/re-evaporation cycles, there should be a moderate amount of higher-boiling components in the lower-boiling fraction, resulting in a more precise separation of the liquids

3.6. Molecular Distillation

Molecular distillation (MD) is a specialized technique used to purify and separate thermally unstable and high-boiling compounds, making it particularly valuable in the pharmaceutical industry. This process operates under high vacuum conditions (10^-3 to 10^-6 mbar) and at relatively low temperatures, minimizing the risk of thermal degradation [16].

The fundamental principle behind MD is the difference in mean free path lengths of the molecules at various pressure and temperature conditions. At high vacuum, the mean free path of the molecules becomes significantly larger than the dimensions of the distillation equipment, allowing for a more efficient separation based on the molecular properties rather than the bulk properties of the mixture [17].

3.6.1. Mechanism of Molecular Distillation

The mechanism of MD involves the following steps:

- Evaporation: The feed mixture is heated, causing the more volatile components to evaporate from the surface into the vacuum chamber.
- Molecular Flow: The evaporated molecules travel in a straight line without colliding with each other due to the high vacuum conditions.

- Condensation: The vapor molecules condense on a cooled surface, typically a condenser, where they are collected as the distillate.
- Residue Formation: The less volatile components remain as a residue on the heated surface or evaporator [18].

3.6.2. Applications in Pharmaceutical Industry

MD finds numerous applications in the pharmaceutical industry due to its ability to handle thermally sensitive and high-boiling compounds. Some examples include:

- Purification of vitamins, steroids, and hormones
- Separation of isomers and enantiomers
- Removal of high-boiling impurities from drugs and APIs
- Purification of fatty acids and natural products
- Separation of polymer additives and plasticizers [19]

3.6.3. Recent Advancements in Molecular Distillation

Researchers have focused on improving the efficiency and scalability of MD processes. Some notable advancements include:

- Centrifugal Molecular Distillation: This technique employs a rotating evaporator and condenser to enhance the separation efficiency and throughput [20].
- Wiped-Film Molecular Distillation: A thin film of the feed mixture is continuously spread over a heated surface, improving heat and mass transfer rates [21].
- Short-Path Molecular Distillation: This approach uses a reduced path length between the evaporator and condenser, minimizing intermolecular collisions and improving separation [22].
- Membrane-Assisted Molecular Distillation: Combining MD with membrane technology to enhance selectivity and energy efficiency [23]

4. Current State of Distillation in Pharmaceutical Engineering

Distillation processes play a vital role in various stages of pharmaceutical manufacturing, including the purification of active pharmaceutical ingredients (APIs), intermediates, and the removal or exchange of solvents. The pharmaceutical industry has continuously sought to improve distillation techniques to enhance product quality, process efficiency, and environmental sustainability.

4.1. Integration with Other Separation Processes:

Distillation is often integrated with other separation processes to achieve more efficient and cost-effective purification. For instance, chromatographic techniques, such as preparative high-performance liquid chromatography (HPLC) and simulated moving bed (SMB) chromatography, are commonly used in conjunction with distillation for the purification of APIs and their intermediates [31].

4.1.1. Process Intensification and Miniaturization

There is a growing interest in the intensification and miniaturization of distillation processes to improve energy efficiency, reduce footprint, and enhance safety. Techniques such as reactive distillation, dividing-wall columns, and microstructured distillation units have been explored in pharmaceutical applications [32].

4.1.2. Solvent Selection and Recovery

The selection of appropriate solvents and their recovery is crucial in pharmaceutical manufacturing. Distillation plays a key role in solvent recovery and recycling, reducing waste generation and environmental impact. Advanced distillation techniques, such as azeotropic and extractive distillation, are employed for the recovery of solvents from azeotropic mixtures [1, 3].

4.1.3. Regulatory Considerations

The pharmaceutical industry is highly regulated, and distillation processes must comply with stringent quality and safety standards. Good Manufacturing Practices (GMP) and regulatory guidelines from agencies like the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) govern the design, operation, and validation of distillation equipment and processes [34].

5. Future Prospects and Challenges

The future of distillation in pharmaceutical engineering is driven by the need for more efficient, sustainable, and cost-effective processes. Several areas are expected to receive significant attention in the coming years:

5.1. Energy Efficiency and Sustainability

Improving the energy efficiency of distillation processes is a key focus area. Strategies such as heat integration, process intensification, and the use of alternative energy sources (e.g., solar, geothermal) are being explored to reduce energy consumption and environmental impact [3, 5].

5.2. Advanced Distillation Technologies

Researchers are continuously developing and refining advanced distillation technologies, such as membrane distillation, reactive distillation, and hybrid distillation-membrane systems. These technologies offer improved separation efficiency, selectivity, and the ability to handle complex mixtures [2, 7, 9].

5.3. Process Modeling and Optimization

The application of advanced modeling and simulation techniques, combined with process optimization algorithms, can significantly improve the design and operation of distillation processes. This includes the development of predictive models for thermodynamic properties, mass transfer, and phase equilibria [2, 5].

5.4. Continuous Manufacturing

The pharmaceutical industry is moving towards continuous manufacturing processes, which offer numerous advantages over traditional batch processes. Distillation processes must be adapted and integrated into continuous manufacturing frameworks, requiring innovative equipment designs and control strategies [2, 8].

5.5. Interdisciplinary Collaboration

Advancements in distillation for pharmaceutical engineering will require interdisciplinary collaboration among researchers from various fields, including chemical engineering, pharmaceutical sciences, materials science, and computational sciences. Knowledge exchange and synergistic efforts will drive innovation and address complex challenges [9, 11].

6. Conclusion

Distillation is an indispensable separation technique widely employed in the pharmaceutical industry for the purification of active pharmaceutical ingredients, intermediates, and solvent recovery. This article provides a comprehensive understanding of the fundamental principles governing distillation processes, including mass transfer and phase equilibrium. It explores various distillation methods utilized in pharmaceutical engineering, such as fractional distillation, azeotropic/extractive distillation, steam distillation, vacuum distillation, membrane distillation, and molecular distillation. Recent advancements in distillation technology, including process intensification, miniaturization, and integration with other separation processes, are highlighted. The current state of distillation in pharmaceutical engineering, addressing regulatory considerations, solvent selection, and recovery challenges, is discussed. Future prospects emphasize the need for energy-efficient and sustainable processes, advanced distillation technologies, process modeling and optimization, continuous manufacturing integration, and interdisciplinary collaboration to drive innovation and address evolving industry needs.

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