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Antisolvent Crystallization (ASC) in Aqueous System: Fundamentals, Sustainability Aspects, and Applications

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ABSTRACT

The present perspective focuses on fundamental and applied attributes of antisolvent crystallization (ASC) in aqueous systems and establishes its potential for various industrial applications. In the ASC method, supersaturation is attained by adding a secondary solvent (antisolvent) to a solution leading to the crystallization of the solute. ASC offers the advantages of increasing yields, and conserving energy over the conventional evaporative or cooling crystallization, and thus appears to be a growing industrially important and sustainable process. The insights on the role of phase equilibrium thermodynamics and kinetics in controlling the crystallization process and crystal properties during ASC are discussed. The choice of solvents is a critical factor in ASC, and the solvent type, properties, and selection are considered briefly. The evaluation of the sustainability aspect of ASC by assessing the environmental benignity of solvents, the impact of their life cycles on the ecology, and associated economic costs are presented. A comprehensive list of solvents used for ASC and their usage pattern is also included. Successively reintegrating ASC into process design and developing different process configurations (stand-alone and hybrid) are reviewed. Finally, the paper highlights the opportunity for more widespread application of ASC in the fields of salt extraction, water treatment, hydrometallurgy, bioprocessing, and the pharmaceutical industry.

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1. Introduction

Crystallization has been practiced since the dawn of civilization, for example, making common salt (NaCl) from brines. Hence, it can be classified as one of the oldest separation processes in the history of separation science and technology [1]. Crystallization is a unique process of industrial importance because it provides high-purity separation and technology widely used in the petrochemical, chemical, food, pharmaceutical, fertilizer, detergent, and explosive industries. In the past few decades, the development of the crystallization process has accelerated due to the increasing application of crystals with unique properties [2].

Different crystallization methods have been developed over the years. The solubility of the solute in a solution significantly affects the choice of the crystallization method to achieve supersaturation. Pure crystals are recovered from impure solutions by inducing supersaturation through cooling, solvent evaporation, or salting out with an antisolvent [3]. Crystal properties such as purity, morphology, mean size, and size distribution can be influenced by how crystallization occurs. These crystal properties, in turn, can affect the material's performance and its applications [4].

Considering the industrial importance of the crystallization process, different methods of crystallization have been developed. These methods include evaporative crystallization, cooling crystallization, antisolvent crystallization, precipitation/reactive crystallization, adductive crystallization, and sublimation crystallization. Different crystallization techniques are briefly discussed to understand their advantages and limitations.

1.1. Evaporative Crystallization

In evaporative crystallization, the solvent is evaporated to increase the solute concentration above its solubility to form crystals. Evaporative crystallization is a well-suited method for a compound that does not show differential solubility with temperature. For example, it has been a standard method for common salt production from sea brine using solar evaporation or vacuum evaporation [5]. Poor control over supersaturation during evaporation (or heating) may limit the crystal quality in terms of purity and crystal size [6].

1.2. Cooling Crystallization

In cooling crystallization, the driving force is the difference in solubility of the solute at different temperatures. This method of crystallization is thus suitable for compounds whose solubility changes appreciably with temperature. As the saturated solutions are cooled, the mixture becomes supersaturated, and crystallization begins [1]. The main advantage of cooling crystallization is the high uniformity of the crystal size. A common method of crystallization cooling is flash cooling, in which part of the liquid evaporates, dissipating the latent heat and enabling the cooling.

1.3. Reactive Crystallization

In this crystallization method, a chemical reaction produces a specific crystallizable species in solution to provide the driving force for forming a crystalline product. The multiple species present as the reactants and products of the reaction impact the species solubility, pH and temperature of the solution, reaction kinetics, and crystallization [4]. A search for suitable reactants and possible contamination by the reaction side products can limit the application of reactive crystallization in some instances.

1.4. Adductive Crystallization

Adductive crystallization is a process where a crystalline compound is formed through the interaction of two or more substances, often resulting in a complex with distinct properties from the individual components [7]. In this crystallization, an adduct is formed when two or more molecules interact to create a new entity. This adduct typically has a different structure and properties compared to the original compounds. For example, an adduct might be a complex between a solute and a solvent or between two different solutes.

The resulting crystals are characterized by their unique structure, which can be different from that of the individual components. Techniques like X-ray diffraction, scanning electron microscopy, and infrared spectroscopy are used to analyze the crystal structure and confirm the presence of the adduct. This technique is useful in various fields, including pharmaceuticals, where it can be used to create drug formulations with improved properties, or in materials science, where it can help develop new materials with specific characteristics.

1.5. Sublimation Crystallization

Sublimation is the phase transition where a substance changes from a solid to a gas without going through a liquid phase. Conversely, sublimation crystallization is a process where a substance transitions directly from a gaseous state to a solid state without passing through a liquid state. This technique is often used to purify compounds or to grow high-quality crystals and is a highly effective method for purifying substances because impurities generally do not sublime along with the pure substance. Sublimation of inorganic salts involves high temperatures, and the substance may dissociate or degrade in the process. Reports on organic salts are rare, and recent studies have attempted the crystallization of organic salts and co-crystals by sublimation [8, 9].

1.6. Antisolvent Crystallization

In this method, supersaturation is attained by adding a miscible/immiscible solvent to a solution leading to the crystallization of the solute. The solvents added are referred to as secondary solvents or antisolvents [10]. By applying suitable control, antisolvent crystallization (ASC) can provide constraint supersaturation leading to superior crystal quality in terms of purity and size [11, 12]. Concerning aqueous solutions, the solvent employed acts antisolvent to water, and therefore the process is called antisolvent crystallization [13]. In a reverse occurrence, the addition of salts in an oil/organic-rich aqueous solution causes a decrease in the aqueous solubility of organic compounds. This phenomenon is called the “salting-out effect” [14]. Therefore, adding organic solvents in salt solutions (aqueous) to crystallize/precipitate salts is known as “solventing-out”.

Although thermal (evaporative and cooling) crystallization can offer many advantages, the evaporation and cooling process entails significant energy consumption (heating and refrigeration, respectively) and limits the profitability of the process. In addition, heat-sensitive materials, which decompose at high temperatures, cannot be subjected to evaporative crystallization. In this context, antisolvent crystallization (ASC), subjected to optimum solvent recovery, can be a potential alternative to reduce energy costs associated with evaporative and cooling crystallization [15].

The present review aims to leverage the potential of antisolvent crystallization (ASC) in aqueous systems for unconventional applications like water treatment, hydrometallurgy, inorganic chemicals, salt extraction, bioprocessing, etc. Earlier review studies have been focused on the progress in ASC for the pharmaceutical industry and crystal property optimization [16]. The perspective of integrating both fundamentals and applied aspects of ASC towards a potential separation and purification strategy are not reported adequately in earlier work. In this work, fundamental aspects including phase equilibrium and thermodynamic behavior of solute-solvent-antisolvent systems, kinetics, antisolvent selection, sustainability, etc. in the context of ASC are critically discussed. Towards the commercial implementation of ASC for alternative applications, various configurations (stand-alone and hybrid) were examined.

2. Antisolvent Crystallization: Fundamentals

Antisolvent crystallization (ASC) or solvent-assisted crystallization is described by names like solvent displacement crystallization, drowning out crystallization, extractive crystallization, etc. ASC offers an advantage where the substance to be crystallized is highly soluble, has solubility that does not change with temperature or heat-sensitive materials [17]. Also, these operations can generally be carried out at an ambient temperature and can produce crystals of high purity and yield [10]. Researchers have exploited the use of the ASC effect, which modifies the solute distribution in a mixed system, for various applications reported in Table **1**.

Table 1: Selected references on antisolvent crystallization (ASC) related applications.

Reference	Focus of the Study	Potential Application
Moldoveanu and Demopoulos [12]	• Organic solvent-assisted crystallization of sulphate and chloride metal salt (K^+, Na^+, Mg^{2+}, Fe^{2+}, Cu^{2+}, Ni^{2+}, Co^{2+}, Zn^{2+}, Fe^{3+} and Al^{3+}) systems in acidic media • Establishing selection criteria for organic solvent selection	• Inorganic processing • Hydrometallurgy
Mayer [13]	• Extractive crystallization of salt with antisolvents having crystal growth/scale inhibiting properties	• Crystallization of alkali or alkaline earth salts
McNally *et al*. [18]	• Ternary water–NaCl–solvent phase boundaries • $CaSO_4$ recovery from aqueous-$CaSO_4$ solution using dimethyl ether (DME)	• Water treatment • Water softening
Karunanithi *et al*. [3, 23]	• Computational framework for design and selection of solvent and/or antisolvent for crystallization of ibuprofen	• Pharmaceuticals • High molecular weight chemical recovery
McGinty *et al*. [24]	• Crystal shape modification of Lovastin (API) using continuous antisolvent crystallization	• Crystal morphology alteration for pharmaceutical application
Feng *et al*. [25]	• Recovery of petroleum sulfonate from high-salt wastewater using alcohols as extractants	• Enhanced oil recovery generated wastewater treatment
Shabani *et al*. [26]	• As, Sb and Fe removal from the copper electrolyte by solvent displacement crystallization employing isopropyl alcohol	• Refining of industrial electrolytes
Lozano [27]	• Potassium-magnesium sulphate double salt production from sea bittern using methanol as an antisolvent	• Added-value mixed salts recovery from sea bittern (a by-product of the solar salt industry)
Kokes *et al*. [28]	• Precipitation of copper sulfate pentahydrate from malachite ore using methanol and ethanol	• Hydrometallurgical metal extraction from ores
Oosterhof [29]	• Phase equilibrium studies of sodium carbonate aqueous solutions in the presence of solvent (ethylene glycol and diethylene glycol) at atmospheric conditions	• Production of anhydrous salts from hydrated salts at room temperature
McGarvey and Hoffmann [30]	• Solubility of the mineral salts NaCl, KCl, CsCl, KBr, K_2SO_4, and $CuSO_4$ in mixed binary solvent (PEG 200 and water)	• Green solvent for chemical synthesis involving mineral salts as reagents

While this technique has several advantages, the challenge of secondary solvent (antisolvent) removal and recovery may lead to increased costs [18]. A recent study comparing evaporative, cooling and antisolvent crystallization routes for selective separation reveals the higher associated economics for ASC over cooling crystallization [19]. Another issue arises due to the high supersaturation attained during antisolvent addition, that can cause deleterious effects on crystal products and supersaturation control in batch processing. ASC is reported to produce fine and variously shaped crystals, which tend to agglomerate and affect product quality [20]. Understanding the molecular mechanism, thermodynamics, and kinetics aspects of ASC can help overcome the associated limitations and establish its potential for future applications. A detailed examination is carried out on the mechanism, phase equilibrium thermodynamics, and kinetics of ASC.

2.1. Mechanism

When a salt is dissolved in a solvent (for example, water), the salt ions form solvation shells through dipole-dipole (ionic) interactions with water, resulting in salt dissolution in water to form a solution. Adding a secondary /antisolvent (organic solvent) to the solution lowers the dielectric constant since solvents have a much lower dielectric constant than water. This results in breaking water-water hydrogen bonds and the formation of water-organic solvent hydrogen bonds. With the reduction in 'free-water' molecules, a force of attraction (Columbic) between the cations and anions of the salt allows the cations to penetrate the water solvation shells, neutralize the anions, and aggregate and precipitate as salt crystals out of the solution [21, 22].

Depending on the solvent (primarily water) and antisolvent (mostly organic solvents) interactions, the crystallization can be carried out in a single- or a two-phase system. The presence of multiple polar functionalities of organic solvents (e.g., alcohol, amides, amines, etc.) generally increases their water solubilities [31]. In the single-phase system, the antisolvent with a high affinity for water molecules starts binding with water by forming hydrogen bonds. This reduces the quantum of free-water molecules for ion hydration leading to solubility reduction and salt crystallization [32]. In the two-phase system, the organic solvent-rich phase and aqueous phase form simultaneously in addition to a solid salt phase. The driving force for crystallization is created by the water extraction from the aqueous phase into the organic solvent-rich phase and by the dissolution of organic solvent in the aqueous phase [13]. Further, the mechanism and rate by which crystallization occurs can depend on thermodynamics, kinetics, and molecular recognition [33].

2.2. Thermodynamics and Phase Equilibrium

During the antisolvent crystallization (ASC) process, the secondary solvent is continuously added to the solution, and the solubility of the solute is influenced by the composition of the solvent mixture [34]. ASC processes, therefore, involve solute+solvent+secondary solvent systems having multi-component (>3) interactions in two or more phases. Therefore, solution-thermodynamic and phase equilibrium analyses of these systems are crucial. The antisolvent crystallization of solute from a solution (primary solvent) by the addition of the secondary-solvent can be formulated as follows:

$$(\text{Solute})_{\text{Solution}} + \text{Secondary-solvent} \rightarrow \text{Solute}\downarrow + (\text{Secondary solvent})_{\text{Solution}}$$

Adding the secondary solvent to the primary solution modifies the entire system's solid-liquid/liquid-liquid phase behavior [35]. Solubility and phase diagrams of ternary systems of solvent, solute, and antisolvent are extensively studied in the context of ASC with a wide range of applications [36-44]. In experimental studies, the solubilities of salts were affected by the nature of the solvent (reflected by the polarity, bulk dielectric constant, mobility, and solvation) and the properties of the solute (mainly the size, the charge, and the ionic association) [36, 37, 44]. The presence of a mixed organic solvent affects water's thermodynamic activity and influences the solute's solubility in aqueous solutions [45]. The usefulness of experimentally determined solubility data to measure the salting-out effect using the Setschenow equation was also reported [46]. The Setschenow equation relates the aqueous activity coefficient, aqueous solubility, and partitioning coefficient with the salt concentration [14]:

$$\log\left(\frac{\gamma_{\mathrm{w}}^{\mathrm{salt}}}{\gamma_{\mathrm{w}}^{\mathrm{DI}}}\right) = \log\left(\frac{S_{\mathrm{w}}^{\mathrm{DI}}}{S_{\mathrm{w}}^{\mathrm{salt}}}\right) = \log\left(\frac{K_{\mathrm{l}}^{\mathrm{salt}}}{K_{\mathrm{w}}^{\mathrm{DI}}}\right) = K_{\mathrm{s}}^{\mathrm{i,k}}[C_{\mathrm{salt}}] \quad (1)$$

where $\gamma_{\mathrm{w}}^{\mathrm{DI}}$ and $\gamma_{\mathrm{w}}^{\mathrm{salt}}$ are the aqueous activity coefficient in deionized water and saltwater, respectively; $S_{\mathrm{w}}^{\mathrm{DI}}$ and $S_{\mathrm{w}}^{\mathrm{salt}}$ are the solubility of organic compounds in deionized water and saltwater, respectively; $K_{\mathrm{w}}^{\mathrm{DI}}$ and $K_{\mathrm{l}}^{\mathrm{salt}}$ are the partitioning coefficient in deionized water and saltwater, respectively; $K_{\mathrm{s}}^{\mathrm{i,k}}$ is Setschenow constant and $[C_{\mathrm{salt}}]$ is the salt concentration.

Setschenow equation presents a log-linear increase in aqueous activity coefficient, reduction in aqueous solubility, or increase in partitioning coefficient with increasing salt concentration. Salt added to an aqueous solution causes a decrease in the solubility of organic molecules, thereby accelerating the separation of organic molecules from the aqueous solution. A salt with a larger positive Setschenow constant provides better separation and prevents mixing between the electrolyte solutions.

As per the thermodynamics definition, crystallization occurs when the chemical potential of a species (μ) is higher than the chemical potential at equilibrium (μ^{sat}) and expressed as the difference in chemical potential (dimensionless) as [47]:

$$\frac{\mu - \mu^{sat}}{RT} = ln\left(\frac{\gamma x}{\gamma^{sat} x^{sat}}\right) \quad (2)$$

where x and x^{sat} are the solute mole fraction in the supersaturated solution and the saturated solution

respectively; γ and γ^{sat} are the activity coefficients of the solute in a supersaturated solution and the saturated solution, respectively. Depending upon the nature of the solute, i.e., charged/non-charged, electrolyte/non-electrolyte, suitable activity coefficient models are used to represent the solubility and supersaturation behavior. Various thermodynamic models, including UNIQUAC, NRTL/electrolyte-NRTL [39], Pitzer model with Bond equation [40, 43], modified Pitzer model [42], ePC-SAFT [48], and semi-empirical thermodynamic models [38], e.g., LIQUAC [41], were proposed for predicting the phase behavior in salt-water-solvent systems. Further adjustments, such as the incorporation of the Debye-Hückel term for electrolytic interactions, have also been considered. Compared to non-electrolyte models such as UNIQUAC or NRTL, electrolyte models (e.g., extended electrolyte NRTL) have been found more appropriate as they account for the interactions arising from charges [48].

By studying twelve miscible organic solvents (MOS) systems, McNally *et al*. [18] have identified the trends in aqueous phase boundaries of ternary water–NaCl–MOS. Two models of ideal solvation scenarios were presented and compared with the experimental data. The first scenario considers minimal energetic interactions between MOS–NaCl, and MOS–water by modelling MOS as a diluent. Consequently, the solubility of NaCl in the ternary mixture decreases proportionally with the addition of MOS, as shown in Fig. (**1a**). Thus, the solubility of NaCl is proportional to the moles of water regardless of the presence of MOS, with no competition between the salt and MOS molecules.

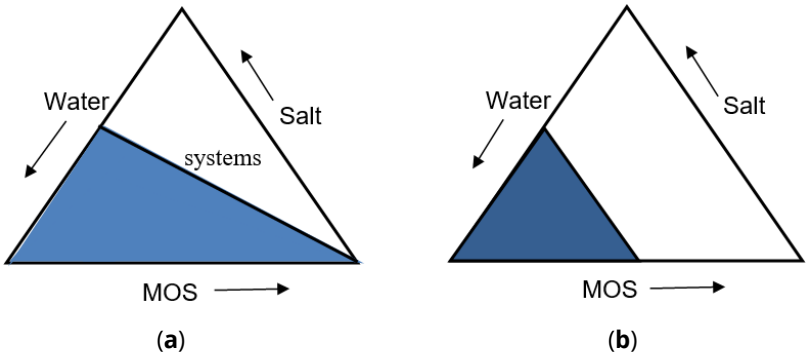


Figure 1: (**a**) Scenario 1 – minimal MOS interaction (**b**) Scenario 2 – solute displacement mechanism (Adopted from [18]).

The second scenario reflects the identical energetic interactions between MOS–water and NaCl – water while assuming no interactions between MOS and NaCl. In this framework, solute and MOS will compete for the common solvation agent of water. In a limiting scenario, adding MOS to a saturated aqueous salt solution will induce salt crystallization by an equivalent molar quantity, as depicted in Fig. (**1b**). Interestingly, most of the MOS studied by McNally *et al*. were found to follow scenario 2, i.e., solute displacement model, at low MOS concentration and high NaCl concentration. On the other hand, as MOS concentrations increase, the ability of the solute displacement mechanism to describe the system diminishes due to competing effects from self-solvation.

From the two scenarios discussed above, it can be comprehended that for the systems following the first scenario, supersaturation by organic solvent can be estimated a priori. Under the second scenario, the supersaturation will depend on the extent of interactions between the MOS – water and salt – water.

More recently in the context of inorganic salt recovery from aqueous solution using ASC, Sahu *et al*. correlated the solubility behavior with phase balance to assess the potential performance of the antisolvent by estimating the attainable yield and attainable suspension density at equilibrium. The feed concentration and solubility data as a function of an antisolvent composition were used to calculate the attainable suspension density and yield for different antisolvent fractions [49]. Solubility relationships should be understood for effective design and optimization of ASC process.

2.3. Kinetics of Antisolvent Crystallization

At a macroscopic scale, the ASC progresses by contacting the solution and antisolvent followed by the invasion of the solvent and the increased supersaturation of the microenvironment around the solute. However, at a microscopic scale, the solute, solvent, and antisolvent interacted to yield combined effects on the crystal

characteristics [50]. The kinetics of crystal formation in ASC are often estimated by experimental determination and compared with nucleation and growth models. The significant kinetics indicators are the crystallization rates, particle size distribution, crystal morphology, and degree of agglomeration, which influence the overall crystallization process and subsequent applications [51].

2.3.1. Nucleation and Crystal Growth

For crystallization to occur, nucleation is required to form the crystal seeds and subsequent crystal growth [52]. In the antisolvent crystallization process, nucleation is possible when the supersaturation condition is achieved. Nucleation involves developing a solid crystalline phase by combining constituent units to create entities until a stable nucleus is formed from a liquid solution. Conventionally nucleation is described by homogeneous and heterogeneous mechanisms (both referred to as primary nucleation as existing crystals do not contribute to the nucleation mechanism) [53]. In primary nucleation, once the solution becomes supersaturated, a period elapses until nuclei formation is observed (recognized by turbidity formation). This period is known as the induction period (I_p), and it depends on factors including temperature, degree of initial supersaturation, agitation, impurities, etc. [54]. After the induction period, the particle size may increase by molecular growth and crystal agglomeration [51].

A solute tends to remain in solution until a sufficient level of supersaturation is created to induce spontaneous nucleation. To optimize the crystallization process, it is desirable to overcome this metastable limit (or metastability), as indicated in Fig. (**2**). The metastable zone width (MSZW) is essential in designing and optimizing any crystallization process [55]. In ASC, MSZW measures the maximum supersaturation value necessary for the spontaneous occurrence of three-dimensional nucleation generated by the antisolvent [56]. During ASC, the antisolvent strongly influences the nucleation kinetics, resulting in broader metastability zones and changes in the crystals' particle size distribution and morphologies [57]. The increased MSZW on antisolvent addition makes ASC an efficient separation method.

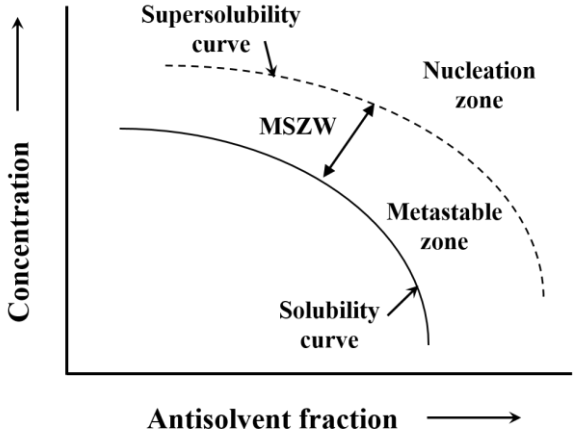


Figure 2: Solubility and metastable zone for ASC.

It is reported that the primary nucleation may be the dominant mechanism for crystal formation in antisolvent crystallization due to high supersaturation. Consequently, ASC often results in tiny crystal formation and crystal aggregation, which make the subsequent separation cumbersome [20]. Controlling the nucleation kinetics can reduce or eliminate the agglomeration [58].

Nowee and co-workers have developed, simulated, and experimentally validated the antisolvent crystallization model. A growth kinetic model as a function of supersaturation, antisolvent mass fraction proposed by them is presented below [59]:

$$G = k_g S^g \tag{3}$$

where S is the relative supersaturation estimated as the ratio of supersaturation (ΔC) and saturated solution

concentration (C^*):

$$S = \frac{\Delta C}{C^*} \tag{4}$$

The parameters k_g and g in the growth rate power-law model Eq (3) are defined as a function of antisolvent mass fraction in the solute-free mixture (z):

$$k_g = k_0 + k_1 z + k_2 z^2 \tag{5}$$

$$g = g_0 + g_1 z \tag{6}$$

Parameters contained in the kinetic sub-model Eqs (4) and (5)-(7) were estimated by experimental data fitting. The proposed models can be used for pharmaceutical and chemical crystallization operations [59].

In this regard, understanding the effect of various operating parameters on crystallization kinetics (nucleation and crystal growth) is critical and discussed in section 2.3.2.

2.3.2. Factors Affecting Crystal Growth and Morphology

Antisolvent crystallization from a solution often displays a small mean particle size; however, controlled operating conditions may retrieve crystal products with good filterability [51]. Various operating parameters like supersaturation, agitation, solvent type, and content were reported to influence the nucleation mechanism, crystal growth, MSZW, and morphology in solvent-assisted crystallization [54, 60-62]. Seeding and solvent dosage rate are other important parameters reported to remarkably improve the rate of crystallization.

Seeding: The seeding of a solution helps to stabilize the crystallization process. For strongly soluble inorganic salts, the mass and size of seeds are adjusted, so that seed growth is allowed when the saturation level is maintained well below that extensive nucleation is possible [63]. In pharmaceutical applications, the overall crystallization process is controlled by achieving reasonable control over the properties of seed crystals [24].

Supersaturation: The solution to antisolvent ratio affects the supersaturation and the equilibrium solubility. The well-known Gibbs-Thomson equation relates the supersaturation and solubility with the particle size [64]:

$$\ln\left(\frac{c(r)}{c^*}\right) = \ln S = \frac{2\gamma V}{kTr} \tag{7}$$

where $c(r)$ is the solubility of the particles of size (radius) r, c^* is the equilibrium solubility of the solute, S is the supersaturation ratio, γ is the surface energy, V is the molecular volume, k is the Boltzmann constant, and T is the absolute temperature.

To characterize the supersaturation driving force in the crystallization system, initial supersaturation (S_i) or degree of supersaturation (ΔC) is used [10, 58]. Initial supersaturation is defined as the ratio of the initial concentration of the solution to be crystallized (C_0) and the equilibrium concentration/solubility in the solute-solvent-antisolvent system (C^*), i.e.,

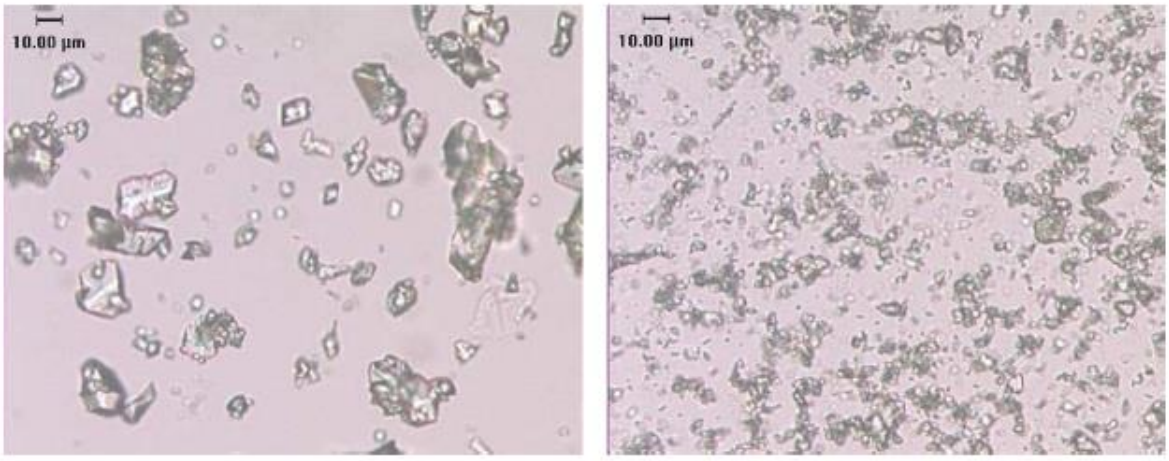
$$S_i = \frac{C_0}{C^*} \tag{8}$$

The degree of supersaturation is the difference between C_0 and C^*. Therefore, the extent of initial supersaturation can be governed by varying the solution concentration or the ratio of solution to antisolvent in ASC processes. Super-saturation can influence crystal growth, size, and shape. For instance, Oosterhof *et al*. reported a linear dependence on the growth of sodium nitrate crystals by increasing the concentration difference in water – isopropoxyethanol mixed system. No change in crystal morphology, however, was observed by investigators [65]. Studies on nucleation behavior during ASC of paracetamol in acetone – water mixture have shown that higher initial supersaturation conditions generate a larger total growing crystal surface area. The interrelation between the surface energy and the solubility to describe the nucleation kinetics was also reported

[66].

Mixing/agitation: The mixing effects during the contact of solvent-solution can strongly influence the nucleation, MSZW, and crystal size distribution [10]. However, too intense mixing should be avoided, leading to a less uniform product. The intense mixing facilitates secondary nucleation, inhibits aggregation, and results in undesirable fines [63]. These conflicts in antisolvent systems can be compounded by the need to continuously blend the antisolvent and solution phases rapidly. Suitable turbulent mixing conditions during crystallization processes improve crystal suspension and impurity profile with a reduction in settling [67]. The location of antisolvent addition during mixing (close to the impeller or close to the vessel wall) also influences nucleation kinetics [55].

Rate and mode of solvent addition: The supersaturation rate in ASC depends on solvent addition/dosage rate [59]. Consequently, the solvent dosage rate (or amount) can control the nucleation rate. Solvent dosage and average particle size are also interrelated. Diluting the antisolvent/secondary solvent with the primary solvent is another way to control nucleation [63]. Kaneko *et al*. [20] proposed high antisolvent operational conditions to relieve high local and bulk supersaturation that causes the formation of fines and agglomeration. The method of solvent addition, by operating under two different modes–forward addition and reverse addition, can also affect the supersaturation and particle size (illustrated in Fig. **3**). In the forward addition mode, the antisolvent is added to the solution resulting in lower supersaturation and large-sized particles. On the other hand, in the reverse addition mode, the solution is added to the antisolvent causing high supersaturation and smaller crystals [68].



(**a**) (**b**)

Figure 3: (**a**) Larger particles obtained from forward addition (**b**) Smaller particles obtained from reverse addition "Reprinted with permission from [68]. Copyright (2024) American Chemical Society."

Inhibition: The application of crystal growth-inhibiting antisolvent and crystal growth inhibitors from suppressing primary nucleation has also been reported. Growth inhibitors are compounds (also known as additives) other than the solute added to the solute-solvent/antisolvent system. The use of crystal growth inhibitors resulted in relatively coarse salt crystals with uniform and narrow size distribution, easing salt crystal separation from slurry [13].

2.4. Antisolvents

Antisolvent plays a vital role in the ASC design and can influence the success or failure of the operation. Among the different solvents, i.e., organic, ionic, organic, or inorganic complex, organic solvents are used most preferably. Table **2** summarizes the list of the organic solvents and their usage pattern as reported in various literature papers cited in this work.

Table 2: List of organic solvents and their usage pattern.

Solvent Category	Usage Pattern		
	High	Moderate	Low
Alcohols	methanol ethanol n-propanol iso-propanol	butanol ethylene glycol	diethylene glycol pentanols butane diols
Ketones	acetone	-	methyl ethyl ketone butanone
Ethers	-	1,4-dioxane	1,2-dimethoxyethane 2-methoxyethanol isopropoxyethanol dimethyl ether
Amines	-	iso-propylamine di-isopropylamine ethylamine	diethylamine triethylamine ethylenediamine butylamine diethylenetriamine
Hydrocarbons	-	-	cyclohexane n-decane n-pentane 1,2,4-trimethyl benzene
Nitrile	-	acetonitrile	-
Heterocyclic	-	tetrahydrofuran (THF)	-
Acetate	-	-	butyl acetate methyl acetate
Amide	-	-	dimethylacetamide n-methyl pyrrolidine dimethylformamide
Acid	-	-	acetic acid

The judicious choice of antisolvents can change the outcome of ASC significantly. Antisolvent composition influences the mechanism that governs the crystal characteristics [66].

2.4.1. Types, Properties, and Selection of Antisolvent

The solubility of solutes in a mixed solvent system depends primarily on the solvation of the solute or its constituent ions by the components of the solvent mixture [69]. The essence of ASC is to select a suitable antisolvent, which can reduce the solubility of the solute in the solution and promote selective precipitation. According to McNally *et al*., antisolvent interacting with the solution can be either implicit-solvent or explicit-solvent based on its interaction with solute and solvent. An implicit solvent may change the solution's dielectric properties, inducing a change in solubility characteristics. On the other hand, an explicit solvent may act as a solute in the solution, thereby competing with the dissolved solute for explicit interactions with the primary solvent [18].

The physical and chemical properties of the antisolvent directly affect the nucleation and growth of the crystal, particle size distribution (PSD), and the final crystal shape [70]. Considering solubility as a primary selection criterion, researchers have outlined the strategy for choosing solvents for cooling crystallization and antisolvent

crystallization [71, 72]. Progressively, Karunanithi and co-workers [3, 23] have considered other factors such as solvent effect on crystal morphology, solvent ability to solubilize impurities, inflammability, and toxicity of solvent for design and selection. A computer-aided molecular design (CAMD) technique was used for crystallization-based separation in pharmaceutical applications in solvent design. Such predictive studies of solvent effects are critical to facilitate solvent screening efforts [73].

The dielectric constant, which reflects the polarity of the solvent, is an important parameter to predict solvent behavior, which in turn can influence the solubility of solutes. Zhang *et al*. [34] proposed a new model (based on experimental data) describing the effect of the dielectric constants on the solubilities of pharmaceutical compounds. In their model, the natural logarithm of the solubility was correlated linearly with a negative reciprocal of the dielectric constant similar to the Arrhenius equation. The solubilities were found to increase with increasing dielectric constant and water content in a binary solvent system. Apart from the dielectric constant, a solvent's polarity and functional group are critical factors in influencing the crystal habit and shape in ASC [2]. ASC can have a broader combination of suitable solvents and antisolvent as well as their component ratio to control nucleation and crystal growth [50]. In another study, the amount of solvent volume enhanced the extent of crystallization [28].

Other important properties of antisolvents to be considered are toxicity, flammability limit, reactivity, cost, solvent loss, partition coefficient, heat of vaporization, dielectric constant, difference in boiling point with primary solvent, azeotrope behavior with primary solvent at application temperature range [22]. The diffusion rate of the antisolvent is another parameter governed by mass transfer phenomena [74]. These properties of the antisolvents are used in phase equilibrium and process calculations, sustainability analysis, and risk assessment [49].

2.5. Antisolvent Recovery Methods

Antisolvent crystallization of solutes in an aqueous system will result in a mixed aqueous-organic solution. Recovery and reuse of antisolvent from the remaining mother liquor after crystallization is an integral part of making the overall ASC process environmentally sustainable. To make the overall crystallization process economically viable, the antisolvent recovery must be carried out at lower energy and operational costs [75]. Industrially applicable solvent recovery methods include:

2.5.1. Evaporation and Distillation

This method is applied when the solvents under application have a difference in volatility and boiling points. Heating or decompression (expansion) of the solution results in the vaporization of the lighter solvent. The boiling point and heat of vaporization dictate this recovery process. The organic solvents with lower boiling point than water can be separated using various distillation methods (flash distillation, pressure-swing batch distillation, fractional distillation, vacuum distillation, etc.) or evaporation methods (vacuum evaporation, multi-effect evaporation, etc.) [76].

2.5.2. Gravity Separation/Decantation

In this method density difference between the liquid phases act as the driving force. Antisolvent is recovered by bringing the mixed system to a temperature level, where two liquid phases (one antisolvent-rich and the other water-rich) with a considerate density difference are formed. Gravity separation/decantation of these two phases can yield a relatively dry solvent and water [77].

2.5.3. Filtration/Membrane-Separation

The separation of specified solvent from other solvents and solutes using filtration is based on the particle/molecular size and pressure. Using a nano-filtration unit comprising a membrane permeable to an aqueous salt solution but impermeable to antisolvent has also been reported [13]. Solvents with larger molecules (like amines) and with high boiling points can be considered for membrane-based separation methods [22].

2.5.4. Aqueous Two-Phase Extraction

In this method, the separation of antisolvent from residual aqueous solution takes place by the 'salting-out' effect [78]. For water as a primary solvent in aqueous solutions, the organic solvent can be classified as fully water-miscible, partially water-miscible, polar protic, and polar aprotic based on solubility chemistries [18]. Temperature-induced liquid-liquid phase split-based regeneration of the antisolvent phase is also achieved for certain solvent-antisolvent combinations [77].

3. Antisolvent Crystallization Process Configurations

A generic ASC process (Fig. **4**) will consist of (i) mixing an antisolvent with the original solution, (ii) filtering and separating the crystals from the mother liquor, and (iii) recovering solvent for reuse.

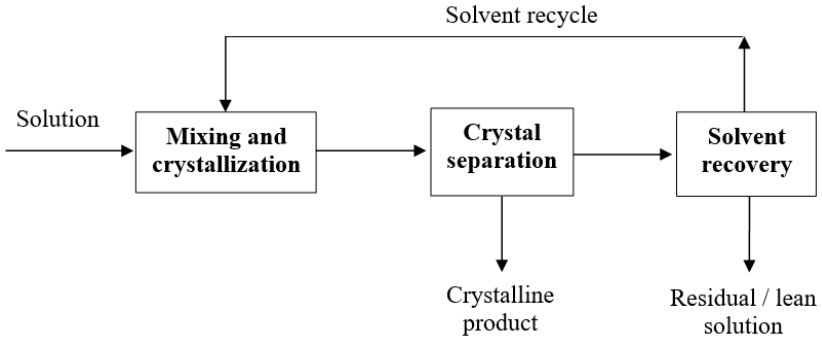


Figure 4: Schematic of a generic ASC process.

Depending on the properties and composition of the feed under study, different process configurations can be designed. For example, in the case of ASC of salt from an aqueous solution, salt crystals are formed by one or a combination of two possible actions; water is transferred from an aqueous phase to the solvent phase, which leads to a direct reduction of the aqueous phase, or solvent enters the aqueous phase, which leads to the lower solubility of the salt in the aqueous phase. Both actions lead to precipitation and crystal growth of a solid salt phase.

Berry and co-workers presented the synthesis of ASC-based separation schemes for two types of systems. In the first system, the antisolvent causes the solute to become sparingly soluble. In the second system, the solute is extracted into a phase rich with respect to the antisolvent. Several possible alternatives to separate feed into pure components and antisolvent recovery were proposed, and guidelines for selecting an extractor type and choosing between crystallizer-extractor and extractor-crystallizer trains were given. Dominant costs of proposed configurations were also identified [79].

Fig. (**5**) shows a process for purified salt recovery from mixed/impure feed salt. The feed salt is fed to the dissolver, together with a recycled water stream. After the dissolver, an optional filtration unit (not shown in Fig. **5**) can be employed to remove insoluble matter. The concentrated aqueous salt solution (from the dissolver) is mixed with a dry solvent in the crystallizer (at a temperature T_C) to induce ASC of the salt. The crystallizer has two outlets: one mother liquor and one slurry outlet. The crystal slurry undergoes downstream filtration and drying to produce pure salt crystals [80]. The mother liquor stream is fed to the solvent regenerator.

As discussed in section 2.5, the water-to-solvent phase separation can be accomplished in different ways. For example, in the solvent regenerator described by Weingaertner *et al*., water is removed from the wet solvent phase by changing the temperature to a level at which two liquid phases are formed, a solvent-rich and a water-rich phase. The regenerator is operated at a temperature T_R, which differs from the crystallizer temperature T_C. The two temperatures must be chosen carefully, but the primary criterion is that the solvent must be more hydrophilic for Tc and more hydrophobic for T_R. Hydrophilicity with temperature rises over temperature ranges that are of interest for ASC, the most promising are oxygen-containing compounds such as common alcohols [77].

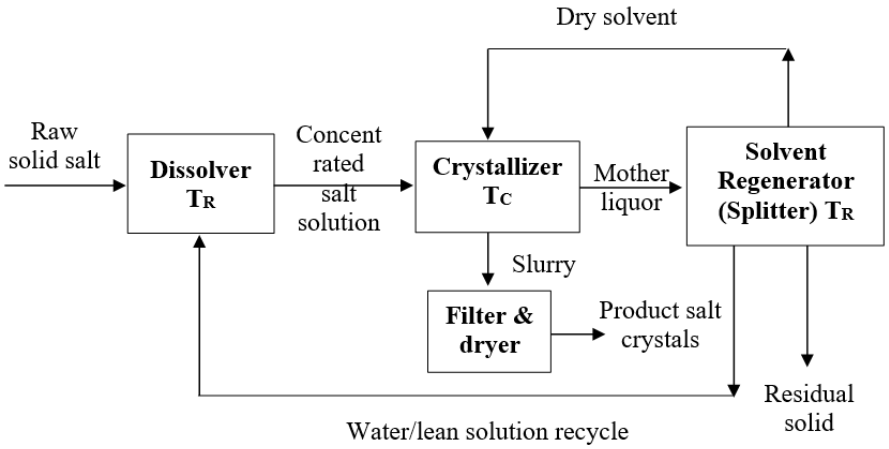


Figure 5: Salt extraction from raw solid salt using ASC with water/lean solution recycle (Based on the work of Weigaertner *et al*. [77] and Taboada *et al*. [80]).

In another instance (Fig. **6**), Taboada *et al*. [80] have used a distillation column as the solvent regeneration unit to separate antisolvent having lower density (lighter component) and water (heavier component) for potassium sulphate purification using propanol.

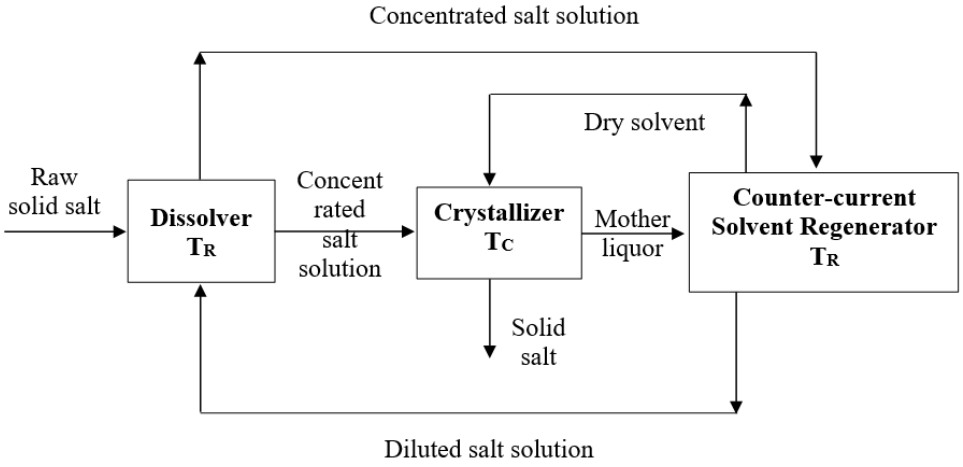


Figure 6: Salt extraction from raw solid salt using ASC with solvent-drying (Redrawn from Weingaertner *et al*. [77]).

Hybrid configurations combining antisolvent crystallization and other crystallization (evaporative/cooling) have also been suggested in the literature [35]. Two flowsheets of hybrid structures are presented in Fig. (**7a**) and (**7b**). The difference between the two configurations lies in the sequence in which thermal (evaporative/cooling) crystallization and antisolvent crystallization can be arranged. In type one, the solvent is added in crystallizer 1 at T_{C1} to crystallize product 1.

After separating product 1, the mother liquor is fed to the solvent recovery column to separate the solvent. The stream after solvent recovery is fed to the crystallizer 2 maintained at T_{C2}. The second product is crystallized and separated by filter 2. The mother liquor from the second crystallizer contains both components 1 and 2. It is recycled back to complete the cycle. In the case of type two, the recycled solvent is added to the feed of the second crystallizer, and ASC takes place in crystallizer 2 (Fig. **7b**).

The choice of the crystallization sequence depends on the phase behavior of the solution in the presence and absence of a secondary solvent. The effect of temperature on phase separation also plays a vital role in choosing process configurations for a given system. The integration of ASC in hybrid configurations can significantly facilitate the recovery of multiple high-purity products with minimal changes to an existing thermal crystallization process and is operationally simple.

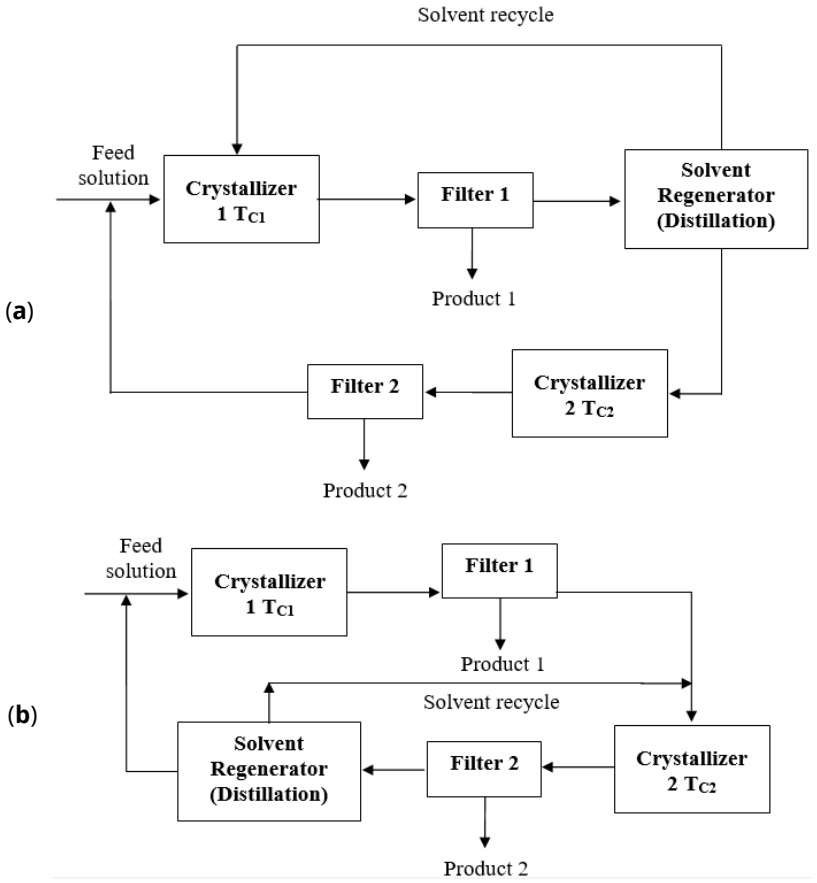


Figure 7: (**a**) Type one-hybrid crystallization configuration, (**b**) Type two-hybrid crystallization configuration (Redrawn from Rajagopal *et al*. [35]).

4. Sustainability Aspects of Antisolvent Crystallization

4.1. Solvent Recycling and Regeneration

The ASC process consists of adding a secondary solvent (antisolvent) that is miscible with the original solution to decrease the solubility of the solute of interest [42]. Consequently, solvent recycling and regeneration are the two important challenges of the ASC process. The organic solvents used in various methods are often disposed of after one cycle due to purity concerns. The solvent recovery practices in the chemical industry are not implemented regularly to minimize waste, and suitable waste recovery methods are needed to reduce the environmental footprint. Chea *et al*. have reported solvent recovery options through a superstructure-based optimization framework, and a generic solvent recovery framework containing multiple technology options is shown in Fig. (**8**) [81].

Interestingly, the different ASC process configurations presented in section 3 include some of the solvent recovery methods portrayed in Fig. (**8**). The solvent recovery framework can aid in designing a sustainable process by recycling materials, reducing emissions, and enhancing the economics of the overall ASC process. A suitable antisolvent with a high potential recovery can significantly improve the process economics and environmental impacts. The additional energy requirements for solvent recycling and regeneration can be offset by several advantages of ASC, including increased yields, operation at ambient temperature (saving energy), higher purity of crystals, and selectivity [64]. Sustainability and life cycle assessment (LCA) for an ASC process with three case scenarios (i) antisolvent recovery and reuse, (ii) direct disposal without antisolvent recovery, and (iii) antisolvent disposal by incineration is reported in a recent work [49]. End-point assessment categories of human health, ecosystem quality, climate change, and resources were evaluated. The ASC process with solvent recovery and reuse was established to be a much greener process using the LCA assessment.

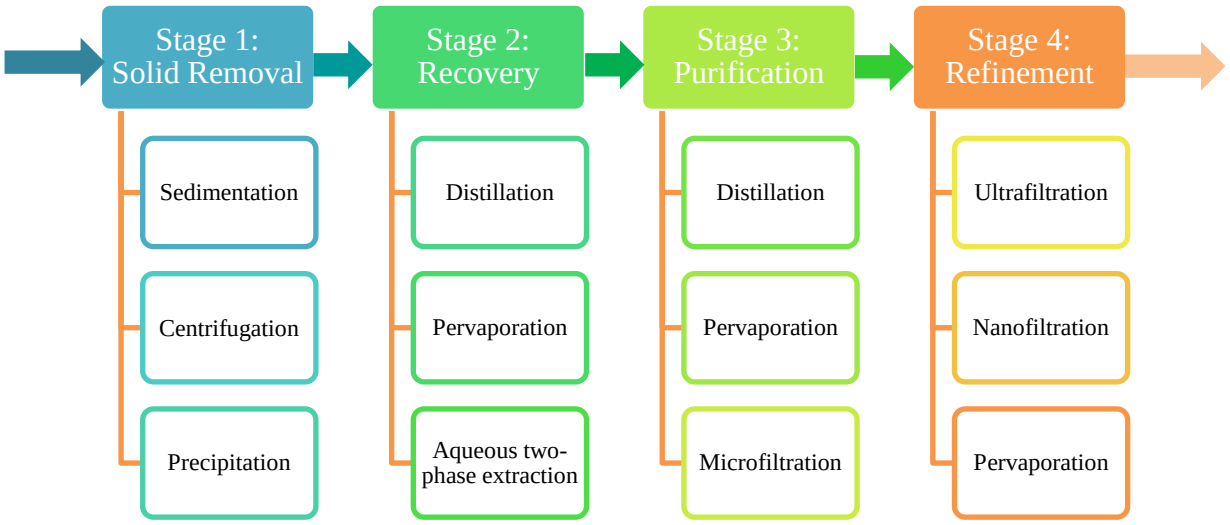


Figure 8: A generic framework for recovery and purification of solvents.

4.2. Environmental, Health, and Safety Considerations

The environmental, health, and safety impact of a solvent is one of the key design criteria in the ASC process, as the traces of the solvents could be present in the final products. Antisolvent properties, including bio-concentration factor (BCF), toxicity, and flammability, are considered by environmental regulations to assess its suitability. The ecological and health impact of a solvent is correlated to the octanol-water partition coefficient (K_{ow}). The safety requirements of a solvent can be quantified by its flash point [82]. A health metric LC_{50} is used to quantify the lethal concentration of a chemical. The solvent toxicity is measured quantitatively as – log(LC_{50}), where the higher value indicates the high toxicity of the antisolvent [3]. Organic solvents are generally harmful to some extent when their vapor is inhaled or when they are injected.

The Innovative Medicines Initiative (IMI) has listed several dipolar aprotic solvents (i.e., NMP, DMF, DMSO, DMA, HMPA, etc.) as hazardous for processing and developing active pharmaceutical ingredients (API) [83]. Given this, efforts towards replacing dipolar aprotic solvents used in the API industry with solvent pair mixtures of hydrogen-bond donor and hydrogen-bond acceptor have been reported [84]. More recently, solvents that are derived from biomass, namely bio-derived solvents, have attracted intensive investigations due to their advantages over conventional volatile organic compounds (VOCs), such as low-toxicity, biodegradability, and renewability [85]. Common examples of bio-derived include ethanol from fermented sugars, esters derived from fatty acids, and terpenes like limonene from citrus peels. These solvents are promising alternatives to petrochemical counterparts for their environmental benefits, including reduced carbon footprint and enhanced biodegradability. However, challenges such as higher production costs and variable performance compared to conventional solvents persist.

4.3. Energy and Economic Savings

Concerning energy requirements and economic evaluation for the ASC process, limited studies are available in the literature. In an early study, Alfassi and Mosseri [86] indicated the possibility of using low boiling point organic solvents for electrolyte precipitation from their aqueous solution using a relatively low-temperature heat source in the ASC process. This can be preferable to using a more expensive higher-temperature heat source in the evaporative crystallization process. In the context of sodium chloride production via crystallization, Weingaertner *et al*. [77] estimated that replacing ASC (under optimal conditions) with a three-effect evaporation process could result in an energy savings (in dollar terms) of 63%. Also, the estimated cost of the ASC plant was reported to be half the cost of a similar size three-effect evaporation plant. However, the capital investment for the ASC plant was found to be high, with a return of investment (ROI) of only 18.7% [77]. The usefulness of existing equipment and processing technology for ASC is another desirable consideration. Rajagopal *et al*. [35] presented the economic trade-offs of the ASC process in the context of the complete separation of para-xylene from meta-xylene using n-pentane as the extractive solvent. An equipment cost comparison of the proposed process has shown an

economic advantage over the conventional process reported in the literature. In another study on ASC as an alternative to evaporation crystallization for sodium chloride production, Zijlema *et al*. reported an energy cost reduction of nearly 29%. Further, the estimated fixed capital costs were 8 – 55% higher for ASC of NaCl, depending on the process configuration used [75]. While for low-value inorganic salts, the overall economics does not seem favorable, for specialty chemicals and pharmaceutical product processing, ASC may be a more viable alternative.

5. Potential Applications of Antisolvent Crystallization-based Separation

ASC technique has great-untapped potential for developing processes with the advantages of controlled crystal growth and improved selectivity. Some of the well-reported applications of ASC in the literature are presented to support its commercial relevance. Niche applications of ASC toward the formation of micron and submicron-size particles in material research and processing are worth-mentioning [58]. ASC for separation and purification of biomolecules during bioprocessing is also gaining attention in recent years. Conventional and emerging application areas of ASC are discussed below.

5.1. Hydrometallurgy

The usefulness of organic solvent-induced metal-salt crystallization is well-established for hydrometallurgical applications. Exemplary investigations on the extraction of cobalt salts [45, 87], copper salt [88], nickel salt [6], and alumina [89, 90] from different sources (spent battery, spent Bayer liquor, etc.) have been reported. Some novel applications like metallic value recovery (Co, Mn, Cu, etc.) from lithium-ion batteries (LIB) and printed circuit boards from obsolete mobile phones are also being explored [91].

ASC was also found to work well in acidic media [12]. Towards the metal recovery application, adding alcohols (propanol and butanol) in dilute hydrochloric acid improved the acid leaching of Cu, Fe, Mn, Ni, and Co from sea nodules [92]. Compared to classical techniques of metal-salt crystallization, these alcohol-assisted precipitation offer advantages like no need for temperature shift, rapid process, and easy implementation [88].

5.2. Salt Extraction

Commercially, many inorganic salts are produced from aqueous solutions or concentrates (having co-solute or impurities) using various crystallization or precipitation-based methods [13, 93, 94]. However, the presence of co-solutes and/or contaminants can impact the solubility of the species of interest and its subsequent extraction [4]. ASC has attracted attention as an efficient method for salt extraction from aqueous solutions. Alfassi and Mosseri have carried out several pioneering fundamental studies to establish the potential of solvent-assisted crystallization/precipitation for salt recovery from aqueous solutions [86, 95-97]. Alfassi [95] examined the feasibility of a miscible organic solvent (MOS) to precipitate electrolyte (or salt) by correlating the solubility of an electrolyte in a mixed water - MOS system to a characteristic constant termed “the precipitating constant: λ.” Experimental values of λ for a large combination of the salt-solvent system were reported. It was reported that two salts in aqueous solutions might be separated using MOS if the two electrolytes have different λ values for the given MOS. The study outcomes were realized as appropriate for singly charged cations. In a subsequent study, Alfassi and Mosseri [86] pointed out the possibility of low boiling point MOS to enable the recovery of electrolytes from their aqueous solution using low-cost energy sources (low-temperature heat source, vacuum without heating, etc.). Several low boiling point MOS, e.g., acetone, propylamine, and isopropylamine, were tested on electrolytes (K_2SO_4 and KIO_3), and isopropylamine was found most suitable. It was suggested that the method could be used for many electrolytes in which a significant fraction of salt is expected to precipitate by a relatively small volume of organic solvent.

Further, in a successive work, Mosseri and Alfassi [97] studied twenty water–MOS–electrolyte systems and derived analytical expressions to describe the relative solubility (of electrolyte) as a function of MOS amount. The general expressions for predicting the solubility constants and MOS relative volumes from precipitation constants λ were found, which applied to the entire range of concentrations. In summary, the fundamental water–MOS–electrolyte phase studies and analytical expression presented by this group have strengthened the prospect of

using solvent-assisted crystallization/precipitation of salts from their solutions.

Weingaertner *et al*. [77] have established extractive crystallization as an alternative to evaporation in processes to recover salts from their concentrated aqueous solutions. In their process, the concentrated aqueous solution is mixed with a selected solvent, and salt is forced to crystallize by mutual solubility of water and solvent. After salt removal, the residual liquor of solvent, water, and remaining salt is re-formed into a regenerate dry solvent phase and a diluted aqueous phase either by changing the temperature or contacting with an additional concentrated solution. The recycling of both phases within the process allows the conception of a continuous industrially applicable process. The extractive crystallization of sodium carbonate and sodium chloride was investigated, and detailed process configurations were discussed.

5.3. Desalination and Water Treatment

The capability of the ASC method to remove water-soluble salts from an aqueous solution has been exploited in desalination and water treatment applications [22, 98]. Govind and Foster [22] patented a system, method, and apparatus for the reclamation of water through precipitating salts from salt solutions by adding the water-miscible solvent (e.g., ethanol, acetone, ethanolamine, etc.). Separation methods for the recovery of precipitated salt and solvent were also presented in their study. Another patent showed an integrated process for making inorganic salt from a crude aqueous solution using antisolvent and the production of drinking/process water [13]. The integrated system comprises a crystallizer and membrane units, wherein the ASC in the crystallizer acts as a primary salt removal unit followed by membrane separation of residual liquid into two streams, i.e., solvent and water. More recently, McNally and co-workers have conceptualized a miscible organic solvent-driven fractional precipitation of solutes from the saline brine solution to augment the water treatment system. A simplified water softening process using dimethyl ether (DME) as the antisolvent is depicted in Fig. (**9**).

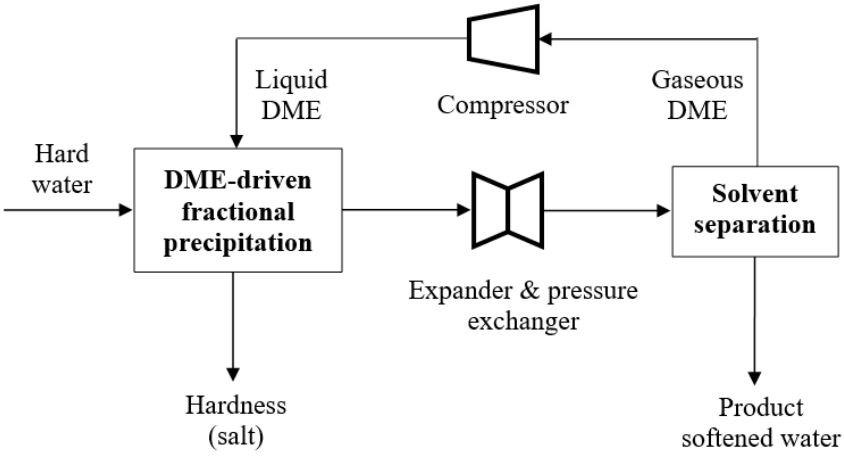


Figure 9: Conceptual scheme of DME antisolvent-driven water treatment (adapted from McNally *et al*. [18]).

The solute-laden hard water is mixed with compressed DME, driving the fractional precipitation of solutes from the hard water. The precipitated solids are separated, and the water – DME mixture undergoes expansion (using an expander) to vaporize DME for solvent and water separation. Vaporized DME is compressed and recycled back in the process, while the softened product water is passed to the next stage in the water treatment process [18].

5.4. Pharmaceutical

ASC has been widely used in pharmaceutical industries to produce various polymorphic drug compounds with desired crystal size distribution [99, 100]. “Polymorphism is defined as the ability of a single constituent to exist in more than one crystallographic arrangement [101].” In the pharmaceutical industries, Polymorphism is an important point of comparison for various physicochemical characteristics such as solubility and dissolution, and both factors influence the other properties, say, bioavailability, compaction, flow, and stability of polymorph. The analogous strength of polymorphism is determined under the aegis of thermodynamic properties concurrently;

the kinetics of polymorphic forms such as nucleation, crystal size distribution, and crystal growth depends upon the crystallization process. ASC is a primary method of purification during the intermediate and final stages of drug synthesis [33]. Kumar and co-workers have classified antisolvent precipitation as one of the particle size reduction techniques of pharmaceutical compounds to enhance their dissolution rate and bioavailability [102]. Various active pharmaceutical ingredients (APIs), including bisacodyl, griseofulvin, curcumin, silibinin, apigenin, etc., crystallized using organic solvents (acetone, ethanol, n-methyl pyrrolidone, dimethyl sulfoxide, and dimethylformamide) and water as antisolvent was reported in their study. By tuning the ASC process conditions, the particle size, crystal habit, particle morphology and degree of crystallinity of the product could be controlled. A recent review has highlighted the applications of ASC in crystal engineering and process intensification pathways in the pharmaceutical field [16].

5.5. Bioprocessing

Application of ASC in bioprocessing industries is realized in twenty first century, in the context of separation and purification of biochemicals/biomolecules like proteins, peptides, enzymes, biopharmaceuticals, etc. [103]. Gerstweiler *et al*. reported crystallization as an important unit operation to store biopharmaceuticals as protein crystals [104]. In a recent work on the application of ASC for bioprocessing, recovery and purification of xylitol from the cashew apple bagasse feedstock using antisolvent is reported. Isopropanol, ethanol and the protic ionic liquid 2-hydroxyl-ethylammonium acetate were evaluated as antisolvents. Isopropanol was found to be the best antisolvent with crystal yield and purity of 70% and 85% respectively [105]. In a recent review on upstream and downstream bioprocessing in enzyme technology, antisolvent crystallization is discussed as an efficient product purification method in conjunction with chromatography [106]. A high-selectivity associated with ASC makes it particularly useful for isolating valuable biomolecules from complex mixtures.

6. Conclusions

In this review, we concentrate on the potential application of antisolvent crystallization (ASC) for unconventional applications and promote its use for inorganic chemical/salt extraction and water treatment. The focus is on the profound understanding of phase equilibrium and thermodynamic behavior of solute, primary solvent (water), and antisolvent systems for the performance of an ASC process. Next, the selection of a suitable antisolvent with desirable characteristics is the key to the successful development and implementation of the ASC technique. Among the gamut of recommended solvents, monovalent alcohols (methanol to butanol), acetone, and other hydrocarbons have been studied extensively and used as antisolvents. Developing a more efficient antisolvent crystal extraction would require investigating other less applied solvents (like glycols, ketones, ethers, amines, nitriles, esters, etc.) as antisolvent with a deep understanding of the underlying thermodynamics and kinetics occurrence. The sustainability aspects of ASC, considering the environmental benignity of solvents, associated economic costs, and efficiency in terms of resilience, evaluation of waste streams, and toxicology, are equally critical for its practical realization. Towards the commercial implementation of ASC, various configurations (stand-alone and hybrid) highlighted in this study provide crucial technical contributions for pure crystalline product recovery from liquid solutions or solid mixtures. ASC is well-adopted in pharmaceutical applications and is expected to grow in the areas of industrial hydrometallurgy, mineral salt recovery, and water treatment. Future work is required to develop and test new greener/environmentally benign solvents and study the performance of ASC at the pilot scale.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Nomenclature

Abbreviation

API	active pharmaceutical ingredient
ASC	antisolvent crystallization
BCF	bio-concentration factor
CAMD	computer aided molecular design
DLS	dynamic light scattering
DMA	dimethylacetamide
DME	dimethylether
DMF	dimethylformamide
DMSO	dimethylsulphoxide
ePC-SAFT	electrolyte perturbed-chain statistical associating fluid theory
HMPA	hexamethylphosphoramide
IMI	innovative medicines initiative
*I*p	induction period
LCA	life cycle assessment
LIB	lithium ion batteries
LIQUAC	liquid phase quasi-chemical activity coefficient
MOS	miscible organic solvent
MSZW	metastable zone width
NMP	N-methylpyrrolidone
NRTL	non-random two liquid
PSD	particle size distribution
ROI	return of investment
THF	tetrahydrofuran
UNIQUAC	universal quasi-chemical activity coefficient
VOCs	volatile organic compounds

Greek Letters

$\gamma_{\mathrm{w}}^{\mathrm{DI}}$	aqueous activity coefficient in water
$\gamma_{\mathrm{w}}^{\mathrm{salt}}$	aqueous activity coefficient in saltwater
γ	activity coefficient of the solute in a supersaturated solution
γ^{sat}	activity coefficient of the solute in the saturated solution
γ	surface energy
μ	chemical potential
μ^{sat}	chemical potential at equilibrium

Symbols

c^*	equilibrium solubility of the solute
$c(r)$	solubility of the particles of size (radius) *r*
C^*	equilibrium concentration

C_0	initial concentration
C_{salt}	salt concentration
ΔC	degree of supersaturation
k	Boltzmann constant
$K_{\text{l}}^{\text{salt}}$	partitioning coefficient in saltwater
K_{ow}	octanol-water partition coefficien
$K_{\text{s}}^{\text{i,k}}$	Setschenow constant
K_{w}^{DI}	partitioning coefficient in deionized water
S	supersaturation ratio
S_i	initial supersaturation
S_{w}^{DI}	solubility of organic compounds in deionized water
$S_{\text{w}}^{\text{salt}}$	solubility of organic compounds in saltwater
x^{sat}	solute mole fraction in saturated solution
T	temperature
T_{C}	solute crystallizing temperature
T_{R}	solvent regeneration temperature
V	molecular volume
x	solute mole fraction in supersaturated solution

References

[1] Ulrich J. Crystallization. Kirk-Othmer Encyclopedia of Chemical Technology, 2002. https://doi.org/10.1002/0471238961.0318251918152119.a01.pub2

[2] Zhou X, Shan J, Chen D, Li H. Tuning the crystal habits of organic explosives by antisolvent crystallization: the case study of 2,6-dimaino-3,5-dinitropyrazine-1-oxid (LLM-105). Crystals. 2019; 9(8): 392. https://doi.org/10.3390/cryst9080392

[3] Karunanithi AT, Achenie LEK, Gani R. A computer-aided molecular design framework for crystallization solvent design. Chem Eng Sci. 2006; 61: 1247-60. https://doi.org/10.1016/j.ces.2005.08.031

[4] McDonald MA, Salami H, Harris PR, Lagerman CE, Yang X, Bommarius AS, *et al*. Rousseau, Reactive crystallization: a review. React Chem Eng. 2021; 6: 364-400. https://doi.org/10.1039/D0RE00272K

[5] Westphal G, Kristen G, Wegener W, Ambatiello P, Geyer H, Epron B, *et al*. Sodium Chloride. Ullmann's Encycl Ind Chem. 2012; 319-65. https://doi.org/10.1002/14356007.a24_317.pub4

[6] Moldoveanu GA, Demopoulos GP. Producing high-grade nickel sulfate with solvent displacement crystallization. JOM. 2002; 54: 49-53. https://doi.org/10.1007/BF02822606

[7] Tavare NS. Crystallization techniques and phenomena bt - industrial crystallization: process simulation analysis and design. In Tavare NS, Ed., US, Boston, MA: Springer; 1995, pp. 465-99. https://doi.org/10.1007/978-1-4899-0233-7_12

[8] Lombard J, Smith VJ, le Roex T, Haynes DA. Crystallisation of organic salts by sublimation: salt formation from the gas phase. CrystEngComm. 2020; 22: 7826-31. https://doi.org/10.1039/D0CE01470B

[9] Volkwyn AL, Haynes DA. Crystallization of organic salts and co-crystals by sublimation: the effect of experimental conditions. Cryst Growth Des. 2023; 23: 8212-20. https://doi.org/10.1021/acs.cgd.3c00931

[10] Takiyama H, Otsuhata T, Matsuoka M. Morphology of NaCl crystals in drowning-out precipitation operation. Chem Eng Res Des. 1998; 76: 809-14. https://doi.org/10.1205/026387698525559

[11] Mydlarz J, Jones AG. Solubility and density isotherms for magnesium sulfate heptahydrate-water-ethanol. J Chem Eng Data. 1991; 36: 119-21. https://doi.org/10.1021/je00001a034

[12] Moldoveanu GA, Demopoulos GP. Organic solvent-assisted crystallization of inorganic salts from acidic media. J Chem Technol Biotechnol. 2015; 90: 686-92. https://doi.org/10.1002/jctb.4355

[13] Mayer MJJ. Processes involving the use of antisolvent crystallization. US patent US20060150892A1, 2006.

[14] Burant A, Lowry GV, Karamalidis AK. Measurement and modeling of setschenow constants for selected hydrophilic compounds in NaCl and CaCl2 simulated carbon storage brines, Acc Chem Res. 2017; 50: 1332-41. https://doi.org/10.1021/acs.accounts.6b00567

[15] Thorson MR, Goyal S, Gong Y, Zhang GGZ, Kenis PJA. Microfluidic approach to polymorph screening through antisolvent crystallization. CrystEngComm. 2012; 14: 2404-12. https://doi.org/10.1039/C2CE06167H

[16] Jia S, Yang P, Gao Z, Li Z, Fang C, Gong J. Recent progress in antisolvent crystallization. CrystEngComm. 2022; 24: 3122-35. https://doi.org/10.1039/D2CE00059H

[17] Doki N, Kubota N, Yokota M, Kimura S, Sasaki S. Production of sodium chloride crystals of uni-modal size distribution by batch dilution crystallization. J Chem Eng Jpn. 2002; 35: 1099-104. https://doi.org/10.1252/jcej.35.1099

[18] McNally JS, Foo ZH, Deshmukh A, Orme CJ, Lienhard JH, Wilson AD. Solute displacement in the aqueous phase of water–NaCl–organic ternary mixtures relevant to solvent-driven water treatment. RSC Adv. 2020; 10: 29516-27. https://doi.org/10.1039/D0RA06361D

[19] Bhatti S, Sahu P, Masani HR, Dinesh AK, Upadhyay SC, Vyas BG, *et al*. Process integration and techno-economic assessment of crystallization techniques for Na2SO4 and NaCl recovery from saline effluents Chem Eng Process. 2024; 203: 109879. https://doi.org/10.1016/j.cep.2024.109879

[20] Kaneko S, Yamagami Y, Tochihara H, Hirasawa I. Effect of supersaturation on crystal size and number of crystals produced in antisolvent crystallization. J Chem Eng Jpn. 2002; 35: 1219-23. https://doi.org/10.1252/jcej.35.1219

[21] Peeters D. Hydrogen bonds in small water clusters: A theoretical point of view. J Mol Liq. 1995; 67: 49-61. https://doi.org/10.1016/0167-7322(95)00865-9

[22] Govind R, Foster R. Systems, apparatus, and methods for separating salts from water. US patent US20140158616A1, December 6, 2014.

[23] Karunanithi A, Achenie L. Solvent design for crystallization of pharmaceutical products. Comput Aided Chem Eng. 2007; 23: 115-47. https://doi.org/10.1016/S1570-7946(07)80007-1

[24] McGinty J, Chong MWS, Manson A, Brown CJ, Nordon A, Sefcik J. Effect of process conditions on particle size and shape in continuous antisolvent crystallisation of lovastatin. Crystals. 2020; 10: 925. https://doi.org/10.3390/cryst10100925

[25] Feng ZY, Li QS, Song YH, Sun XT, Sun LY. Recovery of petroleum sulfonate from wastewater by extractive crystallization. Adv Mater Res. 2012; 524-527: 1852-5. https://doi.org/10.4028/www.scientific.net/amr.524-527.1852

[26] Shabani A, Hoseinpur A, Yoozbashizadeh H, Vahdati Khaki J. As, Sb, and Fe removal from industrial copper electrolyte by solvent displacement crystallisation technique. Can Metall. 2019; 58: 253-61. https://doi.org/10.1080/00084433.2018.1549346

[27] Lozano JAF. Recovery of potassium magnesium sulfate double salt from seawater bittern. Ind Eng Chem Process Des Dev. 1976; 15: 445-9. https://doi.org/10.1021/i260059a018

[28] Kokes H, Morcali MH, Acma E. Dissolution of copper and iron from malachite ore and precipitation of copper sulfate pentahydrate by chemical process. Eng Sci Technol. 2014; 17: 39-44. https://doi.org/10.1016/j.jestch.2014.03.002

[29] Oosterhof H, Witkamp G-J, van Rosmalen GM. Antisolvent crystallization of anhydrous sodium carbonate at atmospherical conditions. AIChE J. 2001; 47: 602-8. https://doi.org/10.1002/aic.690470310

[30] McGarvey PW, Hoffmann MM. Solubility of some mineral salts in polyethylene glycol and related surfactants, Tenside Surfactants Deterg. 2018; 55: 203-9. https://doi.org/10.3139/113.110555

[31] Hyde AM, Zultanski SL, Waldman JH, Zhong Y-L, Shevlin M, Peng F. General principles and strategies for salting-out informed by the hofmeister series. Org Process Res Dev. 2017; 21: 1355-70. https://doi.org/10.1021/acs.oprd.7b00197

[32] Moldoveanu GA. Crystallization of inorganic compounds with alcohols. Thesis, McGill University; 2005. Available from: https://escholarship.mcgill.ca/concern/theses/jm214p530

[33] Miller JM, Rodríguez-Hornedo N, Blackburn AC, Macikenas D, Collman BM. Solvent systems for crystallization and polymorph selection. In: Augustijns P, Brewster ME, Eds., Solvent systems and their selection in pharmaceutics and biopharmaceutics. biotechnology: pharmaceutical aspects. vol VI. New York: Springer; 2007, pp. 53-109. https://doi.org/10.1007/978-0-387-69154-1_3

[34] Zhang X, Yin Q, Cui P, Liu Z, Gong J. Correlation of solubilities of hydrophilic pharmaceuticals versus dielectric constants of binary solvents. Ind Eng Chem Res. 2012; 51: 6933-8. https://doi.org/10.1021/ie202624d

[35] Rajagopal S, Ng KM, Douglas JM. Design and economic trade-offs of extractive crystallization processes. AIChE J. 1991; 37: 437-47. https://doi.org/10.1002/aic.690370313

[36] McNaney JA, Zimmerman FM, Zimmerman HK. Influence of solvent polarity upon salt solubilities, II: Solubilities of two potassium carboxylates at 85°C in aqueous 1,4-dioxane. Monatshefte Für Chemie / Chem Mon. 1984; 115: 1039-45. https://doi.org/10.1007/BF00798770

[37] McNaney JA, Zimmerman FM, Zimmerman HK. Influence of solvent polarity upon salt solubilities, III: Solubilities of KCl in water/tetrahydrofuran at 25°C. Monatshefte Für Chemie / Chem Mon. 1986; 117: 1-6. https://doi.org/10.1007/BF00809166

[38] Kolker A, de Pablo J. Thermodynamic modeling of the solubility of salts in mixed aqueous−organic solvents. Ind Eng Chem Res. 1996; 35: 228-33. https://doi.org/10.1021/ie9406207

[39] Olaya MM, Marcilla A, Serrano MD, Botella A, Reyes-Labarta JA. Simultaneous correlation of liquid−liquid, liquid−solid, and liquid−liquid−solid equilibrium data for water + organic solvent + salt ternary systems. Anhydrous Solid Phase. Ind Eng Chem Res. 2007; 46: 7030-7037. https://doi.org/10.1021/ie0705610

[40] Jimenez YP, Taboada ME, Galleguillos HR. Solid–liquid equilibrium of K2SO4 in solvent mixtures at different temperatures. Fluid Phase Equilib. 2009; 284: 114-117. https://doi.org/10.1016/J.FLUID.2009.06.017

[41] Li M, Constantinescu D, Wang L, Mohs A, Gmehling J. Solubilities of NaCl, KCl, LiCl, and LiBr in methanol, ethanol, acetone, and mixed solvents and correlation using the LIQUAC model. Ind Eng Chem Res. 2010; 49: 4981-8. https://doi.org/10.1021/ie100027c

[42] Lovera JA, Padilla AP, Galleguillos HR. Correlation of the solubilities of alkali chlorides in mixed solvents: Polyethylene glycol+H2O and Ethanol+H2O. Calphad. 2012; 38: 35-42. https://doi.org/10.1016/j.calphad.2012.03.002

[43] Kan AT, Fu G, Tomson MB. Effect of methanol and ethylene glycol on sulfates and halite scale formation. Ind Eng Chem Res. 2003; 42: 2399-408. https://doi.org/10.1021/ie020724e

[44] Hernández-Luis F, Rodríguez-Raposo R, Galleguillos HR, Morales JW. Solubility of sodium halides in aqueous mixtures with ε-increasing cosolvents: formamide, N-methylformamide, and N-methylacetamide at 298.15 K. Ind Eng Chem Res. 2016; 55: 812-9. https://doi.org/10.1021/acs.iecr.5b04614

[45] Aktas S, Gürcan H, Keskin A, Hakan Morcali M, Özbey S, Yücel O. Investigation of cobalt sulfate precipitation by alcohol and influencing factors, Mining, Metall. Explor. 2013; 30: 174-9. https://doi.org/10.1007/BF03402265

[46] Gomis V, Ruiz F, Boluda N, Saquete MD. Liquid−liquid−solid equilibria for ternary systems water + sodium chloride + pentanols. J Chem Eng Data. 1999; 44: 918-20. https://doi.org/10.1021/je990071h

[47] Schall JM, Capellades G, Myerson AS. Methods for estimating supersaturation in antisolvent crystallization systems. CrystEngComm. 2019; 21: 5811-7. https://doi.org/10.1039/C9CE00843H

[48] Mohammad S, Grundl G, Müller R, Kunz W, Sadowski G, Held C. Influence of electrolytes on liquid-liquid equilibria of water/1-butanol and on the partitioning of 5-hydroxymethylfurfural in water/1-butanol, Fluid Phase Equilib. 2016; 428: 102-111. https://doi.org/10.1016/j.fluid.2016.05.001

[49] Sahu P, Gao B, Bhatti S, Capellades G, Yenkie KM. Process design framework for inorganic salt recovery using antisolvent crystallization (ASC). ACS Sustain Chem Eng. 2024; 12: 154-65. https://doi.org/10.1021/acssuschemeng.3c05243

[50] Kitayama A, Kadota K, Tozuka Y, Shimosaka A, Yoshida M, Shirakawa Y. Molecular aspects of glycine clustering and phase separation in an aqueous solution during anti-solvent crystallization. CrystEngComm. 2020; 22: 5182-90. https://doi.org/10.1039/D0CE00542H

[51] Mydlarz J, Jones AG. Crystallization and agglomeration kinetics during the batch drowning-out precipitation of potash alum with aqueous acetone. Powder Technol. 1991; 65: 187-94. https://doi.org/10.1016/0032-5910(91)80181-H

[52] Pirrung MC. Purification of Products. In Smith MB Ed., Handbook of Synthetic Organic Chemistry. Academic Press; 2017, pp. 151-64.

[53] Kalikmanov V. Nucleation Theory, 2013. https://doi.org/10.1007/978-90-481-3643-8

[54] Barata PA, Serrano ML. Salting-out precipitation of potassium dihydrogen phosphate (KDP). I. Precipitation mechanism. J Cryst Growth. 1996; 160: 361-9. https://doi.org/10.1016/0022-0248(95)00740-7

[55] O'Grady D. Barrett M, Casey E, Glennon B. The effect of mixing on the metastable zone width and nucleation kinetics in the anti-solvent crystallization of benzoic acid. Chem Eng Res Des. 2007; 85: 945-52. https://doi.org/10.1205/cherd06207

[56] Sangwal K. Antisolvent crystallization and the metastable zone width. In: Nucleation cryst. Growth Metastability Solutions and Melts. Wiley; 2018: pp. 267-324. https://doi.org/10.1002/9781119461616.ch6

[57] Pina CM, Fernández-Dıaz L, Prieto M, Veintemillas-Verdaguer S. Metastability in drowning-out crystallisation: precipitation of highly soluble sulphates, J Cryst Growth. 2001; 222: 317-27. https://doi.org/10.1016/S0022-0248(00)00937-4

[58] Tóth J, Kardos-Fodor A, Halász-Péterfi S. The formation of fine particles by salting-out precipitation, Chem Eng Process. 2005; 44: 193-200. https://doi.org/10.1016/j.cep.2004.02.013

[59] Mostafa Nowee S, Abbas A, Romagnoli JA. Antisolvent crystallization: Model identification, experimental validation and dynamic simulation. Chem Eng Sci. 2008; 63: 5457-67. https://doi.org/10.1016/j.ces.2008.08.003

[60] Barata PA, Serrano ML. Salting-out precipitation of potassium dihydrogen phosphate (KDP) II. Influence of agitation intensity. J Cryst Growth. 1996; 163: 426-33. https://doi.org/10.1016/0022-0248(95)00987-6

[61] Barata PA, Serrano ML. Salting-out precipitation of potassium dihydrogen phosphate (KDP): III. Growth process. J Cryst Growth. 1998; 194: 101-8. https://doi.org/10.1016/S0022-0248(98)00655-1

[62] Barata PA, Serrano ML. Salting-out precipitation of potassium dihydrogen phosphate (KDP): IV. Characterisation of the final product. J Cryst Growth. 1998; 194: 109-18. https://doi.org/10.1016/S0022-0248(98)00656-3

[63] Budz J, Karpinski PH, Mydlarz J, Nyvlt J. Salting-out precipitation of cocarboxylase hydrochloride from aqueous solution by addition of acetone. Ind Eng Chem Prod Res Dev. 1986; 25: 657-64. https://doi.org/10.1021/i300024a017

[64] Lacmann R. Crystallization, third edition. j. w. mullin, butterworth-heinemann, oxford 1997, 527 seiten, zahlr. abb. und isbn 0-7506-3759-5. Chemie Ing Tech. 1998; 70: 1468. https://doi.org/10.1002/cite.330701126

[65] Oosterhof H, Geertman RM, Witkamp GJ, van Rosmalen GM. The growth of sodium nitrate from mixtures of water and isopropoxyethanol. J Cryst Growth. 1999; 198-199: 754-9. https://doi.org/10.1016/S0022-0248(98)01156-7

[66] Granberg RA, Bloch DG, Rasmuson ÅC. Crystallization of paracetamol in acetone–water mixtures. J Cryst Growth. 1999; 198-199: 1287-93. https://doi.org/10.1016/S0022-0248(98)01013-6

[67] Barrett M, O'Grady D, Casey E, Glennon B. The role of meso-mixing in anti-solvent crystallization processes. Chem Eng Sci. 2011; 66: 2523-34. https://doi.org/10.1016/j.ces.2011.02.042

[68] Tung H-H. Industrial Perspectives of pharmaceutical crystallization. Org Process Res Dev. 2013; 17: 445-54. https://doi.org/10.1021/op3002323

[69] Marcus Y. Solubility and solvation in mixed solvent systems. Pure Appl Chem. 1990; 62: 2069-76. https://doi.org/doi:10.1351/pac199062112069

[70] Lonare SR, Patel AA. Antisolvent crystallization of poorly water soluble drugs. Int J Chem Eng Appl. 2013; 4: 337-41. https://doi.org/10.7763/IJCEA.2013.V4.321

[71] Mahdavi M, Mahvi AH, Nasseri S, Yunesian M. Application of freezing to the desalination of saline water. Arab J Sci Eng. 2011; 36: 1171-7.

[72] Frank TC, Downey JR, Gupta SK. Quickly screen solvents for organic solids. Chem Eng Prog. 1999; 95: 41-61.

[73] Yu Z-Q, Tan RB. Anti-solvent crystallization. Crystals. 2020; 10: 748. https://doi.org/10.3390/cryst10090748

[74] Konstantakou M, Perganti D, Falaras P, Stergiopoulos T. Anti-solvent crystallization strategies for highly efficient perovskite solar cells. Crystals. 2017; 7: 291. https://doi.org/10.3390/cryst7100291

[75] Zijlema TG, Geertman RM, Witkamp G-J, van Rosmalen GM, de Graauw J. Antisolvent Crystallization as an Alternative to Evaporative Crystallization for the Production of Sodium Chloride. Ind Eng Chem Res. 2000; 39: 1330-7. https://doi.org/10.1021/ie990221h

[76] McCabe W, Smith J, Harriott P. Unit operations of chemical engineering, 6th ed. Boston: McGraw Hill; 2001.

[77] Weingaertner DA, Lynn S, Hanson DN. Extractive crystallization of salts from concentrated aqueous solution. Ind Eng Chem Res. 1991; 30: 490-501. https://doi.org/10.1021/ie00051a009

[78] Hanson DN, Lynn S. Method of crystallizing salts from aqueous solutions. US patent US4879042A, 1989

[79] Berry DA, Dye SR, Ng KM. Synthesis of drowning-out crystallization-based separations. AIChE J. 1997; 43: 91-103. https://doi.org/10.1002/aic.690430112

[80] Taboada ME, Cisternas LA, Cheng YS, Ng KM. Design of alternative purification processes for potassium sulfate. Ind Eng Chem Res. 2005; 44: 5845-51. https://doi.org/10.1021/ie0503390

[81] Chea JD, Lehr AL, Stengel JP, Savelski MJ, Slater CS, Yenkie KM. Evaluation of solvent recovery options for economic feasibility through a superstructure-based optimization framework. Ind Eng Chem Res. 2020; 59: 5931-44. https://doi.org/10.1021/acs.iecr.9b06725

[82] Sinha M, Achenie LEK, Ostrovsky GM. Environmentally benign solvent design by global optimization, Comput Chem Eng. 1999; 23: 1381-94. https://doi.org/10.1016/S0098-1354(99)00299-9

[83] Prat D, Wells A, Hayler J, Sneddon H, McElroy CR, Abou-Shehada S, *et al*. CHEM21 selection guide of classical- and less classical-solvents. Green Chem. 2016; 18: 288-296. https://doi.org/10.1039/C5GC01008J

[84] Duereh A, Sato Y, Smith RL, Inomata H. Methodology for replacing dipolar aprotic solvents used in api processing with safe hydrogen-bond donor and acceptor solvent-pair mixtures. Org Process Res Dev. 2017; 21: 114-24. https://doi.org/10.1021/acs.oprd.6b00401

[85] Li Z, Smith KH, Stevens GW. The use of environmentally sustainable bio-derived solvents in solvent extraction applications—A review. Chinese J Chem Eng. 2016; 24: 215-20. https://doi.org/10.1016/j.cjche.2015.07.021

[86] Alfassi ZB, Mosseri S. Solventing out of electrolytes from their aqueous solution. AIChE J. 1984; 30: 874-76. https://doi.org/10.1002/aic.690300539

[87] Aktas S, Fray DJ, Burheim O, Fenstad J, Açma E. Recovery of metallic values from spent Li ion secondary batteries. Miner Process Extr Metall. 2006; 115: 95-100. https://doi.org/10.1179/174328506X109040

[88] Aktas S. A novel purification method for copper sulfate using ethanol. Hydrometallurgy. 2011; 106: 175-8. https://doi.org/10.1016/j.hydromet.2011.01.001

[89] Zhang Y, Zheng S, Du H, Wang S, Peng Y, Zhang Y. Alumina recovery from spent Bayer liquor by methanol. Trans Nonferrous Met Soc China. 2010; 20: s165-s168. https://doi.org/10.1016/S1003-6326(10)60033-7

[90] Zhang Y, Zheng S, Du H, Xu H, Wang S, Zhang Y. Improved precipitation of gibbsite from sodium aluminate solution by adding methanol. Hydrometallurgy. 2009; 98: 38-44. https://doi.org/10.1016/j.hydromet.2009.03.014

[91] Wang F, He F, Zhao J, Sui N, Xu L, Liu H. Extraction and separation of cobalt(II), copper(II; and manganese(II; by Cyanex272, PC-88A and their mixtures. Sep Purif Technol. 2012; 93: 8-14. https://doi.org/10.1016/j.seppur.2012.03.018

[92] Jana RK, Singh DDN, Roy SK. Alcohol-modified hydrochloric acid leaching of sea nodules, Hydrometallurgy. 1995; 38: 289-98. https://doi.org/10.1016/0304-386X(94)00069-F

[93] Le TM, Pham PTH, Hoang ND. A double salt formation from seawater bittern and ammonium sulfate. J Chem Eng Res Updat. 2022; 9: 30-8. https://doi.org/10.15377/2409-983X.2022.09.4

[94] Sahu P. Clathrate hydrate technology for water reclamation: Present status and future prospects. J Water Process Eng. 2021; 41: 102058. 102058.https://doi.org/10.1016/j.jwpe.2021.102058

[95] Alfassi ZB. The Separation of electrolytes in aqueous solution by miscible organic solvents. Sep Sci Technol. 1979; 14: 155-61. https://doi.org/10.1080/01496397908062552

[96] Mosseri S, Alfassi ZB. Separation of the KX-KXO3-KXO4 (X = Cl, Br, I) System by “Solventing-Out” Processes. Sep Sci Technol. 1983; 18: 165-75. https://doi.org/10.1080/01496398308055666

[97] Mosseri S, Alfassi ZB. The measurement of the solubility of electrolytes in water—miscible organic solvent mixture by using the “solventing out” process. Chem Eng Sci. 1985; 40: 1695-701. https://doi.org/10.1016/0009-2509(85)80030-0

[98] Govind R, Foster R. Dissolved air flotation, antisolvent crystallisation and membrane separation for separating buoyant materials and salts from water. US patent WO2014089443A1, December 6, 2014.

[99] Digarse H, Sarkar D. Production of the metastable δ-polymorphic form of pyrazinamide by isothermal internal seeding anti-solvent crystallization. J Cryst Growth. 2019; 526: 125245. https://doi.org/10.1016/j.jcrysgro.2019.125245

[100] Zhang Y, Jiang Y, Zhang D, Qian Y, Wang XZ. Metastable zone width, crystal nucleation and growth kinetics measurement in anti-solvent crystallization of β-artemether in the mixture of ethanol and water. Chem Eng Res Des. 2015; 95: 187-94. https://doi.org/10.1016/j.cherd.2014.10.018

[101] Holaň J, Skořepová E, Heraud L, Baltes D, Rohlíček J, Dammer O, *et al*. Polymorphic Crystallization and structural aspects of agomelatine metastable form X prepared by combined antisolvent/cooling process. Org Process Res Dev. 2016; 20: 33-43. https://doi.org/10.1021/acs.oprd.5b00241

[102] Kumar R, Thakur AK, Chaudhari P, Banerjee N. Particle size reduction techniques of pharmaceutical compounds for the enhancement of their dissolution rate and bioavailability. J Pharm Innov. 2022; 17: 333-52. https://doi.org/10.1007/s12247-020-09530-5

[103] Kirwan DJ, Orella CJ. Crystallization in the pharmaceutical and bioprocessing industries. In: Myerson AS, Ed., Butterworth-Heinemann, Woburn; 2002, pp. 249-66. https://doi.org/10.1016/B978-075067012-8/50013-6

[104] Gerstweiler L, Bi J, Middelberg APJ. Continuous downstream bioprocessing for intensified manufacture of biopharmaceuticals and antibodies. Chem Eng Sci. 2021; 231: 116272. https://doi.org/10.1016/j.ces.2020.116272

[105] Marques JEJr., Rocha MVP. Development of a purification process via crystallization of xylitol produced for bioprocess using a hemicellulosic hydrolysate from the cashew apple bagasse as feedstock. Bioprocess Biosyst Eng. 2021; 44: 713-25. https://doi.org/10.1007/s00449-020-02480-9

[106] Guajardo N, Schrebler RA. Upstream and downstream bioprocessing in enzyme technology. Pharmaceutics. 2024; 16(1): 38. https://doi.org/10.3390/pharmaceutics16010038