Drying and Crystallization

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1. Abstract
Crystallization is a typical downstream processing method for high quality products with high purity requirements. It is an established method used in the initial recovery of organic acids and amino acids, and more widely used for the final purification of a diverse range of compounds (Stanbury et al., 2013). Crystallisation is based on supersaturation, and crystal growth and nuclei formation processes are important aspects on this phenomena. The most common crystallisation techniques are evaporative and vacuum cooling crystallization. Elimination of moisture is a very important step for the product to go through, since moisture is responsible for corrosion and instability of the product. Drying process is usually done by emitting heat on the final product. There is also non thermal drying like adsorption by desiccant and extraction. Drying is unlike evaporation as it deals mainly with solid materials like powders.

2. Drying

2.1 Mechanism

Drying involves the final removal of water from a heat-sensitive material ensuring that there is minimum loss in viability, activity or nutritional value. Drying is undertaken to reduce the cost of transport and to package and handle material more easily.

Contrary to evaporation, drying is defined as the removal of small amounts of water from solids at a temperature below its boiling point. Moreover, water is solely removed in drying process by circulating air over the final product, whereas, in evaporation the water is removed alongside other gases in vapor form.

Monitoring of drying parameters (eg temperature) is vital to improve quality attributes such as moisture content and product appearance. Some conventional drying system does not apply process control, causing the system to encounter problems such as uneven product quality, over-dry and low energy efficiency.

2.2 Classification

Dryers may be classified by the method of heat transfer to the product (direct and indirect-IR dryers) and the degree of agitation (Stanbury et al., 2013). For example, in contact dryers (a drum dryer), the product is contacted with a heated surface, which may be used for more temperature stable bio-products. A slurry is run onto a slowly rotating steam heated drum, evaporation takes places and the dry product is removed by a scraper blade. In indirect drying the products are not in direct contact with the hot air. Instead the dryer vessel is heated from outside which makes the heated drum shell work as a heat conductor to dry those product. The indirect option is very efficient in dealing with
combustible and fine materials. However, most of the industrial dryers are direct-contact dryers, since they are more efficient than indirect dryers in most of the applications.

Dryers can also be classified based on solid handling like, static bed dryer, fluidized or moving bed. Specific types known as rotary, tray, flash, spray, fluidized bed, vacuum, and freeze dryer are explained by Mujumdar et al., 2010.

In tray dryers, materials are placed on trays and directly make contact with drying medium (typically hot air) and the heat transfer mode is typically convective. In rotary dryers, a cylindrical drying chamber rotates with material tumbling inside, with a drying medium contacting the material in cross flow and internal heat exchangers installed to allow conductive heat transfer. A flash dryer has material charging into a fast moving drying medium stream. Spray dryers have atomizers mounted on top of a drying chamber, spraying liquid/suspension that forms droplets. Hot air exits the chamber at the chamber outlet carrying dried powder, followed by the separation of hot air and powder in a cyclone.

Fluidized bed dryer is similar to fixed bed dryer but with higher operating hot air velocity to ensure the suspension of particles and larger contacting areas. In vacuum dryers, there is no drying medium (hence no convective heat transfer) but the vacuum in drying chamber reduces boiling point of solvent, reducing the operating temperature. Freeze dryers freeze the material and then reduce the surrounding pressure to allow the frozen water in the material to sublime directly from the solid phase to the gas phase.

3. Crystallization

3.1 Mechanism

Crystallization is a natural phenomena that is utilized in different artificial separation and purification processes. It is also considered as a typical polishing process in bioseparation. Those processes responsible for the production of 10^8 tonne/year of different materials, including sodium and aluminium sulfates, sodium chloride and sucrose worldwide. Purification of organic liquids using crystallization is more favorable than distillation. Crystallization process require low temperature and low energy consumption. Compared to distillation the lateral enthalpy of crystallization is lower than in distillation (evaporation enthalpy). Industrially crystallization is responsible for about 70% of solids produced. Table 1 compares the energy requirements of crystallization and distillation processes in production of various substances. (M.Giulietti, M.M.Seckler, S.Derenzo, M.I.Réand E.Calinski 2001)
Crystals formation can be achieved from liquid and vapor phase. Supersaturation is a key parameter in crystallization, since the more the dissolved materials in the solution the higher probability of crystal formation. Nuclei formation and crystal growth are the two stages in any crystallization process. The rates of those two stages determine the capacity and residence time of a crystallizer. Which makes crystallization a rate process. (Coulson and Richardson 2002).

Nuclei formation can be divided into two different cases, primary nucleation and secondary nucleation. Primary nucleation happens in crystal free systems, when concentration of solution reaches metastable limit. It can be homogenous which is spontaneous, or heterogenous which depends on the presence of foreign particles. Industrial perspective homogenous are very rare, because there is almost always some foreign object, like the dust, which makes crystallization heterogenous (Liang, J.K., 2003). Secondary nucleation is a process which start to happen when there is a presence of crystals in a supersaturated liquid, beyond metastable limit. The rate of the secondary nucleation depends on the generation of the near solid phase, cluster removal and growth to form new solid phase. Most common sources for this kind of nucleation are crystal-crystal and crystal-impeller contact. Factors affecting this phenomenon are degree of agitation, degree of saturation, cooling and presence of impurities. This happens in lower supersaturation levels which makes it the main nucleation style in industry. (Mersmann, A. 2001) Difference on effect and kinetics of these nucleation processes can be seen in picture 1.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Melting point (K)</th>
<th>Enthalpy of crystallisation (kJ/kg)</th>
<th>Boiling point (K)</th>
<th>Enthalpy of vaporisation (kJ/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>o-cresol</td>
<td>304</td>
<td>115</td>
<td>464</td>
<td>410</td>
</tr>
<tr>
<td>m-cresol</td>
<td>285</td>
<td>117</td>
<td>476</td>
<td>423</td>
</tr>
<tr>
<td>p-cresol</td>
<td>306</td>
<td>110</td>
<td>475</td>
<td>435</td>
</tr>
<tr>
<td>o-xylene</td>
<td>246</td>
<td>128</td>
<td>414</td>
<td>347</td>
</tr>
<tr>
<td>m-xylene</td>
<td>225</td>
<td>109</td>
<td>412</td>
<td>343</td>
</tr>
<tr>
<td>p-xylene</td>
<td>286</td>
<td>161</td>
<td>411</td>
<td>340</td>
</tr>
<tr>
<td>o-nitrotoluene</td>
<td>268.9</td>
<td>120</td>
<td>495</td>
<td>344</td>
</tr>
<tr>
<td>m-nitrotoluene</td>
<td>288.6</td>
<td>109</td>
<td>506</td>
<td>364</td>
</tr>
<tr>
<td>p-nitrotoluene</td>
<td>325</td>
<td>113</td>
<td>511</td>
<td>366</td>
</tr>
<tr>
<td>water</td>
<td>273</td>
<td>334</td>
<td>373</td>
<td>2260</td>
</tr>
</tbody>
</table>

Table 1: Enthalpies of crystallization and distillation in substance productions.
Crystal growth rate is the pace of transporting molecules from the solution to the critical sized crystal surface which cause the formation of crystal lattice (M. Giulietti, 2001). Surface tension of the solution and relative crystal velocity are few of the factors that affect crystal growth rate, in addition to pressure, temperature and Reynolds number. (Coulson and Richardson’s, 2002).

There is also nucleation rate which effects on crystal growth rate. This ratio depends on amount of nucleons which take part for crystal forms and attrition rate, what tells how easily crystals breaks and how small those broken crystals then reacts. In picture 2 is shown how with right nucleon rate, large circular crystals can be obtained.

3.2 Classification
Crystallization has two methods: evaporative, and cooling crystallization. These techniques are commonly used, due to their tendency for larger crystals formation. The basic principle behind these techniques is the change of temperature, which affects the evaporating/cooling rate. Supersaturation also depends on heating/cooling power, and component individual solubility. The heat effects on crystallization process can be evaluated with either heat or enthalpy balance of process. (Myerson, A. S. 2002).

Crystallizers can be divided into continuous and batch crystallizers. There is possible to do crystallization in a multiple stages. Batch processes are normally basic jacketed tanks, where different style impellers can be used. There are methods for crystal size controlling for batch crystallization, like seeding techniques, programmed cooling and ultrasound. Seeding is the most used technique of these, and its purpose is to prevent new nuclei forming in batch process, by adding tiny seeds in the tank. This decreases time which is crystallization takes, because now crystals don’t have to form in randomly interactions, recrystallization can start immediately.

The most used continuous crystallization methods are forced circulation (FC), draft tube baffle (DTB) and fluidised bed (Oslo) crystallization. With forced circulation technique you can have large or small capacity, with small or long retention time and it’s very stable process. DTC method is used for producing many organic products, due its large crystal forming and its usability for soft and fragile crystals, for example amino acids. (Myerson, A. 2002)

### TABLE 1. Comparison between different continuous crystallization methods (Mershmann, 2001)

<table>
<thead>
<tr>
<th>Type</th>
<th>Suspension density, kg/m³</th>
<th>Volume ratio of crystals to suspension, m³/m³</th>
<th>Residence time, h</th>
<th>Specific power input, W/(kg suspension)</th>
<th>Δc/ρc</th>
<th>L₅₀, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forced-circulation, FC</td>
<td>200 - 300</td>
<td>0.1 - 0.15</td>
<td>1 – 2</td>
<td>0.2 - 0.5</td>
<td>10⁻⁴ - 10⁻²</td>
<td>0.2 - 0.5</td>
</tr>
<tr>
<td>Draft-tube baffled, DTB</td>
<td>200 - 400</td>
<td>0.1 - 0.2</td>
<td>3 – 4</td>
<td>0.1 - 0.5</td>
<td>10⁻⁴ - 10⁻²</td>
<td>0.5 - 1.2</td>
</tr>
<tr>
<td>Fluidized-bed, FB</td>
<td>400 - 600</td>
<td>0.2 - 0.3</td>
<td>2 – 4</td>
<td>0.01 - 0.5</td>
<td>10⁻⁴ - 10⁻²</td>
<td>1.5(-10)</td>
</tr>
</tbody>
</table>
When choosing crystallization method, starting point is of course characters of the feed system equilibrium and production capacity. Most of the cases the focus is producing large those crystals, because those are easier to handle, more purified and there is positive impact product’s marketability. After choosing the usable crystallization method, the operation conditions have to be selected to achieve larger crystal size. These operation methods are control of supersaturation is important that it does not exceed metastable region, maximize growth rate and optimize mixing energy input so secondary nucleation is minimized. After essential mass & energy balance calculations, there should be potential crystallizer type in our mind for chosen process. When designing and testing these crystallization equipments, kinetic and population parameters of planned process should be optimized to get final product which satisfies a customer.

4. Utilization in a bioprocess technology
4.1 Insulin manufacturing (Crystallization case study)

Biosynthetic insulin is a recombinant biotherapeutic used to treat diabetes since 1982. In insulin manufacturing application, bulk crystallization and freeze drying make up an integral part of the entire manufacturing process, both employed as finishing steps in insulin manufacture process. Insulin manufacture process is a typical bioprocess, involving an upstream step and several downstream steps performed continuously to ultimately yield pure insulin crystals (Gutka and Prasad 2015).

There are several ways to employ these methods. In one process, insulin obtained from pork pancreas is dissolved under acidic conditions using acetic acid (Jackson, 1973). The pH of insulin solution is adjusted to 8.2 with sodium hydroxide solution. Insulin begins to crystallize at pH 8.2 within about 15 min, and the crystallization is complete after the solution is stirred for about 18 h at 22 °C.

Another method to obtain zinc-free insulin crystals for pulmonary use involves using sodium acetate (Havelund, 1998). Based on this method, purified human insulin is dissolved in TRIS buffer, pH 8.0, and ethanol mixture. A precipitate forms immediately after the addition of sodium acetate to this solution. The crystals then form after about 2 days, which are then washed with cold ethanol, isolated by centrifugation, and dried.

In a process for manufacture of a modified insulin intended for oral delivery (Dave et al., 2008), a modified insulin is synthesized using covalent conjugation of native insulin followed by purification. The purified insulin is crystallized by adding phenol and zinc chloride at a pH of about 4.8. The crystals were washed with cold water to remove excess zinc and phenol and dried into powders.

In the described processes, the residual moisture in the insulin crystals is removed by vacuum drying or bulk freeze-drying. Typically, post-crystallization involves a washing step to retain important quality traits of freeze-dried insulin. Successful washing step ensures that inorganic salts, buffer residues and residual organic solvent are removed for the final freeze-dried insulin to have its ideal quality properties.

There are several advantages when it comes to freeze drying and crystallization of insulin as a formulation. A crystalline/freeze-dried solid at the end of a long manufacture process is a storage handling and logistics process advantage with less volumes to store and handle at the end, compared to liquid products. The availability of the insulin in a freeze-dried solid form also presents a unique advantage, as it can be used for manufacture of
4.2 Drying techniques (Case study)

Biomass is a form of renewable energy for heat and power generation. In industries, biomass drying is important because dry biomass provides considerable benefits for combustion, such as increased boiler efficiency, lower flue gas emissions and improved boiler operations, compared to fuels with high moisture. An initially low level of fuel moisture however could recover much of the energy used during combustion for water evaporation.

The various dryer types used are rotary dryers, flash dryers, fluidised-bed dryers and belt dryers. Rotary dryers, for instance, are the most common type for biomass applications and have low maintenance costs. They are robust, flexible and easy to construct, enabling this type of dryer to operate under the most arduous conditions.

In one application, waste heat from process industries is used to dry biomass as it reduces energy consumption (H. Li et al., 2012). Here, belt dryers are more suited since they can operate at a lower temperature, which suits the usage of low grade waste heat as heating source. The diagrams of how this is implemented is shown in Figures 2 and 3.

![Figure 2: Schematic of the biomass drying process using waste heat](image-url)
Figure 3 shows that moist wood is indirect contact with heated flue gas. Usually the dryers are positioned with slight inclination, as the dried products are in a lower level than the input end. In order to transport the materials through the dryer using gravity.

5. Conclusion

All industry processes have their pros and cons. Depending on the application, we should select the optimal downstream process to formulate our products. To do this, we must very well understand what the advantages and disadvantages of our processes are for a wiser selection.

To compare between the selection of different driers, we see that rotary dryers are the simplest to install and maintain hence have low costs during construction, but compared to flash dryers and belt dryers, rotary dryers have higher fire risk owing to higher operating temperatures. Flash and belt dryers have high heat and mass transfer rates to remove moisture rapidly, but their high installation costs make them less favourable. Freeze dryers are commonly used in food industries because nutrients and flavours are retained and rehydration is easy. However, the equipment used are very costly, and not all foods can be freeze dried (pre-treatment may be needed). Depending on the application or process, engineers need to know which method would best benefit the company and consumers.

In crystallization the purity and size of the crystals can be controlled which makes it very common in different sectors of the industry. High supersaturation prerequisite is considered one of its drawbacks, since a decrease in concentration can cause the ability to recover pure materials to decrease. Another disadvantage is the requirement for large amount of solvents during the process and crystal wash. Furthermore, consecutive crystallizations are needed to achieve more pure crystals.
6. References


