ChE 4162

CRYSTALLIZATION EXPERIMENT – Salicylic Acid Crystallization

Note: Read your assignment first. Not all sections below are relevant to all assignments.

Introduction

The processing of biochemicals and pharmaceuticals is just as important to Chemical Engineering today as petrochemical production and oil refining. Such processing involves operations such as crystallization, ultracentrifugation, membrane filtration, preparative chromatography and several others, all of which have in common the need to separate large from small molecules, or solid from liquid. Of these, crystallization is the most important from a tonnage standpoint; it is commonly employed in the pharmaceutical, chemical and food processing industries. Important biochemical examples include chiral separations (Wibowo et al., 2004), purification of antibiotics (Genck, 2004), separation of amino acids from precursors (Takamatsu and Ryu, 1988), and many other pharmaceutical (Wang and Berglund, 2000; Kim et al., 2003), food additive (Hussain et al., 2001; Gron et al., 2003) and agrochemical (Lewiner et al., 2002) purifications. The control of crystal morphology and size distribution is critical to overall process economics, as these factors determine the costs of downstream processing operations such as drying, filtration, and solids conveying. If you are unfamiliar with crystallization, you should consult a specialized textbook, e.g., Ch. 17 of your Unit Operations textbook (Seader et al., 2011) or Chapter 27 of the previous Unit Operations textbook (McCabe et al., 2005), and/or notes on Crystallization from ChE 4151.

Our experimental crystallization apparatus enables study of key facets of crystallization: (a) effects of key parameters such as supersaturation and cooling/heating rates on solids content, morphology and crystal size distribution; (b) on-line control of crystallization processes. The different classifications of crystallization include cooling, evaporative, pH swing and chemical modification. We use an offline microscope to measure from 10-1000 μ crystal sizes, a typical size range for crystallizations of biologicals.

The current experiment is a “chemical modification” crystallization, generating salicylic acid (precursor of aspirin) crystals from the rapid reaction of aqueous solutions of sodium salicylate (NaSAL) and H₂SO₄ (Franck et al., 1988, see the Appendix for the chemistry). The byproduct sodium sulfate remains (mostly) soluble. This “chemical” crystallization has many facets in common with crystallizations of other biologicals such L-ornithine-L-aspartate (LOLA), used to treat chronic liver failure (Kim et al., 2003). However, whereas the precursor L-ornithine hydrochloride costs >$300/kg and is difficult to recycle, we buy sodium salicylate for ~$50/kg, and the salicylic acid can be reused by rinsing and draining out the byproduct sodium sulfate, and then reacting the salicylic acid with NaOH solution, followed by recycle.
System Overview

The crystallization apparatus consists of two feed tanks, two variable speed (peristaltic) pumps, a crystallizer, a circulating bath for temperature control, power controller, product tank, a makeup tank for feed regeneration, and a recycle pump. There are pH and temperature probes on the crystallizer. There is also a UV/VIS spectrophotometer for offline analysis of dissolved salicylate concentration, along with miscellaneous other instruments, valves and variable speed agitators. A complete list of the equipment tag designations can be found below.

The crystallization itself takes place in a baffled ~5 L glass vessel equipped with an air-driven agitator, thermocouple, pH probe, sampling port and extra ports. Temperature is controlled by a thermostated bath and power controller with its own thermocouple. Air is supplied to the agitator after filtering. The crystallizer normally does not require cleaning. If you are told to clean it, use soap and hot water and rinse with DI (deionized) water. This is true as well for all other glassware used in this experiment. To disassemble the crystallizer, remove the agitator unit using a box wrench, slide it up the stand, remove all probes and place them on towels (remove pH probe slowly and carefully - easy to break). Rinse the pH probe with DI water only and put it back in its plastic container (contains KCl solution). Leave everything else on a CLEAN (e.g., towels) surface. Then disconnect the overflow line, feed lines and hot water lines (quick-connect fittings) and lift the internals from the glass vessel.

There are organic (sodium salicylate, NaSAL) and acid (sulfuric acid, 0.25 M = 0.50 N) solutions fed to the crystallizer. A base (NaOH) solution can be fed to the product tank from a base makeup tank, or instead added to washed solid salicylic acid product + fresh water, after filtration to separate the salicylic acid crystals (which procedure to use depends upon the assignment). Water can be fed to the makeup tank from the city water supply. The NaSAL can be added to the feed tank from either a bottle of the pure solid or by recycle of used NaSAL solution from the product tank. You should wear latex gloves when handling NaSAL, salicylic acid or their solutions. The NaOH is available as a 2 N solution (base makeup tank), which should be handled with latex gloves. Sulfuric acid (0.25 M, 0.5 N) is available from a large tank near the center of the lab and can also be handled with latex gloves.

Some physical properties of the key chemicals can be found in crystallizer.xls. Typical pH values for both NaSAL solutions and saturated salicylic acid slurries can also be found there. These values were measured using the same probe used in the crystallizer.

Operating the Crystallization Experiment

1. Using the Honeywell Experion PKS Control System

Honeywell’s Experion is a distributed control system (DCS) widely used in industry and on many lab experiments here at LSU. In Experion, each process variable is represented by an entity called a Control Module (CM). Each CM is a collection of Function Blocks (FB). And each FB consists of many values called parameters. Within a CM (and
sometimes between CM’s), the FB’s are “wired” together in various ways to monitor and control the process. Desired values of many parameters may be entered via the computer keyboard. The purpose of the next few sections is to explain how to use Experion to run this equipment.

2. Logging in to Honeywell System

Access to the Honeywell Experion DCS application is through ChE-UO Lab. A splash screen should appear with an OK button. Click OK, then open the Honeywell Station software by double-clicking the Station icon. Select “Enter”. Then from “Units” on the toolbar, select “CRU”. The CRU P&ID schematic will appear. There is also a schematic (obtained by clicking the Trend 40 button) which shows trends of the analog values associated with the unit.

![Crystallization Unit](image)

Figure 1. P&ID for CRU – Crystallization Unit

3. Understanding Experion PKS Control System Terminology

On the main schematic, each measurement transmitter and continuous controller is represented by a circle containing its tagname. The first letter of the tagname indicates the type of measurement: A for analyzer (pH in this case), T for temperature, L for level,
or F for flow. There are also four device controllers (sometimes called discrete controllers): solenoid valves which either start/stop the flow in a line, or switch the flow from one line to another. When you click on a circle representing any measurement or continuous controller, or a square representing a solenoid valve, a faceplate will appear in the lower right corner of the schematic. It contains the tagname, engineering units, description, and PV for transmitters. For continuous and discrete controllers, additional values and controls are available (see below).

To change an analog value from a schematic or from a faceplate, single click the value (if change is allowed, its background color will change), and then enter the new desired value. To change the mode of a continuous controller, use the combo box labeled MD near the bottom of its faceplate (more about controller modes below). To change the output of a device controller, use the OP radio buttons on the right side of its faceplate.

At the start of a run, all continuous controllers should be in manual mode (yellow backgrounds), and all solenoids should be either closed or in recycle (green backgrounds). Open the Drain Solenoid (D402) for practice. Notice that the solenoid valve changed from green (closed) to to red (open) when you open the valve. When you close the solenoid, the color sequence will be from red to green.

A transmitter’s most important value is the measurement of the process variable itself, abbreviated as PV. This value is shown in cyan (light blue) near the circle.

Controllers have several additional values, the most important of which is the setpoint or SP. This is just like the speed setting on a cruise control - the controller will manipulate its output (e.g., speed on a variable speed pump, or stem position on a valve) to move the PV to the SP and hold it there. The SP (in green) and the PV (in cyan) are shown near the circle representing the controller. The OP always has units of percent (0-100%) and the SP has the same engineering units as the PV. On the crystallizer, pH is measured in pH units, flow rates are in mL/min, levels are measured in percent full, and temperatures are measured in °C.

When the controller mode is MANUAL, the OP is held until the operator changes it. If you want to change the OP, simply click the OP in the faceplate, type in the new value, and press ENTER. The new OP will be held until you change it again. Note that you can change an OP only while a controller is in MANUAL. For practice, click the NaSAL flow rate controller (to call up its faceplate) and change the output to 50%, then to 100%, and back to -6% (-6% is known as “tight shutoff” in the PKS system). Notice the small bar under the control valve on the schematic – its length is proportional to the output.

When the mode is AUTO, the controller uses the PV, SP and tuning constants to calculate a new OP. You may enter a new SP to be used for control. Note that changing an SP affects the OP only while a controller is in AUTO. If the mode is CAS (“cascade”), this means that one controller’s OP (the “primary” controller) is sent to become another’s SP (the “secondary” controller). In this system, T401 (reactor T controller) is a primary, while T402 (bath T controller) is a secondary. T401 should be in AUTO mode. T402 should be in CAS mode. The SP for T401 should be set 2-3°C higher than the desired reactor T at first, and if this proves too high you can always lower it later.
Notice that the circle representing a continuous controller is filled with a background color, which indicates the current mode of the controller - yellow means the mode is **MAN**, and white means the mode is **AUTO**.

**Display Navigation**

When you logged into Flex Station, you used an item from the menu bar to call up the main PDU schematic. There are several additional ways to go from one display to another. For example, you can enter the tagname of a CM in the Command field at the top of the screen and press **F12** to call up the detail display. Try it with your bath temperature controller (T401). For continuous and discrete controllers, the detail display has 7 tabs, and for a measurement, only three.

Most of the toolbar buttons are used for navigation – some require a name or number to be entered, and some go directly to the display. Most of the same functions are on the function keys. For example, to return to the previous display, click ◼️, or press **F8**. To return to the display before that, do it again.

From most displays (both system displays and custom schematics such as CRU), double clicking any value associated with a CM will take you to its detail display. From a detail display, click ◼️ or press **F2** to return to the main CRU schematic. On most custom schematics there may also be buttons to quickly get you from one display to another.

**Understanding Trend Schematics**

There is a button on the CRU schematic to call up trends. The button is labeled Trend 40 and displays **PVs** and **SPs** of the principle variables on the unit.

At the bottom of the trend is the legend with all the **tag.block.parameters** associated with the traces. The checkboxes in the **Pen** column indicate which traces are currently on the trend. Click on the chart area of the trend and a white hairline cursor appears on the chart and the values at the hairline cursor appear in the **Reference** Value column of the legend. Along the bottom of the chart area is a horizontal scroll bar which allows you to scroll the chart area back and forth. Along the left axis are the low and high ranges of the selected trace. These ranges allow you to change the range of the trace for the selected parameter. Practice by changing the range of one of the flow controllers to 20-80.

Immediately above the left side of the chart area is a combo box which allows you to select one of the traces (you may also click anywhere on the line for this trace in the legend area). When you select an active trace, it is highlighted (thicker) in the chart area. Above the right side of the chart area is the **Period** combo box which allows you to select how much data (time-wise) is displayed in the chart area. To the right of that is the **Interval** combo box which allows you to select the interval between points in the chart area. Practice changing to a different period and interval. Leave the period set to 1 day and the interval at 1 minute for now.
For practice, scroll back until some variation in some of the traces appears. Notice that the timestamps below the chart area change as you scroll. Find some local max or min in one of the traces and click or drag the hairline to it. Now change the period back to one hour and notice that the cursor is centered on (or at least near) the local max or min. If necessary, move the hairline so it is exactly on the peak or valley and notice that the values, as well as the date and time, are shown in the **Reference Value** column in the legend. Now return the trend to the current time by clicking.

All changes you make to the trend can be saved by clicking the familiar Windows Save icon just above the right end of the chart area next to the word **(Modified)**.

**Saving Data into Excel**

You will collect a great deal of process data. To save these data, an Excel workbook containing a Visual Basic Add-In is provided. In Windows Explorer, navigate to APPS\CHE4162\CHE4162-HW Excel Data Recorders\snr and select **CRURecorder.xls**. The workbook will open with a **Start** button, the experiment name, a collection frequency **Combo Box**, and a **Stop** button on the top line. Click on the **Start** button, and the workbook will start collecting the relevant data at the specified collection frequency. These data will be extremely useful in analyzing your results. While the workbook is collecting data, it may be scrolled, but you should not attempt to do anything else in this instance of Excel until after you click on the **Stop** button. If you do, the collector may stop and you may lose valuable data.

**Tag Descriptions with Engineering Units – Table 1**

<table>
<thead>
<tr>
<th>TagName</th>
<th>Description</th>
<th>EngrUnit</th>
</tr>
</thead>
<tbody>
<tr>
<td>A401</td>
<td>Reactor pH</td>
<td>pH</td>
</tr>
<tr>
<td>D401</td>
<td>Product Recycle Solenoid</td>
<td>Open/Closed</td>
</tr>
<tr>
<td>D402</td>
<td>Product Drain Solenoid</td>
<td>Open/Closed</td>
</tr>
<tr>
<td>D403</td>
<td>Product Water Supply Solenoid</td>
<td>Open/Closed</td>
</tr>
<tr>
<td>D404</td>
<td>NaSAL Feed Solenoid</td>
<td>Recycle/Feed</td>
</tr>
<tr>
<td>D405</td>
<td>H2SO4 Feed Solenoid</td>
<td>Recycle/Feed</td>
</tr>
<tr>
<td>F404</td>
<td>NaSAL Flow Rate Control</td>
<td>mL/min</td>
</tr>
<tr>
<td>F405</td>
<td>H2SO4 Flow Rate Control</td>
<td>mL/min</td>
</tr>
<tr>
<td>L403</td>
<td>Product Tank Level</td>
<td>Percent</td>
</tr>
<tr>
<td>T401</td>
<td>Reactor Temperature</td>
<td>Deg C</td>
</tr>
<tr>
<td>T402</td>
<td>Bath Temperature Control</td>
<td>Deg C</td>
</tr>
<tr>
<td>W400</td>
<td>Feed weigh scale</td>
<td>Kg</td>
</tr>
</tbody>
</table>

**4. Startup and Shutdown**

1. Be sure the crystallizer is full to the overflow level, with either water or salicylic acid slurry (in crystallization literature, the slurry is often called “magma”). Turn on agitator for the crystallizer. Turn on thermostated bath and pumps. Set the temperature controller T401 to AUTO and T402 to CAS, and the setpoint for T401 to the desired T. Usually works best if you make the SP for T401 a little hotter than the desired reactor T (by 2-3°C) – can always lower it later.
2. The default setting on the 3-way valves for the feed tanks is recycle. Leave them in recycle for now. Set desired flow rates.

3. Verify that both feed pumps are operating. Sometimes the tubing at a pump head will leak. In this case the tubing must be replaced. Find the lab coordinator.

4. If you make up your sodium salicylate (NaSAL) solution in the feed tank, run the pump in recycle for a few minutes to ensure homogeneity in the tank.

5. Confirm that the product tank is not full and that the drain valve is closed.

6. Switch to feed mode on both 3-way valves. This is time zero for an experiment.

7. Periodically check the overflow line. Under certain conditions it may block up. If so, squeeze the flexible tubing connecting the crystallizer and product tank, and use a spatula or piece of steel tubing to ream out the line entering the product tank. If the blockage is at the exit of the crystallizer, use a piece of steel tubing (there is a hole in the overflow tube to fit the tubing). Samples can be collected from the overflow line, or directly from the crystallizer through the sample port using a wide-mouth pipette.

8. To shut down the system, set the 3-way valves to recycle, set the pump outputs to 0%, return the T-controllers to room T, and shut off the pumps, agitators and thermostated bath.

9. If using the spectrophotometer, remember to shut off the lamps.

**Recycling NaSAL**

NOTE: There is a filter station set up near one of the sinks. If you don’t know how to use a Buchner funnel/aspirator, your Instructor will demonstrate.

ALL solid salicylic acid must be collected and eventually added to the waste pail for ultimate recycle. This means all slurry product must be filtered, even if your assignment doesn’t call for using recycled material. The filtrate should be mostly Na₂SO₄ and can be discarded in the drain near the DI water station, or down the sink. The solid salicylic acid should be washed with DI water to remove any Na₂SO₄ adhering to the crystals. The salicylic acid should then be dried at 70°C for at least 1 day before re-use. Also collect the solid in the bottom of the product tank (scoop); wash it also.

The drying must be for one day (or more). To convert back to sodium salicylate, weigh the dried solid acid, return it to the product tank or to a large flask, then add the required water and about half the (estimated) required amount of 2 N NaOH from the makeup tank. Turn on the agitator for a few minutes to homogenize. Sample the liquid and check the pH. Repeat this process (adding small amounts) until you have reached the theoretical amount of NaOH, at which time the pH should be in the 8.0-8.5 range. All of the salicylic acid should disappear.

Sample your recycle material, diluting appropriately, and check its NaSAL concentration by UV/Vis (see below). Then calculate how much fresh NaSAL solid must be added to the feed tank with the recycled material. You can store excess recycle
solution in the plastic bottles provided. Be sure to label properly and give the NaSAL concentration on the label.

**Using the spectrophotometer**

Dissolved NaSAL and salicylic acid concentrations can be measured simultaneously by UV/Vis spectroscopy. An on- and off-line analyzer probe (Ocean Optics) is provided for this purpose. Handle this probe with care. Nothing should ever enter the liquid tip except the (diluted) process fluid or distilled water for cleaning. Don’t place the probe on a dirty surface. The absorbances of dissolved salicylate and salicylic acid can be assumed additive (why?). **Be sure to turn off the lamps at the end of a lab period, to prolong their life.**

The Ocean Optics spectrometer itself resides in a module (connected to the network through a USB port) near the experiment. Fiber-optic cables transmit the radiation from the DT-1000 source to the probe and the detected signal to the network.

1. From a separate computer, click either “OO1” or “OO2”. Locate the SX Virtual Link icon on the desktop and double-click to display the main application window for the SX Server Link application, as shown in Figure 2. This display should show two Ocean Optics USB 2000 devices, one for the Permeameter (given by location 2.41.0) and one for the Crystallizer (given by location 2.41.3). If these do not appear on this display, disconnect and reconnect the power to the field USB hub. After the hub completes its self-test cycle, these two devices should appear on this display. If not, contact the lab coordinator.

![Figure 2. SX Virtual Link main application screen.](image-url)
2. In the SX Virtual Link window, select the desired Ocean Optics device by double clicking on it. The Available wording on the item in question should change to You are Connected. And the right arrow head should change to a green check mark. At the end of use on any lab day, disconnect the USB connection by clicking the rightmost of the two round buttons on the bottom of the window.

Please be sure to perform this disconnect operation as no other computer will be able to connect to the spectrophotometer until your connection is closed!

3. Double click the SpectraSuite© icon on the desktop to start the SpectraSuite application file. The pdf manual can be obtained from START ➔ Ocean Optics ➔ SpectraSuite (START button at lower left of computer’s display). What is given below is the capsule version of this manual.

4. Switch on both the UV and VIS lamps on the source. The red light at the top will come on when the UV lamp is warmed up and ready for a test. (Be sure to turn the lamps off at the end of the lab period.) Set the acquisition mode to Scope.

With this main window open, ensure that you are in Scope mode by clicking on the Scope button – the blue “S” button on the toolbar directly above the graph.

5. On the top menu bar, change the Integration Time to 250 ms, the Scans to Average to 10, and the Boxcar Width to 2 (unless otherwise instructed). Check the boxes for Strobe/Lamp Enable, Electric Dark Correction, and Stray Light Correction. No other boxes should be checked or parameters changed on the top menu bar.


The spectrometer – in order to give you meaningful results from your work – will require the generation of a Dark Spectrum file and a Reference Spectrum file.

a) Immerse the probe into a test tube filled with DI water. Be sure that the probe mirror/cap is completely secured to the probe. A partially secured mirror/cap (i.e., not completely screwed on) will negatively affect your readings.

b) To create a Dark Spectrum file, unplug the probe from the light source (white box). Your graph should nearly trace the x-axis. When the probe has no light source and the detector has no light reaching it, the spectrum generated is called a Dark Spectrum. To save your newly created Dark Spectrum, click on the grey light bulb (labeled Store Dark Spectrum). You can also save this spectrum through File -> Store -> Store Dark Spectrum.

c) To create a Reference Spectrum file, plug the probe connection back into the light source. Some peaks should appear on the graph in SpectraSuite. To save this Reference Spectrum, click on the yellow light bulb button (labeled Store Reference Spectrum). You can also save this spectrum through File -> Store -> Store Reference Spectrum.
d) Both of these saved files – the dark and reference spectra – serve as reference points. You will have to re-generate them every time you open the SpectraSuite software unless you also save them on a flash drive. But it is recommended that you do so once/day anyway.

e) If ANY settings are ever changed (e.g., Integration Time, etc.), both the Dark Spectrum and Reference Spectrum must be generated again.

7. Switch from Scope to Absorbance mode. For NaSAL solutions, you should see absorbance at <400 nm, usually two peaks. A wavelength near the second peak (~300 nm) is usually adequate for quantification. For some old data on these solutions, see crystallizer.xls.

8. Note that quantification is only possible if NaSAL/salicylic acid solutions follow the Beer-Lambert law (absorbance in the “linear region”). For the salicylate ion, this region is A < ~0.9-1. Examining the data in crystallizer.xls, this criterion suggests that you MUST dilute NaSAL solutions (with DI water) to ~0.05 g/L or less in order to quantify them. Then you quantify the unknown solutions by comparing to the absorbance of an appropriately diluted standard solution:

\[ \frac{C_u}{C_s} = \frac{A_u}{A_s} \]

Where C is concentration, A absorbance, “u” an unknown, and “s” a standard solution of NaSAL. Note that BOTH “u” and “s” must show absorbance inside the linear range. The absorbance at the cursor is read at the bottom left corner of the display.

9. In spectroscopy, the absorbance depends on a couple of factors. First, the type of chemicals, second the concentration. Third, the path length in the fluid, which in turn depends on what probe tip is installed.

10. The SpectraSuite program has a tendency to freeze up such that it can’t even be closed. When this happens, use the “Task Manager” (press CTRL-ALT-DEL simultaneously to get it) in order to close it. When you re-start, you will need new “Dark” and “Reference” files unless you stored them on a flash drive.

**Spectrophotometer Trouble-Shooting Tips**

1) The following are possible problems: a) The probe window is coated with something other than the standard. Wash with a lot of DI water. b) The lamp has failed and its raw signal intensity is < 1000 in the Scope mode. c) The optical fiber connecting the probe to the USB 2000 unit is broken or frayed. See the lab coordinator for a replacement probe if no other problem can be found.

2) Never let the PC go into standby or hibernation mode as the USB communication will be lost when this occurs.

**Gravimetric analysis for salicylic acid**
The salicylic acid (solid) concentration can be determined gravimetrically. Use labeled test tubes to collect the samples. Centrifuge for 5 min, unless otherwise instructed. Then decant most of the water (without losing crystals); this liquid can be used for NaSAL spectrophotometric analysis. Dry the test tubes upright in the Blue M oven at 60ºC, for one day or more. Weigh, clean out the tubes, then re-weigh. Alternative procedures may also be part of your assignment.

**Size determination of salicylic acid crystals**

Use a microscope slide to mount your samples. It’s OK to dry the samples first. Make sure the slide is clean by polishing it with a Kimwipe™. Do not put too many crystals onto the slide; too many crystals will make it difficult to see the individual crystals under the microscope. Use the spatula to center the crystals on the slide.

The Leitz Wild microscope communicates with the computer next to it (log in as usual), which contains software (AMSCOPE) to measure the sizes. Switch on the microscope power source, then increase stage illumination (voltage meter) by turning the knob on the power supply. Set the voltage to at least 10 V by adjusting the knob. You can go to 12 V later if necessary to get adequate illumination.

The microscope itself has four different objectives (6x, 12x, 25x, and 50x). The appropriate objective (often 25x) depends on the size of the crystals in the sample. To aid in the measurement of particles, the Leitz Wild is equipped with a USB microscope camera. Since the camera is not parfocal with the microscope’s eyepiece, its focus must be set independently of the eyepiece focus. This is done through the camera’s included software.

**Connecting the microscope camera to the network**

Click “Connect” and log in as usual. Double-click the SX Virtual Link application desktop icon. The microscope camera is shown as the ScopeTek DCM500. Double-click. It should say “You are connected.” At this point, you can minimize the SX Virtual Link interface. Remember to disconnect at SX Virtual Link at the end of the day. The “Disconnect” button is on the bottom right of the SX Virtual Link display.

**Camera operation and picture taking**

Open the AmScope 64 software by double-clicking its icon. The start Page opens, on which should be seen ScopeTek DCM500 listed under the Live Capture link. Single click that link. A Video window should open. If microscope illumination is powered on, and its settings are appropriate, and a slide with crystals is on the microscope stage, then crystals should appear in that window. However, initially, the image may look unfocused.

Focus the camera image using the large focusing knobs on the vertical mount of the microscope. Once the image is focused, check to see if the magnification of the crystals being viewed is appropriate. Hint: they must be large enough for you to be able to draw a line from one side to another – a technique you will use later in crystal sizing. If the crystals appear too large choose a smaller objective, if too small choose a larger one. The image will need to be refocused with every objective change. You can also use software.
zoom (see drop down box near top of program screen) to bring the field into large view on the computer’s monitor. A value of 40 to 50% usually works well.

Now the crystals are ready to be photographed. This can be done either individually or sequentially. Under the Capture menu item, find the Capture a Frame button, to take an individual photo. Pictures can also be taken at set intervals by clicking the timer toolbar button. This will open a window that will ask you where the files are to be saved. It will also ask you what type of image file you want. Save pictures in .tiff format. Picture files can be named to keep track of sample, slide, and photo number. The other options dictate how often the camera will take pictures and how many it will take. Note that the timer option will automatically save the photos while the individual method requires manual saving for each picture taken.

**Analysis of crystal size from a photo**

After opening a photo, open a new layer by clicking on the LAYER toolbar and choosing NEW. Click OK on the window that opens. Next, go to the OPTIONS toolbar and click the Annotations option. In the new window select “line” under the object heading. Switch the line color to a color other than black. Look at the bottom of the window and look for a yellow ruler. Make sure the word ‘**pixels**’ is displayed next to it. If it is not then right click on the yellow ruler and select pixels.

Measure the crystals by clicking the line icon on the toolbar and choosing any line. Left click on one side of your crystal and move the line to the other side of the crystal. Left click a second time to finish the line. The photograph in Figure 3 is an example of the results of this process.

![Figure 3 - Sized crystals (NaCl)](image)

The line details should show up on the bottom of the picture in the Annotations Manager window. Under the column called Length are the numbers of pixels that each line drawn contains. If you do not see this then click on VIEW toolbar and make sure that Annotations Manager is checked. An example of the contents of the Annotations Manager window can be seen in Figure 4.
Repeat the measuring process for all of the crystals in the frame. Selecting crystals to measure would establish a bias in sizing – not something one would want to do.

Once the crystals are measured, right click on the Annotations Manager pane at the bottom and select “Export”. The data can either be sent to Excel™ or to the clipboard via the current layer option. If the Excel™ option is selected a new Excel window is opened, containing the data from the Annotations Manager, as shown in Figure 5.

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In order to convert line length in pixels to an actual length in microns, the following table is used. The particular value depends on the objective that was used when the photograph was taken.
Table 1: Pixel size versus microscope objective power¹

<table>
<thead>
<tr>
<th>Objective</th>
<th>Microns per pixel¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>6x</td>
<td>3.23</td>
</tr>
<tr>
<td>12x</td>
<td>1.62</td>
</tr>
<tr>
<td>25x</td>
<td>0.775</td>
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<td>50x</td>
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</tbody>
</table>

¹Data are for a full resolution 2592 x 1944 pixel image. If you are using images of lower resolution (e.g., 864 x 600 pixels), then an additional multiplier (e.g., 3, in the case of a 864 x 600 pixel image) – over and above the ones indicated above – will be required to convert from pixels to microns.

Theories of Crystal Growth

Unit Operations textbooks (e.g., Seader et al, 2011; McCabe et al., 2005) discuss the common mechanisms for initially generating (“nucleating”) crystals, but only heterogeneous nucleation takes place here. It is the more common mechanism. Both existing crystals and other solid surfaces such as the agitator can catalyze heterogeneous nucleation. If “n” is the number density of crystals (mol/volume), then the nucleation rate $B^0$ is often expressed as initial growth in the key linear dimension (L) per unit time (t) times the number density of just-formed crystals ($n^0$). The subsequent growth rate $G$ is expressed as $dL/dt$. An example of L would be the radius for a spherical crystal. The relation between $B$ and $G$ is then by definition:

$$B^0 = n^0 G$$

where $n^0$ is the number density for just-formed crystals. The birth rate can be empirically correlated with key physical and operational parameters by (Garside, 1985):

$$B^0 = K_B F(\text{geometry}) \Delta C^b M_j N^h$$

where $\Delta C$ is the supersaturation (liquid concentration of solute is excess of equilibrium solubility), $N$ is stirrer speed, and $M_j$ is the jth moment of the crystal size distribution (called $M_T^j$ in Seader et al., 2011). For typical agitated crystallizers, j and h are both ~3, and the geometry function is:

$$F(\text{geometry}) = \frac{p D_s^5}{V}$$

where $p$ is propeller pitch, $D_s$ is stirrer diameter, and $V$ is liquid volume.

The crystal growth rate is primarily a function of supersaturation, and is usually correlated as:
This can in turn be written in terms of series mass transfer and kinetic resistances (McCabe et al., 2005). The powers $b$ and $g$ are system specific. The ratio of the two, $b/g$, is often called the “relative kinetic order”, i. Because $B^0$ and $G$ both depend upon $\Delta C$, if $\Delta C$ is constant at constant $T$, $N$, geometry etc. (as is possible for a MSMPR, or perfectly stirred tank, crystallizer), then $B^0$ and $G$ can be related:

$$B^0 = K_R G^i$$

(5)

Examples of such correlations for specific crystallizers are known. Note that the power “i” in these correlations varies between 2.8 and 6.

Because the number density $n$ is a probability (differential) density function with respect to $L$, then $n \, dL/(\Sigma n \, dL)$ represents the fraction of crystals at a particular value $L$ to $L+dL$. Let this fraction be called $\psi$. Then a mass balance on the fraction in any control volume gives:

$$\frac{\partial}{\partial t} (\psi n) + \nabla \cdot (\psi Q/V) = -\nabla \cdot (\psi G' \psi)$$

(6)

For an MSMPR crystallizer there is no accumulation, $Q_{in} = Q_{out}$, and, because we are perfectly mixed, $G$ is a constant. So the general population balance becomes:

$$\frac{dn}{dL} = -\frac{n}{G \tau}$$

(7)

Where $\tau$ is the space time ($V/Q$). Using the initial condition and eq. (1) this is easily solved to give:
\[ n = \left( \frac{B^0}{G} \right) \exp\left[ -\frac{L}{G \tau} \right] \] (8)

Eq. (8) predicts an exponential distribution for the number density produced in an MSMPR, with an average \( L = G \tau \). In all likelihood, your observed distribution will be exponential but truncated at small \( L \). There are several reasons for this. First, very small crystals have a higher solubility and so are re-dissolved. Second, the microscope cannot distinguish crystals of below a certain size. Therefore when determining \( B^0 \) and \( G \) from a crystal size distribution, it is best to do so by regression, not by using the moments. However, the cumulative and differential distribution equations, and moment equations, for an MSMPR are well known. Some are given in the Crystallization notes provided, and in Table 17.9 of Seader et al. (2011). Note that the zeroth moment of an already precipitated and separated crystal size distribution is the crystal’s molar volume, while in the magma the zeroth moment is the crystal molar concentration.

References


APPENDIX - The Chemistry of Salicylic Acid Crystallization

The reaction presumably is:

\[ \text{Na}^+\text{SAL}^- + 0.5 \text{H}_2\text{SO}_4 \rightarrow \text{SAL} \text{ (ppt)} + \text{Na}^+ + 0.5 \text{SO}_4^{2-} \] (1)

The chemistry implied by reaction (1) is actually a quite simplified description of the actual crystallization. The reactions taking place are as follows (the K’s will be used to denote the reaction equilibrium constants, and \( \text{H}_2\text{SO}_4 \) dissociates completely to \( \text{H}^+ \) and \( \text{HSO}_4^- \), as does \( \text{Na}^+\text{SAL}^- \) to its ions).

**Nomenclature used:**

- \( C(RM) \): Concentration of NaSAL in feed (mol/L)
- \( C(H_2\text{SO}_4) \): Concentration of \( \text{H}_2\text{SO}_4 \) in feed
- \( C(S) \): Concentration of salicylic acid crystals
- \( C(L) \): Concentration of salicylic acid in solution
- \( C(\text{SAL}) \): Concentration of \( \text{SAL}^- \) ions
- \( C(\text{SO}_4) \): Concentration of \( \text{SO}_4^{2-} \) ions
- \( C(\text{HSO}_4) \): Concentration of \( \text{HSO}_4^- \) ions
- \( Q_{RM\text{feed}} \): Flow rate of NaSAL feed (L/min)
- \( Q_{H\text{feed}} \): Flow rate of \( \text{H}_2\text{SO}_4 \) feed
- \( Q_{out} \): Flow rate of product or effluent.

**Unknowns:** \( \text{pH}, \text{pOH}, C(S), C(L), C(\text{SAL}), C(\text{SO}_4), C(\text{HSO}_4) \)

**Equations used to predict the concentrations at equilibrium:**

Equilibrium of water:

\[ \text{pH} + \text{pOH} = pK_w \] (1)

Dissociation of \( \text{SAL}^- \):

\[ K[\text{SAL}] = \frac{[\text{H}^+][C(\text{SAL})]}{C(L)} \] (2)

Dissociation of \( \text{HSO}_4^- \):

\[ K[\text{HSO}_4] = \frac{C(\text{SO}_4)[\text{H}^+]}{C(\text{HSO}_4)} \] (3)

SAL balance:

\[ Q_{out}(C(\text{SAL}) + C(S) + C(L)) = Q_{RM\text{feed}} C(RM) \] (4)

\( \text{SO}_4^{2-} \) balance:

\[ Q_{out}(C(\text{SO}_4) + C(\text{HSO}_4)) = Q_{H\text{feed}} C(\text{H}_2\text{SO}_4) \] (5)

Electroneutrality:

\[ [\text{Na}^+] + [\text{H}^+] = C(\text{HSO}_4) + 2C(\text{SO}_4) + C(\text{SAL}) + [\text{OH}^-] \] (6)

It is seen that there are at least 7 independent variables ([Na\(^+\)] can be treated as known because NaSAL completely dissociates in water). However, we have only 6 mass balances, so there is one degree of freedom. For example, the pH of the crystallizer could
be specified, or the yield to crystals (leading to C(S)). You can solve for the missing concentrations and ultimately the yield to crystals, as a function of pH, over the range 2-5. You can then determine how close you are to the predicted equilibrium in the actual crystallizer, by computing the yield on a product basis:

$$Y = \frac{\text{mols crystal product}}{\text{mols crystal product} + \text{mols dissolved salicylate product}}$$  \hspace{1cm} (7)

You can use the sodium mass balance:

$$[Na^+] = C(S) + C(SAL) + C(L)$$  \hspace{1cm} (8)

as a check on your answers.

Because the SAL solubility in water, $K_{HSO_4}$, $K_{SAL}$ and $K_W$ are all known over the temperature range of crystallization (Nordstrom and Rasmuson, 2006; Dickson et al., 1990; Meloun et al., 2010; Bandura and Lvov, 2006), while Na$^+$SAL$^-$ dissociates completely at these conditions, it is actually possible to solve the equilibrium relationships in conjunction with the SAL solubility relationship and the reactor mass balances. In this manner the yield of crystals as a function of pH (or vice versa) can be predicted at equilibrium. The application of this analysis is shown below; the equations are implemented in “crystallizer_new.xls”.

There are many ways to solve the equilibrium model. One way is to cast the problem as a nonlinear regression with the sum of squares objective function:

$$\Sigma (\text{left hand side} - \text{right hand side})^2 = \Sigma (\text{LHS} - \text{RHS})^2$$

Convergence to what appears to be a global minimum is rapid using some of the equations in the objective function, but the rest as constraints. An attempt to include all 6 equations in the objective function proved unsuccessful under a normal range of initial guesses. The “Solver” program included in Excel 2013 was used to perform the minimization. The equations included in the objective function were Eqs. 4-6, while Eqs. 1-3 were used as equality constraints. Other combinations are possible, but some will
give convergence problems. Another constraint can be added that also improves convergence:

\[ C(S) + C(SAL) < C(Na+) \]

Setting lower bounds (zero) on the smallest concentrations also helps. Convergence was improved by using pH and pOH in the equations, instead of \( C_{H^+} \) and \( C_{OH^-} \). Obviously the choice of initial guesses in Solver is important, but the correct concentrations are easily bounded using the inequality given above and the experimental results, so it’s easy to get good starting guesses.

The main problem with this analysis is that the bulk pH and T (by necessity) must be used, but at the interface the true pH can be lower due to some limited solubility of salicylic acid, and the true T higher due to the exothermic \( \Delta H_{\text{cryst}} \). If this is the case, would the equilibrium-predicted yield be higher or lower, or can you tell?