Scaling up – teacher note

**Teachers’ notes on scaling-up a chemical process**

# (Answers to questions are in italics)

Over the years one A-level chemistry course has provided two different experimental procedures of how to synthesis aspirin in the school laboratory. They both are successful but both have pros and cons.

## Activity 1

An initial aim for students is to consider both procedures and decide which would be the most suitable for carrying out on 10,000 times the scale on a pilot plant as opposed to the 2g lab scale. Are they equally good or does one have significant problems?

### Procedure A.

1. Weigh out 2g of 2-hydroxybenzoic acid and place it in a conical flask. (The starting material is an irritant fluffy white solid).
2. Add 4cm3 of ethanoic anhydride and agitate to mix the 2 chemicals. (The anhydride is a colourless liquid with a pungent smell of vinegar).
3. Add 5 drops of concentrated sulphuric acid (hazardous viscous liquid – causes burns) and continue agitating the flask for 10 minutes. Crystals of aspirin will be produced and form a crystalline mush.
4. Dilute by adding 4cm3 of cold glacial ethanoic acid and cool in ice.
5. Collect the crystals using vacuum filtration and wash once with cold water.
6. Recrystallise the product from water. Dry and weigh the product.

### Procedure B.

1. Weigh out 2g of 2-hydroxybenzoic acid and place it in a pear shaped flask. (The starting material is an irritant fluffy white solid).
2. Add 4.0 cm3 of ethanoic anhydride (a colourless liquid with a pungent smell of vinegar).
3. The reaction mixture will get slightly warm so cool it by swirling the flask under running water.
4. When cool, add 2 anti-bumping granules.
5. Heat under reflux for 30 minutes.
6. Cool the mixture.
7. Pour into 100cm3 of cold water containing 10cm3 of dilute sulphuric acid. Stir and allow the resulting suspension to stand for 15 minutes.
8. Filter off the crystals that form. Dry and weigh the product. Recrystallise if required

*Although Procedure A is a very good method for a small scale preparation on a 2g scale, and quite safe, it is not suitable for significantly larger amounts.*

* *There are inherent mixing problems through adding a very reactive reagent (ethanoic anhydride) to a solid. It is impossible to get homogeneity on a scale much larger than 20g.*
* *Concentrated sulphuric acid is very dangerous and not an easy chemical to handle on a large scale.*
* *Its drop-wise addition as described would almost certainly create local regions of high concentration and therefore local exotherms with the potential for severe risks.*
* *The procedure has the potential to create a "run-away" reaction since the sulphuric acid is a catalyst and the reaction is exothermic. It is very difficult to remove heat rapidly from a reaction on a large scale (why?) and once the first few drops of sulphuric are added all external control has been lost.*
* *The formation of a "crystalline mush" would also give rise to non-homogeneity and problems with mixing on the subsequent dilution with ethanoic acid.*

*Procedure B uses heat to initiate the reaction rather than a catalyst. This allows much more external control and makes it safe to carry out on a large scale. It may be possible to carry out this procedure at a lower temperature but this would need to be investigated. It may also be possible to add ethanoic acid for example as a co-solvent and diluent.*

## Activity 2

How could Procedure B could be scaled up 10,000 times the scale to 20kg of starting materials?

The typical school preparation would probably use a reflux apparatus of the type shown below using a Bunsen burner to heat it. Vacuum filtration would be used to isolate the product.

|  |  |
| --- | --- |
| reflux | filter |

Think about every operation in this procedure and work out how you would do each phase of the reaction on 10,000 times the scale i.e. starting with 20kg of the 2-hydroxybenzoic acid. Safety and protection of the environment are always the most important things to consider. Work out how you would weigh 20kg of an irritant fluffy powder. Decide how you could cool and heat the reaction and then how to filter off the product. Don't forget - the product is designed to be biologically active - you can not ignore the potential hazards of the product nor how to dispose of any waste materials from the process.

The material being made is going to be taken as a medicine. It must be pure.

Draw the apparatus that you think you could use to carry out the operations and describe each step. Remember that you can not lift apparatus once you get to that size and you should try to do as much as possible in one vessel. Think about how to do every step safely. Think about how you would clean the apparatus for the next set of reactions. Think about costs - what are the costs and how might they be minimised?

Once chemists have worked out how to make a drug safely and effectively on a 20kg scale it is relatively "easy" to scale the reaction up further. Aspirin is made in batches of 6000kg at a time. That's enough for 20 million tablets!

**How would you do each phase of the reaction on a 20kg scale?**

|  |  |
| --- | --- |
| Draw the apparatus you would use in the space at the side. Make notes below. Think about everything you need to do first. Try to minimise the amount of equipment used and make it versatile so that it can be used for other reactions. Consider safety. Fire is one of the biggest hazards; naked flames and electric heaters and motors are banned. | |
| **Step 1:**  Weigh solid |  |
| **Step 2:**  Measure & add liquid |  |
| **Step 3:**  Swirl & cool flask |  |
| **Step 4:**  Add anti-bumping granules |  |
| **Step 5:**  Reflux |  |
| **Step 6:**  Cool |  |
| **Step 7:**  Pour into water |  |
| **Step 8:**  Filter & dry the product |  |

**Notes on PowerPoint slides**

*Answers to questions are in italics*

|  |  |
| --- | --- |
| Slide 1 | Scaling up a chemical process involves more than just using bigger equipment.  There are numerous safety considerations to look at. The risks involved in using a hazardous material on a fraction of a gram scale is totally different to using large amounts.  Heat transfer through large volumes of solvent is significantly different to small scale work. |
| Slide 2 | Students should think about a typical school preparation of aspirin. It is easy to do on a small scale of a couple of grams but less easy on a big scale.  Typical lab apparatus is a pear shaped flask and reflux condenser.  The product is isolated by vacuum filtration.  The aim of this activity is to work out how to do a preparation like this on a large scale (10,000 times scale) and develop ideas of what the equipment might look like to be capable of being used for a variety of reactions. This is what a pilot plant is for. It is not designed for one specific reaction as some production plants would be.  The pilot plant uses many flammable solvents and all forms of sparks and naked flames must be eliminated. |
| Slide 3 | This is easy to do within a couple of hours.  The most likely reason why the reaction sometimes fails at school is due to poor quality ethanoic anhydride. |
| Slide 4 | What are the likely contaminants in the crude product once it is isolated before purification?  *Ethanoic acid*  *Water*  *Unreacted 2-hydroxybenzoic acid*  *Perhaps a trace of sulphuric acid*  *Ethanoic anhydride is unlikely as it should all get hydrolysed.* |
| Slide 5 | What are you going to weigh the solid into?  How are you going to protect the chemist from irritant solid?  How big is the balance?  Where do you locate it?  *Solids are often weighed into plastic bags, one inside the other as a fail safe.*  *The whole area has a laminar clean airflow and the chemist wears a chemical resistant suit and is connected to a breathing air line. The suit takes 10-15 minutes to put on. Chemists work in pairs. After use the chemist goes into a shower and the suit is scrubbed to remove contaminants. Only then is the suit removed. Weighing 20kg could take over 30 minutes – unlike a minute in the lab for a couple of grams.*  *Chemists only wear this protective clothing when they are actually working in the pilot plant modules. At other time they will be wearing lab coats.*  *Balance pans are usually on the floor for ease of use. The read-out is at eye level.*  *Getting a supplier to weigh it out does not really solve the problem!*  *Doing it by volume is not accurate for a fluffy solid. It might work for a nice dense granular material like salt or sugar but it is still very complicated to work out bulk density as opposed to real density. The bulk density of sea salt (big crystals) is less than table salt (small crystals).* |
| Slide 6 | Adding the solid to a reaction vessel. The wide yellow tube is a local extract (like a vacuum cleaner) to remove any chemical dust from the mouth of the vessel.  Half of the reaction vessel is below floor level.  The deep blue coating is mainly insulation. |
| Slide 7 | This is a schematic diagram of a reaction vessel.  It has a temperature probe and a number of inlets and ports.  What do you think these reaction vessels are made of? What chemically resistant materials are there? What are their limitations?  *Various materials might be considered e.g. plastics, glass, steel, stainless steel, titanium, carbon fibre etc. All have their merits and problems but a balance between chemical resistance, strength and cost must be made.*  *The pilot plant vessels are made of steel for strength and have a 2 mm thick pale blue glass lining which is resistant to most chemicals except for hydrofluoric acid and hot sodium hydroxide solution. If necessary, these reagents can be used in a few vessels made of “hastelloy”, a special nickel-chromium alloy. This is not the perfect material either – it is attacked by acids.*  How will you measure out 30litres of nasty liquid? |
| Slide 8 | *The easy way is to use a large measuring cylinder attached to the reaction vessel via a tap (like a burette).*  *The liquid is pumped or sucked into it using pressure or partial vacuum.*  *It can be possible to use flow meters especially in a dedicated production plant where the same liquid is being used repeatedly.* |
| Slide 9 | Develop ideas of how to cool a slightly exothermic reaction on a 30 litre scale.  These reaction vessels are large and lowering them into cooling baths is not really practical.  Immersion coils (cooling pipes) inside the vessel would work but they do create problems during crystallisation or precipitation processes and impede cleaning. |
| Slide 10 | *The best way to cool the vessel is to have a jacket all round it with cooling liquid flowing through it (most students think of water at this stage). It is very similar in concept to a Leibig condenser.*  How will you swirl it to move the liquid about to get it mixed and cooled? |
| Slide 11 | *The easy solution is to use a paddle stirrer.*  *The motor used a hydraulic turbine which eliminates the spark hazard of electric motors. Compressed air stirrer could be used but are normally noisier.*  Magnetic stirring, as commonly used on a lab scale, is not technically feasible on a large scale due to the problem of creating sufficient magnetic flux. |
| Slide 12 | What do anti-bumping granules do?  *They prevent “explosive boiling” happening. For a pure liquid it is possible to heat it above its boiling point without it physically boiling. This is because bubbles of vapour have to form within the liquid and these sometimes need a “seed” to start bubble formation. Anti-bumping granules are usually rough pieces of glass with a multitude of surface cavities on which bubbles can form.*  *On a pilot plant scale this solution become impracticable, and unnecessary. The paddle stirrer causes enough turbulence to allow bubbles to form at the boiling point.*  How are you going to heat the reaction mixture?  *The easy solution is to put a hot liquid through the jacket. The maximum temperature that you can get to with water (superheated steam) is about 120°C but that is very hazardous. It is better to use a liquid other than water to get to high and low temperatures.*  *What 3 properties does such a liquid need?*  *High boiling point. Low melting point. Low viscosity at low temperatures.*  The liquid that is used is quite special – diethylbenzene - chosen because it has a large liquid range (about -30°C to 160°C).  Draw the structure of diethylbenzene. How many isomers are there?  *There are 3 isomers: 1,2-diethylbenzene, 1,3-diethylbenzene, 1,4-diethylbenzene*  A mixture of isomers is used in the pilot plant. How does this affect its melting point and what is the advantage?  *The melting point of a mixture is lower than the pure substance. This means that reactions can be done at lower temperatures.* |
| Slide 13 | The big problem of scaling up reactions is the time taken to heat and cool liquids. Heating and cooling is dependant upon the surface area of the container and surface area of simple objects does not increase linearly with volume. Doubling volume does not double surface area – it is less than double. This means that heating and cooling rates are slower for larger volumes.  In the lab you can boil a small volume ethanoic anhydride (b.p. 140°C) with a Bunsen burner in a few minutes.  It is more complicated on a large scale in a big reaction vessel. |
| Slide 14 | Getting the heat energy into the reaction mixture is slow, partly due to the surface area effect but also because the transfer is from the diethylbenzene through the steel and glass layers and into the solvent.  The maximum rate of heating or cooling is 2°C per minute.  How long will it take to get from room temperature (20°C) to the boiling point?  *60 minutes* |
| Slide 15 | *If the large reaction mixture were heated up and refluxed for 30 minutes this gives a totally different heat / time profile for the reaction. It could easily give different products or some thermal decomposition might occur. The reaction would be over 80°C for 90 minutes.*  Process research chemists look at such reaction profiles very carefully and check how the reaction is progressing under a variety of conditions using special apparatus in which accurate heating rates can de defined.  Reflux is often used on the lab scale for convenience. It gives a constant temperature and is a way of dissipating exotherms using the latent heat of boiling – but it is a bit ad hoc. |
| Slide 16 | The mixture is cooled by lowering the temperature of the liquid in the jacket.  How do you add the reaction mixture to acidified water?  *It could be pumped via a dip pipe into another vessel containing water. Alternatively water could be added via the large measuring cylinder. But note that this is a significant change to the reaction procedure and could lead to complications.*  How do you get the suspension out of the vessel and into the filtration unit? |
| Slide 17 | *The solution is to have a tap in the bottom of the vessel and let gravity do the work.*  *The suspension is stirred to maintain a homogeneous mixture whilst it is run off through the tap (mushroom valve). This prevents clogging of the valve.*  The diagram shows the condenser assembly. It is versatile and allows the chemists to carry our reflux and distillation without having to change the apparatus. Vapour goes up the vertical pipe and past a pressure relief valve and into the top of a condenser (the square block). Liquid condensate runs down through the U-bend back into the reaction vessel – this is reflux.  By closing the tap above the U-bend and opening the outlet tap a distillation set up is created. |
| Slide 18 | Filtration is carried out on the lower floor. The suspension is led down the black pipe from the bottom of the vessel on the upper floor. The pipe is connected to the lid of a steel drum and the suspension is delivered via a spreading funnel to give an even spread over the “filter paper”.  The vacuum filtration unit is a large stainless steel drum on wheels with hinged lid. About 50cm below it is a steel mesh to support the “filter paper” (a porous polypropylene bag is used as paper is too weak). Suction is applied under the mesh and the filtrate is sucked through rapidly and led off via a tap at the base of the unit to be stored separately. The solid residue left on the “paper” can be washed with clean solvent and partially dried by sucking dry nitrogen through it. |
| Slide 19 | Once a solid product has been filtered off it needs to be dried to remove residual solvent. Since the material will be used for further research in either volunteer patients of for pharmacy studies to see how it can be best made into a medicine (tablets, solutions etc) it is crucial that no solvent contaminants are present. Any residual traces could give patients side effects or give misleading results in compression (tabletting) and solubility studies.  The circular door of the oven is hinged on the left and locked in place with the 8 hinged screw down bolts. There are two small “port holes” for looking inside the oven when it is closed.  The “damp” solid is placed in trays onto shelves in the oven. The door is closed, locked and the air sucked out to give a partial vacuum. The oven is then gently warmed. It does not have to get very hot since the boiling point of a solvent is affected by the pressure. Lowering the pressure also lowers the boiling point. This has 2 benefits for drying solids on this scale. Vacuum drying is fast and the modest temperature prevents thermal breakdown of the product. |
| Slide 20 | Once the solid is dry it is sampled for purity and checked that there are no residual solvents. |