aspirin
the wonder medicine

background
Aspirin (2-ethanoyloxybenzenecarboxylic acid) was first produced in 1897 by Felix Hoffmann at the Bayer Company in Germany. It is still one of the most widely-used medicines in the world today. Nowadays aspirin is not only used as a pain killer but is used effectively in treating various forms of arthritis and in reducing the incidence of heart disease.

pre-planning required
weeks before
Ensure that all facilities are booked – ie laboratory space, time on the analytical instruments and relevant staff, and all chemicals are prepared.

days before
Brief your demonstrators and technical staff. It may be an idea to highlight areas where the students are likely to ask questions based on previous events. You may also like to prompt the students to ask questions by indicating this on the student sheets.

facilities required
General chemistry laboratory, infrared (IR), nuclear magnetic resonance (NMR) and high pressure liquid chromatography (HPLC) instruments, chemicals, lecture theatre or seminar room for welcome and debriefing/careers session.

This activity is based on an event run by Dr Ian Bradshaw, Liverpool John Moores University and Dr Paul Birkett, Manchester Metropolitan University.

SAFETY
A risk assessment must be done for this activity.

materials required

• 250 cm³ round bottom flask
• reflux condenser
• Buchner flask
• Buchner funnel
• water bath
• watch glass
• 250 cm³ conical flask
• ethanoic anhydride
• concentrated sulfuric acid
• 2-Hydroxybenzoic acid
• ethanol
• TLC solvent – acetonitrile/ethanoic acid/water
• TLC solvent tanks
• infrared (IR) instrument
• nuclear magnetic resonance (NMR) instrument
• high performance liquid chromatography (HPLC) set-up
Suggested timings for the day

10.00 Arrive
Introduction to the day and a description of the format

10.15 Laboratory session 1
- set-up the aspirin synthesis reaction
- opportunity to run an IR sample
- demonstration of thin layer chromatography (tlc)

11.30 Break

11.45 Laboratory session 2
- continue with synthesis of aspirin
- opportunity to run an IR sample
- set-up a thin layer chromatography (tlc) experiment

13.00 Lunch

13.45 Further briefing session on spectroscopic techniques

14.00 Laboratory session 3
- determine the melting range
- run a tlc of your aspirin sample
- demonstration of HPLC
- run an IR spectrum of your aspirin sample
- demonstration of NMR spectroscopy

15.30 Debriefing session and careers talk. For information on approaching an industrialist contact your RSC local section www.rsc.org/Membership/Networking/LocalSections/index.asp

15.45 Finish

It is helpful to provide the teachers with copies of spectra and chromatograms that are run on the day.

Further information


The history of aspirin www.aspirin-foundation.com


For more information on spectroscopy resources and other resources visit the RSC website at www.chemsoc.org/networks/learnnet/index.htm
Nearly all of us have used aspirin at some time in our lives, but not many people know that for hundreds of years a related compound from willow bark was used to relieve pain and treat fevers. Ancient Asian records show it was used 2400 years ago.

In the 1890s Felix Hoffman of the Bayer Company in Germany made aspirin, which was found to have good medicinal properties. In 1898 aspirin was sent for clinical trials and Bayer patented the process. In 1915 during World War One the British very much wanted aspirin and the British government offered a substantial reward to anyone who could develop a manufacturing process. A Melbourne pharmacist, George Nicholas, did just that.

Approximately 35,000 metric tonnes are produced and consumed annually, enough to make over 100 billion standard aspirin tablets every year. Nowadays aspirin is not only used as a pain killer but has also been proposed as effective in reducing the incidence of heart disease.

This practical session aims:

• to introduce you to the synthesis of one of the oldest medicines, aspirin
• to analyse the purity of your aspirin using techniques you will not have used in school.

### Synthesising aspirin

Aspirin is a relatively simple molecule containing an ethylated phenol group and a carboxylic acid group. In your experiment you will make aspirin from an acid called 2-hydroxybenzoic acid by esterification with ethanoic anhydride under acid catalysed conditions. Ethanoic anhydride is an ‘activated’ form of ethanoic acid which most of you will have encountered in its dilute form as the vinegar you put on fish and chips. Using ethanoic anhydride ensures that the esterification reaction goes to completion much more quickly than if you use ethanoic acid. Why is ethanoic anhydride more effective than ethanoic acid? Also, why is H⁺ added? Once you’ve made the aspirin you’ll then need to purify it by recrystallisation from a suitable solvent.

Materials that are made for human consumption must be checked thoroughly to ensure that:

• the material is the correct product; and
• it is highly pure.

Checking the purity of a sample can be done in a variety of ways and you will be using traditional ‘wet’ chemistry techniques as well as more advanced spectroscopic techniques to determine the purity of your sample.
The experiment

1. Collect a 250 cm$^3$ round bottom flask containing ethanoic anhydride (8.0 g) and concentrated sulfuric acid (3 drops).

2. Collect 5 g of 2-hydroxybenzoic acid. Add the 2-hydroxybenzoic acid in small portions to the ethanoic anhydride/concentrated sulfuric acid mixture. Gently swirl the flask after each addition of 2-hydroxybenzoic acid so that it is mixed with, and dissolves in, the ethanoic anhydride. When all the 2-hydroxybenzoic acid is added there may be some solid which will not dissolve – do not worry as this is normal.

3. Connect a reflux condenser to the round bottom flask and heat the reaction mixture under reflux in a water bath for 15 minutes.

4. Then add water (60 cm$^3$) and swirl the reaction mixture to ensure complete mixing.

5. Leave the reaction mixture to cool for about 10 minutes. The crude aspirin should crystallise from solution at this stage. If you do not have a solid, do not panic this can happen to even the most experienced organic chemists! The problem can be overcome by "scratching" the reaction flask with a glass rod – one of the demonstrators will show you how to do this.

6. Filter off the white, crude aspirin solid under vacuum using a Buchner flask and funnel, wash the product with ice cold water (20 cm$^3$) and then leave the solid to suck as dry as possible.

7. Save a small portion of the crude aspirin (about 0.1 g).

8. Recrystallise the rest of the product as follows.

9. Carefully transfer your crude aspirin into a round bottom flask then connect the condenser. Gradually, add ethanol and heat the mixture under reflux using a water bath until the solid dissolves. This should require approximately 15-20 cm$^3$ of ethanol.

10. Transfer the solution to a 250 cm$^3$ beaker and leave the clear, colourless solution to cool to room temperature slowly, during which time crystallisation of aspirin should begin.

11. Collect the recrystallised aspirin, which should be white, using the Buchner flask and funnel.

12. Use the filtrate to transfer any remaining crystals from the beaker to the funnel.

13. When all of the solid has been carefully collected in the Buchner funnel, wash the crystals with ice cold ethanol (10 cm$^3$) and allow the solid to suck as dry as possible for about five minutes.

14. Transfer the crystals to a watch glass and allow to air dry for at least 15 minutes.

15. Weigh the dry, purified aspirin product.

16. Measure the melting range of your dried product.

SAFETY

The reaction should be done in a fume cupboard.
The results

Weight of recrystallised product = ______ g
Melting point range = ______ - ______ °C
Literature m.p. = 138-140 °C

Theory and percentage yield of product

An organic chemist always calculates the % yield of the product obtained using the following procedure.

1. The number of moles of each reagent used in the reaction is worked out.
2. The limiting reagent, the reagent that is present in the lowest number of moles, is identified.
3. We then assume that if every single molecule of this reagent was converted to the product this is the maximum amount of product that could be obtained. This is known as the 100% or theoretical yield.
4. The actual % yield is calculated.

The following steps are followed to obtain the required information:

Molecular formula of ethanoic anhydride = C₂H₂O₃
Molecular weight of ethanoic anhydride = (4 x ) + (6 x ) + (3 x )
Number of moles of ethanoic anhydride = weight of ethanoic anhydride used ÷ molecular weight of ethanoic anhydride
Number of moles of ethanoic anhydride = ______ mol
Molecular formula of 2-hydroxybenzoic acid = ________________
Molecular weight of 2-hydroxybenzoic acid = __________________
Number of moles of 2-hydroxybenzoic acid = __________________
The limiting reagent = __________________
Molecular formula of aspirin = _________________
Molecular weight of aspirin = _________________
Theoretical yield = no. of moles of limiting reagent x molecular weight of the product
.: Theoretical yield = ______ g
% yield = (actual yield/theory yield) x 100
% yield = ______ --- ______ x 100
Purifying and identifying aspirin

Thin layer chromatography (tlc)

You’ve probably used simple chromatography as part of your earlier studies to separate the dyes in coloured ink. In this activity you investigate the purity and identity of your laboratory prepared aspirin samples using thin layer chromatography (tlc).

Thin layer chromatography is a rapid separation technique, which means that a pure substance gives ‘one spot’. However, if extra spots are observed as well as the characteristic pattern of the known compound, then impurities are likely to be present in the sample. (What impurities are likely to be present in your sample?) You can also identify ‘unknown’ compounds by comparing their Rf values (the distance travelled by the component spot/distance travelled by the solvent front) with an authentic standard running on the same plate.

You’ll see a demonstration of how to run a tlc of your product. The solvent system used to run your tlc is a mixture of acetonitrile/ethanoic acid/water (why do the different components travel different distances on the TLC plate?).

<table>
<thead>
<tr>
<th>Sample</th>
<th>Crude Aspirin</th>
<th>Recrystallised Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of spots observed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distance travelled by solvent front (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distance travelled by UV active spots (mm)</td>
<td>1 2 3</td>
<td></td>
</tr>
<tr>
<td>Rf Values</td>
<td>1 2 3</td>
<td></td>
</tr>
</tbody>
</table>

You will also run an infrared (IR) spectrum of the product and compare it with the spectrum of pure aspirin. If they are identical your synthesis of aspirin has been successful. You will also see demonstrations of both a nuclear magnetic resonance (NMR) spectrometer and high performance liquid chromatography (HPLC).

The theory of each of these analytical techniques is available on a separate sheet.