# Polymer films – an alternative to antibiotics?

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## Aims

The project was to develop a novel polymer designed to bind to the surface of bacteria that could be synthesised cheaply and easily in laboratory conditions. This polymer was then tested to see if it collapsed into a **single-chain nanoparticle (SCNP)** with dynamic covalent bonds that allow the compound to form larger structures and reconfigure their bonds to suit a template (e.g bacteria).

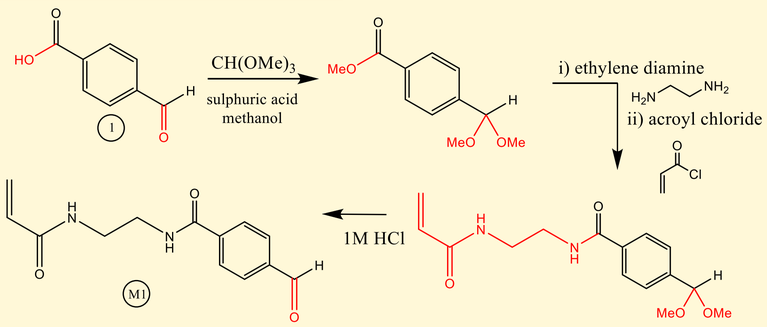
## Background

Antibiotic resistance is an increasing global crisis. Resistance occurs when mutated populations with resistance come into contact with antibiotics. Most are killed, but the resistant strain begins to thrive. So newer antibiotics are needed – however, antibiotics are costly in time and money, with little return and as resistance is seen as inevitable companies are less likely to fund research and development.

To combat this we needed "non-lethal" approaches[1] that do not cause resistant populations. **Polymer nanoparticles** that bind to the surface of bacteria can be made inexpensively. Once bound to the surface they bond with each other, forming a film around the bacteria. This film will be highly specific and complementary to the shape of the bacteria and when isolated, will selectively recognise the strain it was templated around, which may aid in diagnosis and even inactivation of the bacteria using the film.

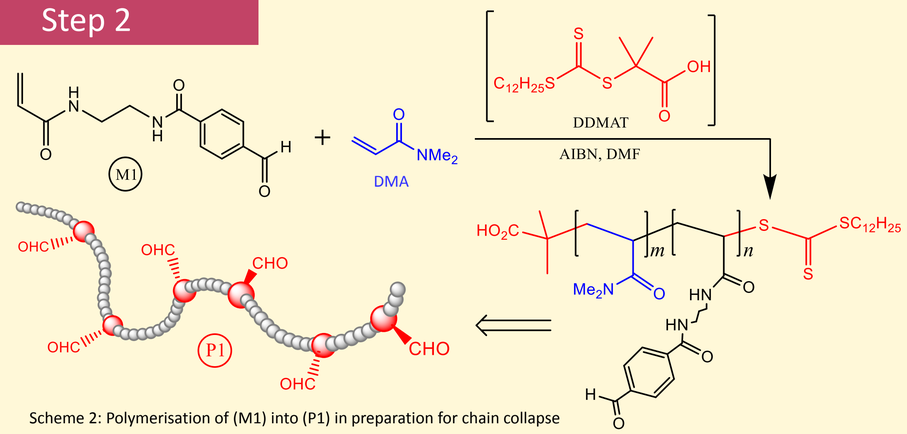
## Synthesis of SCNP

### Step 1[2]



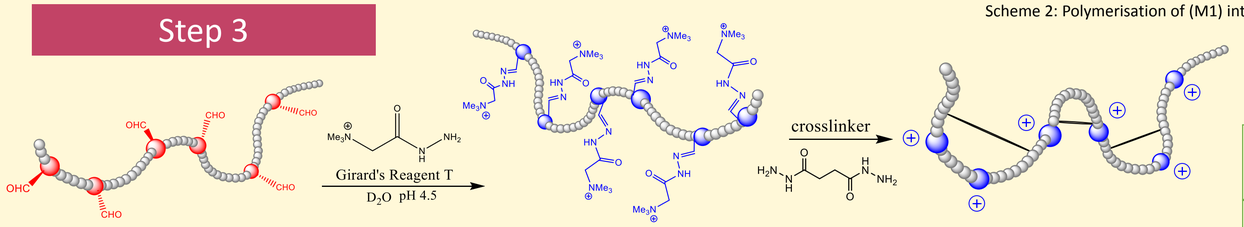

Scheme 1: Synthesis of the monomer (M1) from 4-carboxybenzaldehyde (1).

### Step 2




Scheme 2: Polymerisation of (M1) into (P1) in preparation for chain collapse

### Step 3




Scheme 3: Adding positive charges to (P1) by removing the aldehyde groups. The cationic polymer was then crosslinked using succinic dihydrazide

Positive charges aid in binding to the bacteria. The nitrogen hydrazone bonds are pH sensitive - in acidic conditions they can reorganise and reconfigure. Varying amounts of cross-linker was added.

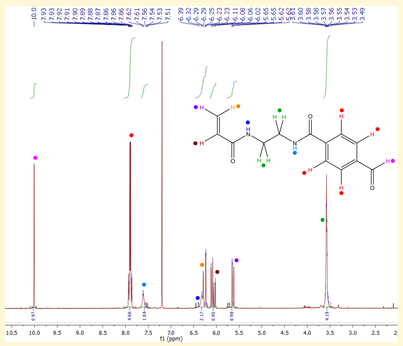
### Polymers

Three polymers were made, all with the same structure:

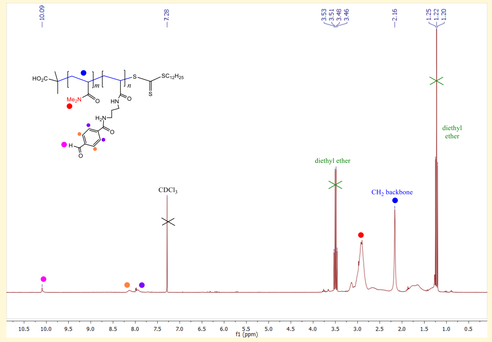
| Polymer | [m]:[n] | $M_n$ (Da) | | $M_w$ (Da) | PDI |
|---|---|---|---|---|---|
| | | $^1$H NMR | GPC | | |
| P1 | 10:1 | 6,500 | 12,000 | 14,500 | 1.25 |
| P2 | - | - | 9,000 | 11,500 | 1.23 |
| P3 | 15:1 | 14,000 | 23,000 | 37,000 | 1.58 |

## Data Analysis & Results

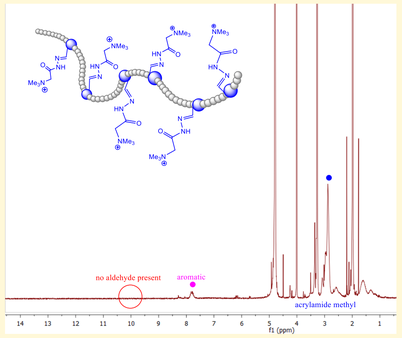
A technique known as $^1$H NMR (nuclear magnetic resonance) was used to assess whether the compounds had been made. $^1$H NMR instruments detect all the hydrogens in a compound and plot this on a graph. These peaks can then be assigned and found to correlate with the expected structure using reference values for different hydrogen environments.



$^1$H NMR of (M1)




$^1$H NMR of (P1). Solvents used are found as impurities.



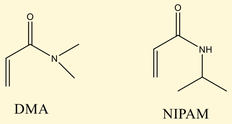

$^1$H NMR of cationic (P1). Weak signal

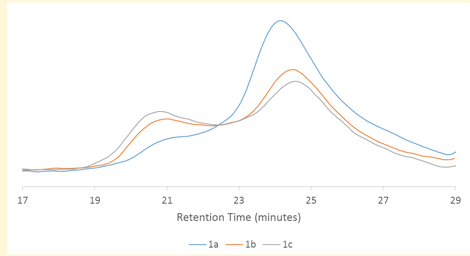
Each sample of varying cross-linker was ran through a gel-permeation chromatogram (GPC), which separates molecules based on size. Smaller compounds get caught in pores, so they elute more slowly. Therefore the cross-linking process can be proved as a success if the more cross-linked SCNPs have a longer retention time:

| Polymer | Equivalents of cross-linker | Retention Time (max) |
|---|---|---|
| 1a | 0.75 | 24.057 – 24.225 |
| 1b | 1.50 | 24.478 – 24.528 |
| 1c | 2.25 | 24.410 – 24.713 |

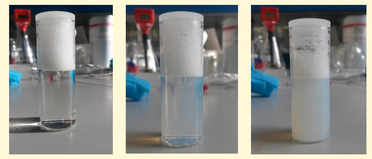
- **Retention time increases slightly – evidence for decreasing size, and therefore the formation of SCNPs.**

One polymer was made with NIPAM rather than DMA (co-monomer in Step 2 of the synthesis). This polymer was found to be thermo-responsive (changes physical properties based on the surrounding temperature).




Graph 1 : GPC results showing varying retention times based on amount of cross-linker



Thermo-responsive polymer warming to room temperature

## Conclusion

- SCNPs successfully synthesised and showed evidence of interlinking
- To achieve more reliable results reduce bonds with $NaCNBH_3$ before running through GPC **or** kinetically fix the hydrazone bonds by adding sodium bicarbonate to increase pH

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Project title: "Synthesis of 'Smart' Polymer Nanoparticles for the Inhibition of Biofilm Formation

References:
1. E. P. Magennis, F. Fernandez-Trillo, C. Sui, S. G. Spain, D. J. Bradshaw, D. Churchley, G. Mantovani, K. Winzer, C. Alexander *Nature Materials,* 2014, **13**, 748-755
2. Method adapted from: B. S. Murray, D. A. Fulton, *Macromolecules*, 2011, **44**, 7242-7252

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