

Body, heal thyself

Education in Chemistry

July 2017

rsc.li/EiC417-medical-plastics

Nina Notman walks us through the recent research exploring the use of biodegradable polymers in orthopedic implants

Let's start with an experiment; take a quick glance around your immediate environment and count roughly how many different types of polymers there are. I'm noting cotton in my clothing, nylon in the carpet, poly(ethylene terephthalate) (PET) in a drink bottle, acrylonitrile butadiene styrene (ABS) in my keyboard ... the list easily runs into double digits. And the fact I can see any of these clearly at all is thanks to the polycarbonate in my spectacle lenses!

But did you remember to include the biopolymers – polynucleotides, polysaccharides and polypeptides – that make up your body in your list? After all, the average human is 17% protein, another word for polypeptide. It is estimated there are more than 50,000 different proteins naturally present in the human body, with collagen being the most abundant.

Polymers are therefore a logical choice for building medical implants designed to go inside the body. 'With so much of our body being made up of some sort of polymer, synthetic polymers are a natural fit,' explains Davide De Focatiis, a polymer engineer based at the University of Nottingham. And while the best known polymeric implants are indisputably the silicone ones used for breast enlargements, polymers are also widely used for artificial heart valves and lenses (following cataract removal) and in knee and hip replacements.

Polymers are long chain molecules made up of repeating units, called monomers, covalently bonded together. In the case of proteins these monomers are amino acids, and in non-natural polymers they are typically alkenes. The ability to vary the structure of the monomers and also the length of the monomer chains means the number of different polymers that could potentially be made is almost infinite. And, as tweaking the design of a polymer changes its properties, it should also be possible to design a polymer to behave exactly as you want it to.

Mending bones

The implants being designed by Davide's research group contain polylactic acids, made by polymerising the chiral molecule lactic acid. Davide selected these polymers because of their biodegradability. While you wouldn't want your new knee or hip breaking down over time, there are instances where implant degradation is very useful indeed.

The team is developing replacements for the internal metal plates and screws used to support fractured bones as they heal. Normally, after a person fractures a bone, immobilising that body part using a cast is sufficient to ensure the bone heals properly again, but sometimes a patient needs to undergo surgery so that metal hardware such as plates and screws can be attached to the bone to support correct healing. This hardware is typically comprised of steel or titanium.

'Fracture fixation plates and screws made out of metals have a whole host of issues,' Davide explains. Importantly, many patients need a second operation to remove them again once the bones have healed. It is not normally desirable to leave metal in the body long term because it can react with body tissues. Fracture fixation plates and screws made of biodegradable polymers would eliminate the need for a second operation, as they would be broken down by the body slowly over time.

'Another reason why there's been a lot of interest in using degradable polymers [for this application] is that metals are much stiffer than bone, and also carry all the body's load as the bone is healing. This can result in the bone healing poorly because it doesn't sense any need to take loads while it heals,' explains Davide. There is therefore a risk a bone will refracture once its metal support has been removed. 'This is similar to the problems that astronauts have after spending time on the space station; their bones start to weaken because of the absence of gravity.'

The degradable polymeric implants are designed to carry the entire load while the bone is first healing but as the bone gets progressively stronger, the plates and screws get progressively weaker, and let the bone carry more and more weight. 'The end result being they disappear altogether and so you also don't need a second operation, but most importantly you've healed the bone in a way that is healthier long-term,' Davide says.

Better together

But while the relative weakness of polymers compared to metals is a plus for this application, the polylactic acids can be a little too weak to do the job alone. Davide's team are therefore reinforcing the polymers by adding ceramic particles. 'Pure polymers are fine for bones that are not terribly load-bearing, such as a finger bone, but if you break a thigh bone then it's a much more challenging operation to try and support it,' he explains.

The ceramic particle his team are using in their composite is nano-hydroxyapatite, a crystalline form of calcium phosphate. '[This material is] a building block of bone and teeth so, at the same time as reinforcing the polymer, as the material degrades it actually releases minerals the body needs in order to re-grow the bone. They have this dual function,' explains Davide. Nano-hydroxyapatite is already widely used in oral care products including toothpastes and mouthwashes. The material has been proven to support the natural remineralisation of enamel better than the fluoride traditionally used for this purpose.

The key point here is that the minerals in the ceramic particles are taken in by the body and reused, rather than just being broken down and disposed of as is the case with the polymer.

Testing, testing, one, two, three

As well as perfecting the manufacturing process for these implants, Davide's group have also been working to ensure they degrade at the required rate. How long they need to remain in the body varies depending on which bone has been fractured, but 'typically, these materials would stay in the body for about a year or two, but mechanically, they would probably weaken over a period of months,' he explains.

To do this the group are making model parts and placing them in a phosphate buffer solution to mimic the conditions they would experience inside the body. They then monitor the materials as they degrade, to ensure they are exhibiting the required strength at all stages in the process. Only once they are happy with the degradation process will the team look to move onto clinical studies.

Through the looking glass

Another research group looking to make biodegradable orthopaedic implants is that of Julian Jones, a professor of biomaterials at Imperial College London. Again, Julian is using a biodegradable polymer and a second material that supports bone regrowth. But instead of adding hydroxyapatite, he is using bioglass, also known as bioactive glass.

'Bioglass is a glass that starts to dissolve when put into the body and forms a tight bond to bone. Also, as it dissolves it releases ions that support the growth of more bone,' Julian explains. 'It is similar to window glass in terms of its components, but if you implanted window glass it would be isolated by scar tissue by the body and then pushed out. Whereas the bioglass, because it contains less silica, the body sees it as natural material and it doesn't get pushed out.'

A number of consumer applications already contain bioglass including some toothpastes and anti-aging cosmetics. 'Bioglass in toothpaste is probably the biggest commercial use of any bioactive biomaterial,' explains Julian. Sensodyne Repair & Protect contains bioglass particles that release calcium and phosphate ions when they come into contact with saliva and water. 'When you have sensitive teeth you've got exposed tubules in your dentin that go to the nerve cavity,' he says. When the glass dissolves it forms a calcium phosphate layer over those tubules. Through the natural mineralisation process the body converts this to hydroxyapatite. 'This ends up being the same composition as natural tooth mineral.' Bioglass is also already used in orthopedic surgery to fill holes in damaged bones.

Julian and his colleagues are exploring the use of bioglass for supporting the regrowth of damaged cartilage in knees.

With added bounce

Cartilage is a firm but flexible connective tissue that is found all over the body acting as a cushion between bones. However, it is prone to wearing out, especially in the knee. Patients who suffer from degenerated knee cartilage often undergo knee replacement surgery where the damaged cartilage is replaced with a plastic spacer. With no like-for-like synthetic knee cartilage material yet available, as well as necessitating a major operation with significant recovery time, this plastic spacer does not fully mimic the mechanical properties of natural cartilage with stiffness being the biggest issue.

The potential to repair damaged cartilage with a bioglass that slowly dissolves at the same rate that new cartilage grows is very appealing indeed. However, bioglass alone is not up to the job. 'Bioglass is a brittle material meaning it doesn't take cyclic loads. When we're walking around we're putting weight on our lower limbs. The current clinically-available bioglass can only be used in holes in bone, where it's not actually put under direct load, so we've been making materials called hybrids that are designed to be able to share the body's load,' says Julian.

A hybrid material by definition contains two or more components intimately mixed together throughout its structure (this mixing occurs at a much finer scale than in composites such as those designed by Davide's group). Julian's hybrid is comprised of bioglass plus the bouncy, biodegradable polymer poly(caprolactone). The inclusion of this bouncy polymer, and the way it bonds with bioglass, gives the hybrid the mechanical properties required for this application. 'The intimate relationship between the two parts will also give a controlled biodegradation rate,' he says.

Stand up straight

The proportion of bioglass and polymer in the hybrid can also be tweaked to suit different applications. 'You can dial in the mechanical property and decide whether you want it to be really flexible, or whether you want it to be quite stiff, or anywhere in between,' explains Julian.

Another potential application where he would like to see the hybrid used is in the replacement of damaged discs in the spine. Here the composition of the material is tweaked so it doesn't degrade, but instead exactly matches the mechanical properties of natural discs to act as a permanent 'big cushion'.

Spinal discs are comprised of cartilage shells surrounding a gel-like material and, like all cartilage, this shell is prone to damage. The most well known issue being the herniated – or slipped – disc, where the cartilage breaks down and some of the gel escapes. While the escaping part sometimes goes back in naturally, and can also be removed surgically, the risk of re-slippage is high. Patients with reoccurring issues are typically offered a spinal fusion where the damaged disc is slid out, and the vertebrae in the spine held in place using a metal and plastic cage. 'Inside the cage is put bone graft, either natural bone, bioglass or calcium phosphate,' says Julian. 'The bone will then grow into that cage, fusing the two vertebrae together and giving stability. But because you're growing bone where cartilage was, you're losing mobility.' Artificial discs have been developed recently but are not yet widely used.

Julian is now working alongside Justin Cobb, an orthopaedic surgeon at Imperial, to test the clinical potential of his materials for both knee and spinal disc replacements. 'We are currently setting up preclinical trials for the bouncy hybrids,' says Julian. 'But in reality they're still 10 to 15 years away from clinic.'

Article by Nina Notman, a science writer based near Baltimore, US. Teaching resources by Kristy Turner, a school teacher fellow at University of Manchester and Bolton School, UK