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Chitin, chitosan and healthcare

Clare Connell and **Henry Hunt** of Connell Consulting investigate how fish waste can benefit the healthcare industry

Investors are always looking for new opportunities and fish waste is an unlikely but promising area of interest for the healthcare industry. It offers a renewable source of biomedical products at the cutting edge of research.

Cellulose is the most bio-abundant material on the planet and is used in a vast array of commercial products; from paper to pinstripe suits to gun-powder, cellulose is everywhere. However, the world's second most abundant polysaccharide, chitin, is an underexploited resource with potential use in an equally dizzying array of applications. Although previously restrained to the laboratory, breakthroughs in technology have made chitin, and its most versatile derivative chitosan, a commercially viable product that will revolutionise many fields of healthcare in the near future.

Chitin is the fundamental building block in a huge swathe of the earth's fauna and fungi. Chitin and its derivatives, of which there are over 200, is a chain of sugars. In the natural world it can be found in the cells of fungi, in insects it's the key component of their carapace and forms the exoskeletons of all crustaceans. Organisms generate about 100 billion tonnes of chitin every year. It's both abundant and can be chemically altered into more useful forms for a whole host of industrial applications.

Chitin itself is not a new product in industry. With a little chemical trickery, one can turn chitin, the raw material, into chitosan. In agriculture it is an important ingredient in biofertilizers, biofungicides and biopesticides. It is an integral element in water filtration systems. It can be used to separate components in the recycling of paper. In clothes manufacturing it is used as a 'sizing agent' – changing absorption levels of textiles ready for dyeing. In cosmetics it appears as an anti-ageing agent in a whole host of lotions and creams.

Its prevalence in these industries is the result of a number of the fundamental characteristics of chitosan. For example, it is used in agriculture because it is 'bio-friendly: alternatives to chitin-based pesticides, like DDT to take a well publicised example, have the tendency to be incredibly toxic to animals. One might expect that to be a useful trait in a pesticide. But, it also had the tendency to accumulate in the food chain. DDT made its way through the ecosystem and caused devastation as it failed to be broken down by the animals who consumed it. The original pests were then consumed by predators who were affected themselves. In this way the peregrine falcons of North America accumulated toxic levels of DDT intended for insects. Chitosan-based insecticides have no such danger; chitosan-derivatives break down chitin in the cell structure of insects and fungi, killing them. Mammals do not use chitin in the same way and are unaffected by an environmental overabundance. Mammals, including humans, can safely ingest chitin and chitosan derivatives with no danger of adverse bioaccumulation.

Further proof of the safety of chitosan can be found in a more domestic setting. Perhaps unwittingly many people may use a chitin-based product twice a day, everyday. Sensodyne toothpaste uses chitosan, the processed form of chitin, as an active ingredient. This example displays another of chitin's useful characteristics – chitin and chitosan are bioactive. When you brush your teeth with Sensodyne, tiny particles of chitosan find their way into 'pores' in your teeth's enamel. Here they settle, 'adsorb' and combine with the surrounding enamel. They effectively become part of the tooth's surface and help to strengthen against abrasion and acid erosion whilst actively encouraging your tooth's enamel to regrow.

Chitin and chitosan have proved themselves to be viable in a commercial setting – Sensodyne currently holds second place on Amazon's Best Sellers list of toothpastes and 28,882,000 people in the UK use Sensodyne as their toothpaste of choice. Importantly, chitosan is seen as an accepted, even welcomed additive to a healthcare product; a vital publicity factor when looking to bring new medical products to market.

Other uses of chitosan include 'active' water filtration systems in place of passive membranes because it is bioabsorbent; it is able to bind chemically with harmful aquatic pollutants and acts as a 'flocculation' agent of suspended particulates. That is, it causes sediment to clump together, making it easier to filter and is able to combine with artificial chemicals – harmful or otherwise. This is an important application because current filtration systems use synthetic polymers that are, ironically, pollutants in and of themselves. A chitosan system would be a more natural way to reduce toxins in water supplies.

What value does chitosan hold for the medical industry? Those same factors that are making it useful in other industries make it an intriguing prospect for biomedical research. In and of itself, chitosan is safe for human consumption; it is approved by the FDA of the US and the MHRA of the UK. But, it can also combine with chemicals to perform useful tasks. This makes it a 'holy grail' for medical applications.

There are three interesting uses for chitosan in healthcare today. The first is as a drug delivery system, the second as a coating for medical devices such as hip replacements and the ▶

▶ third as a 3D scaffold for traumatic injuries. All three rely on the versatile combination of non-toxicity, biocompatibility, stability as well as biodegradability. Current cutting-edge technologies are seeking to build on the early commercial success of chitosan and researchers are excited about the prospects chitosan has to offer.

It's important to understand that chitosan does not, and cannot, treat disease or illness on it's own. Instead, it can act as a vehicle to deliver drugs to a patient. For example, antibiotics can be chemically combined with chitosan and ingested; the chitosan releases the antibiotics at a predetermined rate decided by the biodegradation of the chitosan. This is unlike current drug delivery systems where the chemicals used to stabilise drugs have the potential to combine toxically once ingested. When taking alprazolam (Xanax), for example, a patient must be careful to avoid certain foods like grapefruit because the two chemically interact and cause dangerous side effects. The risk might be reduced when chitosan-based delivery systems are used; they biodegrade into biologically and chemically inert by-products. Interestingly chitosan can also form a topical cream and so is very versatile as a drug delivery system.

The second use, in medical devices, is one that exploits the way our bodies deal with 'invasive' treatments. Currently, if one were to have surgery and have a medical device inserted into their body they run the risk of the bodies natural defence mechanisms rejected it outright. This may result in the device having to be removed. This is a costly, and dangerous risk involved in surgery for both patient and hospital. Even if the body does not outright reject the device, there is still the danger that the body overproduces scar tissue as a naturally occurring mechanism to protect against further damage. If one were to have hip surgery to improve mobility a real danger is that uncontrolled scar growth actually does more to harm mobility if left unchecked.

The premise of chitosan coatings for medical devices is the idea that the body recognises chitosan as being biocompatible. In other words, it readily accepts chitosan as an environmentally occurring saccharide – a sugar in essence. The chitosan is accepted by the body but, because mammals don't interact with chitosan in the same way that a crab might, it does not affect any of a human's natural processes. Chitosan, and its derivatives, are almost paradoxically 100% natural products and entirely alien to mammalian metabolism. So, chitosan can act as a safe interface between a titanium device and human tissue.

Once a medical device is coated in chitosan the risk of it being rejected falls and so too does the potential costs of surgery as check-up costs and the likelihood of further surgeries is reduced. Chitosan-coated devices will be welcomed in operating theatres in the very near future.

The last, and perhaps most interesting application for chitosan in healthcare is in the production of 3D scaffolds for use in traumatic wound treatment and various surgeries. Chitosan can be manipulated into a sponge-like scaffold and injected with the patients own stem cells. It is then inserted into the site of the break or wound. Here the scaffold stays while the bodies own processes help to rebuild the bone. Amazingly, because of chitin's bioactive properties, over time the chitosan is gradually replaced by bone with the chitosan actively promoting the growth of the bodies own blood and bone by communicating via ion transfer. Eventually all the chitosan will have degraded safely and the bone has fixed itself entirely with little to no evidence of intervention.

There is still some time yet before this

procedure will be rolled out. There are some technical niggles that are being fixed to make the chitosan, in this case in the form of a gel, into something more robust which will, in turn, make the new bone less brittle and therefore able to bear weight. Once research is complete it will likely be a welcome replacement to the current procedure which involves the use of crushed bones as the scaffold for growth. The source of these bone grafts is either one's own bones or grafts are generously donated post-mortem.

These technological advances, spearheaded by Imperial College London and Nuremberg University, will prove exciting to stakeholders looking for holistic, efficient tools to deliver drugs more efficiently and perform surgeries much more safely. However, there are limits to current research. There is limited funding available to researchers as pharmaceutical companies are perhaps slow to welcome chitin into the healthcare industry; it threatens to cannibalise their core businesses with potentially much cheaper alternatives.

Moreover, while the supply of chitosan is huge, the quality of that supply is a little suspect. Chitosan can be bought for $15-$20 per kilo at the cosmetic, high-grade level you'd find in a tube of Sensodyne toothpaste. The cost sky rockets to $2,000 per kilo for medical grade chitosan. This is, in part, because there are a number of kinds of chitin. Alpha chitin is hyper-abundant, it's what prawn shells are made from, but beta chitin, preferable for biomedical purposes because of the alignment of its polymers, is slightly more difficult to get a hold of. It comes predominantly from squid; specifically, the 'pen' or 'gladius' that runs through its body. Where much of a prawn catch is processed and de-shelled, squid tends to be sold whole with the 'pen' unremoved. Currently there is little incentive for fishermen to fish for squid for just the pens or add a step to their supply chains.

So, there is less beta chitin available and the underdeveloped infrastructure and logistics of getting beta chitin from the sea to the laboratory, as well as the limited number of producers turning chitin into chitosan makes it very expensive. Especially as the centres of research for medical chitin are in Europe, the UK and Germany, but the sources of medical grade chitin are in Africa and Latin America.

One company, Tigmak, is looking to combine the incredible potential of chitosan with access to the raw supply of squid necessary for high-quality chitin and strong links with the expertise of top researchers in Europe. With the backing of sufficient capital they are highly likely to be able to succeed in bringing sought after products to market at the forefront of biomedical research. They are attempting to address the scarcity and inconsistency of pharmaceutical grade chitosan whilst staying in contact with the end product. ■

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