The Revolutionary Solution Transforming the Veterinary Market – Magnesium Alloys

PEER REVIEWED

The veterinary market in the UK alone has grown by 1.9% annually since 2012 (CVS Group plc, 2017) and, looking at other geographies, US Animal Health Institute member companies spend around 10-12% of their sales investing in new innovations in animal health (AHI, 2010). Scientists and those working in the veterinary industry are continuing to look for improvements to maintain the health of animals, whether this be through drug delivery or the implementation of medical implants.

The veterinary industry, however, to some extent, is facing the same challenges as the medical industry. Owners of pets and animals are investing more and it is therefore important that the best possible products reach market through the discovery of innovative solutions to medical and healthcare problems.

A new state-of-the-art solution which has recently been developed for use in the veterinary market, for both drug delivery and in medical devices, is magnesium alloys. Magnesium alloys have already been successfully developed and used in CE marked cardiovascular scaffold implants in humans and are now beginning to be used effectively in veterinary auto wormers, allowing a drug to be delivered over specific intervals rather than at one time. So, what are magnesium alloy's properties and how have they helped with recent market breakthroughs, such as in veterinary auto wormers?

Magnesium for Applications in Animals

Bioresorbable materials, such as magnesium alloys, are beginning to be tested more and more for use within the animal health and veterinary industries. These bioresorbable materials are advantageous and can be used to address a number of challenges, as they achieve optimum healing by resorbing at a steady rate. Other examples of bioresorbable materials include polymers; however, polymers are often associated with low strength, and have been known to cause foreign body reactions. Further disadvantages are the time polymers can take to resorb compared to other resorbable materials.

Magnesium alloys bring to the market a revolutionary alternative to polymers. Magnesium, unlike polymers, is a naturally occurring element within the body. Although it has previously been associated with the aerospace industry, it is biocompatible and has now begun to be tested for and used in a variety of medical devices in both animals and humans.

Research into magnesium is a continuous process; however, it is already clear that magnesium demonstrates bio-compatibility, as well as biosafety. It is proven that magnesium can be used in the treatment of animals, and we now know what the outcome will be and that the material has the potential to be used in a wider range of applications for animals.

Studies of human blood following the use of magnesium within the body revealed little change to the composition and no disorder to the liver or kidneys (Zhang *et al.* 2009). Tests with magnesium alloy implants among rabbits have also revealed that the magnesium scaffold performed very well during degradation and osteogenesis, rendering magnesium a useable material for orthopaedics (Liu *et al.* 2014). This demonstrates its use among both humans and animals.

Magnesium has faced challenges, including its potential to degrade too quickly under physiological conditions. However, the recent advances in magnesium alloy technology mean that magnesium can be tailored to degrade at specific rates, taking advantage of the degradation process. This means that magnesium can now be used within animals for a variety of different applications.

The Manufacturing Process

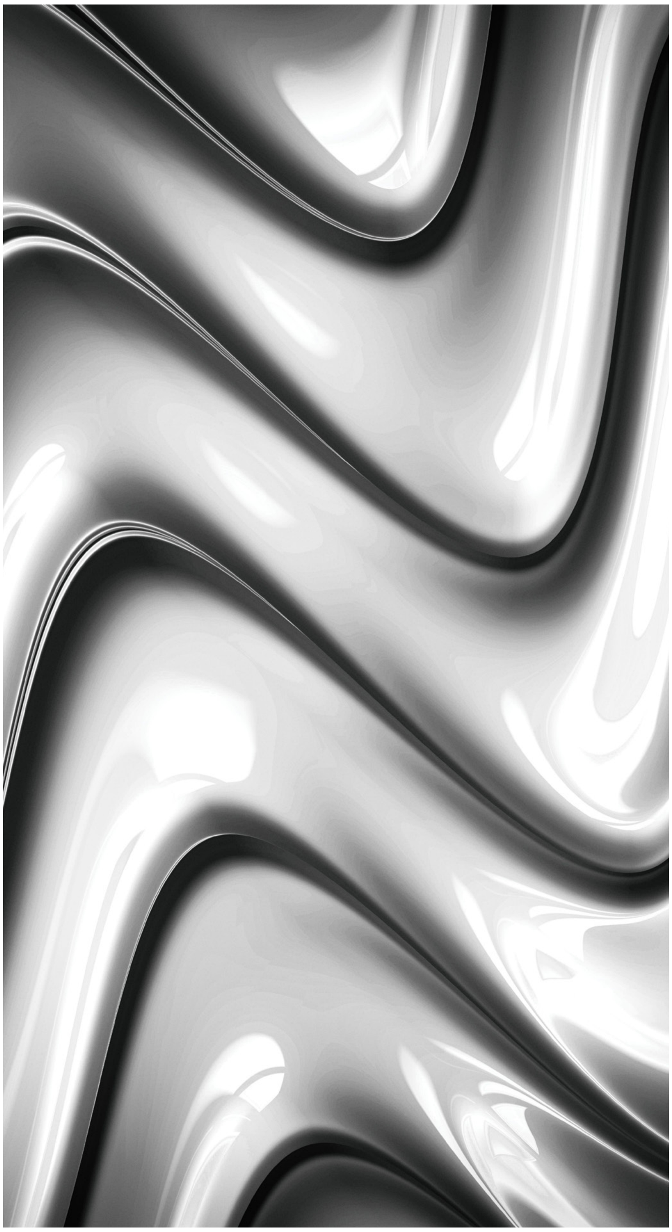
A manageable step-by-step process is implemented for the manufacturing of magnesium alloys, which can then be used within medical applications for animals. A good example of a company implementing a rigid process for magnesium alloy manufacturing is Magnesium Elektron, a Manchester, UK-based developer, manufacturer and supplier of magnesium, across markets including biomedical and pharma.

The bespoke Magnesium Elektron manufacturing process results in the SynerMag® magnesium alloy product for biomedical applications. The SynerMag product is developed in the company's SynerMag® Technology Centre, built as part of a $2.5M investment in 2012. The centre is a dedicated manufacturing facility, incorporating state-of-the-art laboratories, casting, extrusion and heat-treatment facilities. Magnesium Elektron worked to achieve ISO 13485 certification in 2014. The certification is an internationally recognised quality standard for medical devices. SynerMag's alloy designs, manufacturing and business processes – including supplier controls, traceability and documentation – are fully compliant with medical industry standards.

The process begins with magnesium heated in a furnace until molten. The alloying elements are then added to magnesium, with all raw materials selected based on their impurity content. The magnesium used in this process is of the highest grade of commercial volumes available on the market.

Once this step has been implemented, the metal is then cleaned to remove any traces of impurities. Then the molten alloy is cast into billets (a casting produced in the foundry that will need further processing before the finished good is manufactured). The casting parameters are critical in determining the structure of the material. This, in turn, affects the mechanical properties and corrosion rate. Magnesium Elektron uses computer modelling to simulate the casting parameters, in order to develop the very best cooling conditions for each alloy.

The next step of the process involves the cast billets being machined to a smooth surface. They are then



ultrasonically inspected to locate any defects. Following this, the billets are then ready for extrusion and they are heated to a carefully determined temperature. They are placed in a heated extrusion press and then pushed through a die. The die and extrusion press are also at critical temperatures. The heat parameters combined with the speed of extrusion determine the change in mechanical properties of the extruded material, comparative to the cast.

Once the extrusion has occurred, the material is cut into the correct lengths and samples are taken for testing. During melting, casting and extrusion, all the parameters are logged in real time by a central computer system. These parameters are then compared to the end test results for statistical process control. The summary of product characteristics (SPC) was a key aspect in fine-tuning the manufacturing process and removing variation within the product.

All of these processes, from the supply chain, through manufacturing and testing are risk-assessed, set up and controlled according the ISO 13485 standards. So, following the manufacturing process, which applications for animals have magnesium alloys been used in?

Examples of Use

Magnesium alloys have been used effectively within animals for a number of different applications, including osteosynthesis and for drug delivery. Osteosynthesis applications have previously, typically been produced from titanium and stainless steel, however, these are permanent materials and often require removal with secondary operations. Polymers are bioresorbable materials which have been used in this application; yet polymers, as well as taking longer to degrade than magnesium, have the potential to intake water during degradation, which leads to a loss in structural integrity, as well as size (Hofmann *et al.* 2009). For drug delivery, it was hitherto very difficult to control the release of a drug into an animal's system at set intervals, with a drug often released upon entry into the body.

An effective example of magnesium's use in osteosynthesis in comparison with polymers was by Marukawa *et al.* (2016) using Magnesium Elektron's alloy, SynerMag, to evaluate the effectiveness of the magnesium alloy implants in comparison to PLLA polymer implants, within beagle tibia fractures. The study discovered that 100% of the PLLA screws were broken within the timeframe. In comparison, only one in 24 magnesium screws broke. It also found that four out of six PLLA screws loosened within four weeks, whereas all magnesium screws remained tight. This shows both the strength and obvious mechanical benefits of magnesium, which can be used in high load-bearing areas; the study also found magnesium to have good biocompatibility.

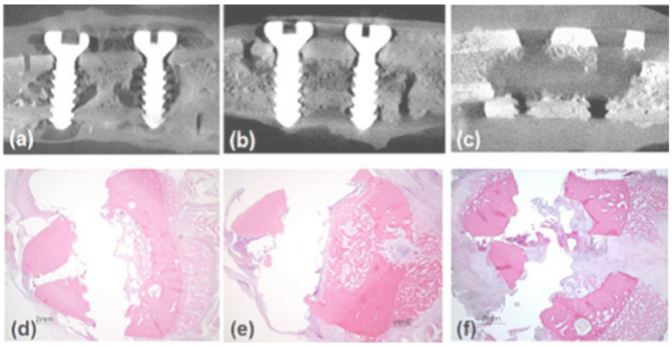


Figure 1. (a) Shows the monolithic magnesium screws, (b) shows the anodised magnesium screw, (c) shows the PLLA screw. Below (d-f), the first two screws (d and e made from magnesium) stayed intact, whereas the PLLA fractures at four weeks after implantation (Marukawa et al. 2015).

A second example once again used SynerMag and was conducted with biodegradable magnesium plate/screw osteosynthesis systems implanted onto the frontal bone of adult miniature pigs. Results showed the implants kept their shape during implantation and stayed in place with no screw loosening (Schaller *et al.* 2016).

Furthermore, a pilot study conducted by Windhagen *et al.* (2013) found that resorbable magnesium screws were radiographically and clinically on a par with titanium screws. They also found that magnesium did not cause any foreign body, osteolysis or inflammatory reaction.

Within drug delivery, magnesium has been equally as successful. A specific example is in veterinary auto wormers, in which a galvanic cell is used. This uses the process of magnesium corrosion to release oxfendazole, over a controlled, set period. In this particular case, an iron weight is coupled with a magnesium rod to form a galvanic cell.

This is held in a polymer cylinder containing several drug capsules. The galvanic corrosion forces the magnesium rod to shorten over time, creating an aperture for drug release. Each capsule releases its load at set intervals as the magnesium rod continues to corrode shorter.

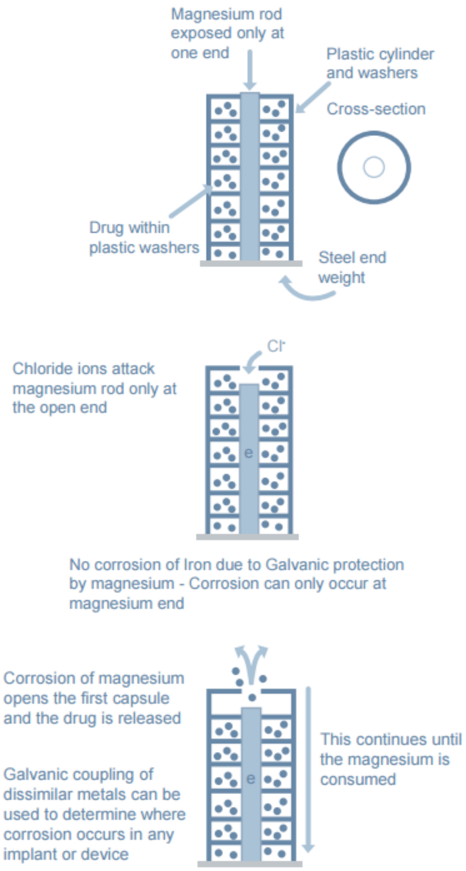


Figure 2. Veterinary auto wormers use magnesium corrosion to give timed delivery of drugs. The device also utilises a galvanic couple (Mg and Fe) to design where the device corrodes first.

Although magnesium alone has a quick resorption time, corrosion can be controlled through alloy design, processing and the coating of the alloy. It is therefore likely to replace problematic polymers in certain applications (Song, 2006), specifically in high-impact areas. As seen in use by Marukawa *et al.* (2015), the PLLA screws were prone to breakage.

Conclusion

Magnesium is therefore a material which can be used within multiple veterinary applications. This includes, among others, for osteosynthesis and drug delivery and offers great promise for other veterinary applications. Magnesium demonstrates biocompatibility, as well as biosafety, and can resorb over specified periods of time. This therefore means it is advantageous for use in animals over other bioresorbable materials such as polymers. Using magnesium, instead of titanium or steel, also eliminates the need for re-operation, saving time and money.

https://www.magnesium-elektron.com/global-downloads/

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