3G5 Crib – 2022

Q1

(a) Balloon expandable stents arrive premounted on a balloon anglioplasty catheter. While mounted, the stent is moved into place and the balloon is inflated to expand the stent to the desired diameter. Balloon expandable stents expand by plastic deformation by an angioplasty balloon.

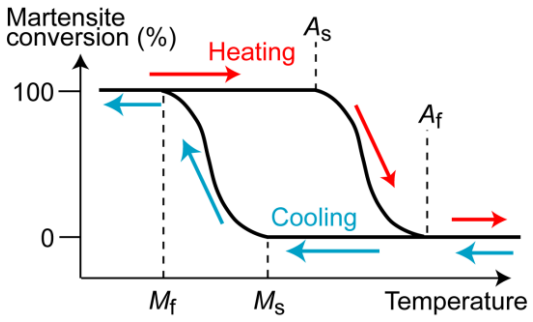
Self-expanding stents come premounted or sheathed. Once deployed to the treatment area, the sheath is pulled back, allowing the stent to expand to its predetermined diameter. Self-expanding ones use the "superelasticity" or the "shape memory" effect.

Balloon expandable stents are manufactured primarily from 316L austenitic stainless steel. Tantalum (Ta), cobalt-chromium (Co-Cr) and cobalt-platinum (Co-Pt) alloys have also been used. Self-expanding stents are made from an equi-atomic alloy of Ni and Ti, known as Nitinol.

The absence of a delivery balloon results in self-expanding stents being more flexible allowing longer length to be delivered through vessels that exhibit relatively high curvature.

(b) The difference between diffusive and martensitic phase transformations is that the latter does not involve any diffusion. In martensitic transformations, each atom moves a small distance relative to its neighbours in a well-defined way. This homogeneous shearing of the parent phase creates a new crystal structure, without any compositional change (no diffusion). The key to such a process is that it is diffusionless, and consequently can happen extremely rapidly. This allows very large recoverable strains, which are much higher than normally expected during conventional elastic deformation. Such effects involve martensitic transformations induced by an applied external strain or a temperature variation.

There is generally a temperature hysteresis associated with the martensitic transformation – see Figure below. On cooling, the parent phase starts to transform into the martensite at a temperature M_s, ending at a second, lower temperature M_f. The reverse transformation commences at some temperature A_s, ending at a final temperature A_f.

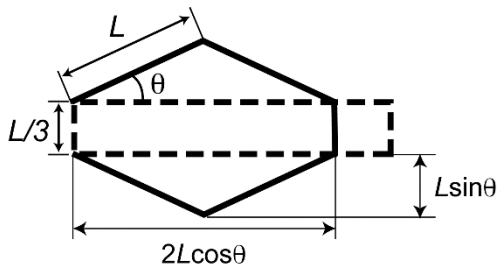


(c)

(i) The unit cell contains four members of length L and two members of length $L/3$. The metal volume fraction is thus given by

$$f = \frac{4\,Lt^2 + \frac{2}{3}Lt^2}{\left(2L\cos\theta\right)\left(2L\sin\theta + \frac{L}{3}\right)t} = \frac{Lt^2\left(4 + \frac{2}{3}\right)}{L^2t\left(4\sin\theta\cos\theta + \frac{2}{3}\cos\theta\right)} =$$

$$= \frac{t}{L}\frac{14}{(6\sin 2\theta + 2\cos\theta)} = \frac{0.2\times10^{-3}}{4\times10^{-3}}\frac{14}{(6\sin 20° + 2\cos 10°)};\ 0.17$$



(ii)

relative decrease in length = 0.2

relative increase in radius = $\frac{2L\sin\theta}{\frac{L}{3}} = \frac{2L\sin 10^{o}}{\frac{L}{3}}$; 1

axial contraction ratio ; 0.20

(iii) A disadvantage of this design is its high axial contraction ratio (i.e. reduction in its length), which prevents precise positioning of the stent. Nowadays, stent wall designs incorporate features that tend to reduce the axial contraction ratio.

This stent design has high axial beam stiffness before expansion because it has horizontal members. This is highly undesirable since stents must often be pushed through vessels, which may exhibit relatively high curvature. Stents with high axial beam stiffness before expansion may apply excessive local pressures causing damage to the vessel wall. The subsequent repair process is complex with inflammatory and thrombotic pathways being activated. Platelets become adherent to the damaged vessel wall due to loss of the protective endothelium (inner layer of the blood vessels). These changes culminate in recurrence of restenosis, and the need, because of luminal renarrowing, for further intervention.

[Comments: This question is on the description and calculation of a stent structure. For descriptive questions of (a), (b) & (c,iii), high marks were awarded for completeness. For part (c,i) and (c,ii), notable mistakes associated with the calculations included putting down the wrong formula, and/ or mis-calculated the geometry. High marks were obtained.]

Q2

(a) A good answer would reference biofunctionality and biosafety as both being important to consider. A very good answer would link this more specifically to this product. For example, noting that there is a function (encouraging rapid healing and growth of bone) and this must be maintained.

The same is true about noting that there is a need to consider safety and it may be that the polymer scaffold will not lead to deleterious effects when it degrades or leaches out materials.

An important point to bring up somewhere in a good answer is the reference to appropriate international standards on biological evaluation. A more complete answer would note there are standards about how to evaluate and test in general and what management processes to follow, and further standards that cover the details (e.g. looking at leachable substances, cytotoxicty, irritation, etc.).

A good answer would note that the assessment would be carried out on the final, finished product, where it has experienced the full manufacturing cycle. An excellent answer would refer to implementing a risk assessment process.

A good answer would note physical lab-tests. A very good answer would consider both lab tests and searching the literature. An excellent answer will link these well to the product described.

In terms of the literature, the candidate may discuss the choice of polymer and any other components within the plastic, and to look for previous clinical experience, animal studies, or even similar devices.

In terms of the lab tests, a brief description is important describing cytotoxicity studies, the direct contact of the final product with cells, the diffusion of materials across a gel layer to reach cells, and the analysis of the effect of any materials leaching out of the scaffold. An excellent answer would also note the importance of doing tests that reflect the relevant timeframe, as the scaffold will be implanted and degrade over time.

(b) (i) A description of sterilisation needs to include the point that any single living or active organism means the product is non-sterile. An very good answer will include additional points that sterilisation is about going from the initial bioburden to the sterility assurance level, because it is not feasible to confirm no active organisms are present and so we rely on a level of probability. An excellent answer would refer to international standards as defining sterilisation when making or manufacturing materials/devices.

In terms of validation, a good answer can include comments about challenge devices such as chemical or biological sensors, or can talk about validating the process by extrapolating from the bioburden to the sterility assurance level by experimentation at different exposure times. The third part of this question is guiding the candidate to specifically think about this product. This is an implantable device and so if it is non-sterile there is the potential for causing infection.

(b) (ii) There are many challenges that can be noted but a good answer would focus on the sterilisation of the scaffold only. With tissue engineering, the final product contains cells and proteins and so would not undergo sterilisation. The porous polymer scaffold would need to be sterile. It will be a challenge to find a way of ensuring sterility of the scaffold and then treating it in a controlled way and transferring it into a bioreactor without risk of contamination. As the 3D printing is happening in the firm, and the bioreactors are in the firm, it is likely an in-house system is needed. It will be challenging to identify the affordable and manageable technique that will penetrate through the porous region. There will be a challenge in ensuring the porous material does not change shape, surface chemistry, reduction in chain length etc. Answers may include considerations linked to safety of staff, affordability, and effectiveness.

(c) (i) A good answer will name two different steps and give a brief description. Examples would include any two from: identifying the regulation, classification, implementing a quality management system, creating the appropriate reporting documentation (design dossier or technical report), undergoing an audit by the Notified Body, Registering with the Competent Authority, affixing a CE

mark. A basic answer will note the step taken, a good answer will convey an understanding of what is going on at this step, and an excellent answer will give some additional details in the description.

(c) (ii) There are many challenges when considering tissue engineered products. A basic answer will name 4, a good answer will name 5 and show an understanding through brief notes on at least 3, a very good answer will provide brief notes on all 5. An excellent answer will include some additional level of detail to show a very good understanding.

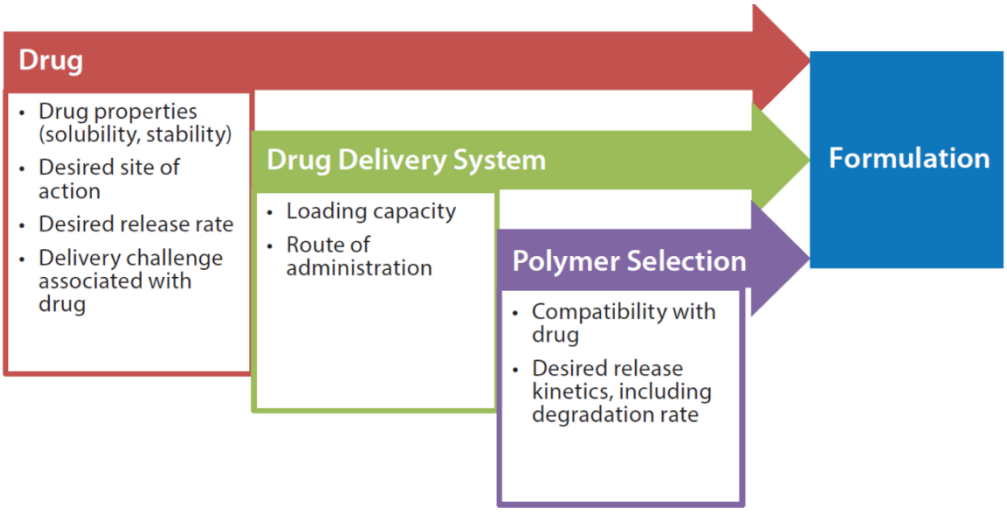
Examples include:

- From an example discussed, a new tissue engineering product can take a very long time to get regulatory approval.
- This product includes software and a physical tissue engineering product. Both components will require approval, which will likely increase the time required and cost.
- Previous tissue engineering products have overestimated the market because the approval was given for use in only specific circumstances.
- We could estimate a manufacturing cycle of 2 weeks, certainly >1 week. A tissue engineering product would likely have a relatively short shelf life and so it would be challenging to ensure it can reach a hospital sufficiently quickly.
- It will be challenging to carry out quality control tests once the product is made and before it is used, because of the relatively short shelf life and the individual nature of each product.
- There will need to be a highly controlled approach to transporting the final product to the hospital, most likely with controlled temperatures and humidities.
- This will be a class III product, and so will need to undergo rigorous testing and approval, including clinical trials. However, it is challenging to carry out trials when there is no equivalent treatment with which it can be prepared.
- The product will need to be both communicated sufficiently and designed carefully to ensure acceptance and adoption by clinicians, to ensure it can be implanted easily.

[Comments: This question is about manufacturing and regulatory aspects of tissue engineering product translation. It consists of a list of short descriptive questions, which involve applying general concepts taught in lectures to a specific case study. This is the most popular question, and also the highest scored question.]

Q3

(a)



The discussion should centre around the above diagram. Ultimately, the carrier polymer selection is dependent on the drug and the delivery route requirement. Thus, the choice of polymer can be dramatically different if the drug and the delivery considerations are different.

(b)

(i) Hydrolysable polymers' main chain/backbones are formed by chemical linkages which can undergo hydrolysis reaction. The key advantages of using co-polymerisation to forma a hydrolysable polymer is that tuning the co-polymerisation ratio, tuneable polymer properties can be resulted, such as in rate of hydrolysis (degradation rate), material mechanical properties, and surface hydrophilicity.

(ii) Brain cancer drugs can be highly cytotoxic. Localised delivery has the advantage of restricting drug delivery to the affected tissue (brain region), reducing systematic and side-effect toxicity. In the case of drug delivery to the brain, due to the presence of blood/brain barrier, many systematically-delivered drugs cannot permeate through. Thus, localised delivery overcome the issue of crossing blood-brain barrier. However, localised delivery requires direct access to the affected tissue region; in the case of brain cancer, the carrier system is implanted in the tumour resected cavity during surgery. The rate of delivery is highly dependent on the property of the carrier, thus less control-able, and adjustable.

(iii) poly(anhydride) is a hydrolysable polymer of which degradation is triggered by water (abundant in the brain tissue). The degradation product is biocompatible. For the wafer-dimension that normally used for the poly(anhydride) carrier, the wafer undergoes surface erosion, leading to drug delivery. Surface erosion gives rise to relatively constant rate of drug release for majority of the time. The overall duration of delivery is over a one-to-two-week period. This is important for localised cancer drug release since burst release is undesirable.

(c)

(i) For practical consideration, a wafer used by clinicians would have thickness ~a few millimetres. Thus the new hydrolysable co-polymer will undergo surface erosion. The plots of rate of drug release over time (dM_d/dt vs t) and total mass of drug released over time (M_d vs t) are shown below.

(ii) It provides a relatively constant rate of release for majority of the time of the wafer. The 'normalised' delivery profile is suitable. However, one does not know the absolute values of dMd/dt, so in a way we cannot say for sure whether the device is suitable from the profile alone.

[Comments: This question was about biodegradable polymers and drug delivery systems, which involves some short descriptions questions and a sketch of the erosion mechanism. This is considered a new question compared to the previous TRIPOS papers. Since the materials have been covered in details in class, most students have answered the question well. Most mistakes occurred for part (a) which required to state and discuss design considerations for selection of polymers for drug formulation. Answers need to cover broad categories of considerations for high marks.]

Q4

(a)

(i) Collagen can be used as a hydrogel/ scaffold to support cell growth. For implantation, the collagen quaternary structures should be avoided, so that the scaffold is throboresistance; thus the collagen would be acid treated and post-crosslinked. Acid treated collagen has some exposed cell attachment sites (e.g. RGC sequence). Collagen can be degraded by naturally occurring enzymes in the human body.

For acid extracted collagen, crosslinking of collagen fibres lead to decelerated degradation rate. Other commonly used forms (different microstructures and micro-architectures), e.g. fibres by electrospinning, sponges by freeze-drying, and as extracted collagen which has its quaternary molecular structure preserved.

(ii) Collagen sponge can be formed by freeze-drying of collagen hydrogel, where the separation of water phase from the collagen proteins lead to the formation of pores in a collagen sponge. The pores in a collagen sponge are micron in size; while for collagen hydrogel, it has an effective mesh network rather than distinctive pores. Thus, three types of water are present in the hydrogel state: free water, freezing bound water, non-freezing bound water. Free water – water that is not intimately bound to the polymer chain and behaves like bulk/pure water, i.e. undergoes thermal transition at temperature analogous to bulk water (at 0˚C). Freezing bound water – water that is weakly bound to the polymer chain and undergoes a thermal phase transition at a temperature lower than 0˚C. Bound water (non-freezing water) – water tightly bound to the polymer, which does not exhibit a first order transition over the temperature range from -70 to 0˚C. For sponge, it is characterised by porosity, and there is only free-water and freezing bound water. Further, collagen sponge is usually more mechanically robust than its hydrogel counterpart.

(b)

(i) The body's response to injury can be divided into three successive phases, which occur on different time scales and serve different functions. First, within a few minutes, blood loss is limited by "plugging" the wound through the process of haemostasis. The end result is a temporary "patch" that partially restores the integrity of the outer boundary of the body, as well. Over the next few hours and days, the site of injury is "cleaned" of infectious agents and small particles that have been introduced, and of dead cells left in the wake of the injury, by the process of inflammation. Finally, the tissue damage is repaired, to the extent possible, over the subsequent days, a process that may continue for weeks or months. The three phases overlap in time and their cellular and molecular components interact with each other in a complex, orchestrated fashion to bring about wound healing.

In summary:

Processes activated in response to injury include:

- Haemostasis (secs-mins)
  - Cells: Platelets
  - Proteins: Fibrin
  - Function: Plug the wound
- Inflammation (hours-days)
  - Cells: Phagocytes (macrophages and neutrophils)
  - Proteins: Complement
  - Function: remove bacteria, debris, blood clot
- Repair (days-weeks)
  - Cells: Keratinocytes, fibroblasts, endothelial cells, macrophages
  - Proteins: Collagen
  - Function: Rebuild tissue
  - Repair may be unsuccessful. Alternative outcomes include scarring (fibrosis) and chronic inflammation.

(ii) The insertion of an implantable glucose sensor into skin represents a skin injury. The sensor is seen by the body as a foreign body. Thus, during the repair process, fibroblasts would tend to secret copious amounts of collagen and other matrix proteins. The production of collagen may be excessive and leave a fibrotic capsule around the glucose sensor. The presence of fibrotic capsule reduces the sensitivity of the sensor thus leading to the failure of the implant.

[Comments: This question is divided into two parts, first on the description of collagen as a biomaterial; and second on the tissue injury and repair process. Most candidates answered both parts well. High marks were awarded for completeness of descriptions.]