3G5 2021 Exam -- Crib

Question 1

(a)

(i) A total hip prosthesis comprises an acetabular component and a femoral component. The acetabular component is usually made of UHMWPE (or Al_2O_3) and fixed in place with PMMA cement. UHMWPE is sometimes backed up with a metal cup (usually Co-Cr) to provide better X-ray visibility. The femoral component (stem and femoral head) is commonly made of Ti-6Al-4V, 316L or Co-Cr alloys. They are chosen because of their mechanical properties (strain tolerance, strength and toughness). Often the stem is coated with HA or porous Ti, Co-Cr coatings (bead-sintered or fibre/wire based ones) to allow bone in-growth as a means of fixation. Femoral heads can also be made of Al_2O_3 and ZrO_2. Femoral heads need to have a low coefficient of friction and high wear resistance.

A hip implant is mainly used to treat osteoarthritis. In osteoarthritis, there is a breakdown in the cartilage covering the ends of bones where they meet to form a joint. As the cartilage wears away, the bones become exposed and rub against each other. The second cause is known as avascular necrosis. In this condition, there is cellular death of the femoral head due to interruption of the blood supply. Without blood, this leads to collapse of the femoral head and degeneration of the joint.

(ii) Balloon expandable stents, are manufactured primarily from austenitic stainless steel (316L) which has very high ductility (~50% in the annealed condition). Tantalum (Ta), cobalt–chromium (Co–Cr), cobalt-platinum (Co-Pt) alloys have also been used. Ta and Pt have good radiopacity, which facilitates precise positioning of the stent. Co alloys allow thinner stent struts without sacrificing strength. Self-expanding stents are made from an equi-atomic alloy of nickel and titanium (NiTi) which exhibits superelasticity and shape memory effects. The latter allow very large recoverable strains. (as high as ~8%).

An endovascular stent is an expandable perforated tube used to widen blocked or occluded vessels.

(iii) An endovascular stent graft is an expandable tube composed of an impervious fabric (ePTFE, PET etc) supported by a stent. The choice of the fabric is driven by the need to prevent any cell adhesion.

Stent grafts are used to treat aneurisms.

(b) In orthopedic implants, cell attachment is required to increase the lifetime of the implant. This is in contrast to cardiovascular stents, in which case cell attachment may lead to

vessel renarrowing (restenosis) known as neointimal hyperplasia. To overcome this problem, the metallic stent surfaces are smoothen, passivated to improve corrosion resistance. Also polymeric coatings (degradable and non-degradable) and drug eluting coatings are applied to prevent neointimal hyperplasia.

In cementless prosthesis, bone-implant attachment is achieved via bone-in-growth into a rough/porous surface. In this case a number of surface engineering approaches are employed to secure the implant. This involves the use of porous coatings such as thermally-sprayed coatings (hydroxyapatite and Ti), bead-sintered coatings (Co-Cr, Ti) and wire/fibre meshes (Ti).

(c)

(i) Figure x shows the unit cell of NIR stent in the unexpanded and expanded forms.

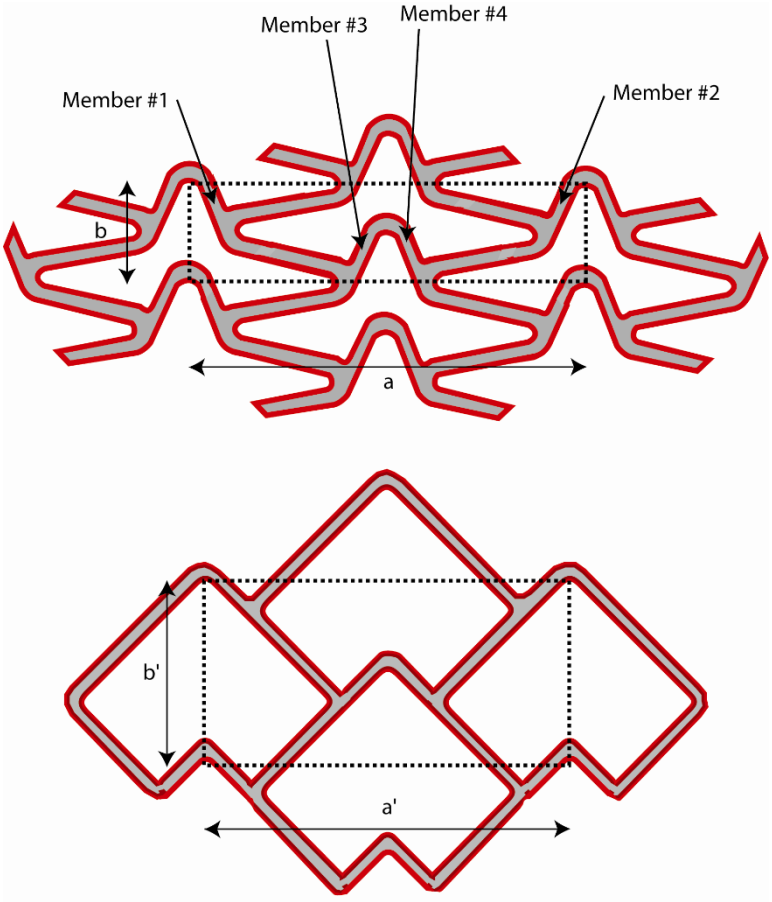


Figure x

(ii) This stent design facilitates deployment by the introduction of pairs of members forming vertical loops. These pairs of members have high orientation angles of around 70˚. They are marked in the Figure x above as two pairs of members, #1 & #2 and #3 & #4. These high angle

members are responsible for the flexibility upon insertion (low axial beam stiffness). This is highly desirable because it allows for conformance of the stent with the vessel curvature.

Examiner's comment:

This was a popular question. For part (a) and (b), all the points shown in the model answer should be addressed and explained for achieving a high mark. Most mistakes took place in part (c), which involved identifying the unit cell of a NIR stent.

Question 2

(a) A basic answer will refer to the key considerations whenever looking into choosing a sterilisation technique, i.e. the technique needs to show a broad spectrum efficacy, the technique complies with standards for medical device manufacturing, it is safe for staff to use and leaves no toxic residues, has a good environmental profile, is straightforward to monitor so sterilisation can be confirmed. It is important to note in a basic answer that material compatibility is considered.

A strong answer will also note that this is for a high throughput manufacturing scenario and so a continuous, rather than batch process is likely to be more useful. In any case, it would be important to consider the economic case when choosing a scenario. Examples would strengthen this, highlighting that ethylene oxide and gamma radiation are often used for high throughput manufacturing. The former is batch and has a long quarantine time, the latter is continuous with immediate release, but the cost and the need to have the system on site will often be the deciding factor.

An advanced answer would also note in more detail about material compatibility, specifically thinking about testing for any chemical or mechanical changes to the syringe and bulb due to the sterilisation technique. An advanced answer would also note that sterilisation is most important within the syringe, which will hold the material being delivered to the body, and also the tip. Sterilisation is effective because it either breaks up or denatures (unfolds, coagulates) proteins. As the vaccine is a protein, the sterilisation technique would be extremely difficult to arrange with the final packaged product without also damaging the vaccine. This would lead to conclusions that it is possible that they arrive sterile from a supplier or are sterilised upon arrival, just before adding the vaccine and sealing.

(b) A basic answer will note that standards assure those auditing the process and consumers that the technical and quality specifications have been met and that regulations have been followed. They also help manufacturers meet the regulatory requirements at the lowest feasible cost, to in turn keep prices lower.

A strong answer will give examples relating specifically to medical devices and highlight in more detail that a standard exists that defines the quality management system, ensuring the firm documents correctly the design, manufacture, and post-market handling of their devices. An international standard can be audited to ensure the firm is conforming to regulations.

An advanced answer may also note that standards exist at multiple stages, such as defining how to check biocompatibility, or defining how to deliver sterilisation.

(c) A basic answer will note three of the points made in the lectures, e.g.

As a Regulation, all countries within the EU or selling into the EU will conform to exactly the same rules, which did not happen when following a Directive.

EU legislation was broadened to include implants for aesthetic purposes, to provide confidence after a number of major issues.

There was a goal to help bring devices to market more quickly.

There were changes to the in-vitro diagnostic device rules, including increasing post-market surveillance. In fact, there was a goal to improve surveillance in general.

There was a move towards harmonisation with FDA in terms of traceability, safety, risk evaluation and clinical evaluation.

A good answer will explain each point clearly and give a brief note about one additional consideration this company will need to take into account when moving from following the directives to following the regulations. An advanced answer will also explain this in detail. It is anticipated that the company will need to recruit a qualified person or persons to be responsible for regulatory compliance, which was not required before. this person needs to have 5 years of regulatory experience and be responsible for batch conformity. The firm may also need to look at existing products and implement unique identifiers on products to help traceability, depending on what else they are producing.

(d) Benefits discussed in lectures include (but are not limited to) the reduced volume of blood required for testing, which is good when patients may have to get many tests at one time. Also, the devices are small and have fast response times and usually an increased sensitivity. Overall, it is anticipated that a move to such devices will reduce healthcare costs because it will reduce the handling, consumables, and infrastructure required to carry out such tests.

Challenges include the complexity of manufacturing techniques, which would mean a significant upfront investment. Also, it was noted in the lectures that often flows need to have mixing to allow a sensing reaction to occur. However, when working with such small dimensions, mixing is extremely difficult to achieve as flows are always laminar (low Reynolds numbers). There may also be comments about the challenge around taking advanced or new

products out to market as regulators are not as familiar with such devices and it is not always clear what scale of market will exist.

A basic answer will provide 1 benefit and 1 challenge in brief, a good answer will note 2 of each as required in the question. An advanced answer will explain these answers clearly and in detail.

Examiner's comment:

This is the most popular question with high marks achieved.

Question 3

(i) Urinary catheter require a material surface to be in contact with urine; it requires adequate structural rigidity to be used as a catheter, but also some flexibility to follow the contour of the urinary tract when being clinically inserted. Polyurethane (PU) provides a relatively non-adhesive, smooth surface required, and PU has good corrosion resistance to be used in a urine environment. The most likely PU polymer form is in a crosslinked PU elastomer, which can improve the strength, toughness and flexibility of the PU.

The likely in vivo degradation mechanisms are surface degradation due to biofilm formation, bacteria contamination, and to a less degree erosion.

(ii) PLGA is a hydrolysable polymer. PLGA co-polymers with composition 50%:50% result in an amorphous structure. An amorphous structure provides a homogenous phase for drug dissolution and release. The 50%:50% composition ratio is expected to have a short degradation half-life (in the order of days). The biodegraded bi-products can be re-absorbed by the body without inducing toxicity, and the degradation life time allows the drugs to be controlled released into the tissue over the time scale of days. Since it is a drug delivery device, more emphasis is placed on the predictability of controlled release rather than the mechanical property. An amorphous structure of the polymer is used.

The in vivo degradation mechanism would be dominated by hydrolysis, and the associated erosion process.

(iii) Alginate is a naturally derived, anionic polysaccharide material. Alginate has a good biocompatibility, and can be made into a hydrogel form (a 3D crosslinked network that can contain over 90% water). The water-rich space in the hydrogel allows cells to be encapsulated within. The crosslinking mechanism of alginate is reversible/ physical, and can

be triggered via Ca2+ in an aqueous environment, this is a mild process which does not damage living cells.

Once the cells are loaded within the crosslinked alginate hydrogels and delivered to the tissue, de-crosslinking (or degradation in vivo) can be triggered by interacting with physiological fluids which have a different ionic composition. As the hydrogel is de-crosslinked, cells are released.

(iv) Fibrin (also called Factor Ia) is a fibrous, non-globular protein involved in the clotting of blood. It is formed by the action of the protease thrombin on fibrinogen, which causes it to polymerize. The polymerized fibrin, together with platelets, forms a hemostatic plug or clot over a wound site. This 'plugging' and 'clotting' property of Fibrinogen/fibrin make them useful as a medical glue. Depending on the composition, fibrin glue can be optimised to give adequate mechanical property to hold the wound of soft tissues.

The in vivo degradation mechanism would be enzymatic degradation as the wound healing takes place. Short peptides are generated which can be bioresorbed.

(v) Non-absorbable, sterile surgical sutures can be made of nylon. The linear, long chains in nylon improves the molecular packing, the polymer crystallinity and thus the resulted fibre suture strength, toughness and durability. Nonabsorbable monofilament sutures incite minimal inflammatory reaction, slide well, and can be easily removed, thus providing ideal running for sensitive soft tissues like the cornea, leaving less scarring tissues. Further, nylon is non-resorbable thus it can remain its strength over time, which is useful for applications requiring the material strength to be maintained due to long tissue healing time. Since the cornea is on the body's exterior, the suture can be more conveniently removed compared to internal organ surgery.

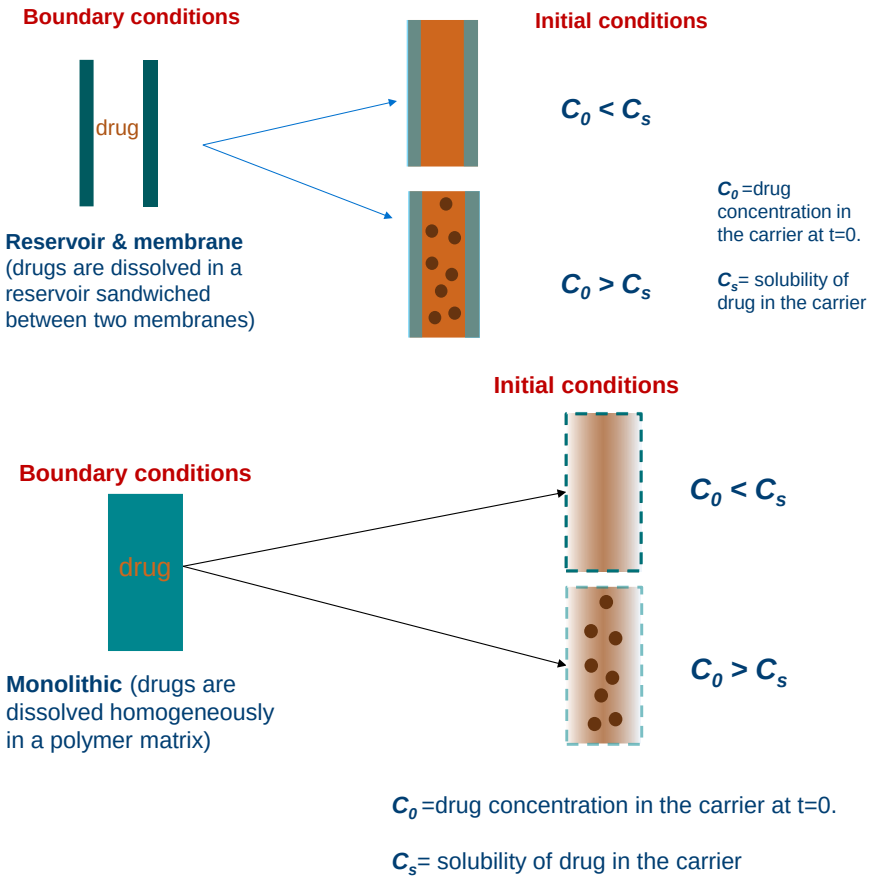
The in vivo degradation mechanisms could be wear and erosion (mechanical), and to a less extent biofilm-induced material degradation.

Examiner's comments

This question was the least popular question. Part (i) and part (iii) required the students to expand the basic knowledge learnt in the lectures and the lab about biomaterial selection to answer the question.

Question 4

(a) **(i)**



(ii) One can think about the factors in the relevant diffusion equations.

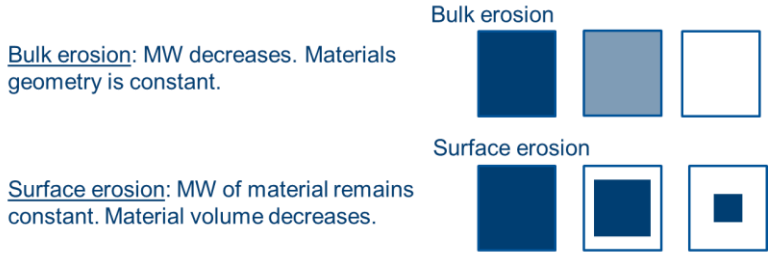
For the Reservoir & Membrane device type, diffusion constant of drug in the membrane, membrane partition function, membrane thickness, solubility of drug in the membrane, surface area of the device, concentration of drug in the carrier, concentration of drug at the surface of the membrane.

For the monolithic device type, diffusion constant of drug in the monolithic matrix, matrix thickness, solubility of drug in the matrix, amount of drug originally loaded (or original drug concentration and surface area of the device), concentration of drug at the surface of the membrane, time.

(b) As this is a hydrolysable polymer, one can look at factors influencing the hydrolysis reaction and erosion.

- Backbone chemistry—Choice of polymer class.
- Side chains that are hydrophobic (slower) or hydrophilic (faster)
- Crystallinity: packing

- Glassy versus rubbery state of the polymer—rubbery state, faster reaction
- Geometry of the implant/material: surface area to volume ratio, implant or coating thickness & porosity. This controls the motion of water into the material and whether the material may undergo surface vs. bulk erosion. When characteristic thickness < critical thickness Wc, bulk erosion takes place. When characteristic thickness > critical thickness Wc, surface erosion takes place.

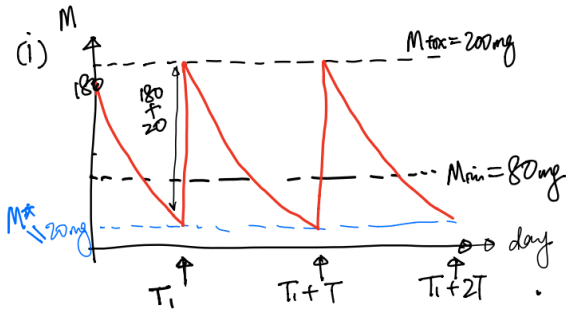


(c)

Comments: Several ways can be used to design the injection, and it might not be possible to maintain the mass of drug level within the window of effectiveness/ safety at all times. The key for obtaining a good mark is to demonstrate one's understanding in the concepts of multiple injection, the meaning of M_tox and M_min, and the assumptions under which his/her suggested result is valid.

Key assumptions for this particular model:

1. The aim is to maintain the drug level lower than M_tox, and it is non-detrimental for the mass of drug in the body to fall below M_min
2. Instantaneous delivery of M0 and drug effects in the body upon injection.
3. Superposition of drug mass at different injection times holds; thus Designate M*=20mg at which re injection takes place (20+180)=200mg giving nearing the toxic level



The first injection will be at T_1
The second injection at T_1+2T, then third injection at T_1+3T, and so on.

To find T_1 and T

Take M_i as the initial drug mass

$M = M_i \exp(-\lambda t)$

$\frac{M}{M_i} = \exp(-\lambda t)$

$\ln(\frac{M}{M_i}) = -\lambda t$

$\lambda = \frac{\ln 2}{4}$ day^{-1}

For T_1:

$\ln(\frac{20}{180}) = -\frac{\ln 2}{4} T_1$

$T_1 = 12.7$ days

For T

$\ln(\frac{20}{200}) = -\frac{\ln 2}{4} T$

$T = 13.3$ days.

(ii)

The approximate average weight of the drug will be dependent on the strategy of drug delivery shown in (i). In general, one should demonstrate his/her understanding of the conditions for approximation, how to mathematically calculate the average mass of drug, and the reasoning for the choice of numerical inputs.

With repeated injection after the first injection, we can assume that the average mass is close to that obtained in one repeated cycle after the first injection.

$$\langle M \rangle = \frac{\int_0^T M\,dt}{T} = \frac{\int_0^T M_i \exp(-\lambda t)\,dt}{T}$$

$$= \frac{M_i - M^*}{\ln\left(\frac{M_i}{M^*}\right)}$$

$M_i = 200\text{mg}$, $M^* = 20\text{mg}$, $\langle M \rangle = 78\text{mg}$

when $M_i = 150\text{mg}$, this is an interesting question, as this depends on whether one would want to change the multiple injection strategy., e.g. after the intial injection, one can cycle between 200mg and 50mg. if we do, then, (150 + 50)

$M_i = 200\text{mg}$, $M^* = 50\text{mg}$, $\langle M \rangle = 108\text{mg}$.

∴ difference ~ 30mg

(d) Subcutaneously implanted glucose sensors trigger a local inflammatory and wound healing response, which results in a fibrotic layer that walls of the implant and impairs diffusion of glucose to the sensor after a few days, thus rendering the implant non-functional.

Examiner's comments:

Students attempted this question have achieved good marks overall. Masks were mainly lost in part (c), for clarifying the conditions for the design of injection mechanisms, and performing calculations based on the conditions chosen.