National Exams December 2019

04-Bio-A1, Biomaterials and Biocompatibility

3 hours duration

NOTES:

1. If doubt exists as to the interpretation of any question, the candidate is urged to submit with the answer paper, a clear statement of any assumptions made.

2. This is an OPEN BOOK EXAM.
   Any non-communicating calculator is permitted.

3. FIVE (5) questions constitute a complete exam paper.
   The first five questions as they appear in the answer book will be marked.

4. Each question is of equal value.

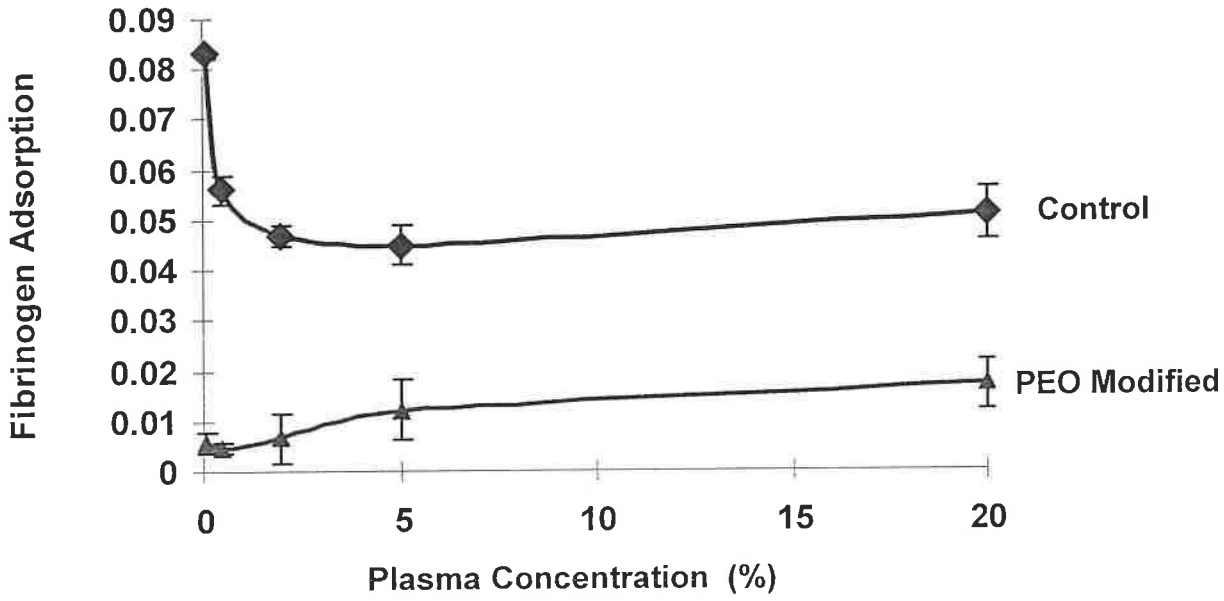
5. Most questions require an answer in essay format. Clarity and organization of the answer are important.

Question 1:

a) Large diameter (>6 mm) vascular grafts made from Dacron or poly (tetrafluoroethylene) (PTFE) have enjoyed significant success for the replacement of diseased or damaged vessels. However, in cases where the vessel to be replaced has a diameter 5 mm or less, the only option for replacement is a patient's native veins. Explain in detail why this is the case, what the challenges are in terms of developing a successful small diameter vascular prosthesis and why you think this goal has yet to be achieved.

b) The following results were obtained for the adsorption of fibrinogen from plasma to two different surfaces, a control and a surface modified with polyethylene oxide. Explain the curves and their significance in terms of developing materials with improved blood compatibility.

c) It has recently been reported that phospholipids, molecules that mimic the membranes of cells, including red blood cells, can be put onto surfaces with high density and that these surfaces show low levels of protein adsorption. Explain why these surfaces may ultimately show promise in developing more blood compatible biomaterials.



Question 2: Answer ANY FOUR (4) of the following questions

(a) A metallic screw used to connect two bones together is made of a single material (stainless steel) but is observed to be undergoing corrosion at the interface between the part of the screw embedded within the bone and the part of the screw exposed to the adjacent soft tissue. State, and briefly explain, two possible mechanisms by which this may happen.

(b) Would a bioactive material always be biocompatible? Briefly justify your answer, referring to the definitions of both these terms, and give one example or scenario that would support your answer.

(c) In a paper, the authors assayed the composition of proteins adsorbed to a particular biomaterial eight hours after implantation using a Western blot and found almost entirely albumin adsorbed to the surface. The authors then argued that the biomaterial was likely to induce low acute and chronic inflammatory responses, given that albumin is the most common protein in blood and thus would not act as an opsinization agent for the biomaterial. Describe two reasons why the authors are wrong, briefly explaining your logic in each case.

(d) Briefly explain the key mechanisms by which cells can self-regulate the degree to which they respond to a paracrine signal using cell membrane receptors. Give one specific example of the importance of this capacity for self-regulation in regulating cell responses.

(e) Describe three specific functions of macrophages in regulating the host response to biomaterials, highlighting in each case the specific biological stimulus that induces this function.

QUESTION 3:

You have been asked to design a new biomaterial intended to replace articular cartilage present in the knee, elbow, shoulder, and other joints that undergo repeated stress and deformation. Such therapies are essential to address the pain experienced by patients suffering from osteoarthritis, which is typically associated with a decrease in the amount of, or an inflammation within, the native cartilage. Given the nature of the tissue it is replacing, your choice of biomaterial should be easy to apply into narrow biological spaces, have high impact strength but also some capacity to reversibly deform under shear (to minimize joint friction), and persist in the body for extended periods of time (ideally years).

(a) Based on these requirements, what biomaterial(s) would you choose to make this implant? Briefly (2-3 sentences or points maximum) justify your answer, specifically connecting your choice to the above design criteria.

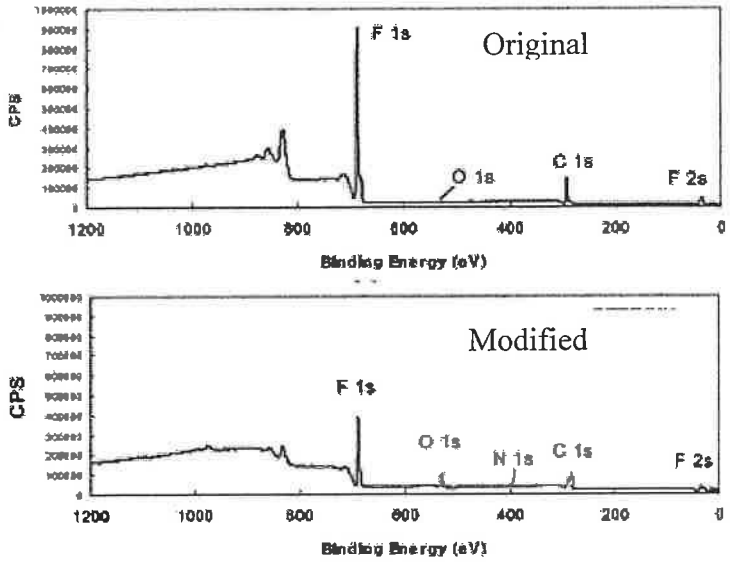
(b) What method would you recommend to sterilize your biomaterial? Briefly justify your answer.

(c) Initial testing of your biomaterial suggested that the mechanical and degradation properties of the material met the design criteria but the implants were prone to slipping out of the joint over time given their weak interfacial interactions with the surrounding bone. Suggest two types of surface modifications (chemical or physical) that would address this problem. *Note*: while it is not expected that you propose complete protocols, you should be specific enough in your answer that we recognize that you understand what you are proposing (e.g. "conjugation" is insufficient; "conjugation of x to y using z" would be sufficient).

QUESTION 4:

Consider the following data, all collected for the same original and then modified biomaterial.

(i)



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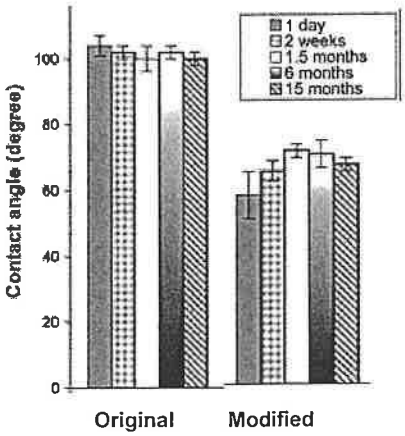
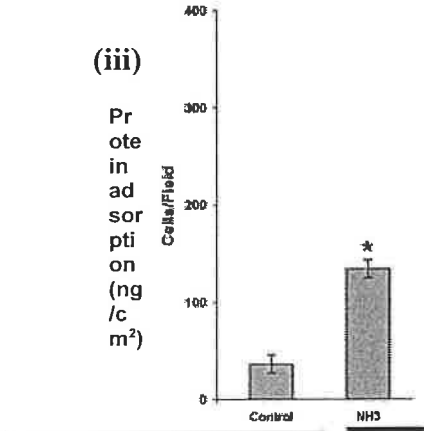
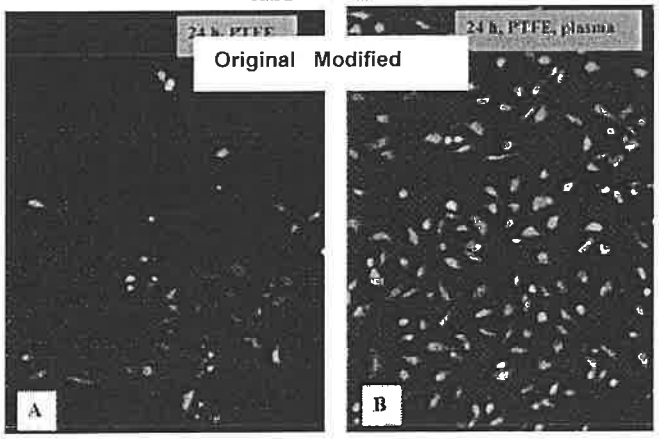


(iii)



(iv)



(a) What characterization methods were used to collect each of the data sets (i) – (iv) above? State the method and, using no more than *one line per method*, indicate what each method is measuring.

(b) Suggest possible identities of (i) the original biomaterial and (ii) the modified biomaterial, briefly justifying your answer (2-3 points maximum).

(c) List two other characterization technique(s) (including one line per technique to clearly indicate what you would be measuring with that technique) you would you use to validate your guess of the identities of the original and/or modified surfaces in (b).

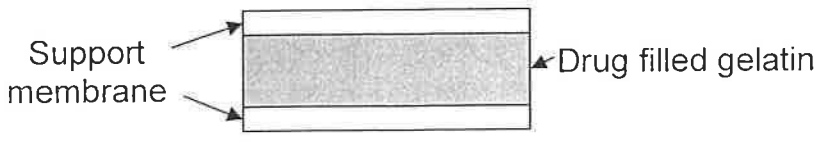
(d) Describe an application for which this type of modification would be useful.

(e) Predict (2-3 lines) the most likely host response to this biomaterial if implanted.

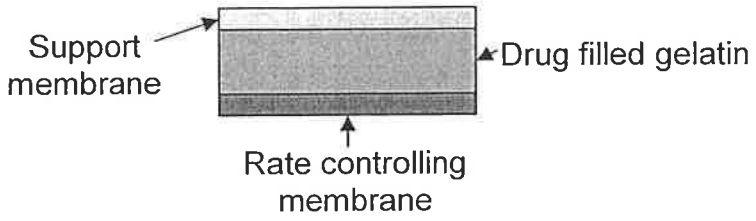
Question 5:

a) Your company holds a patent on a novel and very useful drug. The drug, with a molecular weight of 355, has been dubbed "healitall" and is useful for the treatment of glaucoma, gastrointestinal disorders and surprisingly has been shown to be a useful medication for reducing blood pressure. All of these indications are covered by existing patents. However, these patents will expire within the next one to three years and your company has exhausted all avenues attempting to find other disorders that can be treated by this drug. It has therefore been suggested that you look at the development of a delivery system for healitall in order that the company can continue to dominate these fields and make loads of money (i.e. your job potentially depends on the success of the delivery system). Someone else has been assigned the gastronintestinal and eye problems – it is the job of your group to come up with an appropriate delivery systems for treating high blood pressure. You have shown that the skin is actually quite permeable to this drug and that therefore a transdermal system, similar to the nicotine patches, is likely the best method of delivery in the case of the blood pressure treatment. Two models are proposed by two different members of your team. Given that you require a system that can be applied daily (i.e. every 24 hours), but accounting for patient compliance, should be able to provide a release rate at 28 hours of at least 200 μg/day, and that the device should be a disk with a diameter of approximately 3 cm which of the methods do you select? You can assume that the patches will be applied to a skin region where there is very high vascularization meaning that the concentration of the drug is virtually zero in the skin and tissue beneath the patch. Explicitly state any other assumptions that you make.

Method 1: It is proposed that the drug be dissolved in a thin (0.1-1 cm thick) gelatin film. The film containing the drug is then sandwiched between two thin polymeric membranes – the outer membrane is virtually impermeable to healitall, while the inner membrane offers negligible resistance to the passage of the drug. The diffusivity of the drug in the gelatin is 3×10^{-7} cm^2/s and its solubility is 1.2 mg/mL. You can vary the thickness of the gelatin film



Method 2: The drug is dispersed in a gelatin matrix for support at a concentration of 1000 mg/mL. This drug containing gelatin is then placed between two membranes. As above, the outer membrane is virtually impermeable to healitall. The inner membrane, which has a thickness of 0.2 mm is designed to act as a rate controlling membrane. The diffusion coefficient of the drug in this membrane has been determined to be $2x10^{-8}$ cm^2/s and the solubility of the drug in this membrane is 0.4 mg/mL.



b) Suggest an alternative method that could be used and justify your answer.

Question 6:

Various indications require the replacement or regeneration of bone.

a) Discuss the materials that have been used in the field of bone repair and regeneration.
b) Based on the structure of native bone, discuss what methods have the most promise in the development of new bone.
c) What are the limitations of current osteoinductive materials.

Question 7:

Artificial heart valves can either be made with synthetic materials or natural materials.

a) Discuss the pros and cons of each of the materials.
b) Two patients, a 50 year old male and an 80 year old female are scheduled for valve replacement surgery. Which type of valve would you recommend for each of these patients?