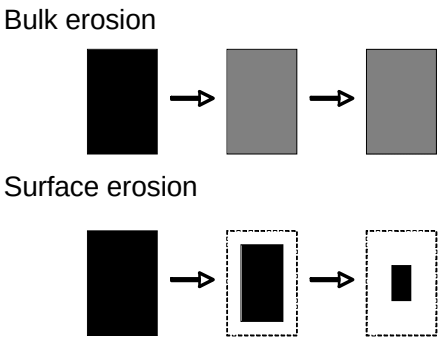
3G5 Biomaterials 2010 Crib Final version

1 (a) Bulk erosion is uniform through the sample while in surface erosion there is an erosion "front" and a degrading region of fixed thickness. In bulk erosion the volume remains constant, there is no change of sample geometry, molecular weight and density decrease linearly with time. In surface erosion the sample shrinks and the molecular weight and density remain constant. Bulk erosion takes place when the sample thickness W is less than a critical thickness W_c, when the time constant for water diffusion in the polymer is less than the time constant for hydrolytic bond cleavage and when the ratio of the diffusion to hydrolysis time constants, epsilon, is less than 1. Surface erosion is for the opposite case. Expressions need to be given for the diffusion and hydrolysis time constants and a means for establishing the critical thickness should be provided. Full details from the notes are provided below.



DP = degree of polymerization, the number of monomers in the polymer chain (note DP can be found from M_n/M_0 where M_0 is the molecular weight of one monomer)

DP – 1 because there are N-1 bonds between N monomers (above 3 and 4, respectively)

The number of polymer bonds in distance $<x>$ is

$n = <x>/V^{1/3}$

The amount of time needed to degrade n bonds is

$$\tau_E = \frac{1}{\lambda}\ln n = \frac{1}{\lambda}\left(\ln <x> - \ln\left(V^{1/3}\right)\right)$$

Make a non-dimensional function to compare the two time frames:

$$\varepsilon = \frac{\tau_D}{\tau_E}$$

Where a trade-off is seen (i.e. from one rate-limiting case to another) for $\varepsilon = 1$

or solve for $<x>$ by setting $\varepsilon = 1$ *to define a critical sample size,* W_c

The critical specimen thickness is proportional to the diffusion constant and inversely proportional to the hydrolysis reaction rate $W_c \propto D/\lambda$

For $W < W_c$ bulk erosion (also $\tau_D < \tau_E$ and $\varepsilon < 1$ *)*
For $W > W_c$ surface erosion (also $\tau_E < \tau_D$ and $\varepsilon > 1$ *)*

Surface vs bulk erosion

Two competing time-scales:

(1) Diffusion time scale: characteristic for water to diffuse into the implant

$$\tau_D = \frac{\langle x \rangle^2 \pi}{4 D_{eff}}$$

D = diffusion constant for water in that polymer, cm^2/s

<x> is the mean distance the water has to travel

(2) Hydrolysis reaction rate time scale

Assume Poisson kinetics for hydrolysis reactions.

The likelihood that a bond has been cleaved at time t is

$$f(t) = \lambda \exp(-\lambda t)$$

where lambda is a rate constant related to the half-life of a polymer bond.

the volume of polymer containing one degradable bond is

$$V = \frac{\bar{M}_n}{N_A \rho (DP - 1)}$$

N_A is Avogadro's number

Rho is the polymer density

(b) PLA and PGA are both esters with relatively short degradation time constants for hydrolysis and thus degradation in the physiological environment. Rough time constants are:

Poly (ortho esters) e.g. PGA: 4 hours

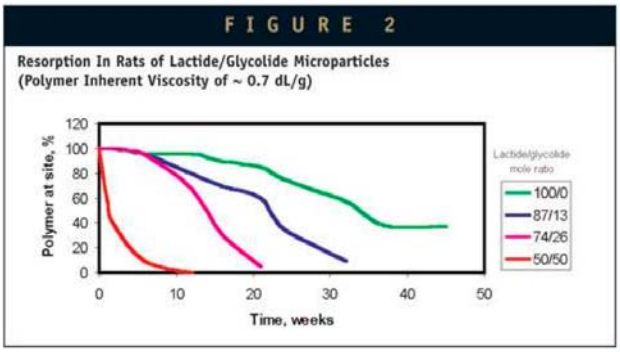
Poly (esters) e.g. PLA: 3.3 years

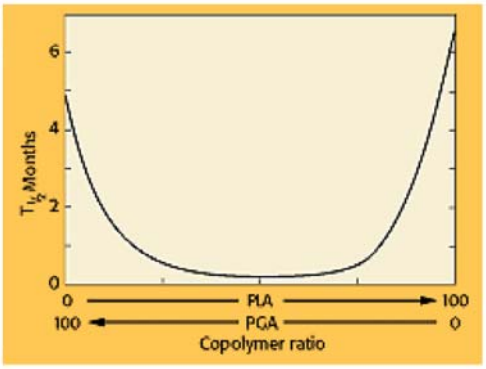
The most important factor affecting chemical stability of polymers in the body is the chemical nature of the hydrolytically susceptible groups in the polymer backbone. Additional critical factors are: the hydrophobic/hydrophilic character of repeat units, crystallinity, glassy vs. rubbery state (faster reactions in rubbery state), geometry (size and surface area to volume ratio) of the device. These are all important because of the relative ease of water reaching the hydolytically susceptible groups in the backbone. Water motion through the material is by diffusion and it is slowed by hydrophobic units, by high crystallinity/low porosity and by large diffusion distances in the case of large parts with small surface/volume ratios.

Factors that cause differences in bioerosion rates for PGA [poly(glycolic acid)], PLA [poly(lactic acid)] and PGA-PLA co-polymers specifically are discussed next.

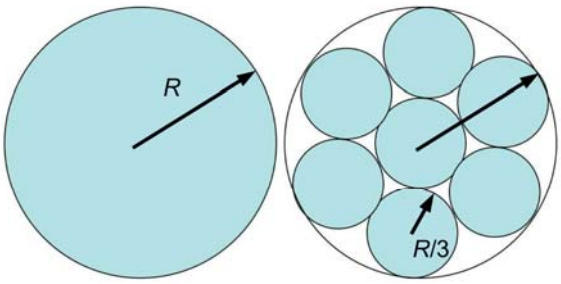
PGA and PLA have the same backbone chemistry (ester), but devices made of PGA erode faster than those made of PLA since PLA side chains are more hydrophobic. PLA-PGA blends in the 50:50 composition range are amorphous, while the pure polymers are semi-crystalline. The bioerosion rates for PLA-PGA blends depend on the crystallinity, polymer molecular weight and specimen porosity. Also affecting the degradation rates are the outward diffusion of hydrolysis by-products; if trapped, they can create pH gradients that accelerate hydrolysis in the center of the sample, leading to gradients in the specimen. Overall, there are a number of factors affecting blends and it is difficult to predict the bioerosion rate, whereas for pure materials a guess can typically be made on their rate ranking based on the polymer backbone, crystallinity, and other factors noted above. Some additional details are in this next image.

PGA	*PLA*	*Morphology*
0-25 mol%	75-100%	Crystalline
25-65%	35-75%	Amorphous
65-100%	0-35%	Crystalline





(ii) Factors to be considered include mechanical properties (bending stiffness, tensile strength). Multi-filament sutures maintain much (typically 70%) of the longitudinal tensile strength of monofilaments while exhibiting a significantly diminished (about 10%) bending stiffness due to the decreased moment of area for the smaller fibrils.



For the same tensile load applied by the physician, the stress in the multifilament is only 28% larger.

However, bending stiffness is S = EI. For the monofilament $I=\pi R^4/4$, whilst for the multifilament $I=7\pi(R/3)^4/4$, so the multifilament is much more flexible.
Other properties are also different.
Multifilaments exhibit higher friction: they tend to cause more damage when being pulled through tissue, but on the other hand the knots tend to be more stable.
Monofilaments are less prone to bacterial contamination.
Multifilaments erode faster than monofilaments made from the same material.
However, there is a wide range of suture types available, with different degradation times, so this parameter can be determined independently. Ultimately, the choice of suture for a particular application comes down to doctor choice.

Examiner's comments:
(a) Most students made a reasonable attempt at this part; marks were lost because of lack of detail.
(b) There was a lot of confusion about the relative erosion rates of the two polymers.

2 (a) A tissue engineered implant will typically have the following components: biological cells and a scaffold to support the cells initially. It can also potentially contain a stimulatory chemical component (which can be coupled to the scaffold) such as signalling molecules or growth factors. Autologous cells are those that come from the patient's own body. There are two advantages of this: one, there is no risk of immune rejection from the cells since the body would see them as "familiar" instead of "foreign"; two, there are no ethical quandaries associated with the use of the cells since they do not come from a separate source, who would have to consent to the use of their cells in another patient's body. A potential disadvantage is to the patient himself or herself, in that the cells have to be harvested in a separate procedure and expanded in culture, and there is thus an additional cost to the procedure and potential complications (e.g. infection) at the site of the other surgery.

(b) There are currently only two types of tissue-engineered products that are FDA/EU approved and commercially available. The first is only peripherally a tissue-engineered product, as it is solely an autologous cell transplant from healthy cartilage within the joint to a defect. Thus, there is no scaffold. The second is monolayer or bilayer skin-like materials, where the cell source is fetal foreskin fibroblasts from donor tissue. The LigaNew product is a hybrid of these two, in that it contains autologous cells but there is a polymer scaffold (as in the skin-type product). As no such product is currently on the market, the challenges associated with commercializing the product are greater. However, the market analyses have shown that the potential for tissue engineering generally is also great and thus this is a high-risk, high-reward prospect.

(c) Prior to sale of any implant, there is a process of regulatory control that varies depending on the country, although the general conditions of the process are similar. The implant is typically developed in a research environment, where studies are done in vitro and in animal models to assess the biocompatibility and efficacy of the implant. The implant is then brought into limited clinical trials, to test the performance of the implant in a human context. This is regulated closely, for example, in the US, the FDA has to authorize an "investigational device exemption" allowing the device to be implanted into humans without it having been fully approved yet. There is an important review of ethical issues to do with any implant before it is used in the human body. Success in limited clinical trials leads to more extensive clinical trials, and eventually an application to the appropriate regulatory authorities in the US and EU prior to clearance for sale.

The process is different in the US and the UK in both philosophy and in details of execution. The duration and rigor of the examination process for the implant depends on the risk it presents to humans, and the existence of a comparable product in the approved implant market. In the US there are three categories of risk in order of increasing risk: class I, class II and class III. In the EU, class II is subdivided into class 2a and class 2b. Long term implants, as would be expected for this tissue engineered replacement, are high risk and considered class III; further, there is little precedent for the approval of such implants such that the approval process will be more rigorous than that for an established class of medical device.

The philosophical difference between the US and EU is that in the US the implant must be proven to be efficacious (benificent) while in the EU the emphasis is on

safety and process control (non-malificence). The governmental body, the FDA, in the US must approve all implants for sale, while in the EU authority is not centralized but is delegated to a "notified body" which is an independent and private organization with authority to grant the CE mark, which approves the device for sale. The FDA procedure is based in federal regulation while the EU process relates to voluntary standards.

Further, and this is critical, because tissue engineered products contain living cells, the existing medical device regulations—designed for non-living implants and devices—have been found to be insufficient for regulating these products. There are thus new rules in both the US and EU. In the EU the new rules only came into effect in 2008, so they have not been tested or used very much yet! This is an evolving area of medical device regulation and we can expect that things will be changing as the next generation of devices and products comes to market.

(d) The typical wound healing process is a three stage process:
Seconds to minutes: Haemostasis ("plug")

- platelet aggregation (seconds), fibrin deposition (minutes) combining to seal off the wound and entrapping microbes
- Triggered by disruption of endothelial cells lining blood vessel walls

Minutes to hours: Acute inflammation ("clean")

- Rubor (redness), tumor (swelling), calor (heat), dolor (pain)
- Phagocyte activation (monocytes become macrophages, polymorphonuclear neutrophils migrate)
- Further activation of endothelial cells triggering increased vascular permeability, vasodilatation
- Complement assists in phagocytosis and can kill bacteria directly by membrane disruption/pore formation

Hours to days or weeks: Termination of acute inflammation and initiation of wound healing followed by resolution ("repair")

- Bacteria being cleared
- Initiation of fibrosis (scarring/collagen deposition) through fibroblast activation by macrophages
- Contraction of wound, restoration of normal tissue architecture and epithelial cell barrier
- Angiogenesis (blood vessel formation)

This is related to implantation because implantation almost inevitably involves the disruption of normal tissue at the implantation site (skin disruption); the body interprets the insertion of an implant as an injury and mounts a wound-healing response directly to it. Long-term problems with implants include chronic inflammation due to incomplete wound healing processes and/or bacterial infection.

(e) Sterile is the complete absence of any micro-organisms, including bacteria, yeasts, molds and viruses. If even a single micro-organism is present, the implant is not sterile.

Since determining the absence of all micro-organisms is actually probabilistic, a sterility assurance level (SAL) is set, typically 10^{-6} (one in a million parts is non-sterile). For sterilization process development, first the original bioburden must be established, that is, how many micro-organisms are present on the original part prior to any treatment. This is established over an average of 10-30 parts, and represents the time-zero point for generating a semi-log plot of log (number of micro-organisms) (y-axis) versus time (linear coordinates, x axis). A fractional sterilization run is performed, where the sterilization process is terminated at a range of intermediate time-points and the number of micro-organisms counted. Again 10-30 parts are examined for each time-point to establish a mean and standard deviation. A line is drawn through the data to establish the x-intercept at the SAL, or the time to achieve the target of one part per million. This can also be characterized by the decimal reduction time constant, the amount of time required for an order of magnitude decrease in the number of micro-organisms. Once the time at SAL is established, an additional factor of safety is typically then applied to account for population variation in resistance to the sterilization technique.

This is all complicated for a tissue-engineered implant due to the need to maintain the viability of autologous cells while preventing the propagation of bacteria or other micro-organisms that would thrive in the same conditions as would be used to keep the cells alive. The scaffold would likely have to be sterilized first, followed by introduction of the cells in a sterile environment.

Packaging must be designed to both suit the sterilization process and to allow for storage (most likely under frozen conditions) and shipping (likewise frozen) of the device/implant.

Examiner's comments:
(a) There was confusion about what was meant by 'autologous'.
(b) Generally poorly answered. Most did not recognise that the proposed product represents an advance into new territory. Few mentioned commercial aspects.
(d) A number of answers made no mention of the relevance to LigaNew.
(e) Very few spotted the need to sterilise the scaffold separately from the living cells.

3 (a)

Removal of the drug from the system at the rate -b as above
input (drip, pump) at a constant rate a (independent of either t or y or C)

$$\frac{dy}{dt} = a - by$$

Initial concentration of 0: y(0) = 0
Equilibrium concentration for

$$\frac{dy}{dt} = a - by = 0$$

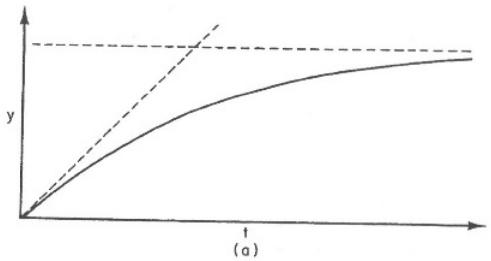
$$y = \frac{a}{b}$$

(note that b can be person specific, while a is set by the delivery method)

The equilibrium concentration is the horizontal dotted line asymptote.

Full solution:

$$y(t)=\frac{a}{b}(1-\exp(-bt))$$

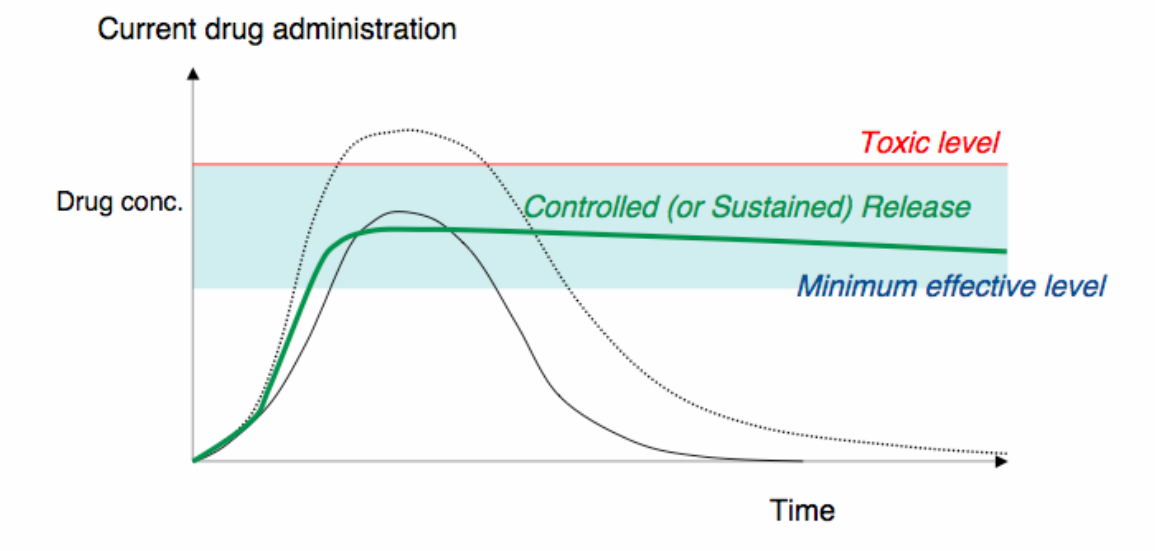


The initial slope is a.

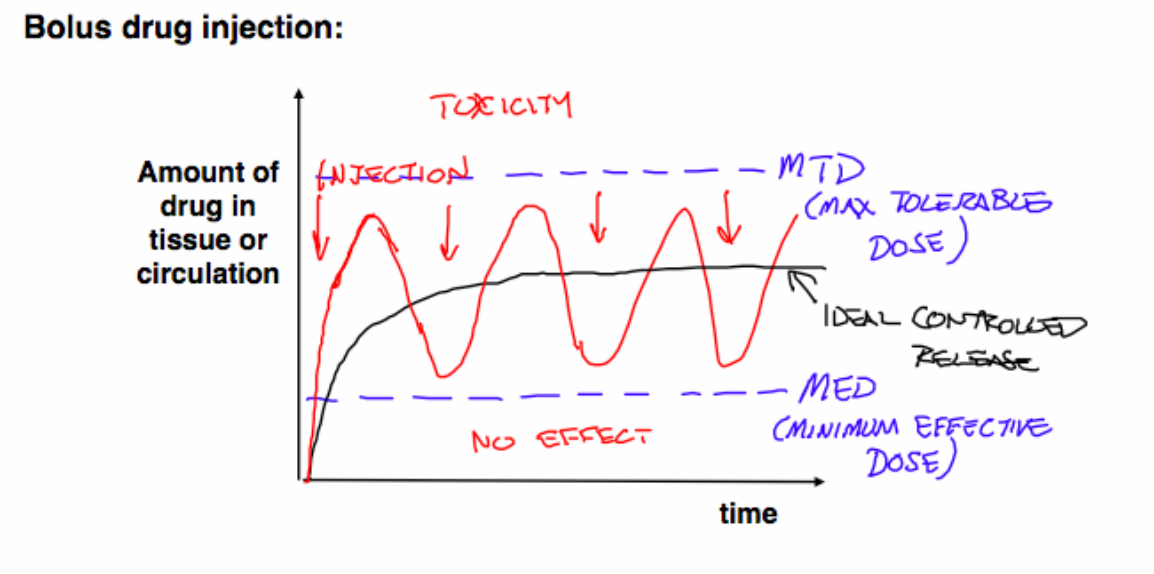
In general there is a minimum effective level and a toxic level (maximum tolerable dose) for a drug. A controlled release mechanism involves the use of a physical or chemical principle engineered into a device such that the drug is released into the body in a sustained manner designed to keep the body concentration of the drug approximately constant (and between the minimum effective level and maximum tolerable dose) over much longer time-scales than that for clearance of a drug after a single or multiple injection(s). Single or multiple injections are the traditional mechanisms of delivery compared with a controlled release or constant infusion mechanism due to either a pump or a new technology (i.e. drug released from polymer microspheres or a patch).

A single injection aims to reach a moderate dosing level (between the minimum effective level and maximum tolerable dose) but the drug's effect diminishes with time and dips below the minimum effective dose as the drug is cleared from the body. To achieve a sustained effect, multiple injections are used by which a periodic increase in the drug is delivered, with the timing of this delivery attempting to occur before the drug concentration falls below the minimum effective dose. This is very difficult to control, especially in light of patient variability in clearance rates. This paradigm of multiple injections is generally not seen as an ideal or sustainable model for patient autonomy and medical independence.

Controlled release versus single dose:



Controlled release versus multiple injections:



(b) Higuchi equation and associated assumptions:

Switch to Planar, not radial, system with a disbursed drug in a patch; this is a classic solution.

$$M_t = A\sqrt{(2C_0 - C_s)C_s Dt}$$

Higuchi 1961

i.e. square root of time behavior
Spherical solution for this case much more complicated.

This is a very useful expression but contains many assumptions that are often neglected (and this expression is over-ly used due to its simplicity); requires

1. $C_0 >> C_s$
2. *thin film with negligible edge effects (large patch)*
3. *size of drug particles << film thickness*
4. *carrier material does not swell or dissolve*
5. *diffusivity of the drug is constant (depends neither on drug concentration, time or position)*

M_t = amount of drug released
A = device (patch) surface area
C_0 = initial drug loading
C_s = drug solubility in polymer
D = diffusion constant for drug through polymer

(c) profile in A is for $M_t = k\,t^{0.7}$
This is an empirical power law that shows a larger exponent than would be expected for diffusion alone, so there is likely some effect of swelling-enhanced diffusion. For linearly increasing diffusivity with time, $M_t \sim kt$ (see Higuchi law above and assume C_s and D_0 negligible) so this is a less extreme increase in the diffusivity with time.

Profile in B is for an erosion controlled case where the initial response looks like diffusion or perhaps swelling-enhanced diffusion but at later times the drug release starts to accelerate due to the extremely enhanced drug diffusion through the polymer due to loss of physical material after hydrolysis of polymer bonds.

Physically there are three types of polymer-based drug delivery systems, in order of increasing complexity:

(1) Diffusion-controlled
(2) Swelling-controlled
(3) Erosion-controlled

Diffusion-controlled systems rely on simple diffusion of a drug through polymer and the kinetics are controlled completely by Fick's second law: the drug released is proportional to the square root of the diffusion constant and the square root of time. There are four sub-cases for diffusion-controlled devices, based on (a) whether the device is monolithic or a "reservoir" system and (b) whether the device is a planar object, such as a patch (nicotine patch) or a spherical object, such as an ingested or implanted microsphere. A further sub-classification is related to whether the drug loading is initially smaller than or larger than the solubility of the drug in the polymer—if larger, some of the drug is present in aggregates and must break up before diffusing out.

Swelling controlled systems are particularly useful when the diffusivity of the drug in the polymer is very low. Water enters the pore spaces in the polymer, opening them up (causing swelling) and the swelling enhances drug diffusion.

Overall the behavior is controlled by two competing diffusivities:
(1) Diffusivity of drug in the polymer (as in diffusion controlled systems, above)
(2) Diffusivity of water in the polymer (to give rise to swelling)

A semi-empirical expression for the drug release shows this to be enhanced drug release compared with pure diffusion-controlled systems: cumulative drug released $M_t = \text{constant}*t^n$

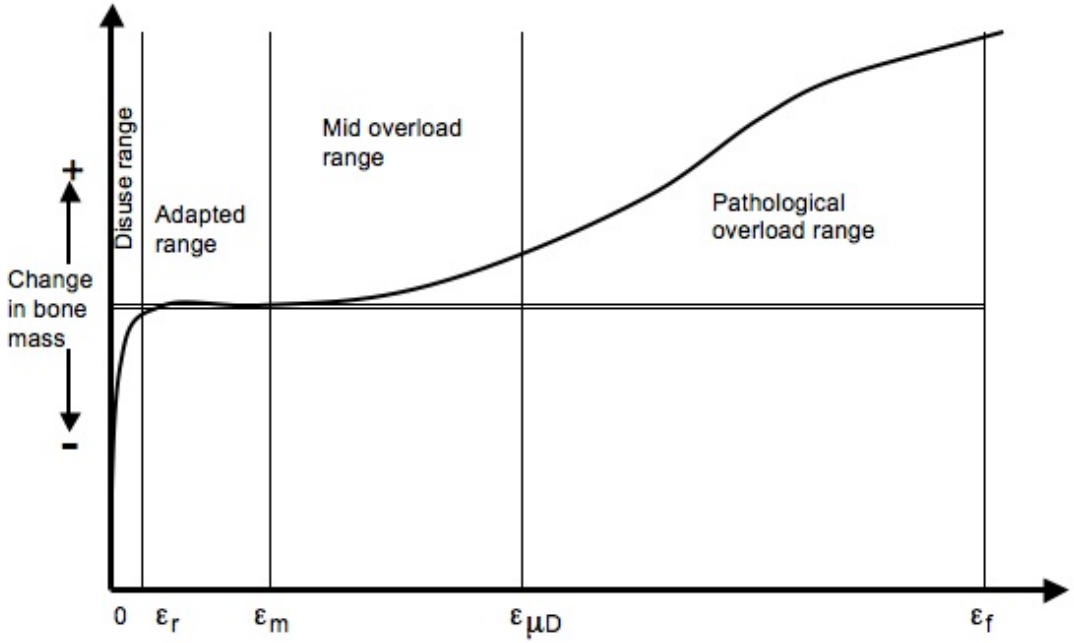
In pure Fickian diffusion, $n = 0.5$ as noted above
if swelling enhanced diffusion, $n = 0.5$ to as high as 1 for the case where the effective diffusivity of the drug in the polymer increases linearly with time, $D = D_0 + \text{constant}*t$

In erosion-controlled drug delivery systems, we see an additional parameter added to the two diffusivities, resulting in a complicated system with three key parameters:
1.Diffusivity of drug in the polymer (as in diffusion controlled systems, above)
2.diffusivity of water in the polymer (as in swelling controlled systems, above)
3.hydrolysis reaction rate (k)

The second and third of these, the water diffusivity and the hydrolysis reaction rate, are what trade off to determine whether surface or bulk erosion is dominant. The kinetics of drug delivery are sufficiently complicated in this case to eliminate the potential for simple analytical models of drug delivery, and typically stochastic approaches such as Monte Carlo simulations are used to create drug release-time profiles for erosion-controlled systems.

Examiner's comments: The first two parts were reasonably well answered, but very few really grasped the significance of the curves in part (c).

4. (a) Mechanical strain has been shown to influence bone mass: bone mass increases in locations where the strain is high, and bone can be resorbed in regions where strain is low. This is illustrated in the *mechanostat* diagram below:



Characteristic strains (millistrain):
adapted range starts at strains of 0.05-0.1;
mild overload range starts at strains of about 1;
pathological overload range starts at strains of about 3

This can cause problems with orthopaedic implants, which are stiffer than the surrounding bone and can therefore shield it from strain; the resultant 'stress shielding' effect results in bone loss which can compromise the stability of the implant.

(b) The hip joint experiences a force F from the pelvis through the femoral head. This force results in moments about the implant neck. A torsion T_t in the transverse plane and a moment M_f in the frontal plane. The torsion is regarded as the most likely to endanger the implant stability.
Measuring forces on a prosthetic hip in service can only be done rather indirectly by instrumenting a prosthesis with transducers (strain gauges). The output is normalised with respect to the patient's body mass. Median values are correlateed with different activities (walking, going up and down stairs, running).

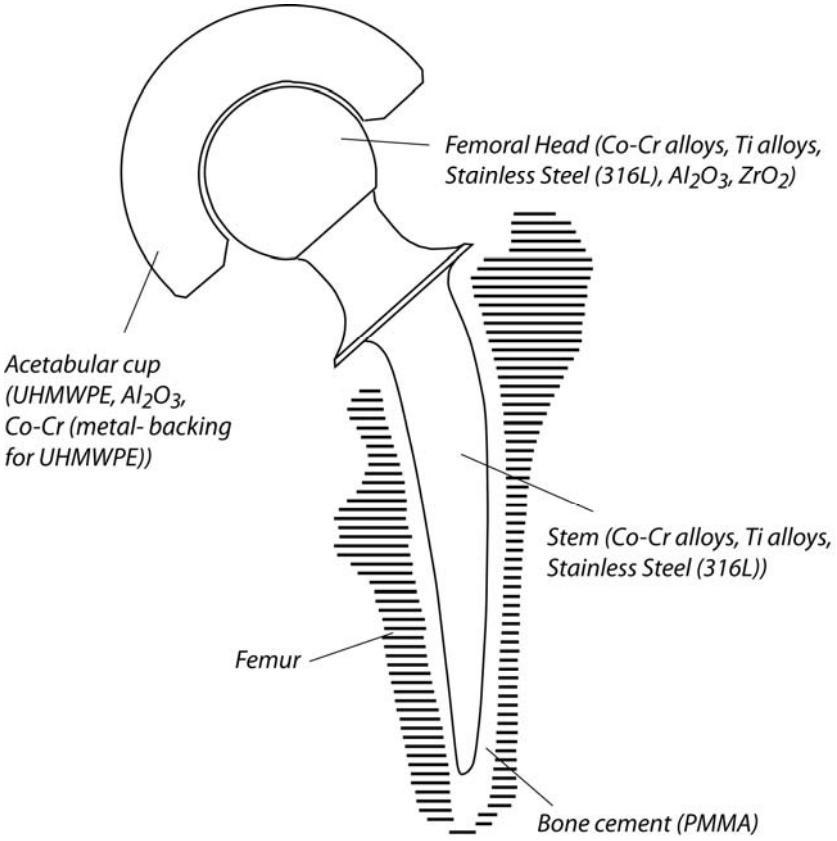
(c) A total hip prosthesis comprises an acetabular component and a femoral component – see schematic below. The acetabular component is usually made of UHMWPE (or Al_2O_3) and fixed in place with PMMA cement. UHMWPE is sometimes backed up with a metal cup (usually Co-Cr) which provides better X-ray visibility. 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 (respectable 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)

which 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.

An advantage of using a ceramic instead of metal for the head is that it is harder and can be made smoother and more wear resistant. The main cause of failure is formation of wear debris from the movement of the head against the acetabular cup. The neck of the stem is subjected to torsion and bending which will induce tensile stresses. Ceramics are weak in tension.

For all materials used in implants the following criteria are important:

- Basic mechanical properties: sufficient strength to avoid plastic deformation, brittle fracture, fatigue crack propagation and wear, preferably with a stiffness at least approximately matching that of bone, to minimise "stress shielding".
- Biocompatible (not toxic, not allergenic, not carcinogenic)
- Manufacturability (readily processed into 3-D shapes)
- Low cost



(d) Porous coatings are often used on stems to encourage bone in-growth and improve fixation.

Titanium or hydroxyapatite can be thermally sprayed; beads of cobalt-chromium or titanium can be sintered on to the stem; steel or titanium wire or fibre meshes can be sintered on to the stem.

Examiner's comments:

(a) Most sketched roughly the right plot, but very few were able to provide any indication of quantitative strains for transition between regimes.

(c) Most answers were rather thin and lacked detailed knowledge.