NOTES OF THE COURSE

in master's programme Biomedical Engineering
Course 308.106 Biocompatible Materials

Exam question from WS 2021

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TU WIEN TECHNISCHE UNIVERSITÄT WIEN

Exam questions from the oral exam held on the
23.02. - 24.02.2022,
03.03. - 04.03.2022.
The exam was held by a tutor via Zoom. There were 5 questions and you had 30 minutes to answer them. It can be seen from the questions that the same topics are always asked. Therefore, I wrote down the questions that dealt with the same topic one after the other.

1. **Definition of Medical Devices and categorization.**

   Medical device means any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings.

   For one or more of the specific medical purpose(s) of:

   a) diagnosis
   b) prevention
   c) monitoring
   d) treatment or alleviation (*Linderung*)
   e) investigation
   f) replacement
   g) modification or support

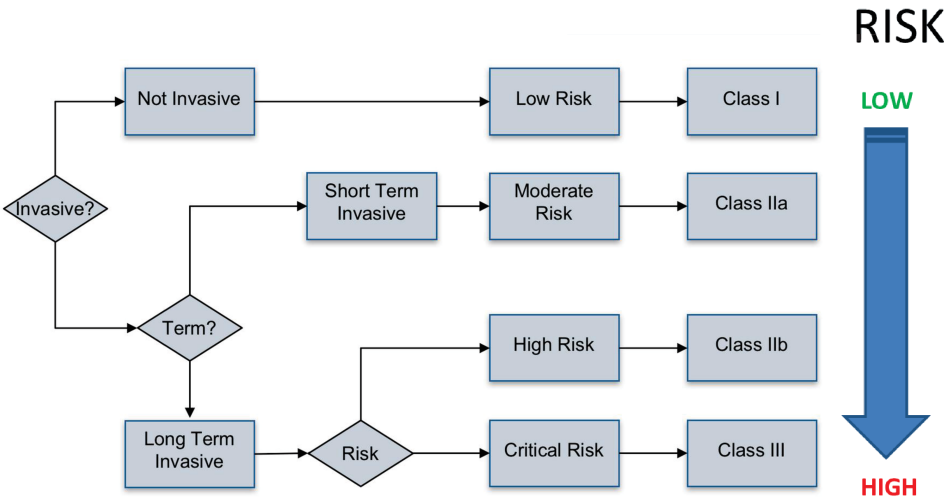

Figure 1: The EU Medical Device Regulation has 4 main categories for Medical Devices classification. Example for Class I: Stethoscope, medical thermometer; Class II a: injection needle, contact lens; Class II b: Orthopedic prostheses, Bone Cements; Class III: Stent, Artificial valves

2. **Medical Devices and European classes. Differences and Examples.**

   See answer above.

3. **EMA (European Medicines Agency) $\longrightarrow$ classed of Medical Devices. What makes a MD class III?**

   The EU Medical Device Regulation has 4 main categories for Medical Devices classification: Class I, II a, II b and III.

   Classe III:

   - Risk for the patients is High/Critical
   - Invasive and permanent contact with the Body

   Important is that the biocompatible for this class is a requirement (*Vorraussetzung*).

4. **Definition Sterility, SAL (Sterility assurance level) What are the procedures? More detailed description of Steam and Dry.**

   Sterility is the absence of viable contaminating microorganisms including highly resistant bacterial endospores; can only be considered in terms of probability, cannot be, cannot be proven empirically.

   SAL (Sterility assurance level) is the probability to detect a viable germ; describes efficacy of a sterilisation process OR the probability that a given sterilisation process has failed to destroy all of the microorganisms.

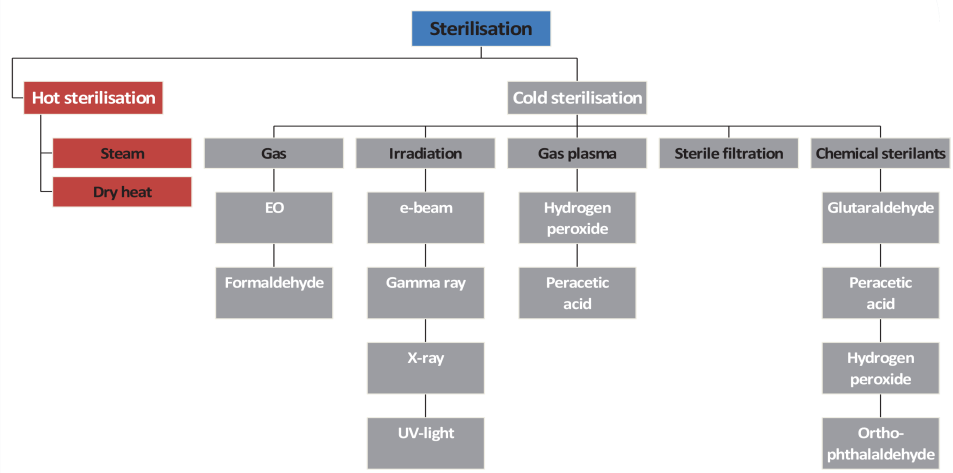

Figure 2: Methods of Sterilisation.

Steam: Realise on the tree parameters time, temperature and pressure. The MD is place in the autoclave. The machine begin to heat up, the temperature and pressure increase, the water begin to become steam (*Dampf*). During the next phase the autoclave must held the temperature and pressure on a constant level for 20 min at 121 ℃. After this step the system starts to cooling. Examples for steam application: gravity, Pre/Post-vacuum.
Destroying the microorganism by coagulation of proteins and oxidative damage.

Dry heat: When steam is a problem for the MD we can use this type of technic. The Sterilisation process include a heating phase whit dry heat >160 ℃ for 2 hours or 170 ℃ for 1 hour. The temperature must be higher as by the steam technic because dry heat conducts less efficiently energy than wet air.
Destroying the microorganism by coagulation of proteins and oxidative damage.

Gas: This technic is suitable for sterilisation of thermosensitive materials and components or materials sensitive to radiation. The MD is exposure to a reactive gas in a high concentration. As gas we use a microbiocidal gas or gas mixture. In the end of process the gas must completely remove, because it is toxic. Important is that the load is package in foils that are permeable to gas. Otherwise the gas can not detect the MD.

Irradiation: This technique offer the great advantage not to need vacuum or desorption as no steam or chemicals are used. They do not rise any toxic issue for the patients due to residues, and function at room temperature. The MD are usually sterilized already in their final packaging, it is of course important to select appropriate materials for this packaging. The MD get only irradiated whit different types of irradiation.
Destroying the microorganism by destroying of the DNA and cell membrane of microorganisms and deactivates them.

Gas plasma: Suitable in case of heat and steam sensitive devices. Plasma is created when a gas is heated sufficiently or exposed to a strong electromagnetic field. Gas Plasma sterilization is considered between 37 and 60ºC under low pressure.
Destroying the microorganism whit the produced free radicals via oxidation.

Sterile filtration: In choosing this sterilization technique, one must be aware of which microorganisms is suspected to be the source of contamination. Because some microorganism can either be too small to be retained (*zurückhalte*n) by the membrane or can be deformable and pass through the holes of the filter. For this kind of sterilisation we use membrane filters.
Sterilization by filtration aims to sterilize liquids or gases by the retention of microorganisms on the surface of filter materials.

Chemical sterilants: Sterilisation with aqueous solutions is rather a disinfection process than a true sterilisation process. Because they do not have completely eliminated the microorganism from the surfaces of the biomaterials.
In fact, by using liquid disinfectant, the microorganisms are only harmed and they can no longer provoke any infections.

5. Sterilization methods (listed). Gas sterilization in detail.

See answer before.

6. Types of sterilization with more complex explanation of hot steam and irradiation.

See answer before.

7. What is a ceramic, glass, glass ceramic? Bonds, structure, differences, areas of application, examples.

Name	Bonds	Structure	Differences	Areas of application	Examples
Ceramic	chemical bond between a semi-metal/metal and a non-metal; covalent and ionic bond	polycrystalline	-	dental restorations, implants	Aluminum oxide, Zirconium oxide
Glass	metals with non-metallic elements; covalent and ionic bond	amorphous	In contrast to ceramics, glasses are completely amorphous.	eyeglasses, diagnostic instruments	Silicon dioxide
Glass ceramic	molten glass; covalent and ionic bond	amorphous and crystalline phase	-	bone replacement, implants in ears	Hydroxylapatite

8. Ceramics $\longrightarrow$ Type of ceramics, ways to change their properties, degradable ceramics is for bones...

From a more functional point of view, ceramics can be grouped into four categories:

Morphological fixation: Dense, non-porous, nearly inert ceramics attach by bone growth into surface irregularities by cementing the device into the tissue or by press-fitting into a defect.

Biological fixation: For porous inert implants, bone ingrowth occurs that mechanically attaches the bone to the material.

Bioactive fixation: Dense, non-porous surface-reactive ceramics, glasses and glass-ceramics attach directly by chemical bonding with the bone.

—: Dense, non-porous, resorbable ceramics are designed to be slowly replaced by bone.

To change the properties of a ceramics we must influenced the grain size, this is done by changing the sintering temperature.
Low sintering temperature + fine starting powder = fine grain size

9. Properties and production of LS2 (Lithiumdisilicate). Components, nucleating agents, recrystallisation.

Listhiumdisilicate is produced by production of two materials. Glass and Lithiummetasilikat. Both materials merged together to the Lithiumdisilicate.
Lithiumdisilicate exhibit a high strength value and good optical properties. This make it possible to process is whit CNCs.

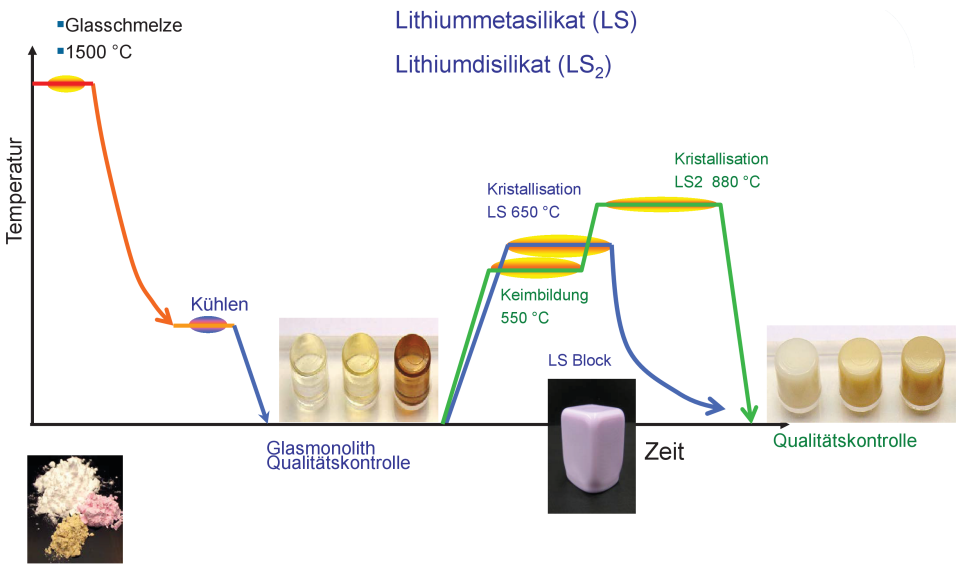

Figure 3: Production steps of LS_2.

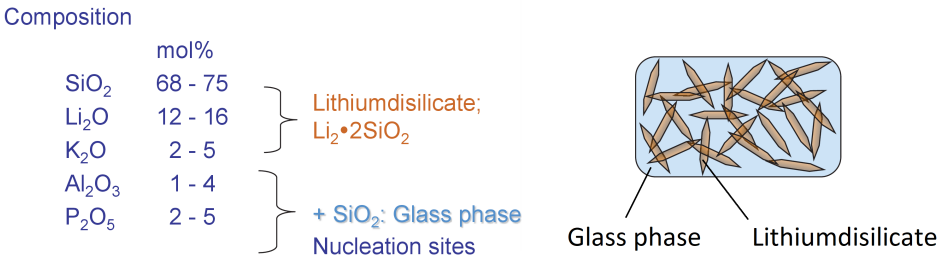

Figure 4: Components and structure of LS_2.

10. **Phase transformation of Zirconium oxide. Allowance (*Zugabe*). How, where and why does the conversion work.**

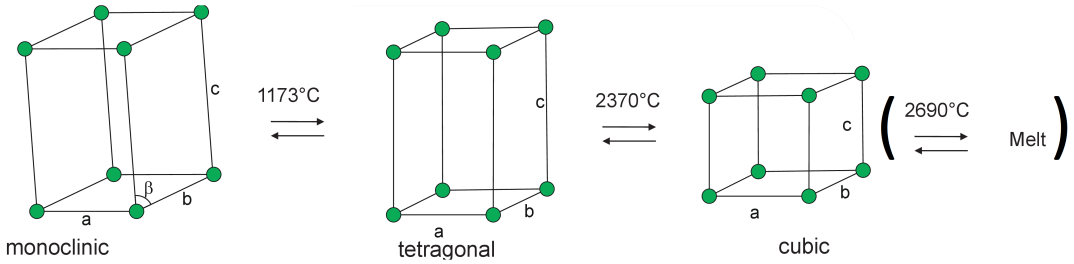

Figure 5: Phase transformation of ZrO_2.

Allowance of MgO, CaO, Y_2O_3 and CeO_2 stabilised the tetragonal transformation at room temperature. This is do because the Additions causes stress in the crystalline structure. The volume is reduction of 3 to 5% during transition from monoclin to tetragonal.

11. **Zirconia strength transformation.**

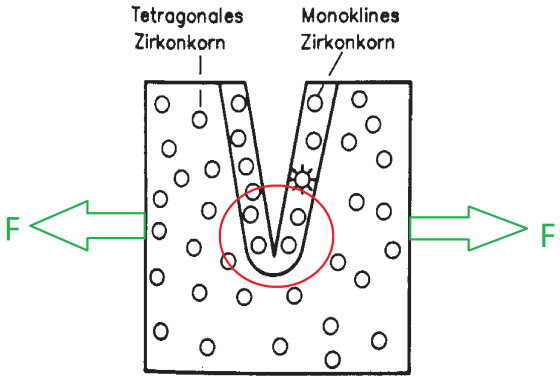

Figure 6: Strength transformation.

From outside we act a force (F) on an tetragonal zirconium cube. In the Middle a crack starts do grow. Do to the new free place, because of the crack, the Zirkoncorns have more place and build up a monolice structure. This structure also indicates a increase of the size form 3-5%. This size growth also reduces the stress by the crack.

12. Zirconia, where used. Why has given properties. Differences between aluminium.

Due to its high strength and excellent toughness, zirconia can be used for dental restorations, including crowns and bridges. Furthermore, it is the standard material in implantology for manufacturing abutments, which connect the metallic (titanium) screw with the final restoration.

Zirconia have given properties because of the phase transformation who he can undergo.

Yttria tetragonal zirconia polycrystal (YTZP), surpass alumina in terms of achievable strength

13. Covalent bonds, physical bonds.

- Irreversible (chemical) bonds:

  Covalent bonds The covalent bond can be characterized by the fact, that a covalently bonded atom interacts primarily with its nearest neighbours. The electrons of two adjacent atoms form a bound pair of electrons. This bond greatly reduces the total energy of the system, compared to the original initial state (unbound atoms). The valence electrons are shared between two atoms (usually metallic element with O, N, C, or B), leading to attractive forces and formation of a stable bond (molecules) $\longrightarrow$ high elastic modulus, high melting point, low coefficient of expansion. Due to the directional bonds, the atoms are not mobile. Covalently bonded materials are very hard and brittle.
  • high meltig point and elastic modulus,
  • brittle and low coefficient of thermal expansion (CTE)
  • poor thermal and electrical conductivity

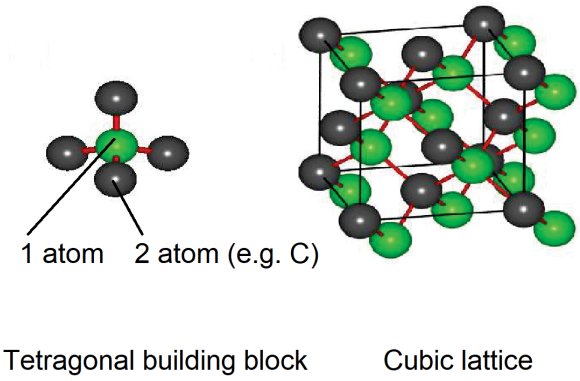

Figure 7: Covalent bond.

Ion bonds In compounds composed of atoms with strongly differing electronegativity, ionic bonding occurs. The chlorine atom is strongly electronegative and could energetically stabilize its outermost shell by adding an additional electron. This required electron is supplied by an Na-atom, which can achieve a stable electron configuration by giving off the outermost electron and in further consequence meeting a noble gas configuration. After the electron exchange, positively charged Na^+ -ions and negatively charged Cl^- -ions are present and attract each other. Electrons detach themselves from the atomic core of one (mostly metallic) partner and migrate to the other partner (halogen). Attracting forces between oppositely charged ions. Repulsive forces between equally charged ions. Most ion crystals crystallize in dense, space-filling crystal structures with a high coordination number. No materials with pure ionic bonds (except salts).
• very brittle

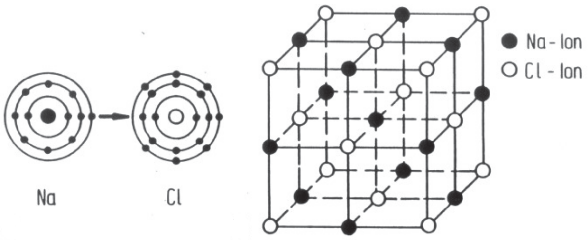

Figure 8: Ion bond.

- Reversible (physical bonds):

Van der Walls Van der Waals bonds are formed by the statistical charge fluctuations within neutral atoms. A short-term charge fluctuation in one atom produces an opposite charge distribution in an adjacent atom. Van der Waals bonds can also be observed, when an existing dipole induces a dipole moment in an adjacent molecule. The resulting dipoles can then attract each other. Van der Waals bonds always occur parallel to other bond types. However, they are only noticed in cases where much stronger chemical bonds are not dominant.
•weak bond
•low melting point/glass transition temperature,
•low elastic modulus and large CTE

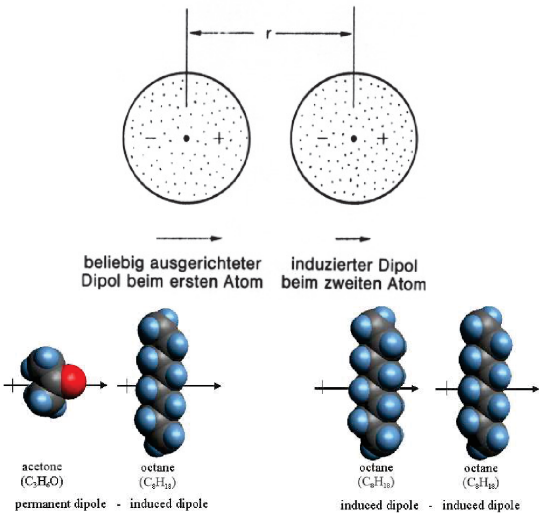

Figure 9: Ion bond.

Hydrogen bonds Hydrogen bridges are responsible for the binding forces between polymer chains. Hydrogen bridges also act between individual water molecules and are therefore the reason for the existence of solid ice. The characteristic feature of hydrogen bridges are hydrogen atoms that are simultaneously bound to two neighbouring atoms. The H atom first forms a covalent bond with a adjacent atom (e.g. O in the case of water). Due to the strong electronegativity of the oxygen atom, the electrons of the hydrogen atom are largely transferred in the direction of oxygen.

- weak bond
- low melting point/glass transition temperature,
- low elastic modulus and large CTE

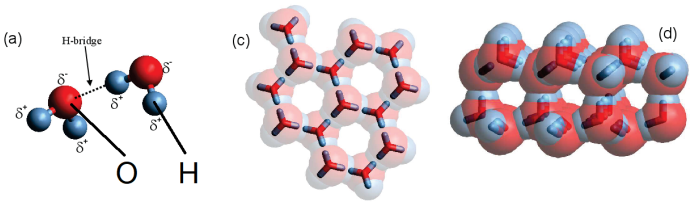

Figure 10: Hydrogen bond.

Metallic bonds The metallic bond is mainly characterized by the fact, that the outer electrons of the individual metal atoms cannot be assigned to a single "parent atom". Rather, these electrons are distributed over a large area with a high probability of being present. These electrons move freely in a quite wide range around the actual "parent atom". The loosely bound outer electrons form a so-called electron gas, which can move freely in the lattice formed by the positively charged atomic nuclei. Due to the anisotropy of the binding forces, most metals crystallize in dense, space-filling crystal structures with a high coordination number. Attracting forces between atomic body (positively charged) and electron gas. Repulsive forces between atomic nuclei (positive ions). Equilibrium potential or derivative of the attractive force (modulus of elasticity) at the atomic position vary substantially. Due to the free mobility of the electrons high thermal and electrical conductivity.

- High packing density due to anisotropic bonding forces
- plastic deformation possible
- large thermal and electrical conductivity due to free electrons

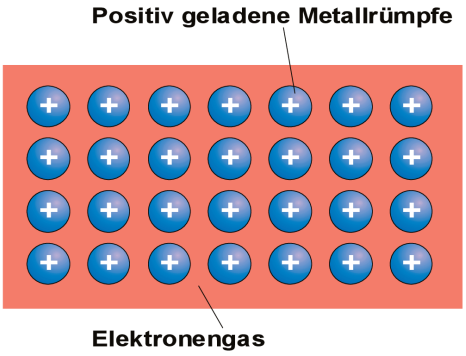

Figure 11: Metallic bond.

14. Polymers (properties, types)

Classification	Structure	Appearance (*Aussehen*)	Behaviour when heat up	Behaviour when treated with solvents (*Lösemittel*)
Amorphous thermoplastics	linear or branched macromolecules	Transparent, hard an rather brittle	softening, becoming clear during melting, forming thin filaments during melting, weldable	generally easily soluble after previous swelling in certain organic solvent
Semicrystalline thermoplastics	linear or branched macromolecules	soft to hard solids, tough due to plastic flow, opaque due to scattering at inner interfaces, only thin films are transparent	softening, becoming clear during melting, forming thin filaments during melting, weldable	swellable, in cold solvents not easily soluble. Becomes soluble at higher temperatures.
Elastomers	loosely cross-linked macromolecules	soft an flexible	flexible, but no plastic flow up to temperature of decomposition	insoluble, but easily swellable due to loose network
Thermosets	tightly cross-linked macromolecules	hard, brittle, transparent when not filled	remain hard, maintain shape up to the temperature of decomposition	insoluble; no or almost no swelling

15. Polymer classification. Elastic modulus/ temperature characteristics of each.

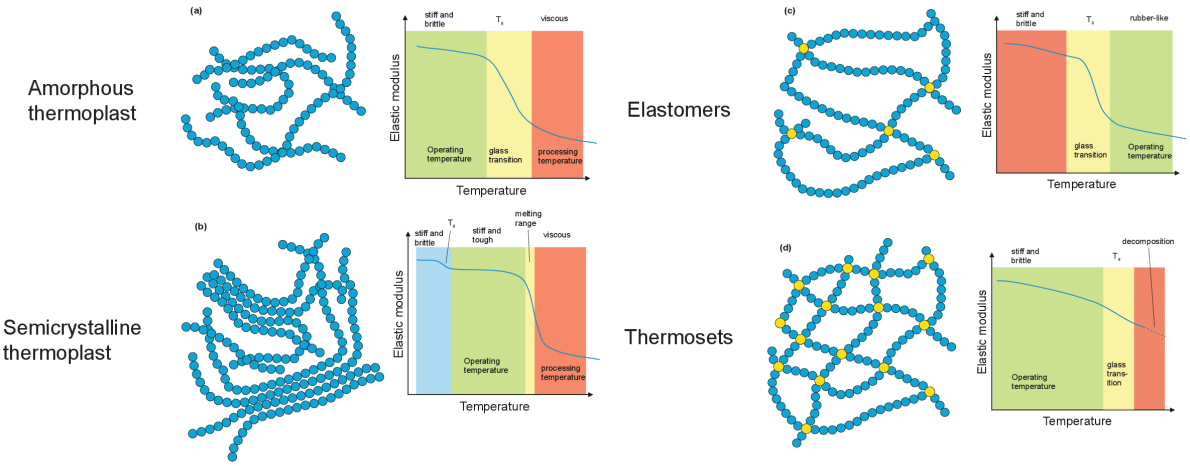

Figure 12: Polymers morphology ans scheme of elastic modulus versus temperature. Operating temperature (green); processing temperature (red); T_g glass transition temperature; T_m melting temperature.

Amorphous thermoplast: Are viscous above (*oberhalb*) their glass transition temperature T_g and stiff and brittle below this. There operating temperature is below T_g.

Semicrystaline thermoplast: These materials exhibit a glass transition as well as a melting point. The melting temperature (T_m) is above (*oberhalb*) the T_g. Below T_g these polymers are very stiff and brittle. Between T_g and T_m the material is stiff and ductile.

Elastomers: Have a low T_g where the operating temperature is above this point. This makes them highly flexible and yield rubber-like properties. the deformation of such polymers is elastic.

Thermoset: The T_g here increases because of the many cross-links. The higher density to covalent bonds lead to an increase of de elastic modulus and strength. The operating temperature is below T_g. The ductility and the fracture toughness is very low.

16. Polymers $\longrightarrow$ types differences, what happens when heated, solubility (*Löslichkeit*).

See answer before.

17. Properties of Polymers (Primary the differences in mechanical/thermal properties)

See answer before.

18. Hydrogels $\longrightarrow$ materials, structure, DDS (Drug Delivery System), what do use in combination with them (Protection).

- Natural materials:
  - Polysaccharide e.g. agar, cellulose
  - Polypeptides e.g. collagen, gelatin
- Synthetic materials:
  - PEG

– PAA

By definition, the hydrogel consists of a 3D network of hydrophilic polymers, formed either by:

- Covalent bonds produced by reaction of one or more copolymers
- hysical cross-links from entanglements, hydrogen bonds or strong van der Waals interactions between chains
- Ionic interactions

Other important features are that Polymer chains of hydrogels interact with the solvent molecule and tend to expand to the fully solvated state. Crosslink structure works as retractive force to pull back polymer chain inside.
Hydrogels are able to retain a large quantity of water within their structure without dissolving (up to 99% of H2O dry weight) -> reason why they are highly biocompatible.

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance into the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body. An equal drug level in plasma and tissue over a defined period is necessary.
Those DDS aim to reach an equilibrium between supply of the drug and its elimination. This equilibrium must be of course within the therapeutic window over a controlled period of time.

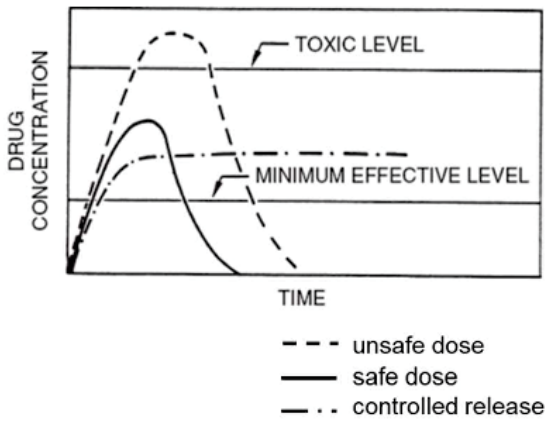

Figure 13: Therapeutic window.

19. Hydrogels.

See answer before.

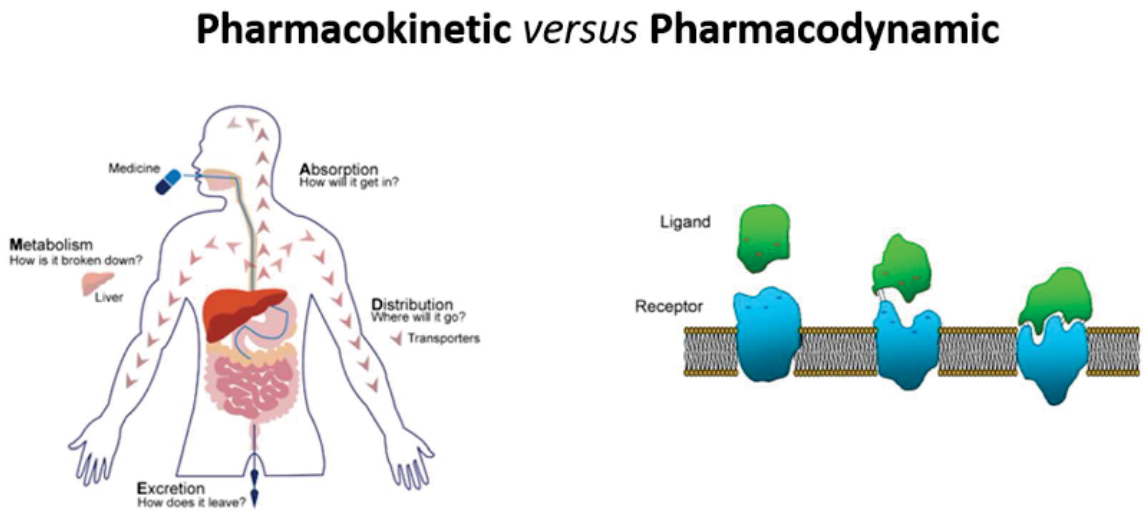

Figure 14: PK vs. PD.

PD is the study of the biochemical, physiologic and pharmacological effects of drugs on the organism. This pharmacological effect is most of the time a result of the drug binding to a specific receptor present on/in the cells. Pharmacodynamics places particular emphasis on dose–response relationships, that is, the relationships between drug concentration and effect. The DDS do not really play a role in PD.

PK is a branch of pharmacology dedicated to determine the fate of substances administered to a living organism (but not its pharmacological activity = PD). PK is directly influenced by the type of DDS carrying the active drug. The PK includes consecutively 5 “phases”, named LADME, for Liberation, Absorption, Distribution, Metabolization and Excretion.

Controlled Release Drug Delivery System:

- Diffusion-Controlled DDS
- Water Penatration-Controlled DDS
- Chemically-Controlled DDS
- Responsive DDS
- Particulate DDS

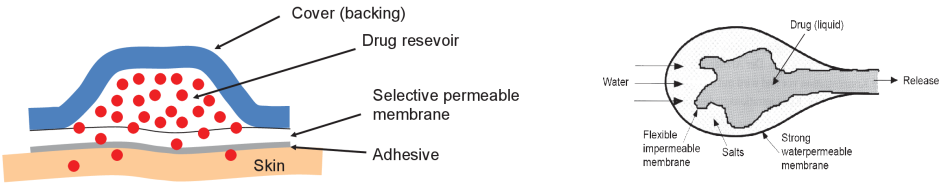

Figure 15: Left: Diffusion controlled drug delivery system. Right: Water penetration controlled drug delivery system.

20. Foreign Body Reaction.

The body’s recognition of self and the aim of containing or destroying the non-self is the basis

of the foreign body reaction (FBR).
What is a “non-self”?

- Non-self can be living agents (infectious agents, infected cells)
- Non-living agents (BIOMATERIALS)

The field of biomaterials has evolved from passive concepts such as biocompatibility and tolerance to a contemporary paradigm of biointegration and bioinduction.

The FBR involves many complex molecular and cellular players but can be broadly categorized into five sequential phases

- Blood biomaterial interaction
- Acute inflammation
- Chronic inflammation
- Foreign body giant cell formation
- Encapsulation

Besides their in vivo functionality, biomaterials also require characteristics that allow their integration into the intended tissue without eliciting an overshooting foreign body reaction (FBR). The host response to implants is essentially an in fl ammatory response that continues as long as there is a foreign body present to which to respond.

The healing cascade happens at the surface of the MD. This means that Surface chemistry and topography are important design considerations during the development of an implant to improve integration and compatibility.

The healing cascade includes the following steps:

- Phase 1 - Blood-biomaterial interaction

  Water comes first: This means that is most of the case, the implant will be covered first with water as soon as it is in contact with tissue during its insertion in the body. The affinity of the molecules of water to the surface of a materials depends on its surface hydration. Known polymers which have non-fouling effect due to high surface hydration are hydrophilic materials.

  Proteins adsorb to the surface: After the water, the second important category of molecules that will come into contact with the implant and, which are present in all the body fluids, are the proteins. The nature of the proteins that will adsorb onto the MD depends of course of the nature of the biological fluids (implantation sites). The most important extracellular fluids are the blood, the saliva, the semen, the vaginal fluid, the mucus and urine. Those fluids are considered CORROSIVE for many MD. There is a certain order in the kinetic of protein adsorption, which is described by the VROMAN EFFECT. This means that the nature of the coated proteins over an implant is dynamic and will evolve over time.

  Cells are now connecting with the implant: Cellular contact and interaction with the adsorbed proteins on the surface of the implant is the third stage, which usually takes from minutes up to days. The adsorbed proteins act as a translator between the surface properties of the material and the cell receptors, determining the fate of the implant in the biological environment. It is important to keep in mind that the recognition of the cells to any surfaces is a phenomenon which is specific -> it is

described as being highly selective. This “recognition” is done via transmembrane receptors, which are called Integrins.

- Phase 2 - Acute inflammation
  Acute inflammation characterized by the infiltration of polymorphonuclear leukocytes (PMN) and mast cells is considered the second phase in the FBR against biomaterials.
- Phase 3 - Chronic inflammation
  During the chronic phase, circulating macrophages, monocytes and lymphocytes respond to platelet-, PMN-, and mast cell derived chemoattractants at the implantation site.
- Phase 4 – Foreign Body Giant Cells Formation
  Macrophages/Giant cells phagocytose the damaged tissue as well as degradation products of the implant and secrete cytokines and growth factors that facilitate inflammation and finally activate fibroblasts, tissue regeneration, and capsule formation.
- Phase 5 – Tissue Remodeling or Encapsulation
  Repair of implant sites involves two distinct processes Regeneration which is the replacement of injured tissue by normal tissue, or replacement by connective tissue that constitutes the fibrous capsule. The last phase is the remodeling phase which involves remodeling of the granulation tissue to form the mature tissue or scar (*Narbe*). Prolonged remodeling may occur in the presence of a foreign body and may lead to exuberant tissue fibrosis and scarring.

21. Description of tensile test graph.

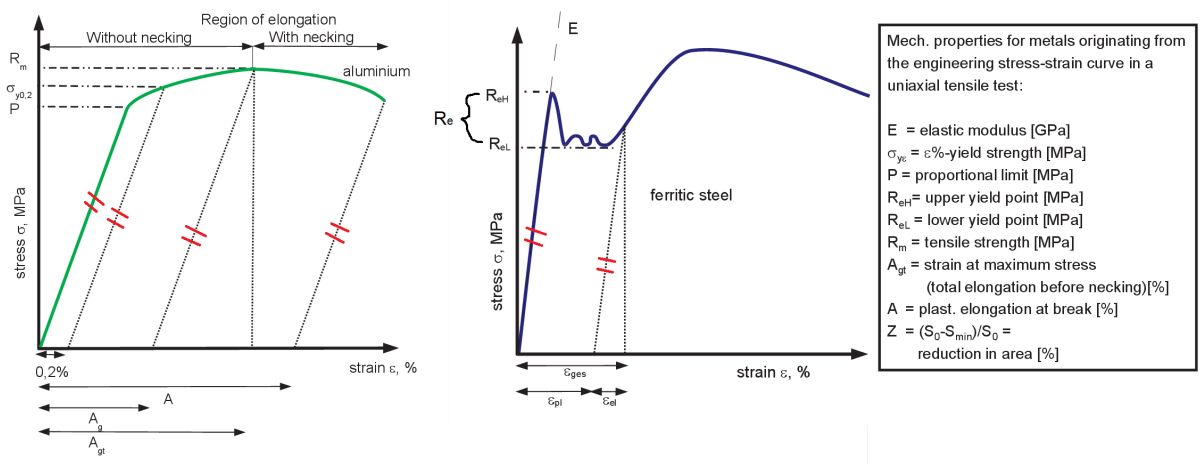

Figure 16: Left: Tensile stress test graph for aluminium. Right: For ferritic steel.

Left graph description.

P: Point at which the elastic deformation occurs. After this point plastically deformation starts. Under this point it forms elastically.

$\sigma_{y0,2}$**:** In the most graphs we can not se the point P. To get a knowing when plastic deformation starts we shift the green line for 0,2% (in case of metal, wood have 2%).

R_m: Point where the material starts to destroy. The end of the green curve marks where the aluminium is broken.

A: Plastically elongation at break.

A_g: total elongation with necking (*Einschnürung*).

A_{gt}: Total elongation before necking.

Right graph description:

R_{eL}: Lower yield Point. Point at which the elastic deformation occurs. After this point plastically deformation starts. Under this point it forms elastically.

R_{eH}: Upper yield point.

R_e: Proportional limit. It this limit is exceeded the specimen does not return to its original state. But a irreversible plastic strain remains.

ε_{ges}: Total strain.

ε_{pl}: Plastic strain.

ε_{el}: Elastic strain.

Hook's Law:

$$\delta = E \cdot \varepsilon$$

$\delta \dots Stress\ [N/m^2]$
$E \dots elastic\ modulus\ (young's\ modulus)\ [N/m^2]$
$\varepsilon \dots elongation\ [-]$

$$\delta = \frac{F}{A}$$

$$\varepsilon = \frac{\Delta l}{l_0}$$

$F \dots Force\ [N]$
$A \dots Area\ [m^2]$
$\Delta l \dots Extension\ [m]$
$l_0 \dots initalgauglength\ [m]$

22. Nitinol Characteristics. Where used and tensile stress graph.

NiTi intermetallics, also termed as Nitinol, exhibit a special microstructure allowing them to serve as shape memory alloy. The shape memory effect can be triggered by exposing the material to a given temperature, or alternatively by applying mechanical stresses. Nitinol is hyperelastic, deformation of more than 10% strain can be elastically recovered. Because of his metal alloys he is biocompatibility and resistant to corrosion.

Used in:

- Stents
- Tools for minimal-invasive surgery
- Wires for orthodontics
- Tools for root canal removal in dentistry

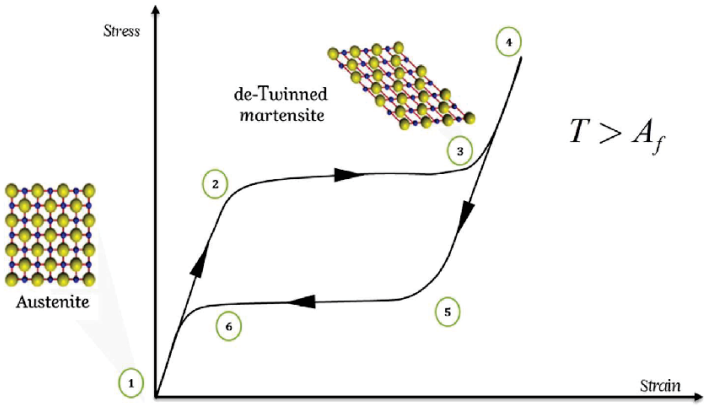

Figure 17: Stress strain curve of a superelastic alloy.