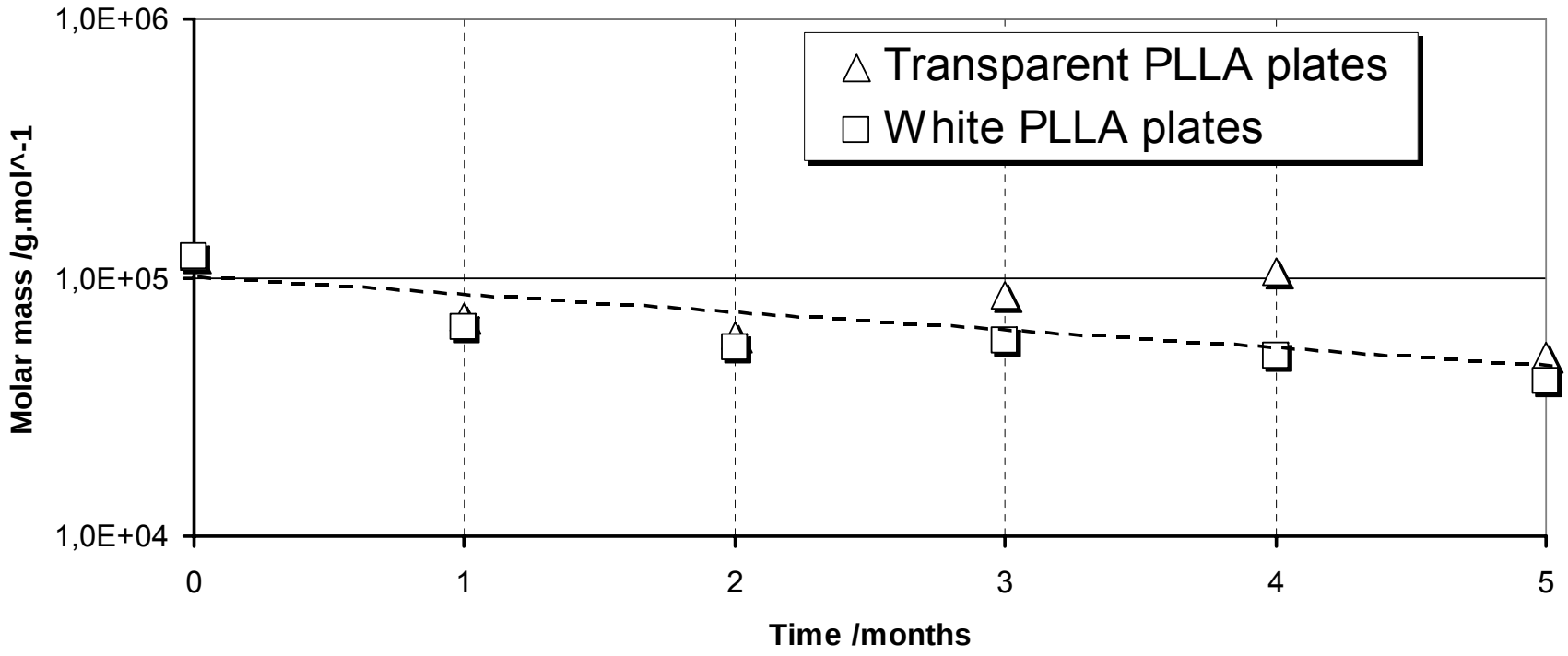
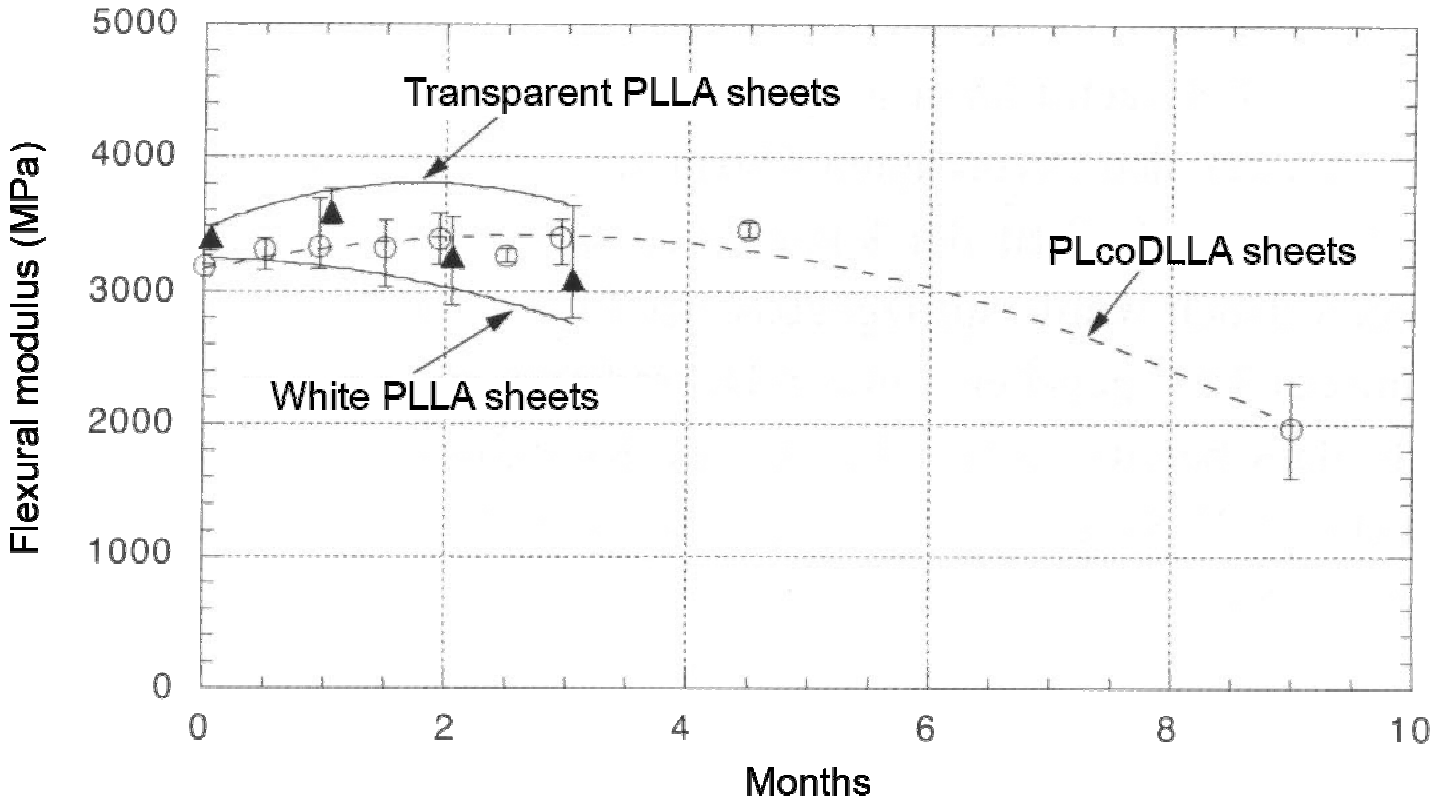
Accelerated Degradation In Vitro in the Whitened PLLA



Hydrolysis of the ester bonds in the polylactide

(E. Wintermantel / S.-W. Ha, 1998)

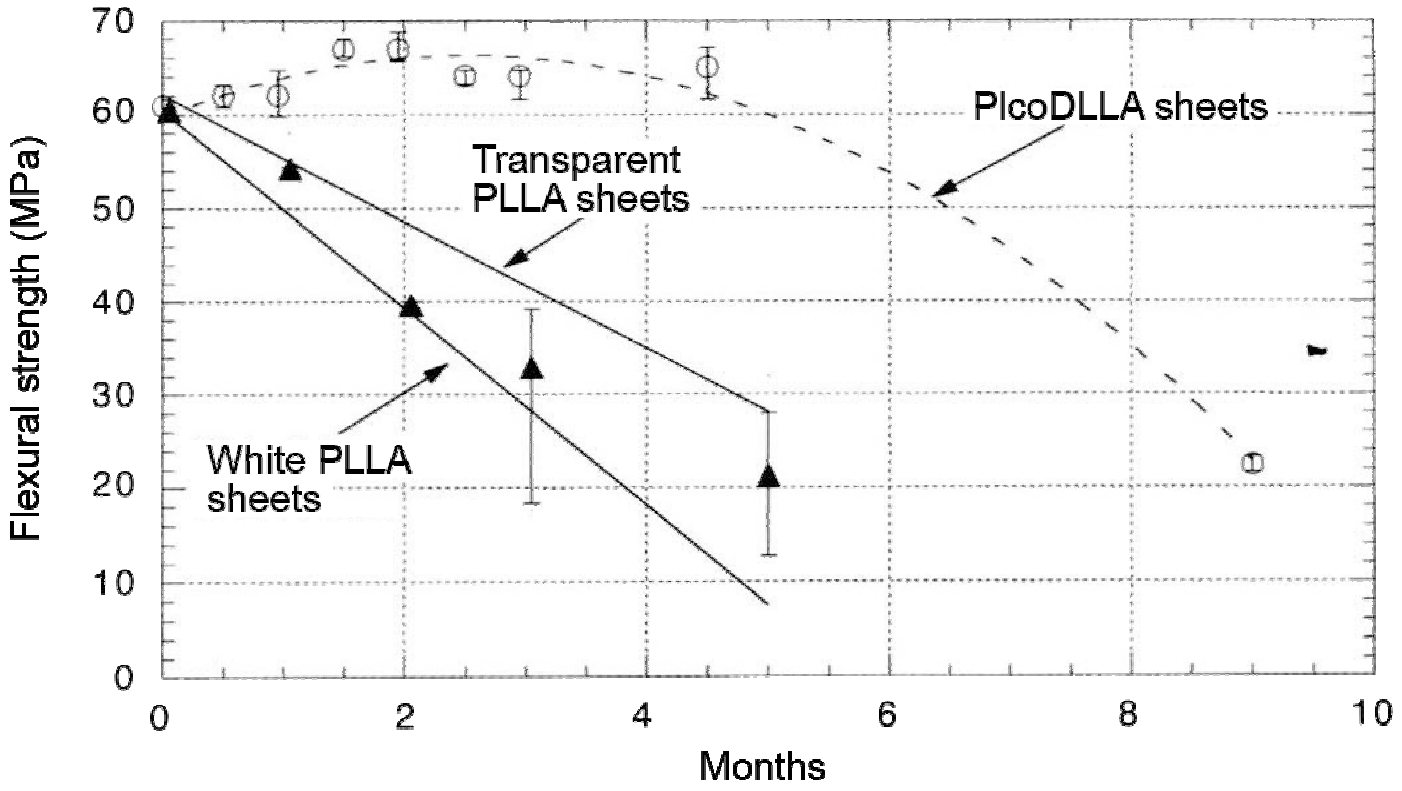
Flexural Modulus in Dependence on Storage Time



After 3 month a determination of the modulus is impossible due to the too low strength of the PLLA

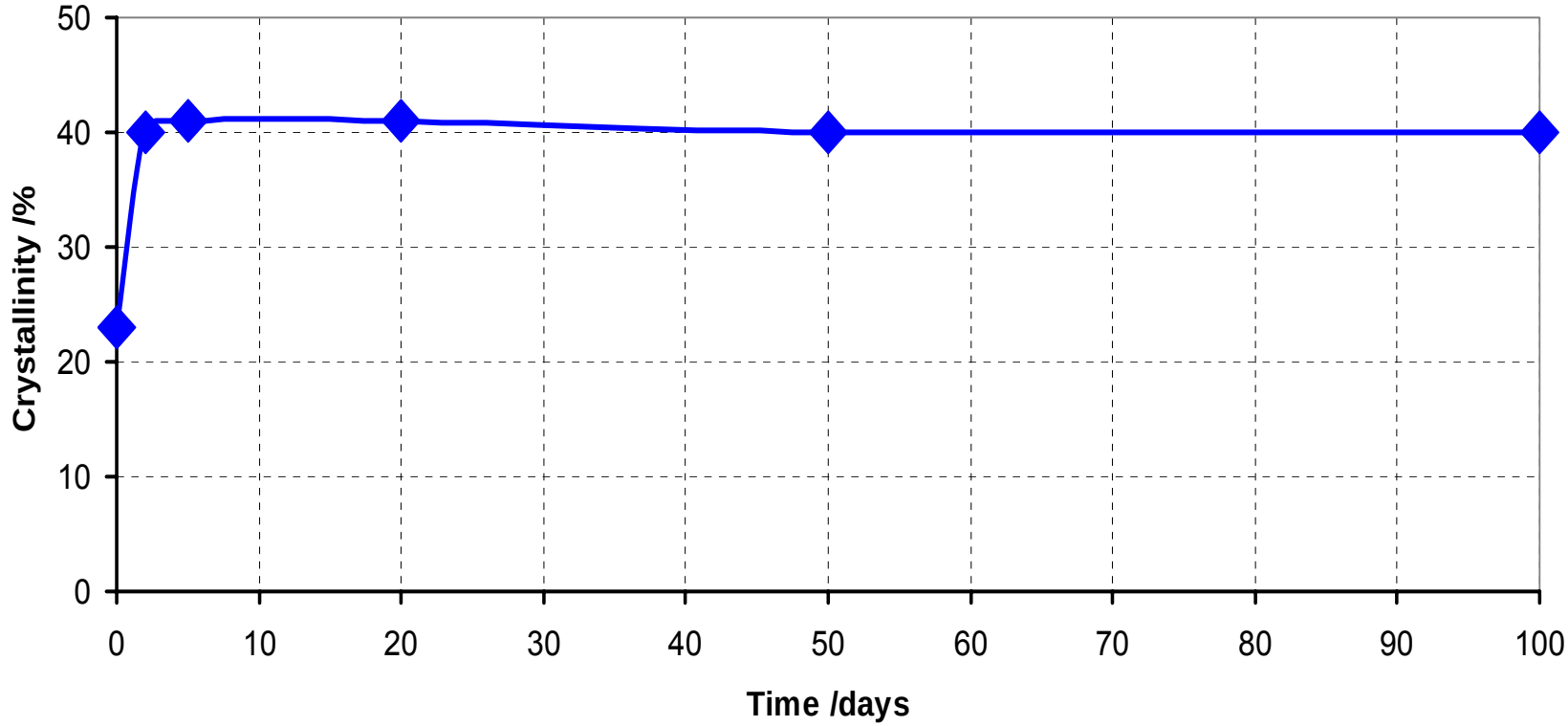
(E. Wintermantel / S.-W. Ha, 1998)

Flexural Strength in the Dependence of the Storage Time



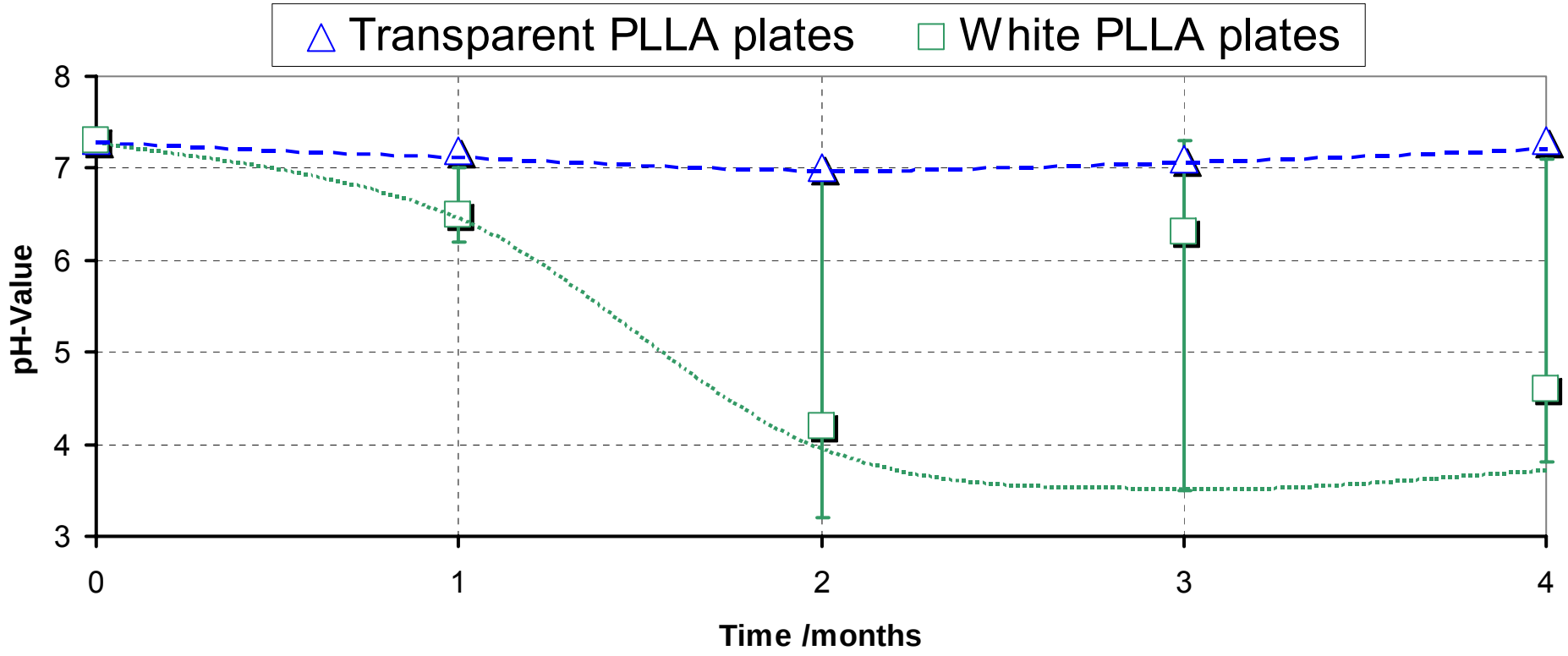
(E. Wintermantel / S.-W. Ha, 1998)

Storage Caused Recrystallisation in the PLLA (Powder)



(E. Wintermantel / S.-W. Ha, 1998)

pH Profile of the Medium (Ringer Solution) During Storage (PLLA)



(E. Wintermantel / S.-W. Ha, 1998)

Conclusions I

- The task of a crystal-free implant from PLA can not be fulfilled with the materials used
- Supercooling from the melt produces amorphous PLcoDLLA, but recrystallisation can occur during degradation
- To prevent the formation of crystallites an intrinsic amorphous polymer has to be used, but degradation rate is faster and mechanical properties are lower

Conclusions II

- Injection moulding has a strong influence on degradation kinetics of the components:
  - Lowest moisture residues reduce clearly M_W during the processing
  - Holding time of the polymer in the molten state, processing temperature and holding pressure have to be minimised
  - A pH decrease as observed in the *in vitro* experiments can lead to inflammation reactions *in vivo* and eventually to a removal of the implant

Conclusions III

- The degradation behaviour of the polylactide has to be modified in the following way:
  - Continuous release of the degradation products into the surrounding tissue or
  - The degradation products have to be buffered before the release, for example, by a second phase that dissolves alkaline

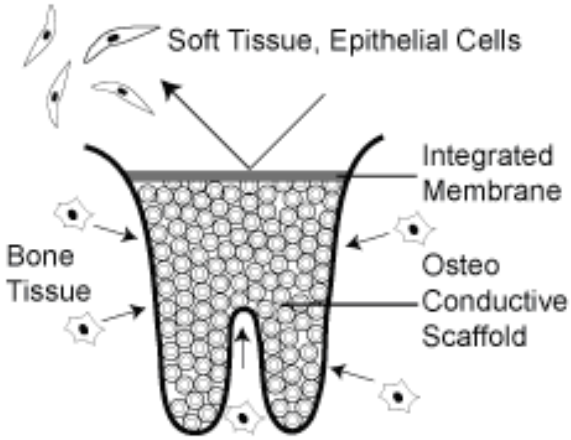
Commercial example of biodegradble composite

RootReplica®

- Open porous biodegradable composite consisting of β-tricalcium phosphate (β-TCP) pellets and polylactide
- Can be shaped and cut at higher temperatures
- After teeth extraction the alveolus is closed with a custom-tailored teeth root shaped biodegradable root replica

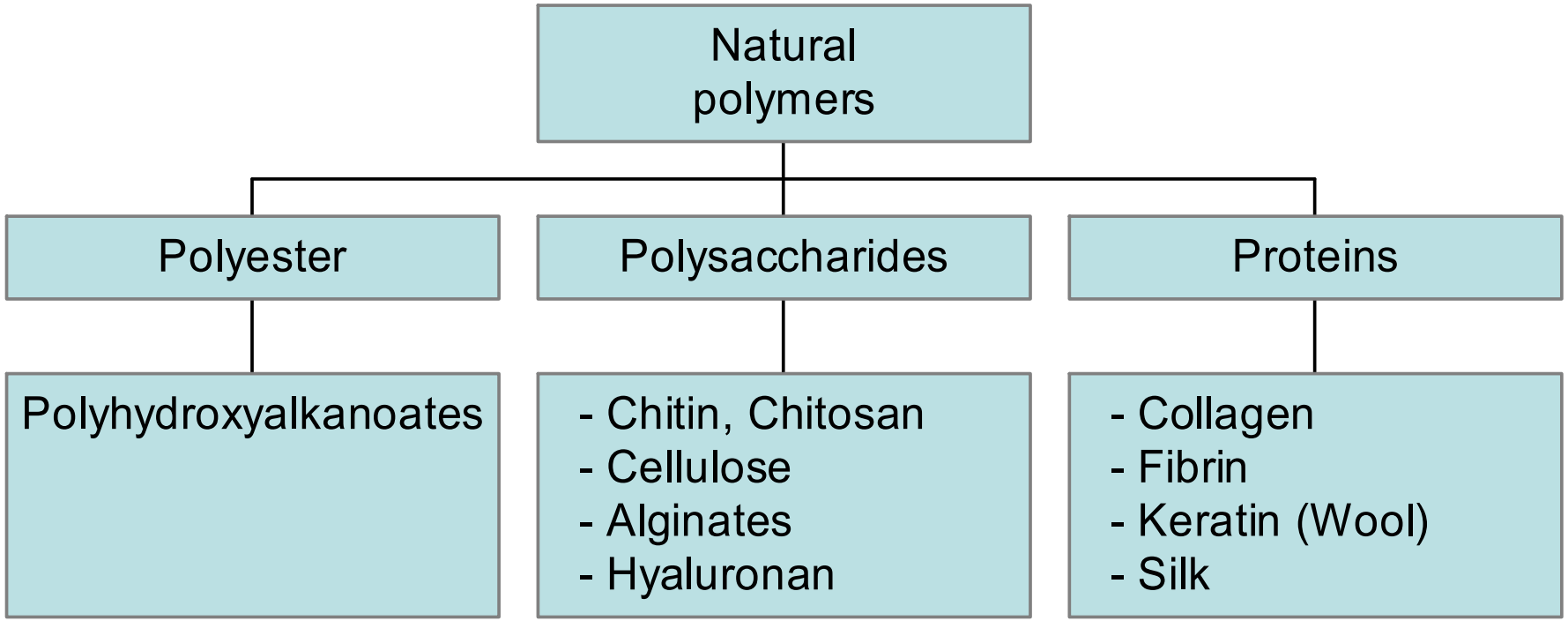
Degradable Solutions AG

Commercial Examples – RootReplica®



- An integrated membrane prevents the ingrowth of soft tissue
- The polylactide in the composite acts against bacterial growth
- The bone wound is closed immediately, the implant acts styptic blutungsstillend
- The porous morphology allows the absorption of blood and with it of important factors for formation of new tissue
- Due to its mechanical stability the bone growth material remains in the defect and supports the defect
- Drugs like pain relieving substances, antibiotics and growth factors can be included and later controlled released
- Duration time: 9 – 15 month

Natural Polymers


Natural polymers
Polyester
Polysaccharides
Proteins
Polyhydroxyalkanoates
- Chitin, Chitosan
- Cellulose
- Alginates
- Hyaluronan
- Collagen
- Fibrin
- Keratin (Wool)
- Silk

Polyester
Polyhydroxyalkanoates (PHA)

Mirel™ from Metabolix

- linear polymer chain
- engery and C reserve in some bacteria
- unsoluble in water
- biodegradable (use as packing material for food)
- biocompatible
- most common PHA are P3HB and PHV
- copolymers -> properties ranging from those of thermoplastics to that of elastomers
- sutures, bone marrow grafts, wound dressings, ...

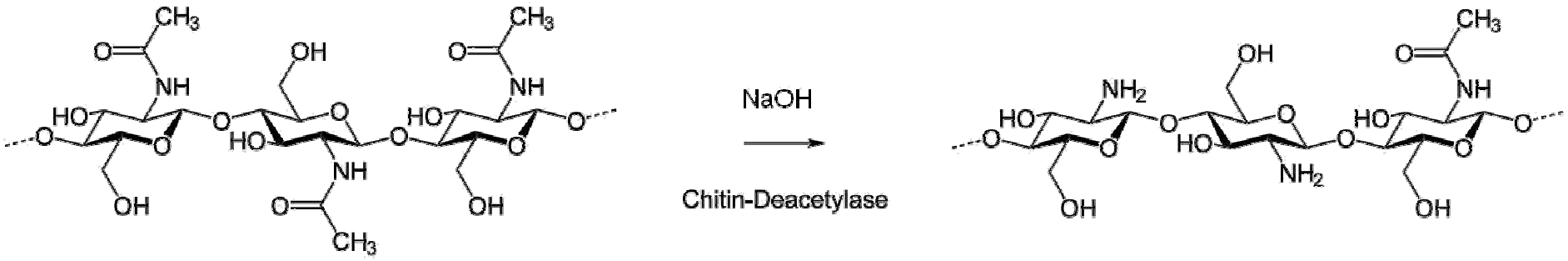
Polysaccharides
Chitin

- Nitrogen containing linear polysaccharide
- Main component of the outer skeleton of arthropods (may beetle „wings“ (elytron) and outer layer of the lobster) and cell membranes of fungi
- Example: outer layers of prawns: Composite consisting of chitin (15 – 20 mass%), calcium carbonate (40 – 50 mass%) and protein (30 – 40 mass%)

Polysaccharides
Chitin and Chitosan

From Chitin to Chitosan:

- Natural occurrence of chitosan in fungi like Oyster mushroom, Zygomycota, Agaricus, ...
- Technical process
  - Deacetylation of chitin with sodium hydroxide
  - Deacetylation of chitin by enzymes



Chitin

Chitosan

(E. Wintermantel / S.-W. Ha, 2002)

Polysaccharides
Transformation from Chitin to Chitosan

- Chitin is insoluble in aqueous and common organic solutions
- Chitosan
  - high solubility in diluted acid solutions
  - amorphous polymer
  - by simple processing different textures can be fabricated:
    - gel-like salves
    - powders
    - pearls
    - fibres
    - membranes

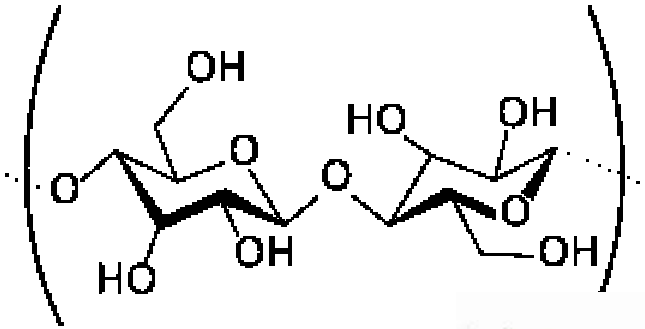
www.medical-chitosan.de

Applications of Chitin and Chitosan

Field	Application
Medicine	· Haemostatic agents (surgery, wound dressing) · Artificial blood vessels, blood dialysis membranes · Wound dressings (films and membranes) · Artificial skin for burn disease · Contact lenses · Biodegradable suture · Controlled release systems · Materials for dentistry, orthopaedics, artificial organs
Biotechnology	· Immobilisation of cells and enzymes · Carrier for affinity chromatography and protein separation · Biosensors (Glucose electrode)
Cosmetic industry	Cosmetics additives for hair conditioners, moisturiser, nail polish
Food industry	· Protection means for fruits and vegetables · Additives for animal feed · Finings Klärmittel for juices

(E. Wintermantel / S.-W. Ha, 2002)

Polysaccharides
Cellulose



- Polysaccharide consisting of a linear chain of linked D-glucose
- Structural component of the primary cell wall of green plants
- most organic compound on earth
- Mostly obtained from wood pulp and cotton
- Raw material for paper, textile (Rayon, Viscose, Lyocell), carboxymethyl cellulose (CMC)

Cellulose derivatives – Application
Wood – Fluff pulp - Cotton

absorbent cotton wool

gauze bandages

fluff rolls

underpads

medical swabs

medical dressing pad

cotton dental rolls

tongue depressors

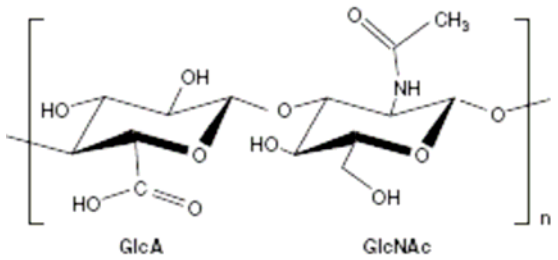
cotton buds, applicators, …

Polysaccharides
Alginates

- derived from seaweed (brown algae)
- produced by soil bacteria
- extracted from the washed algae and precipitated from the solution -> fibrous precipitate of sodium or calcium alginate
- Alginates are linear block copolymers (1,4-linked *β*-D-mannuronic acid (M) with $^4C_1$ ring conformation and *α*-L-guluronic acid (G) with $^1C_4$ conformation)
- Application: food additives, dentistry, wound dressings, cell culture, tissue engineering, ...

Polysaccharides
Hyaluronan (hyaluronic acid (HA))

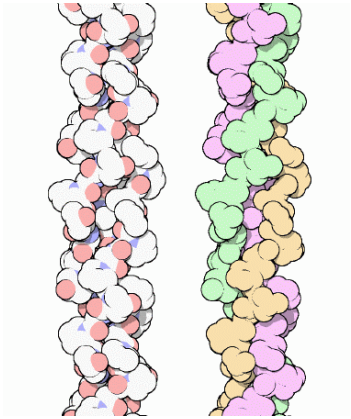
- initially extracted from umbilical cords, rooster combs and bovine vitreous humour -> bacterial production now
- linear copolymer (*β*-(1–4)-D-glucuronic acid (GlcA) and *β*-(1–3)-*N*-acetyl-glucosamine (GlcNAc))
- important polysaccharide occuring in the body
- has biological activity in humans



M. Rinaudo, 2007

- cross-linking -> sponges with increased lifetime for arthrosis treatment
- joint diseases, wound dressings, drug delivery systems

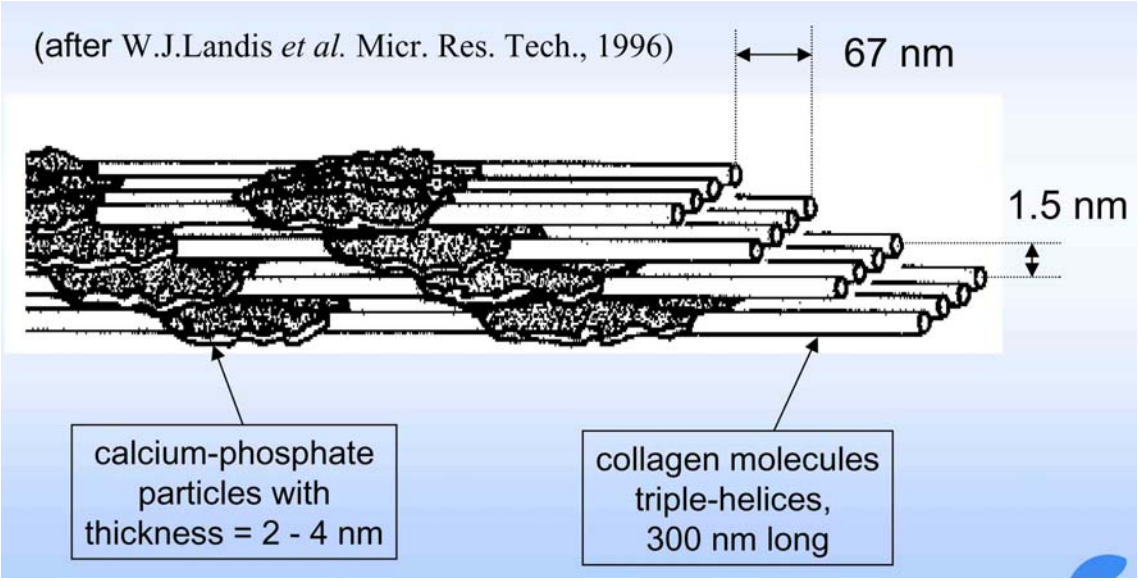
Proteins
Collagen


©DSGoodsell

- Fibre protein in the human body
  (≈ 25 % of the whole protein content)
- Triple helix conformation
- Contains predominantly parts of the amino acid units glycine, proline, and hydroproline that stabilise the helix
  - Every third amino acid within the triple helix is glycine
  - Glycine groups are oriented in helix inside direction and form crosslinking hydrogen bonds Wasserstoffbrücken
- Essential compound in bone, skin, tendon
- Collagen fibres consist of collagen fibrils
  (∅ 0.2 – 0.5 µm)

Protein
Collagen

- The heads of joining tropocollagen fibres are shifted past each other by exact 67 nm
- For the whole length of a tropocollagen fibre (300 nm) 5 distances are needed
- Between head and end of serial arranged tropocollagen fibres are 35 nm free
- In the bone mineralization occurs in this free space



Protein
Collagen

- The order of the collagen fibrils is adapted to the functions of the appropriate tissue:
  - Parallel orientation in tendon (load transformation); fibril diameter 50 ... 500 nm
  - Plane formation in the skin; fibril diameter 40 ... 100 nm
  - Plane network in the sclera (strength at break); fibril diameter in the cornea 25 nm
  - 3D translucent network in the vitreous body (dimensional stability)
- Up to 12 different collagen types can be found in the different tissues of the human body
- Fibril, fibril-associated and non-fibril collagen

Extraction of collagen (I)

- Soluble collagen:
  - Proteolytic separation of telopeptides by enzymes, e.g. pepsin
  - Removal of the telopeptides as intermolecular crosslinks causes the dissolution or dispersion of collagen molecules or aggregates in aqueous buffer solution
  - Reorganisation of soluble collagen in fibrils is possible, but not in such a high order as in the initial state

Extraction of collagen (II)

- Collagen fibres (fibril collagen):
  - Removal of non-collagen parts from collagen containing tissues
  - Extraction in salt solution: elimination of new synthesised collagen molecules, that are not integrated in the fibrils
  - Simultaneous elution of other soluble substances that are bonded onto the fibrils
    - Treatment with ethers and alcohols: elution of lipids
    - Extraction with acids: removal of acid proteins and glycose amino glycanes
    - Extraction with base: elimination of alkaline proteins
  - Such an extraction series supplies purified collagen fibres from tendon and skin

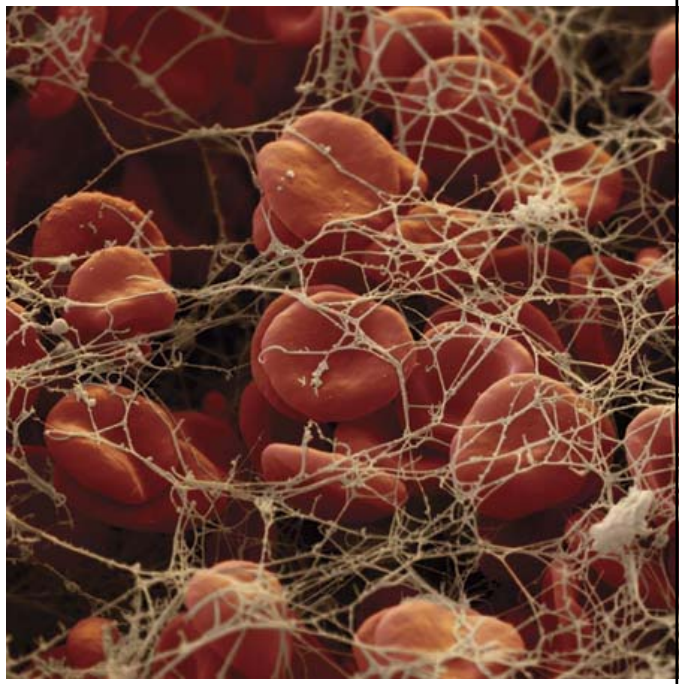
Medical Application of Collagen (Examples)

Cardiovascular surgery	Replacements for blood vessels and heart valves
Orthopaedy	Replacements for bone, ligaments, tendon
Ophthalmology	Cornea implants
Otology	Tympanoplasty
Plastic surgery	Correction of tissue disease
Urology	Dialysis membranes, bladder and ureter implants
Wound dressings	Treatment of burns, bedsores and abscesses

(E. Wintermantel / S.-W. Ha, 2002)

Proteins
Fibrin

- cross-linked activated adhesive" involved in the clotting of blood
- fibrillar protein that is polymerised to form a mesh that forms a clot in conjunction with the platelets
- one of the most elastic fibre out of any naturally occurring fibre



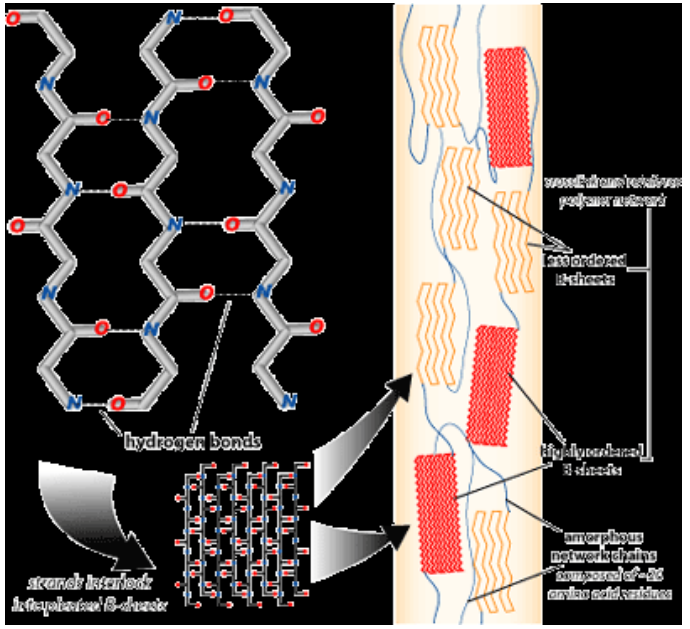
updatecenter.britannica.com/eb/image?binaryId=98328&rendTypeId=4

Protein
Silk

- Natural protein fibre
- obtained from the cocoons from cocoons made by the larvae of the mulberry silkworm (*Bombyx mori , L. 1758*)
- consists of fibroin (fibre) and sericin (coating)
- extruded by the silkworm in form of a double filament cemented by gum.

Silk fibroin

www.kanebo-sa.com



www.scq.ubc.ca

Protein
Silk

- Length 1000 m (unbroken filament); thickness 12-25 µm
- density 1.33 g/cm^3 raw and 1.25 g/cm^3 boiled-off
- Tensile strength 350 MPa; elongation 24 %
- As silk fibroins keep 50 % of their mechanical properties after 2 months of implantation *in vivo*, they are defined as non-degradable
- non-degradable suture material, fibroin based porous scaffolds, ...

www.margaret.com

Lessons learned

- Cranial implants
  - Materials, fabrication of PSI
- Degradable Polymers
  - Definitions relating to (bio)degradation / (bio)erosion
  - Degradation mechanisms
  - Change in the mechanical properties of the component during degradation
  - Application example: osteosynthesis system for maxillo-facial surgery
  - Biocompatibility of (bio)degradable polymers
- Natural polymers
  - Polyester, polysaccharides, proteins
  - Application examples in medical engineering