Classes of Materials Used in Medicine

Composites, Pyrolytic Carbon, Hydrogels

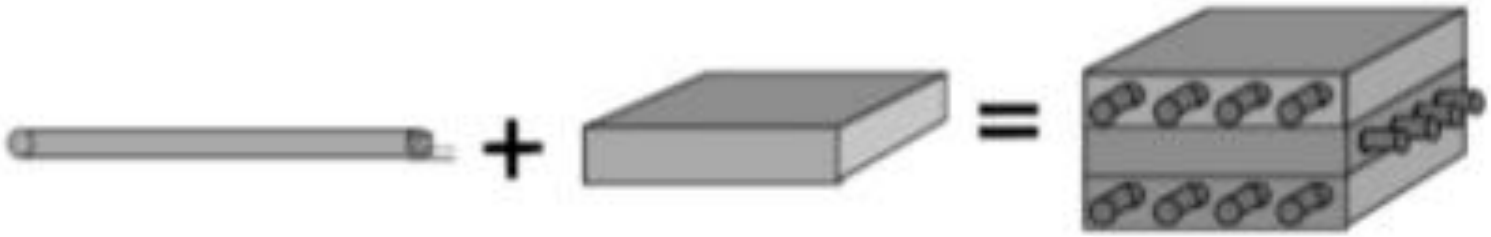
- The word ***composite*** **means** "consisting of two or more distinct parts."

- **At the atomic level,** materials such as metal alloys and polymeric materials could be called composite materials in that **they consist of different and distinct atomic groupings.**

- **At the microstructural level** (about 1 to 10 microns), **constituents may be observed distinctly in the optical microscope.**

- **In engineering**, a composite material usually **refers to a material consisting of constituents in the nano- to micro- to macrosize range, each having a distinct interface separating them**. Such composites usually consist of one or more discontinuous phases embedded within a continuous phase

- The discontinuous phase is usually harder and stronger than the continuous phase, and is called the ***reinforcement*** or ***reinforcing material***, whereas the continuous phase is termed the ***matrix*****.**



Fiber/Filament Reinforcement | Matrix | Composite

- **For example:**

- **In some cases, tough fillers, e.g., rubber particles, are combined with brittle matrices in order to produce higher toughness materials with better impact strength.**

- **In other cases**, the "reinforcement" could be aimed at achieving **specific functional properties**, such as bioactivity in the case of biomedical composites.

- **Many body tissues are composites**, such as extracellular matrix (ECM), tendons, ligaments, skin, bone, and so on, with an additional complexity due to their hierarchical structure.

- Most composite materials are **fabricated to provide desired mechanical properties** such as strength, stiffness, toughness, and fatigue resistance.

- <u>The strengthening mechanism of composites **strongly depends upon the geometry of the reinforcement.**</u>

- **classification of composites are made on the basis of the geometry** of a representative unit of reinforcement more than on the type of matrix, e.g., composites with long fibers, short fibers or particles

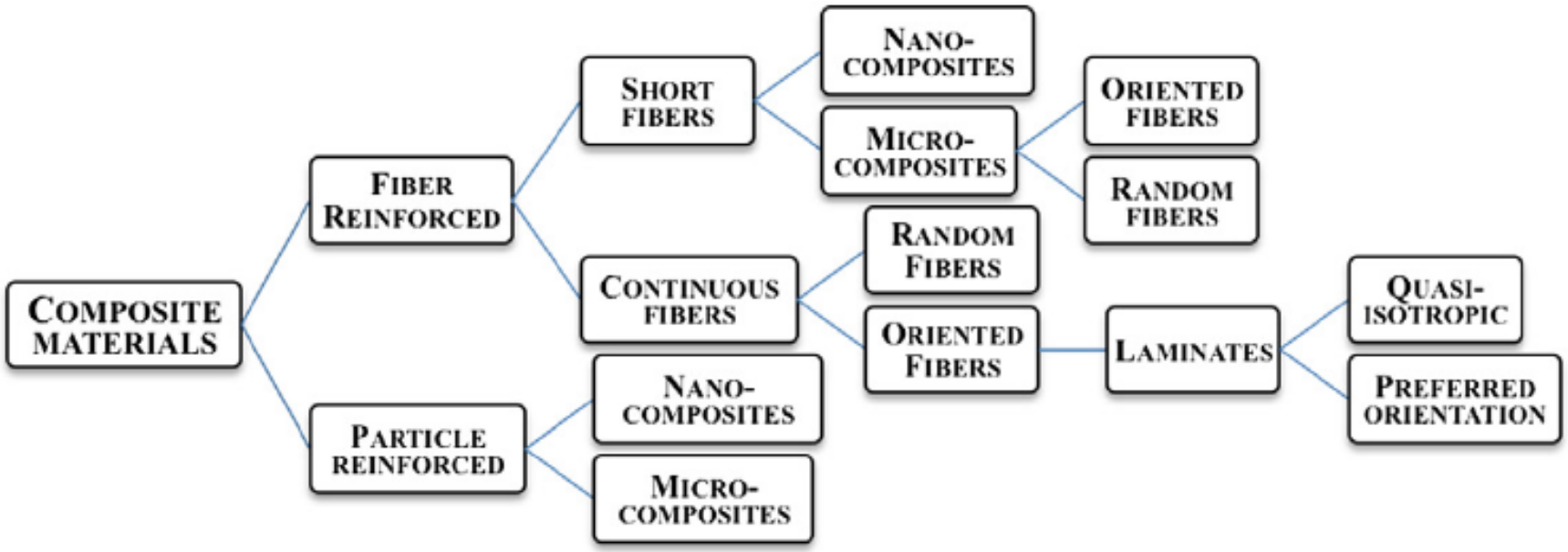


FIGURE I.2.9.1 Classification of composite materials.

REINFORCING SYSTEMS

- **The main reinforcing materials that have been used in biomedical composites are carbon fibers, polymer fibers, ceramic particles, glass fibers & particles**. Depending upon the application, the reinforcements have either been inert or absorbable.

➢ Carbon Fiber

- Carbon fiber is a lightweight, flexible, high strength, and high tensile modulus material .

- Due to their **low density** and **high mechanical properties** (**they can be much stiffer and stronger than steel!**) **these fibers are used in composites in a variety of applications that demand light weight and high mechanical properties.**

- **carbon fibers display unique properties** for the fabrication of loadbearing medical devices.

- Most successful applications are **for prosthetics where carbon fiber composites exhibit unique properties in term of lightness, stiffness, and strength.**

➢ Polymer Fibers

- **Polymer fibers are not comparable to carbon fibers in strength or stiffness** when used to reinforce other polymers.

- For biomedical applications, biocompatibility, high strength and fatigue resistance are compulsory, while **stiffness is a design parameter to be adapted to the specific conditions.**

- Thanks to **their absorbability**, not to their mechanical superiority, certain absorbable fibers have been employed in medical applications such as

    - *aramid*
    - polyethylene
    - Dacron™
    - Poly(lactic acid) (PLA)
    - poly(glycolic acid) (PGA)
    - Copolymers (poly(lactic-co-glycolic acid) PLGA) , Polycaprolactone (PCL)

➢ Ceramics

- A number of different ceramic materials have been used to reinforce biomedical composites.
- Since **most biocompatible ceramics are relatively weak and brittle** materials compared to metals, **the preferred form for this reinforcement has usually been particulate.**
- These reinforcements have included various calcium phosphates, aluminum- and zinc-based phosphates, glass and glass–ceramics, and bone mineral.
- **Tricalcium phosphates and hydroxyapatite are commonly referred as bioceramics**, i.e., bioactive ceramics. The definition refers to their ability to elicit a specific biological response that results in the formation of a bond between the tissues and material
- **The calcium phosphate ceramic systems have been the most intensely studied ceramic systems**. Of particular interest are the calcium phosphates having calcium to phosphorous ratios of 1.5–1.67.
- Hydroxyapatite (HA) ceramic and tricalcium phosphates are used in orthopedics and dentistry, **alone or in combination with other substances or also as coating of metal implants.**

➢ Glasses

- **Glass fibers are used to reinforce plastic matrices to form structural composites and molding compounds.**

- **Commercial glass fiber plastic composite materials** have favorable characteristics such as

  - high strength-to-weight ratio
  - good dimensional stability
  - **good resistance to heat, cold, moisture**, and **corrosion**
  - good electrical insulation properties
  - ease of fabrication
  - relatively low cost.

- For example

  - Glass fibers have also been used to **increase the mechanical properties of acrylic resins for applications in dentistry.**

➢ Nanoparticles and Nanofibers: "Nanofillers"

- Polymers filled with nanoparticles or nanofibers have been proposed for several applications in medicine.

- **nano-reinforcements** that have been investigated **for biomedical use includes** silica nanoparticles, carbon nanotubes etc.

➢ some examples of nanocomposites:

- **nanocomposites for blood contacting applications –**

  - the use of poly(carbonate)– urethane–POSS nanocomposites for blood contacting applications.
  - These materials were found to be thrombo-resistant, biostable, and more compliant than PTFE vascular grafts *in vitro*.

- **Carbon nanotubes**

  - Their exceptionally **high mechanical properties have stimulated numerous researchers to study their application for composites, also for biomedical applications.**

  - For instance, carbon nanotubes have been used to produce electrospun silk fibroin nanocomposites for potential tissue engineering applications

MATRIX SYSTEMS

- **Ceramic matrix or metal matrix composites** have important technological applications, but their use is mostly in **non-biomedical applications** (e.g., cutting tools, power generation equipment, process industries, aerospace), with **just a few examples** for biomedical applications (e.g., calcium phosphate bone cements).

- **Most biomedical composites have polymeric matrices that can be bioabsorbable or not.**

Some Examples of Biomedical Composite Systems

TABLE I.2.9.1 Some Examples of Biomedical Composite Systems

Applications	Matrix/Reinforcement*	Reference
External fixator	Epoxy resin/CF	Baidya et al., 2001; Migliaresi et al., 2004
Bone fracture fixation plates, pins, screws	Epoxy resins/CF	Ali et al.,1990; Veerabagu et al., 2003; Pemberton et al., 1994
	PMMA/CF	Woo et al., 1974
	PSU/CF	Claes et al., 1997
	PP/CF	Christel et al., 1980
	PE/CF	Rushton and Rae, 1984
	PBT/CF	Gillett et al., 1986
	PEEK/CF	Fujihara et al., 2001
	PEEK/GF	Lin et al., 1997
	PLLA/HA	Furukawa et al., 2000 a,b
	PLLA/PLLA fibers	Tormala,1992; Rokkanen et al., 2000
	PGA/PGA fibers	Tormala,1992; Rokkanen et al., 2000
Spine surgery	PU/Bioglass	Claes et al., 1999
	PSU/Bioglass	Marcolongo et al., 1998
	PEEK/CF	Ciappetta et al., 1997
	Hydrogels/PET fibers	Ambrosio et al., 1996
	PLA/PLA fibers/CP	Huttunen et al., 2006
Bone cement	PMMA/HA particles	Morita et al., 1998
	PMMA/Glass beads	Shinzato et al., 2000
	Calcium phosphate/aramid fibers,CF,GF,PLGA fibers	Xu et al., 2000
	PMMA/UHMWPE fibers	Yang et al., 1997
Dental cements and other dental applications	Bis-GMA/inorganic particles	Moszner and Salz , 2001
	PMMA/KF	Pourdeyhimi et al., 1986; Vallittu, 1996
Acetabular cups	PEEK/CF	Wang et al., 1998
Hip prostheses stem	PEI/CF-GF	De Santis et al., 2000
	PEEK/CF	Akay and Aslan, 1996; Kwarteng, 1990
	CF/PA12	Campbell et al., 2008
Bone replacement, substitute	PE/HA particles	Bonfield, 1988; Bonfield et al., 1998
Bone filling, regeneration	Poly(propylene fumarate)/TCP	Yaszemski et al., 1996
	PEG-PBT/HA	Qing et al., 1997
	PLGA/HA fibers	Thomson et al., 1998
	P(DLLA-CL)/HA particles	Ural et al., 2000
	Starch/HA particles	Reis and Cunha, 2000; Leonor et al., 2003
Tendons and ligaments	Hydrogels/PET	Kolarik et al., 1981; Iannace et al., 1995
	Polyolefins/UHMWPE fibers	Kazanci et al., 2002
Vascular grafts	PELA/Polyurethane fibers	Gershon et al., 1990; Gershon et al., 1992
Prosthetic limbs	Epoxy resins/CF, GF, KF	Dawson, 2000

*See Glossary of Terms.

ABSORBABLE MATRIX COMPOSITES

- Absorbable matrix composites have been **used in situations where absorption of the matrix is desired.**

- Matrix absorption may be desired to expose surfaces to tissue or to **release admixed materials such as antibiotics or growth factors (drug release)**

- However, **the most common reasons for the use of this class of matrices for composites has been to accomplish time-varying mechanical properties** and ensure complete dissolution of the implant, eliminating long-term biocompatibility concerns.

- **This type of composite would contain an absorbable matrix as well as absorbable reinforcing fillers**. A typical clinical example is fracture fixation

➢ Fracture Fixation

- **Rigid internal fixation of fractures** has conventionally been accomplished with metallic plates, screws, and rods.

- **During the early stages of fracture healing, rigid internal fixation maintains alignment and promotes primary osseous union by stabilization and compression.**

- Unfortunately, as healing progresses, or after healing is complete, rigid fixation may cause bone to undergo stress protection atrophy. This can result in significant loss of bone mass and osteoporosis.

- Additionally, **there may be a basic mechanical incompatibility between the metal implants and bone**.

    - The elastic modulus of cortical bone ranges from 17 to 24 GPa, depending upon the age and location of the specimen, while the commonly used alloys have moduli ranging from 110 GPa (titanium alloys) to 210 GPa (316L steel). **This large difference in stiffness** can result in disproportionate load sharing, which can lead to relative motion between the implant and bone upon loading, as well as to **high stress concentrations at bone–implant junctions.**

- **Another potential problem is that the metal alloys currently used for plates corrode to some degree.**

    - Metal ions are released and they have been reported to cause adverse local tissue reactions, which in turn raises questions of adverse effects on bone mineralization, as well as adverse systemic responses such as local tumor formation.
    - Consequently, it is usually recommended that a second operation be performed to remove the metal hardware after healing

- **The advantages of absorbable devices are thus two-fold.**

- First, the devices degrade mechanically with time, reducing stress protection and the accompanying osteoporosis.

- Second, there is no need for secondary surgical procedures to remove absorbable devices. The state of stress at the fracture site gradually returns to normal, allowing normal bone remodeling.

  - **Absorbable fracture fixation devices have been produced from poly(L-lactic acid) polymer (PLLA), PGA polymer, and polydioxanone.**

  - **The degradation product of PLLA is mainly lactic acid**, which is nontoxic, biocompatible, easily absorbed into and eliminated from the body.

  - Lactic acid enters the lactic acid cycle of metabolites within cells. Ultimately it is metabolized to carbon dioxide and water.

NON-ABSORBABLE MATRIX COMPOSITES

- **Non-absorbable matrix composites are generally used to provide specific mechanical properties unattainable with homogeneous materials.**

- Because the matrices and fillers are non-absorbable, they are used for “lifelong” implants such as orthopedic appliances and total joint replacements.

➢ Total Joint Replacement

- the **most studied** and potentially the most valuable use of **non-absorbable composites** has been **in total joint replacement.**

- **Bone resorption** in the femur leading to aseptic loosening with the implantation of metallic femoral hip replacement components

- **It has long been recognized that bone adapts to functional stress by remodeling to re-establish a stable mechanical environment.**

- When applied to the phenomenon of **bone loss around implants**, one can postulate that the **relative stiffness of the metallic component is depriving bone of its accustomed load.**

- Clinical and experimental results have shown the significant role that implant elastic characteristics play in allowing the femur to attain a physiologically acceptable stress state.

- **Composite materials technology offers the ability to alter the elastic characteristics** of an implant and provide a better mechanical match with the host bone, potentially leading to a more favorable bone remodeling response.

- **Using different polymer matrices reinforced with carbon fiber, a large range of mechanical properties is possible**

  - Poly(ether-ether-ketone) (PEEK) matrix has been one of the most studied matrices for bone interfacing prosthesis.

  - An *in vitro* study of Scotchford et al. (2003) showed a **similar osteoblast attachment and proliferation on a PEEK/carbon fiber** stem component as referred to Ti6Al4V stems.

Tissue Engineering Scaffolds

- Composites have been widely proposed as tissue engineering (TE) scaffolds. The **aim** of the addition of fillers to a biodegradable polymer matrix is **not only to reinforce the matrix**, **but also to impart to the scaffold specific bioactive properties, such as drug delivery.**

- The role of the scaffold is to **provide a support** to the newly forming tissue through a favorable interaction with cells, but also **fulfilling specific requirements of the implant site**

- Sometimes, polymeric particles have been added to polymeric matrices to promote sustained **release of specific molecules.**

- For instance, **gelatin microparticles** have been added to injectable cross-linked oligo(ethylene glycol fumarate) matrices to **release drugs or growth factors** for regenerating tissue in an **osteochondral defect**

Pyrolytic Carbon

- **Carbon materials are ubiquitous** and of great interest because the majority of substances **that make up living organisms are carbon compounds**.

- Although many engineering materials and biomaterials are based on carbon or contain carbon in some form, elemental carbon itself is also an important and very successful biomaterial.

ELEMENTAL CARBON

- **Elemental carbon is found in nature as two crystalline allotrophic forms:** graphite and diamond.
- Recently **a third crystalline** form of elemental carbon, the **fullerene structure**, has been discovered.
- The crystalline polymorphs of elemental carbon are shown :

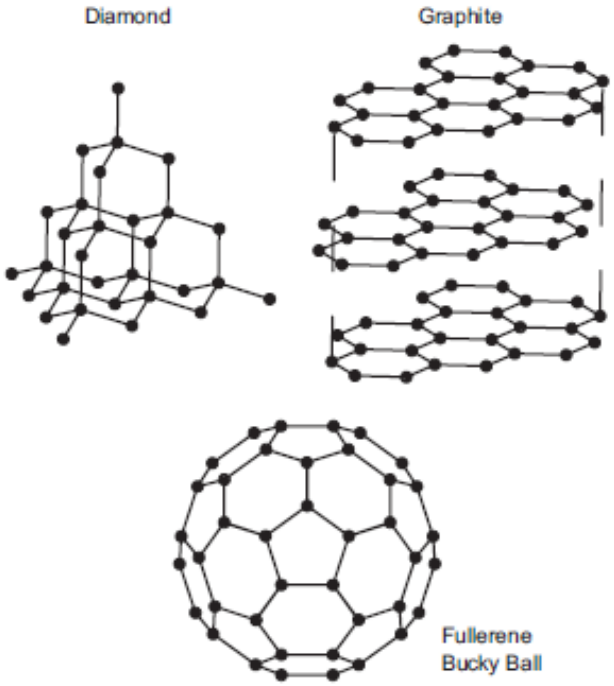


FIGURE I.2.8.1 Allotropic crystalline forms of carbon: diamond, graphite, and fullerene.

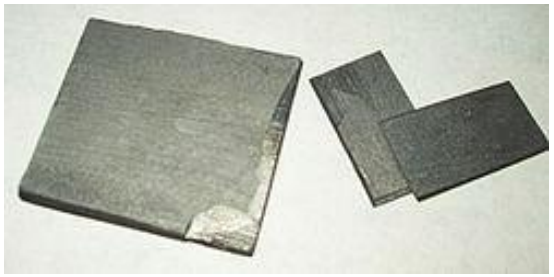
- **The properties of the elemental carbon crystalline forms vary widely according to their structure.**

- **Diamond** is one of the hardest materials known.

- **Graphite** is a soft material and has low hardness and a lubricating property

- **Fullerenes** have yet to be produced in bulk, but their properties on a microscale are entirely different from those of their crystalline counterparts.

PYROLYTIC CARBON (PyC)



- The biomaterial known as **pyrolytic carbon is not found in nature**; it is manmade
    - It is a material **similar to graphite**, but with some covalent bonding between its graphene sheets as a result of **imperfections in its production**.
- Pyrolytic carbon components have been **used in more than 25 different prosthetic heart valve designs** since the late 1960s, and have accumulated a clinical experience in the order of 16 million patient-years.
- Among the materials available for mechanical heart valve prostheses, pyrolytic carbon has the **best combination of blood compatibility, physical and mechanical properties, and durability.**

CLINICAL APPLICATIONS

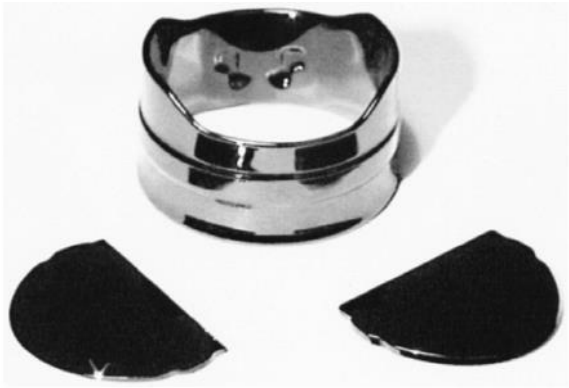
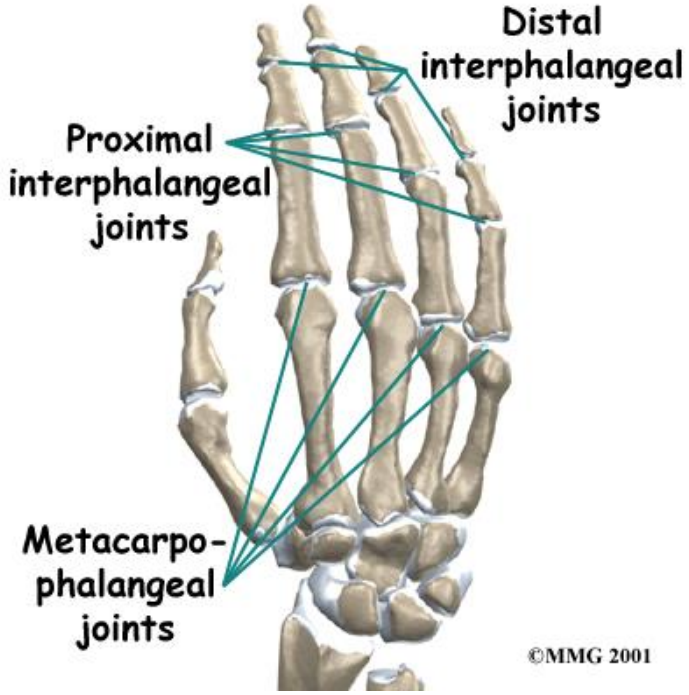


FIGURE I.2.8.9 Components for On-X bileaflet heart valve.

- Widespread clinical use of pyrolytic carbon components for **heart valve replacement** began in October of 1968.
    - However, patients with mechanical valve prostheses require chronic anticoagulation therapy because of the risk of valve-related hemostatic complications.
- PyC has also been used as a **loadbearing material for small orthopedic joint replacement implants**
    - Successful applications for upper limb total joint prostheses include the metacarpophalangeal (MCP) joint and the proximal interphalangeal (PIP) joint



- Pure PyC is a nearly ideal material for orthopedic application with demonstrated advantages over traditional materials such as polymers, ceramics, and metals which include:

  - ✓ Elimination of wear-related failures
  - ✓ Absence of osteolytic adverse tissue reactions
  - ✓ Excellent fatigue resistance
  - ✓ Non-cemented fixation via bone apposition
  - ✓ Minimization of stress shielding effects and bone resorption
  - ✓ Excellent compatibility with joint cartilage and bone tissues.

Hydrogels

- Hydrogels have received significant attention because of their high water contents and related potential for many biomedical applications.

- **Hydrogels are polymeric structures held together as water-swollen gels by**:

  (1) primary covalent cross-links
  (2) ionic forces
  (3) hydrogen bonds
  (4) affinity or “bio-recognition” interactions
  (5) hydrophobic interactions
  (6) polymer crystallites
  (7) physical entanglements of individual polymer chains
  (8) a combination of two or more of the above interactions.

- Many natural polymers such as collagen, gelatin, fibrin, hyaluronic acid, heparin, alginates, pectins, chitosan, and others can be used to form hydrogels, and some of these gels have been used in biomedical application

CLASSIFICATION AND BASIC STRUCTURES OF HYDROGELS

- Depending on their **method of preparation, ionic charge, or physical structure features, hydrogels may be classified in several categories.**

➢ Based on the method of preparation, they may be:

1. ***homopolymer hydrogels***
2. ***copolymer hydrogels***
3. ***multi-polymer hydrogels***
4. ***interpenetrating network (IPN) hydrogels*.**

- ***Homopolymer hydrogels*** are cross-linked networks of one type of hydrophilic monomer unit, whereas ***copolymer hydrogels*** are produced by cross-linking of chains composed of two comonomer units, at least one of which must be hydrophilic to render them water swellable.

- ***Multi-polymer hydrogels*** are produced from three or more comonomers reacting together

- ***interpenetrating network (IPN) hydrogels*** *are produced* with polymerizing one monomer within a different cross-linked hydrogel network. The monomer polymerizes to form a polymer or a second cross-linked network that is intermeshed with the first network.

- ***Ionic hydrogels***, with ionic charges on the backbone polymers, may be classified as:

1. *neutral hydrogels* (uncharged)
2. *anionic hydrogels* (having negative charges only)
3. *cationic hydrogels* (having positive charges only)
4. *ampholytic hydrogels* (having both positive and negative charges).

Ionic hydrogels

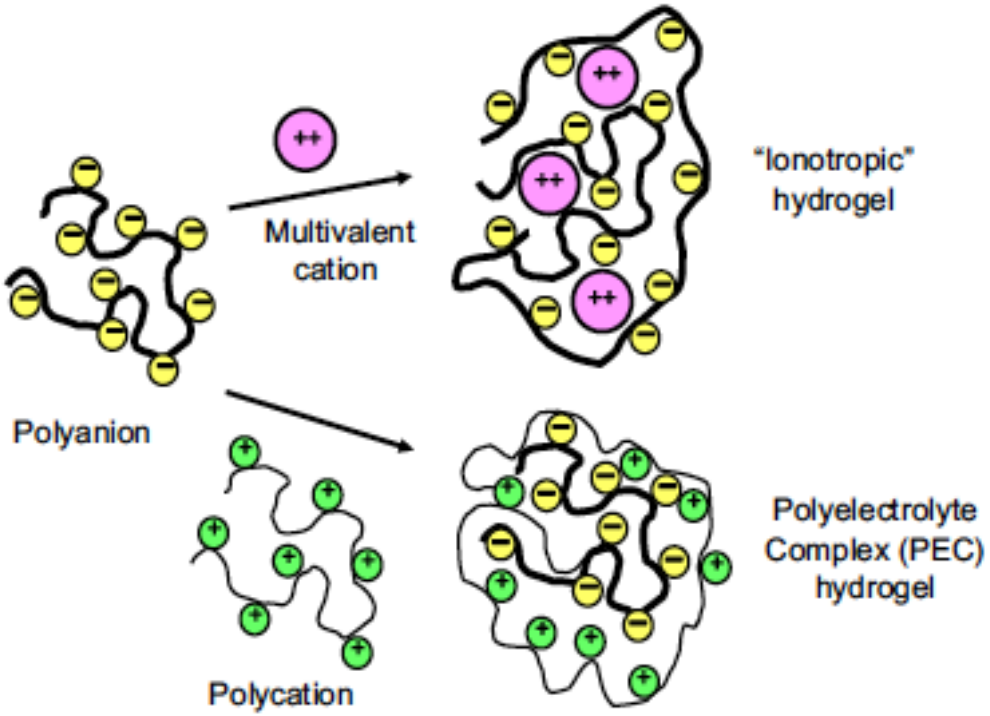


FIGURE I.2.5.5 Formation of ionic hydrogels. (Hoffman, 2002.)

- Based on physico-chemical structural features of the network, hydrogels may also be classified as:

    1. *amorphous hydrogels* (having covalent cross-links)
    2. *semi-crystalline hydrogels* (may or may not have covalent cross-links).

- **amorphous hydrogels**, the macromolecular chains are arranged randomly.

- **Semi-crystalline hydrogels** are characterized by self-assembled regions of ordered macromolecular chains (crystallites).

- Another type of classification of hydrogels includes the "*complexation" hydrogels*, which are held together by specific types of secondary forces.

    - **These include hydrogen bonds, hydrophobic group associations, and affinity "complexes"** (i.e , biotin/streptavidin, antibody/antigen)

Affinity hydrogels

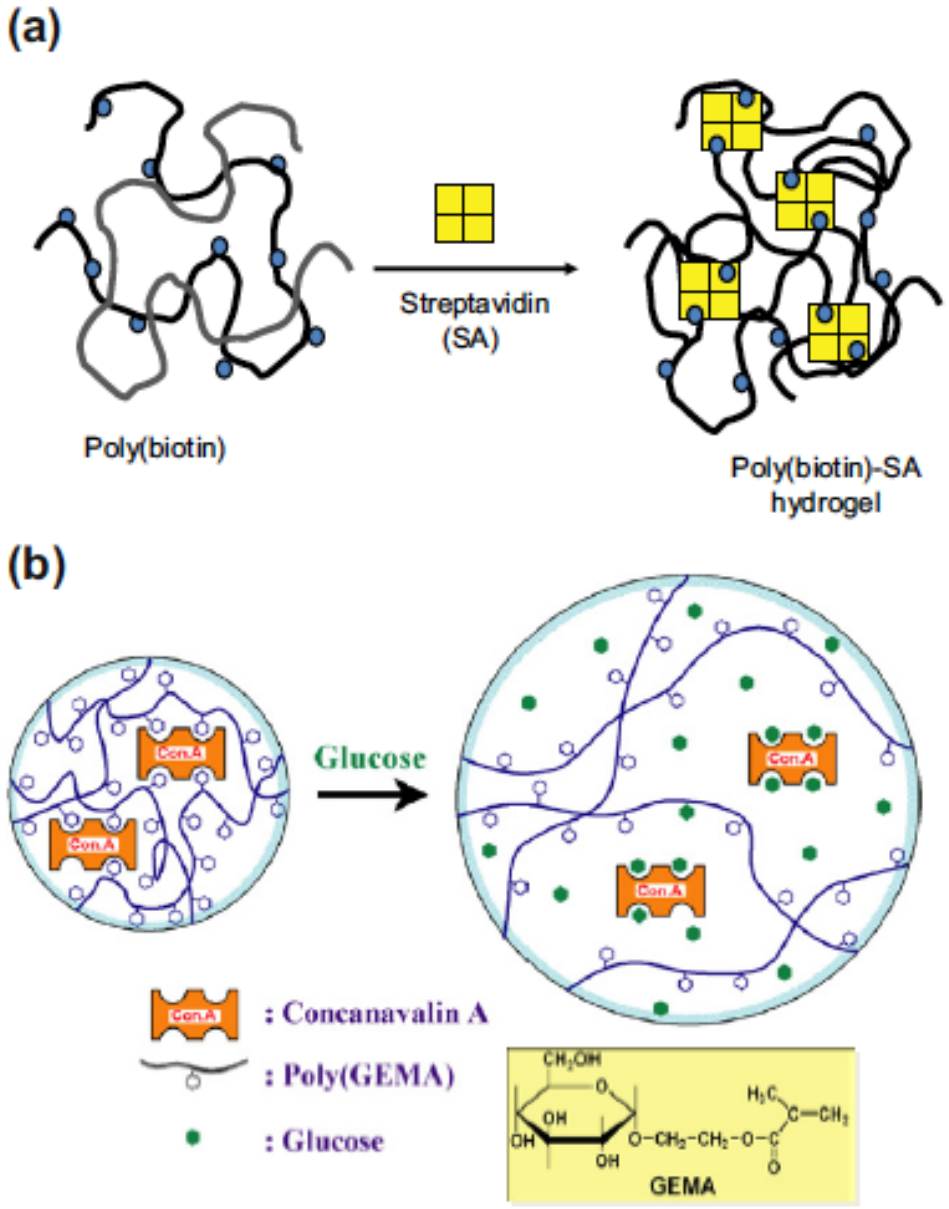


FIGURE I.2.5.6 (a) Formation of an affinity hydrogel between polybiotin and streptavidin. (Morris et al., 1993.) (b) Glucose-responsive hydrogel swells when free glucose competes with polymeric glucose groups in a ConA-cross-linked GEMA hydrogel. (Miyata et al., 1996.)

SWELLING BEHAVIOR OF HYDROGELS

- **The physical behavior of biomedical hydrogels is dependent on their dynamic swelling and equilibrium in water and in aqueous solutions.**

- Knowledge of the swelling characteristics of a polymer is of utmost importance in biomedical and pharmaceutical applications since **the equilibrium degree of swelling influences:**

1. the solute diffusion coefficient through hydrogels

2. the surface properties and surface molecule mobility

3. the optical properties, especially in relation to contact lens applications

4. the mechanical properties.

BIOMEDICAL HYDROGELS

Acrylic Hydrogels
Poly(vinyl alcohol) (PVA) Hydrogels
Poly(ethylene glycol) (PEG) Hydrogels
…

"SMART" OR "INTELLIGENT," STIMULI-RESPONSIVE HYDROGELS AND THEIR APPLICATIONS

➢ pH-Sensitive Hydrogels

- **These hydrogels are swollen ionic networks containing either acidic or basic pendant groups. In aqueous media of appropriate pH and ionic strength, the pendant groups can ionize and develop fixed charges on the gel, leading to rapid swelling.**

- These gels typically contain ionizable pendant groups such as carboxylic acids or amine groups

- The most commonly studied ionic polymers include poly(acrylic acid) (PAA), poly(methacrylic acid) (PMAA), poly(diethylaminoethyl methacrylate) (PDEAEMA), and poly(dimethylaminoethyl methacrylate) (PDMAEMA).

➢ pH-Responsive Complexation Hydrogels

- Complexing hydrogels is a class of hydrogels that exhibit responsive behavior.

- complexing hydrogels exhibit drastic changes in their mesh size in response to small changes of pH, which could be useful for drug delivery in varying pH environments in the body, such as in the GI tract, mouth, and on the skin.

➢ Temperature-Sensitive Hydrogels

- Temperature-sensitive polymers typically exhibit a lower critical solution temperature (LCST).
- Above this temperature, the polymers may lose their hydrophobically-bound water, and phase separate, causing the gel to collapse.
- Below the LCST, the cross-linked gel re-swells to significantly higher degrees because of the increased hydrophobic bonding with water.

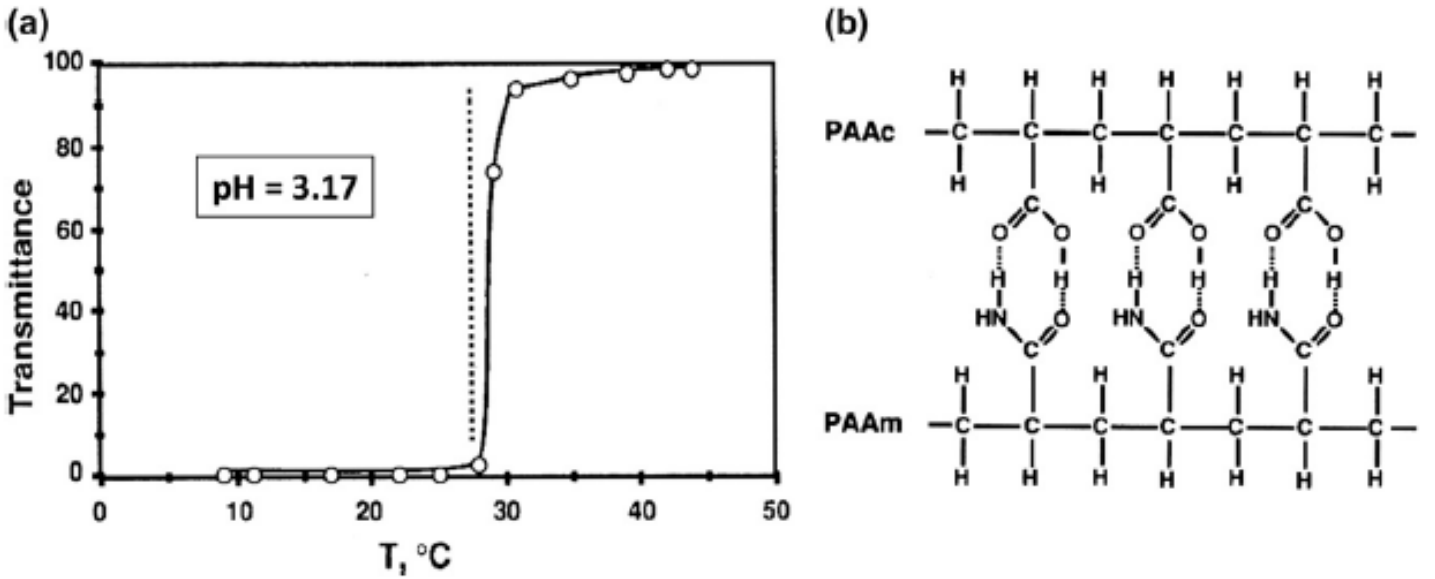


FIGURE I.2.5.7 Temperature dependence of light transmission for two H-bonded polymers, PAAc (Polyacrylic acid) and PAAm (Polyacrylamide) at pH 3.17; (a) shows the temperature dependence of light transmission and (b) shows the hypothetical H-bonded structure that would exist at low pH and at temperatures below 30°C, where the COOH groups are protonated and the polymer chains are complexed. The H-bonding is disrupted as temperature rises above 30°C. Data are for an aqueous solution at pH 3.17 (adjusted by HCl). Polymer concentration (wt. %): PAAc, 0.5%; PAAm, 0.5%. (Katono et al., (1991).

➢ Affinity Hydrogels

- Some hydrogels may exhibit environmental sensitivity due to the formation of complexes between chains that hold them together as a gel

- Sometimes this complexation is due to affinity recognition interactions, such as

  - between streptavidin, with four binding sites for biotin, and a polymer with multiple pendant biotins **or**

  - Concanavalin A with four binding sites for glucose and a polymer with multiple pendant glucose**, or**

  - an antibody with two binding sites for its antigens

BIOMEDICAL APPLICATIONS OF HYDROGELS

➢ Contact Lenses

- One of the earliest biomedical applications of hydrogels was the use of PHEMA hydrogels in contact lenses

- Hydrogels are particularly useful as contact lenses because of their relatively good mechanical stability and favorable refractive index

➢ Blood-Contacting Hydrogels

- Nonionic hydrogels have been prepared from poly(vinyl alcohol), polyacrylamides, PNVP, PHEMA, and poly(ethylene oxide).

- Heparinized polymer hydrogels and heparin-based hydrogels also show promise as materials for blood-contacting applications.

➢ Drug Delivery from Hydrogels

- Applications of hydrogels in controlled drug delivery systems (DDS) have become very popular in recent years

- They include equilibrium-swollen hydrogels, i.e., matrices that have a drug incorporated in them and are swollen to equilibrium, releasing the drug.

➢ Targeted Drug Delivery from Hydrogels

- Promising new methods for the delivery of chemotherapeutic agents using hydrogels have been recently reported.

➢ Tissue Engineering Scaffolds from Hydrogels

- It is driven by the same attractive properties that drive the use of hydrogels for drug delivery applications: high water content gels that may be synthesized with degradable backbone polymers, with an added advantage of being able to attach cell adhesion ligands to the network polymer chains.

- There are a number of natural polymer-based hydrogel scaffolds that have been studied (e.g., collagen, gelatin, alginates, hyaluronic acid, chitosan.

- hydrogels they may stimulate stem cell differentiation; that is, when stem cells are deposited on some hydrogel surfaces, depending on the composition and/or mechanical stiffness of the surface, differentiation of the stem cells into certain phenotypes may occur

➢ Miscellaneous Biomedical Applications of Hydrogels

- Other potential applications of hydrogels include artificial tendon materials, wound-healing bioadhesives, artificial kidney membranes, articular cartilage, artificial skin, maxillofacial and sexual organ reconstruction materials.