LECTURE 7

Synthetic and Natural Carriers Used in PCM and Requirements for Medical Polymer Carriers

Polymer Composite Materials, Carrier Architecture, Biocompatibility Criteria, and Regulatory Compliance

Lecture: acc.professor Kudaibergenova Bates Malikovna.

Lecture Overview: Plan, Aim & Key Tasks

Lecture Plan

1. Introduction: Role of carriers in Polymer Composite Materials (PCM)

2. Natural Carriers: Polysaccharides, proteins & lipids

3. Synthetic Carriers: Polyesters, polyethers & vinyl polymers

4. Requirements: Medical safety, degradation & sterilization

5. Applications: Targeted delivery & tissue engineering scaffolds

Lecture Aim

To evaluate and compare synthetic and natural polymer carrier systems utilized in Polymer Composite Materials (PCM) for biomedical applications, defining stringent pharmacological and materials science requirements for medical clinical use.

Key Learning Tasks

Classify: Synthetic vs. natural carrier architectures

Analyze: ISO 10993 carrier biocompatibility rules

Examine: Degradation kinetics and byproduct safety

Assess: Sterilization impact on carrier structural integrity

Biomedical Paradigm: The polymer carrier dictates the encapsulation capacity, release kinetics, stability, and tissue compatibility of advanced composite drug delivery and tissue engineering systems.

Role of Carriers in Polymer Composite Materials

Carriers serve as the continuous or dispersed matrix phase in PCM, housing active payloads, controlling mass transport, and governing implant mechanics.

Payload Protection & Stabilization

Shields labile pharmaceutical molecules (proteins, DNA, peptides) from enzymatic degradation in biological fluids.

Interfacial Adhesion & Filler Dispersion

Wets and uniformly disperses inorganic nanoparticles (clays, hydroxyapatite) within composite matrices.

Controlled Transport & Release

Modulates solvent ingress and molecular diffusion to achieve sustained, zero-order therapeutic release profiles.

Clinical Impact: Transforms poorly soluble or unstable compounds into viable clinical therapeutics.

Classification of Medical Polymer Carriers

Natural Polymer Carriers

Biological Origin

- **Polysaccharides:** Chitosan, Alginate, Hyaluronic Acid, Starch.
- **Proteins:** Collagen, Gelatin, Albumin, Silk fibroin.
- **Advantages:** High biocompatibility, intrinsic cell-adhesion motifs, enzymatic degradation.

Synthetic Polymer Carriers

Engineered Chemical Synthesis

- **Biodegradable:** PLA, PGA, PLGA, PCL, Polyorthoesters.
- **Non-Biodegradable:** Silicone, PMMA, EVA, Polyurethane.
- **Advantages:** Reproducible molecular weight, tunable mechanical strength, predictable degradation.

Hybrid Paradigm: Combining natural and synthetic polymers yields composite carriers balancing bioactivity and mechanical robustness.

Natural Polysaccharide Carriers: Chitosan & Alginate

Chitosan (Cationic Biopolymer)

Deacetylated Chitin Derivative

- Protonated amine groups (-NH3+) bind anionic drugs and cell membranes.
- Exhibits intrinsic antimicrobial and hemostatic activity.
- Degraded in vivo by lysozyme enzymes.

Alginate (Anionic Biopolymer)

Brown Algae Polysaccharide

- Composed of blocks of β-D-mannuronic (M) and α-L-guluronic (G) acids.
- Instant mild ionic crosslinking with divalent Ca2+ ions ("egg-box" model).
- Excellent cell encapsulation carrier for tissue engineering.

Polyelectrolyte Complexes: Combining chitosan and alginate forms stable hydrogel composite carriers via electrostatic coacervation.

Natural Protein Carriers: Collagen, Gelatin & Albumin

Collagen (Type I)
Triple-Helix ECM Scaffold

Contains RGD peptide sequences promoting cell adhesion and tissue regeneration. Used in hemostatic sponges and bone grafts.

Gelatin
Denatured Collagen Hydrolyzate

Lower antigenicity, excellent water solubility, and tunable crosslinking via glutaraldehyde or genipin for microparticle carriers.

Serum Albumin (HSA)
Plasma Transport Carrier

Readily binds hydrophobic drugs (Paclitaxel nanoparticles - Abraxane). Non-immunogenic and biodegradable via proteases.

Crosslinking Stabilization: Chemical or enzymatic crosslinking is mandatory to prevent rapid enzymatic dissolution of protein carriers in vivo.

Synthetic Biodegradable Carriers: PLA, PGA, & PLGA

Polylactic Acid (PLA) & PGA

Metabolism: Cleaved by backbone ester hydrolysis into natural metabolic acids.

PLA: Hydrophobic, high mechanical strength, degrades slowly over 12–24 months.

PGA: Highly crystalline, fast hydrolytic degradation (4–6 weeks) due to lack of pendant methyl groups.

PLGA Co-Polymers

Gold Standard: FDA-approved for microparticles, nano-carriers, and surgical implants.

Poly(lactic-co-glycolic acid) copolymer degradation is tuned across weeks to months by adjusting the LA:GA monomer molar ratio.

Autocatalytic Effect: Bulk erosion causes acidic oligomer accumulation inside thick PLGA implants, dropping internal pH and risking protein denaturation.

Polycaprolactone (PCL) & Specialty Synthetic Carriers

Polycaprolactone (PCL) Architecture

Semi-crystalline aliphatic polyester with a low melting point (~60°C) and high flexibility. Undergoes very slow hydrolytic chain cleavage, requiring 2 to 3 years for complete bio-absorption.

Specialty Synthetic Carrier Classes

- **Polyorthoesters & Polyanhydrides:** Surface-eroding carriers providing zero-order drug release.
- **Polyphosphazenes:** Inorganic-organic hybrid backbones with tunable amino acid side chains.

Blend Utility: Blending PCL with fast-degrading PLA/PGA balances mechanical toughness and degradation rate.

Non-Biodegradable Synthetic Carriers

Medical Silicone Elastomers

Application: Subdermal contraceptive capsules and intravaginal rings.

Polydimethylsiloxane (PDMS) networks. Highly permeable to small hydrophobic drug molecules (steroids). Inert, flexible, and non-reactive in biological tissue.

Ethylene-Vinyl Acetate (EVA)

Application: Ocular inserts and long-term release reservoir matrices.

Copolymer of ethylene and vinyl acetate. Vinyl acetate content (9–40%) controls carrier crystallinity and drug diffusion rate.

Surgical Retrievability: Non-biodegradable carriers require minor surgical extraction once drug payload is depleted.

Core Requirements for Medical Polymer Carriers

1. Biocompatibility

Zero cytotoxicity, non-hemolytic, non-pyrogenic, and minimal foreign-body inflammatory response.

2. Controlled Degradation

Erosion rate matching tissue healing, yielding non-toxic, easily excretable metabolic byproducts.

3. Sterilization Stability

Withstands thermal, gas, or gamma sterilization without altering molecular weight or release kinetics.

Regulatory Mandate: All medical polymer carriers must strictly comply with ISO 10993 biological evaluation standards and FDA guidance documents.

Biocompatibility Criteria: ISO 10993 Compliance

Cytotoxicity & Hemocompatibility

ISO 10993-5: Carrier extracts must not cause cell membrane lysis or metabolic inhibition (MTT cell viability >80%).
ISO 10993-4: Must exhibit hemolysis rate <2% and prevent platelet thrombus formation upon blood contact.

Sensitization & Genotoxicity

ISO 10993-10: Zero allergic contact dermatitis or delayed-type hypersensitivity.
ISO 10993-3: Zero mutagenic or clastogenic potential (Ames test & chromosomal aberration assays).

Tissue Integration: Carrier surface must promote normal host cell attachment rather than encapsulating fibrous scar tissue.

Controlled Degradation Kinetics & Byproduct Safety

Matching Healing Velocity

The rate of carrier mass loss and strength reduction must precisely match tissue regeneration velocity, ensuring continuous biomechanical load transfer.

Non-Toxic Metabolic Excretion

Degradation species (e.g., lactic acid, amino acids, monosaccharides) must enter natural physiological clearance pathways (renal filtration or Krebs cycle oxidation).

Safety Standard: Zero systemic accumulation of high-molecular-weight polymer fragments in RES organs.

Sterilization Stability of Polymer Carriers

Gamma & E-Beam Irradiation (25 kGy)

Mitigation: Low-temperature irradiation under dry ice or inert atmosphere.

High-energy ionizing radiation achieves terminal sterility. However, it can induce random polymer chain scission in PLA/PGA, dropping molecular weight and accelerating degradation.

Ethylene Oxide Gas (EtO) & Autoclaving

SAL Target: Sterility Assurance Level of 10^{-6} required.

EtO Gas: Excellent for heat-sensitive biopolymers, but requires prolonged vacuum outgassing to remove toxic residual alkylating agent.

Autoclaving: Steam at 121°C causes melting or hydrolysis of low-Tg polymers (PCL).

Quality Control: GPC molecular weight verification mandatory before and after sterilization validation.

Mechanical & Rheological Carrier Requirements

Avoiding Stress Shielding

Carrier elastic modulus (E) must match host target tissue (e.g., cortical bone E ≈ 18 GPa; soft tissue E ≈ 10–100 kPa) to prevent bone resorption around rigid implants.

Injectable Hydrogel Rheology

Carriers designed for syringe injection must exhibit shear-thinning flow behavior under extrusion stress combined with rapid recovery post-injection.

Composite Reinforcement: Adding nanoclays or carbon nanotubes enhances tensile strength and fracture toughness.

Polymer Carriers in Targeted Drug Delivery

Passive Targeting (EPR Effect)

Stealth Shielding: PEGylation prevents reticuloendothelial macrophage clearance.

Nanoscale polymer carriers (50–200 nm) circulate long enough to extravasate through leaky tumor blood vessels and accumulate passively in cancerous tissue.

Active Targeting Functionlization

Internalization: Receptor-mediated endocytosis delivers payload directly into target cells.

Surface-grafting carrier chains with targeting ligands (folic acid, antibodies, peptides) that bind specifically to overexpressed cell receptors.

Therapeutic Index: Maximizes local tumor drug concentration while sparing healthy systemic organs from toxicity.

Polymer Carriers as Tissue Engineering Scaffolds

Interconnected 3D Porosity

Tissue scaffolds require highly porous architectures (pore size 100–300 µm) to permit cell migration, vascular ingrowth, and nutrient perfusion.

Bioactive Molecule Delivery

Carriers co-deliver growth factors (BMP-2, VEGF) sustainedly over weeks to direct stem cell differentiation into bone or endothelial tissue.

Fabrication: Solvent casting, gas foaming, 3D bioprinting, and electrospinning.

Natural vs. Synthetic Carriers: Comparative Analysis

Carrier Comparison Matrix

Natural Carriers

Pros: Excellent biocompatibility, cell recognition sites, non-toxic enzymatic degradation.

Cons: Batch-to-batch variability, potential immunogenicity, uncontrolled rapid degradation.

Synthetic Carriers

Pros: Reproducible molecular weight, tunable mechanical properties, predictable degradation kinetics.

Cons: Lack bioactivity ligands, potential acidic degradation byproducts, hydrophobic surfaces.

Synergistic Blend: Modern PCM design combines synthetic polyesters with natural proteins/polysaccharides for optimal performance.

Toxicological Evaluation & Regulatory Approval

Extractables & Leachables

Residual organic solvents (DCM), catalyst traces (tin octoate), and unreacted monomers must be quantified and minimized per ICH guidelines.

Immunogenic Contaminants

Natural carriers (collagen, chitosan) must undergo rigorous purification to remove endotoxins, residual proteins, and viral pathogens.

FDA Inactive Ingredients (IID)

Polymer excipients must be listed in the FDA IID database for the specific route of administration at approved safety levels.

Clinical Translation: Compliance with ISO 10993 and FDA Quality by Design (QbD) ensures successful human clinical trials.

Future Horizons: Stimuli-Responsive & Smart Carriers

Environmentally Triggered Carriers

Smart polymer carriers designed to respond to physiological triggers (tumor acidic microenvironment, inflammation redox gradients, or enzymatic overexpression).

Bio-Inspired Mussel Adhesives: Catechol-functionalized carriers for robust wet-tissue adhesion.

Gene-Editing Carriers: Lipid-polymer hybrid nanoparticles delivering mRNA/CRISPR machinery.

Theranostic Systems: Carriers combining diagnostic imaging agents with sustained drug delivery.

Clinical Vision: Precision nanomedicine carriers tailored to individual patient genetic and pathological profiles.

Summary: Polymer Carriers & Medical Requirements

01

Diverse Origins

Natural (chitosan, collagen) and synthetic (PLGA, PCL) carriers offer complementary bioactivity and mechanical control.

02

Strict Safety Standards

ISO 10993 biocompatibility, zero cytotoxicity, and non-toxic metabolic byproducts are mandatory.

03

Advanced Applications

Carriers enable targeted cancer therapy, long-acting depot implants, and regenerative tissue scaffolds.

Core Takeaway: Master selection of synthetic and natural polymer carriers coupled with stringent safety compliance is essential for successful biomedical PCM innovation.

Thank You for Your Attention

acc.professor Kudaibergenova Bates Malikovna.