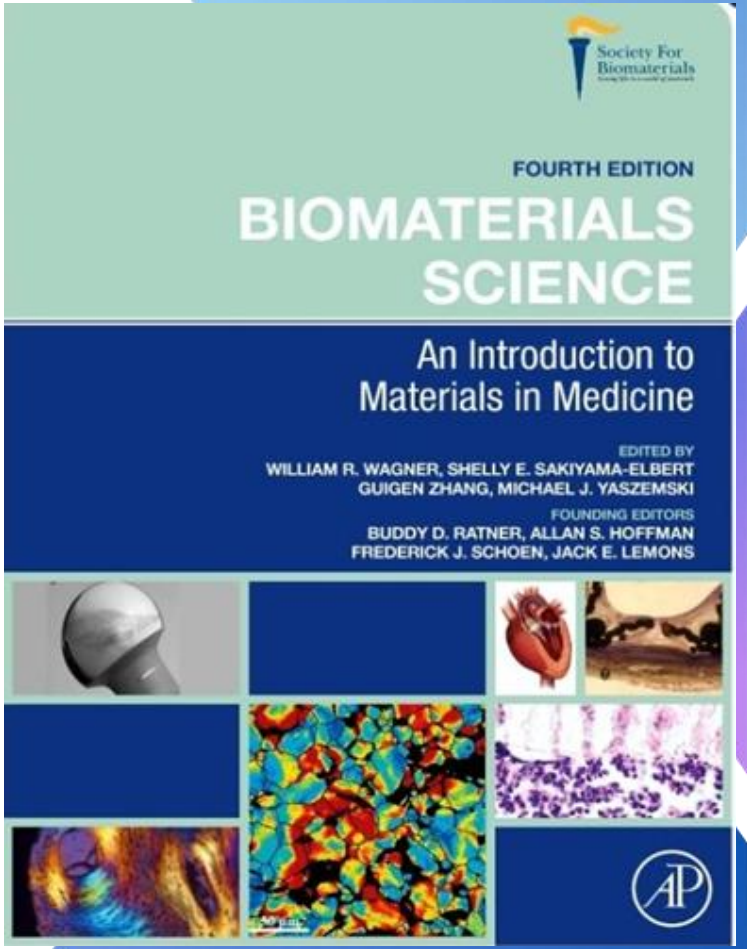
Materials in Biomaterials Science:

Ceramics, HA and Carbons

Part I. Materials Science and Engineering

1.3 Classes of Materials Used in Medicine

22. Ceramics, Glasses, and Glass-Ceramics: Basic Principles
23. Natural and Synthetic Hydroxyapatites
24. Structural Ceramic Oxides
25. Carbon Biomaterials



Defining Biomaterials

Introduction to Biomaterials

Biomaterials are materials used in medical devices to interact with biological systems.

- Replacement of physiologic functions (e.g., cardiac valves)
- Sensing (e.g., ultrasound contrast agents)
- Delivery of materials within the body (e.g., stent-delivery catheters)
- Temporary mechanical support (e.g., sutures)
- Extracorporeal processes (e.g., dialyzers)

Biomaterials: Engineering in Biology

The Unique Challenge of Biomaterials

Unlike automobile parts, the human body is not readily amenable to 'off-the-shelf' compositional and functional equivalence.

- Complexity of biological systems vs. engineered systems
- Integration with living tissue, not just mechanical fit
- Dynamic and adaptive environment

Grafts are classified by their source and purpose, commonly including
autografts (from the patient),
allografts (from a human donor), and
xenografts (from an animal source).

Other types include;
synthetic grafts, which are man-made materials like ceramics or bioactive glass, composite grafts, which combine different graft types to achieve a specific outcome.

Skin grafts are also categorized by thickness,
as split-thickness or
full-thickness grafts.

Autografts: Optimal Tissue Source

Autografts: The Gold Standard

Autografts use tissues harvested from the patient's own body, representing the '**gold standard**' for clinical needs.

- Muscle flaps for reconstructive procedures
- Saphenous veins/arteries for arterial bypass
- Skin for burn treatment
- Excellent biocompatibility and integration
- Bone for various applications

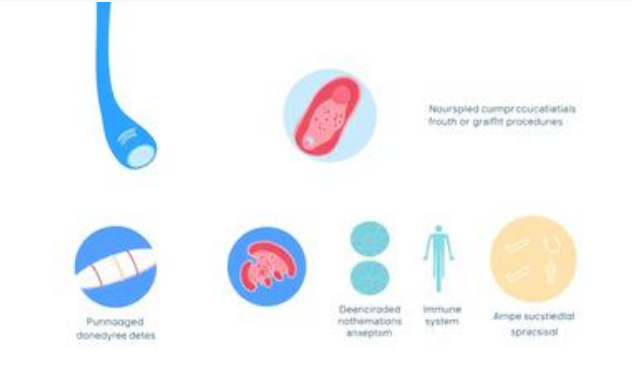
Allografts: Donor Tissue Applications

Allografts: Bridging Critical Needs

Allografts, from organ and tissue donation, fill critical needs when autografts are not feasible.

- Best option for end-stage cardiac, kidney, liver, pulmonary failure
- Used in a minimally processed state
- Quality of life and survival often exceed medical support devices

Challenges of Grafting



Limitations of Grafts and the Need for Engineered Solutions

- Autografts: Donor site morbidity (pain, scarring, infection)
- Allografts: Immunosuppressant therapy, limited supply, ethical considerations
- Biomaterial and medical device technology often fall short of autograft effectiveness

This highlights the persistent need for advanced, engineered biomaterials.

Engineered Biomaterial Classification

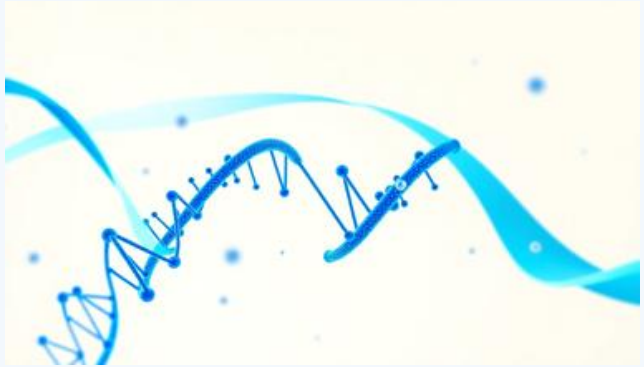
Ceramics, Glasses, and Glass-Ceramics: Basic Principles
Natural and Synthetic Hydroxyapatites
Structural Ceramic Oxides
Carbon Biomaterials
Polymers: Basic Principles
Polyurethanes
Silicones
Fluorinated Biomaterials
The Organic Matrix of Restorative Composites and Adhesives
Hydrogels
Degradable and Resorbable Polymers
Applications of "Smart Polymers" as Biomaterials
Metals: Basic Principles
Titanium Alloys, Including Nitinol
Stainless Steels
CoCr Alloys
Biodegradable Metals
Natural Materials
Processed Tissues
Use of Extracellular Matrix Proteins and Natural Materials in Bioengineering
Composites
Microparticles
Nanoparticles

The Spectrum of Engineered Biomaterials

To fulfill diverse medical device requirements, a broad array of materials is needed.

- Polymers: Flexible, customizable, biodegradable options
- Metals: High strength, fatigue resistance, biocompatibility
- Ceramics: Hardness, wear resistance, bioactivity
- Natural Materials: Biologically derived, often biodegradable
- Composites: Combine properties of different material classes
- Particulates: Nanoscale or microscale materials with specific functions

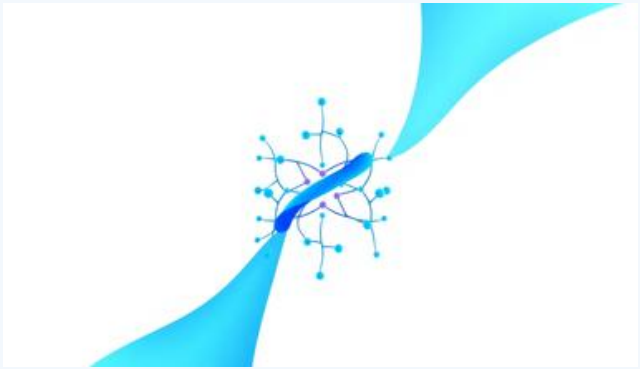
Biomaterials Innovation Drivers



Evolving Trends in Biomaterials: Next Generation Design

- Molecular biology advances: Designing materials with specific biological functionalities (e.g., cell guidance, signaling).
- Particulate biomaterials: Leveraging biological knowledge for targeting, responsiveness to local conditions (e.g., pH), and cellular interactions.
- Biologically derived materials: From highly purified single components to engineered natural materials (e.g., decellularized tissues, ECM-derived).

Convergence of Disciplines



The Merging Material-Biological Interface

As the field progresses, the knowledge bases informing both the material and biological sides are converging.

- Control of biological response is often the critical engineering issue.
- However, many current devices still rely on materials adopted from broader materials community.
- Understanding fundamental materials science remains essential for biomaterials experts.

Overview of Bioceramics

Introduction to Bioceramics

Bioceramics encompass ceramic, glass, and glass-ceramic implant materials.

- Generally hard inorganic components.
- Primarily used to repair, replace, or regenerate bone or teeth.
- Applications are continually broadening.

Bioceramic Classification

Classifying Bioceramics: Bioinert vs. Bioactive

No material implanted in living tissue is completely inert; all elicit a response.

Nearly-Bioinert Ceramics

- Used where a robust hard surface is needed (e.g., joint replacement with articulating bearing surface, dental restoration).
- Tend to be surrounded by fibrous capsules in the body.

Bioactive Ceramics

- Designed to provoke a beneficial biological response from the host environment.
- Traditionally, form a direct bond with bone tissue without fibrous encapsulation.

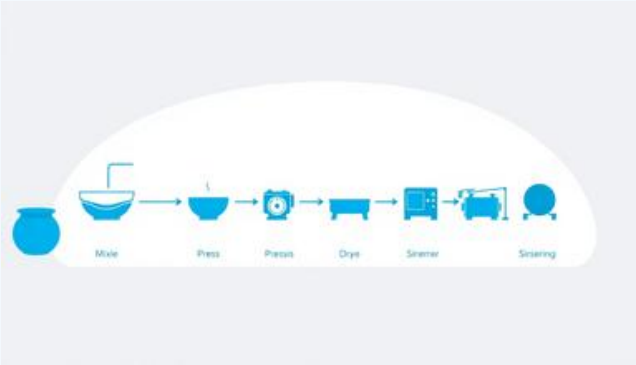
Key Bioinert Materials

Common Nearly-Bioinert Bioceramics

- Alumina (aluminum oxide, Al_2O_3)
- Zirconia (zirconium oxide, ZrO_2)

These materials are chosen for their mechanical robustness and minimal reactivity.

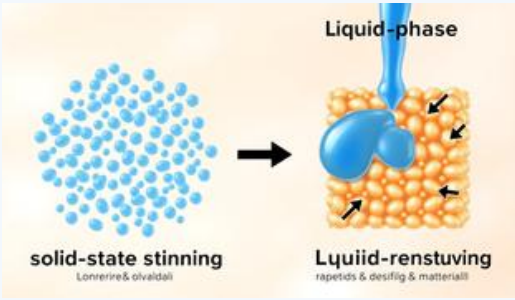
Ceramic Fabrication Steps



Manufacturing Nearly-Bioinert Ceramics: Process Overview

- Starting material: Fine-grained particulate solids.
- Mixing: Combined with water and an organic binder.
- Pressing: Formed into desired shape in a mold.
- Drying: Temperature raised to evaporate water.
- Binder Burnout: Organic binder removed at higher temperatures.

Sintering Techniques in Bioceramics



Sintering is forming a solid mass of material through heat and pressure without melting to the point of liquefaction.

Solid-State Sintering

- Atoms move to fill pores and channels between grains.
- Grains bond more tightly, improving density, strength, fatigue resistance.
- Typically slower, but yields higher purity and uniformity in fine-grained microstructures.

Liquid-Phase Sintering

- Some liquid phases form at grain boundaries at elevated temperatures.
- Liquid penetrates between grains, fills pores, and draws grains together by capillary attraction, decreasing volume (densification).
- Typically faster, resulting microstructure has fine-grained matrix around original grains.

Alumina: Orthopedic Pioneer

Alumina (Al_2O_3): A Legacy in Orthopedics

Alumina has been utilized in orthopedic surgery for over 50 years.

- Characterized by high-density, high-purity (>99.5%), fine-grained polycrystalline α-Al_2O_3.
- Primary application: articulating surfaces of total joint prostheses.

Alumina's Desirable Attributes

Key Properties of Alumina for Medical Use

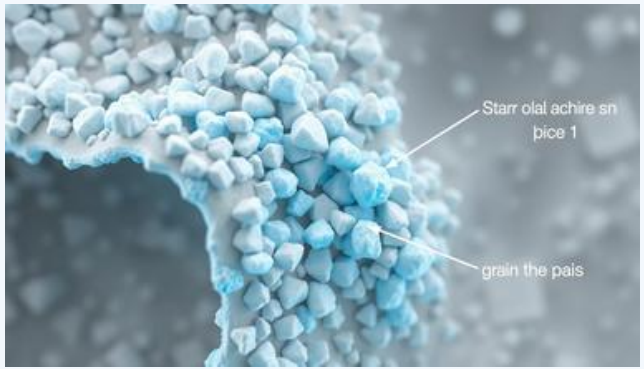
- Excellent corrosion resistance: Stable in physiological environments.
- High wear resistance: Crucial for long-term function in articulating joints.
- High strength: Withstands significant mechanical loads.
- Biocompatibility: Well-tolerated by the body.

Alumina Production Parameters

Manufacturing High-Performance Alumina Ceramics

- Process: Ceramic powder is pressed and sintered.
- Sintering Temperature: Typically 1600-1700°C.
- Sintering Aid: A very small amount of MgO (<0.5%) is used.
- Purpose of MgO: Aids densification and limits excessive grain growth during sintering. Too much can be detrimental.

Microstructural Control of Alumina



Alumina Properties: The Role of Microstructure

- Strength, fatigue resistance, and fracture toughness are functions of:
- Grain size: Smaller grains generally lead to higher strength.
- Percentage of sintering aid (purity): Affects grain boundaries and overall material integrity.
- ISO 6474: Standards for alumina implants specify requirements for flexural strength (e.g., 55 MPa) and compressive strength (e.g., 4.5 GPa).

Alumina: Surface Optimization for Wear

Tribological Excellence of Alumina: Achieving Low Friction

- Motivation: Exceptionally low coefficient of friction and low wear rates.
- Requirements: Superb tribology properties achieved only when grains are very small (<4 µm) and have a very narrow size distribution.

- Result: Leads to very low surface roughness values (Ra <0.02 µm).
- Consequence of large grains: Can be pulled out, leading to rapid wear of bearing surfaces due to local dry friction.

Y-TZP: A Toughened Ceramic Option

Zirconia (ZrO_2) in Articulating Applications

Yttria-stabilized zirconia (Y-TZP) was introduced for articulating applications in hip and knee implants.

- Specifically, 3 mol% yttria-stabilized zirconia (Y-TZP) results in a ceramic with excellent fracture toughness.
- Initially seen as an improvement over alumina due to its toughness.

Y-TZP Failure: Phase Transformation

The Zirconia Recall: Understanding Implant Failures

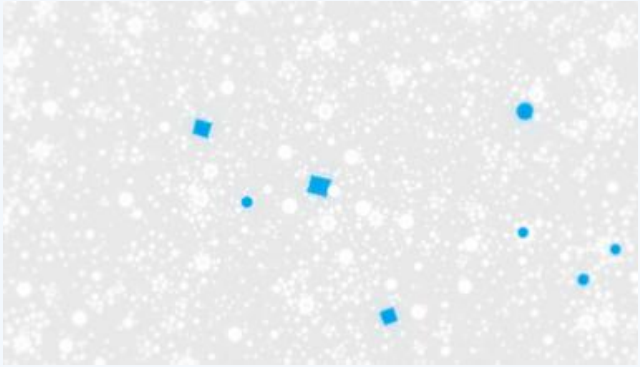
Despite initial promise, a series of implant failures around the year 2000 led to the withdrawal of zirconia for these applications.

- Reason: Unforeseen aging of the ceramic post-implantation.
- Mechanism: Crystal structure of the ceramic changed from tetragonal to monoclinic phase.
- Result: Made the ceramic more brittle and prone to failure.

Introducing ZTA: Strength and Toughness

Zirconia-Toughened Alumina (ZTA): A Robust Hybrid

To overcome the limitations of pure alumina and zirconia, Zirconia-Toughened Alumina (ZTA) was developed.



- ZTA offers enhanced strength and toughness properties over α-Al_2O_3.
- Mechanism: Small zirconia grains within the alumina matrix.
- Benefit: Not only slow down the aging process of zirconia but also prevent crack propagation within the alumina.

ZTA: Advancing Joint Implants

Clinical Impact of ZTA

- Widespread Use: ZTA is now in widespread use for the articulating surfaces of knee implants.
- Ongoing Trials: Currently undergoing trials for hip arthroplasty.
- Patient Benefit: Could significantly benefit younger patients by helping to preserve much of the underlying bone in the femoral head due to improved durability and reduced wear.

Bioactive Materials: Inducing Healing

Bioactive Ceramics and Glasses: Supporting Tissue Repair

In contrast to nearly-bioinert materials, bioactive ceramics and glasses are designed to actively engage with biological systems.

- Purpose: To elicit a specific biological response.
- Primary Goal: Support of tissue repair, especially bone formation and integration.

Host-Implant Interactions

Implant-Tissue Responses: A Spectrum

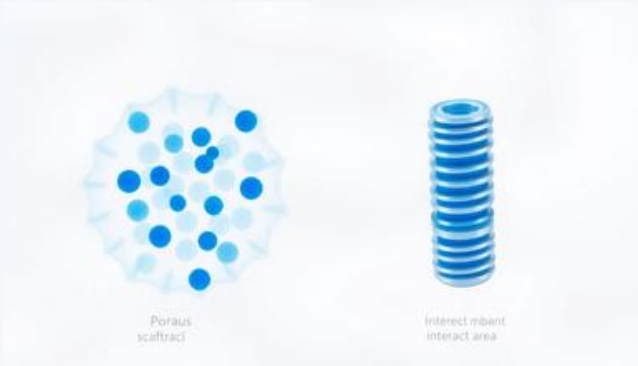
Type of Tissue Response

- Biologically active (bioactive)
- Biologically inactive (nearly inert, or bioinert)
- Resorbable
- Toxic

Description of Tissue Response

- An interfacial bond with tissue forms; may allow/support bone formation (osteoconductive) or induce bone formation.
- Material tolerated by formation of a fibrous tissue layer.
- Implant material resorbed/degraded, typically allowing new tissue to replace it; degradation products should be biocompatible.
- Toxic response, surrounding tissue death (local), with potential systemic toxicity.

Physical Properties & Bioactivity

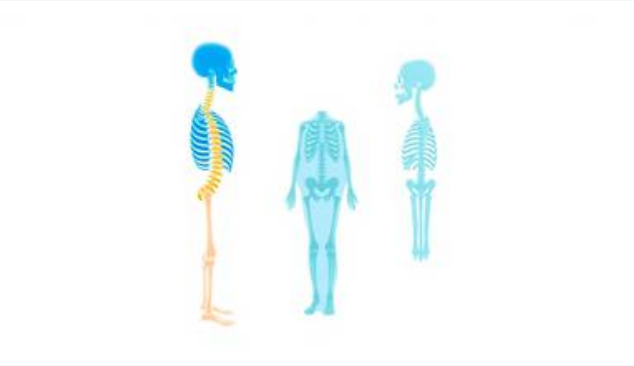


Factors Influencing Biological Response

The biological response to bioactive materials is not solely dictated by the material's chemical composition.

- Physical Form: Whether the material is dense or porous, or has a low or high surface area, significantly influences the local tissue response.
- Beyond Bone Formation: Bioactive materials can also elicit osteoclast resorption, activate proinflammatory responses, or induce new blood vessel formation (angiogenesis), in addition to chemical resorption.

Bioactive Materials: Clinical Scope



Clinical Applications of Bioactive Ceramics and Glasses

- Orthopedics: Filling bone defects, nonunion fractures, spinal fusion (posterolateral, interbody).
- Craniotaxillofacial/Dental: Cranioplasty, orbital floor fracture repair, sinus obliteration, cyst removal, ridge augmentation, periodontal regeneration.

These materials are crucial as synthetic bone graft substitutes.

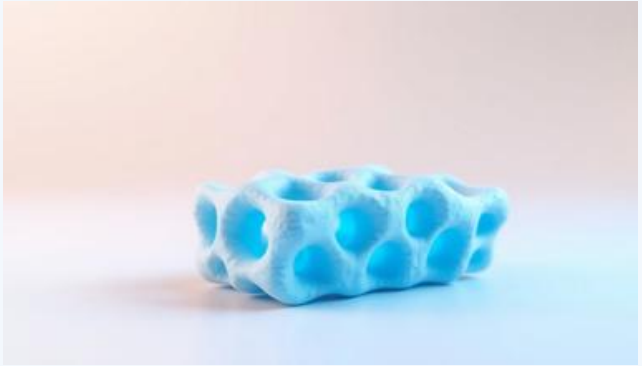
Synthetic Graft Benefits

Advantages of Synthetic Bone Graft Substitutes

Synthetic bone graft substitutes derived from bioactive ceramics and glasses offer benefits over traditional options.

- Avoids donor site morbidity of autografts.
- Circumvents limited supply and immunogenicity of allografts.
- Provide consistent properties, unlike demineralized bone matrix (DBM).
- Properties depend on chemical composition, physical micro/macrostructures, and final form.

Bioactive Scaffolds for Regeneration



Role in Tissue Engineering

Beyond direct grafting, bioactive ceramics and glasses are vital as scaffolds in orthopedic tissue engineering.

- Provide a structural template for cell attachment, proliferation, and differentiation.
- Guide new tissue formation in complex defects.

- Can be designed with specific pore architectures to promote vascularization and bone ingrowth.

Calcium Phosphates: Bone's Mimics

Calcium Phosphate-Based Bioceramics: Foundation for Bone Repair

The most widely studied group of bioactive ceramics due to their chemical similarity to the mineral component of bone and teeth.

- Mimic natural bone mineral, primarily hydroxyapatite.
- Serve as osteoconductive (guiding bone growth) and sometimes osteoinductive (inducing bone formation) materials.

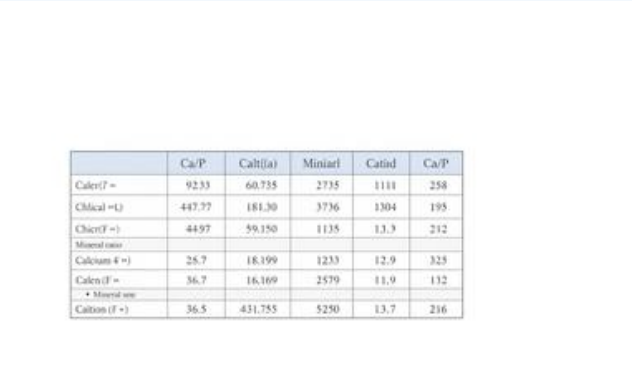
CaP Phase Variations

Diversity of Calcium Phosphate Phases

A wide range of distinct calcium phosphate phases exist, classified by various parameters:

- Molar ratio of calcium-to-phosphorus (Ca/P)
- Polymorphs (same chemical composition, different crystal structure)
- Presence/absence of structural water
- Formation temperature (e.g., phases forming only at high temperatures like tetracalcium phosphate)

Common CaP Phases

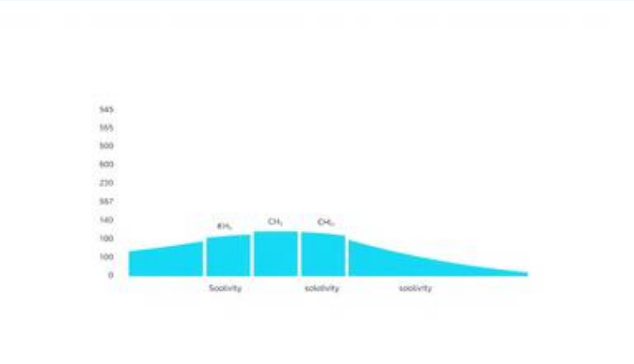


	Ca/P	Calt([a)	Miniarl	Catid	Ca/P
Calcr(7 =	92.33	60.735	2735	1111	258
Chlical =L)	447.77	181.30	3736	1304	195
Chicr(F =)	4497	59.150	1135	13.3	212
Mineral ratio					
Calcium 4 =)	25.7	18.199	1233	12.9	325
Calcn (F =	36.7	16.169	2579	11.9	132
• Mineral ratio					
Cation (F =)	36.5	431.755	5250	13.7	216

Key Calcium Phosphate Phases in Bioceramics (Table 1.3.4.3)

- Dicalcium phosphate anhydrous (DCPA): Monetite
- Dicalcium phosphate dihydrate (DCPD): Brushite
- Octacalcium phosphate (OCP)
- Tricalcium phosphate (α-, β- TCP): Whitlockite (β-TCP)
- Ca-deficient apatite (CDA)
- Hydroxyapatite (HA): Apatite, hydroxyapatite
- Tetracalcium phosphate (TTCP): Hilgenstockite

CaP Solubility Profile

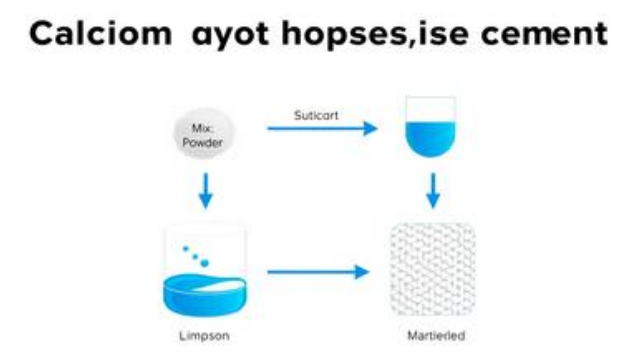


Solubility of Calcium Phosphate Phases

One of the major differences among these phases is their relative solubility, critical for their degradation behavior.

- Solubility order (at physiological pH and 37°C):
- DCPA = DCPD > α-TCP > β-TCP > TTCP > CDA > OCP > HA
- Highly soluble phases are often used as reactants in bone cements.

High Solubility for Cement Reactants



Reactant Phases in Bone Cements

Calcium phosphate phases with high solubility are predominantly used as reactant phases in calcium phosphate bone cements.

- DCPA, DCPD, α-TCP, and TTCP are key components.
- Their inherent high solubility at physiological pH enables rapid setting reactions when mixed with an aqueous solution.

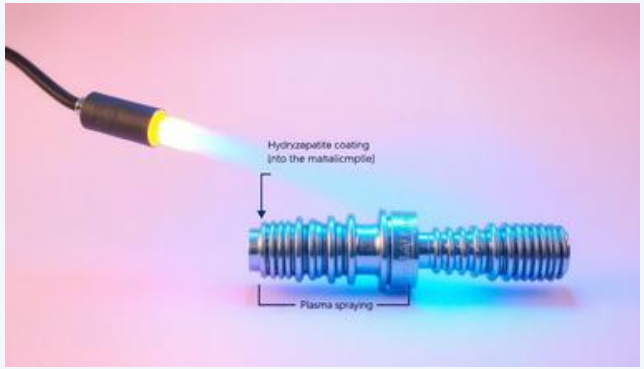
Aqueous Precipitation CaPs

Alternative CaP Bone Graft Substitutes

While not traditionally classed as ceramics due to their formation process, DCPD, DCPA, and OCP have been studied as potential bone graft substitutes.

- Form by aqueous precipitation at or close to room temperature.
- Avoids high-temperature ceramic processing, which would transform them to different phases.

HA Coatings for Osseointegration



Hydroxyapatite Coatings on Implants

Calcium phosphates, especially HA, can be used to coat metallic and polymeric implants.

- Purpose: To provide a bioactive surface on an otherwise biologically inert bulk material.
- Method: Most studied coating method is high-temperature plasma-spraying (HA powder fed into plasma torch).
- Benefit: Enhances osseointegration and biocompatibility.

HA and TCP: Bone Grafting Solutions

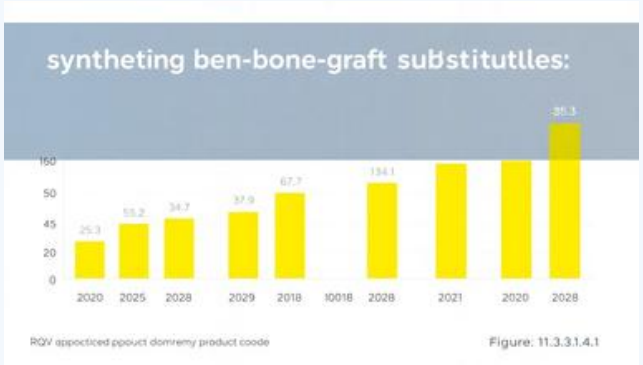
HA and TCP as Bone Void Fillers (BVFs)

Hydroxyapatite (HA) and Tricalcium Phosphate (TCP) are extensively studied as bioactive ceramics for bone graft substitutes, often referred to as bone void fillers (BVFs).

- Typical form: Porous ceramics, often combined within a natural (e.g., collagen) or synthetic (e.g., polyethylene glycol [PEG]) polymeric carrier.

- Also used as cements: Providing distinct advantages depending on the bone defect.

Regulatory Landscape: FDA Approvals



FDA Approvals for Synthetic Bone Graft Substitutes

- Classed by FDA:
- MQV: For orthopedic use (e.g., calcium salt BVFs).
- LYC: For dental applications.
- The number of approved products between 2014 and 2018 highlights the growing market and demand for synthetic bone graft substitutes.

Porous CaP Ceramics Composition

Porous Calcium Phosphate Ceramics: Core Materials

Bone graft substitutes produced from porous calcium phosphates typically consist of:

- Hydroxyapatite (HA)
- β-Tricalcium Phosphate (β-TCP)
- Biphasic Calcium Phosphates (BCPs): A mixture of HA and β-TCP.

CaP Degradation and Bone Growth

Resorption Rates and Osteoconductivity

- Relative Solubility: β-TCP is significantly more soluble than HA.
- Osteoconductivity: Both materials are osteoconductive, providing a surface that encourages new bone formation.
- Degradation Differences:
- β-TCP: Resorbs faster in vivo, suitable when rapid graft replacement is desired, but might resorb faster than bone formation rate.
- HA: Limited solubility can result in a material that, once host bone forms, shows limited further integration and remodeling.

BCPs: Customizing Bioactive Grafts

Biphasic Calcium Phosphates (BCPs): Tailored Responses

The rationale for BCPs lies in providing a material that offers a blend of biological responses from HA and β-TCP.

- Ratio Dependence: The relative amounts of HA and β-TCP in BCPs have been shown to affect:
- Bone formation
- Soft tissue response
- Material degradation/resorption
- Osteoinduction (in some cases)

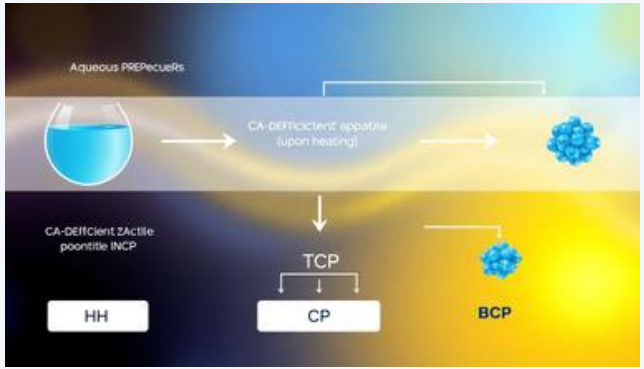
Aqueous Synthesis of CaP

Synthesis of CaP Bioceramics: Aqueous Precipitation

Aqueous precipitation reactions are the preferred method for synthesizing various calcium phosphate phases.

- Involves mixing calcium and phosphate reactants at alkaline pH.
- Example: $Ca(NO_3)_2 \cdot 4H_2O$ and $(NH_4)_2HPO_4$ or $Ca(OH)_2$ suspension and phosphoric acid.
- Key advantage: Ability to control the Ca/P molar ratio of the product by adjusting pH, reactant concentration, and temperature.

CaP Phase Transformation



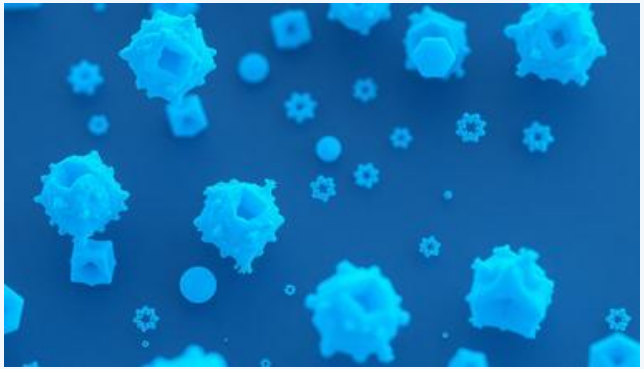
From Ca-Deficient Apatite to HA/TCP/BCP

The initial product from aqueous precipitation is often a Ca-deficient apatite (CDA).

- CDA composition: $Ca_{1018xxxə}(PO_4)_{618xxxə}(HPO_4)_{xxxə}(OH)_{218xxxə}$, where x (0-1) dictates composition.
- Transformation upon heating/sintering (>750°C): Water loss occurs.
- Final Composition: Results in HA (x=0), TCP (x=1), or BCP (1>x>0, with increasing TCP as x increases).

- Impurity Control: Reaction conditions (e.g., pH drops) can lead to other CaP phases (DCPD, DCPA, OCP) in the final product.

Nanoscale CaP Synthesis



Nanoparticles of Calcium Phosphates

There is increasing interest in producing nanoparticles of calcium phosphates, primarily apatites, for advanced applications.

- Synthesis Methods:
- Aqueous precipitation (most common for control over particle size/morphology).
- Biomimetic synthesis: Mimicking natural biomineralization processes.
- Sol-gel synthesis: Formation from colloidal suspensions.
- Hydrothermal methods: High-temperature, high-pressure aqueous synthesis.

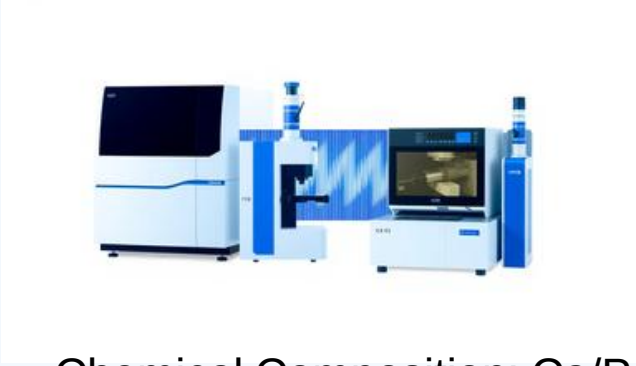
CaP Bioceramics: Quality Standards

Characterization of CaP Bioceramics: Industry Standards

The quality and safety of CaP bioceramics for medical use are guided by international standards.

- ISO 13175-3 (2012): Specifies requirements for hydroxyapatite and beta-tricalcium phosphate bone substitutes.
- ASTM F1185-03 (2014): Standard Specification for Composition of Hydroxylapatite for Surgical Implants.
- ASTM F1088-18 (2018): Standard Specification for Beta-Tricalcium Phosphate for Surgical Implantation.
- These standards ensure consistency and performance for their intended applications.

Analytical Methods for CaP



Chemical Characterization Techniques for CaP

- Phase Composition/Purity: X-ray Diffraction (XRD) — identifies crystalline phases and amorphous content.
- Chemical Composition: Ca/P molar ratio and impurity content — typically using X-ray Fluorescence (XRF) and/or Inductively Coupled Plasma-Optical Emission Spectrometry (ICP-OES).
- Functional Groups: Fourier Transform Infrared (FTIR) and/or Raman spectroscopy — identifies specific chemical bonds and substitutions (e.g., carbonate ions).
- Other: Surface area and density measurements.

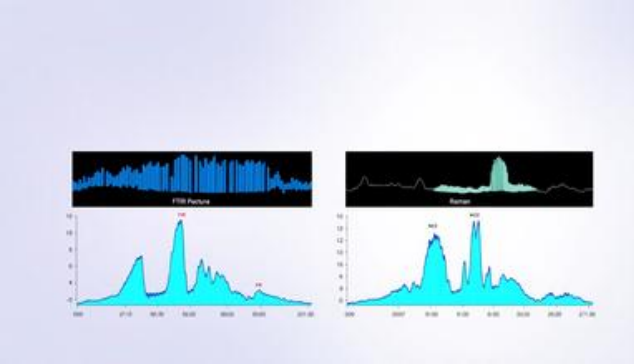
XRD Fingerprints of CaP

X-ray Diffraction (XRD) patterns are identified by reference to standard Powder Diffraction Files (PDFs) from the International Centre for Diffraction Data (ICDD).

Powder Diffraction Files for CaP Phases (Table 1.3.4.4)

- Hydroxyapatite (hexagonal): 00-009-0432
- β-Tricalcium phosphate: 00-009-0169
- α-Tricalcium phosphate: 00-009-0348
- Dicalcium phosphate anhydrous: 00-009-0080
- Dicalcium phosphate dihydrate: 00-009-0077
- Octacalcium phosphate: 00-026-1056
- Common Impurities: Calcium oxide (lime), Calcium carbonate (calcite, aragonite).

FTIR and Raman for CaP Analysis



Spectroscopic Insights: IR and Raman

Infrared (IR) and Raman spectroscopy provide complementary data for characterizing CaP materials.

- Identify different CaP phases and subtle changes during synthesis/processing.
- Detect inclusion of carbonate ions or loss of structural water.
- IR provides specific vibration peaks for PO_4^{3-}, OH^-, and CO_3^{2-} groups (Table 1.3.4A.3).
- Raman offers advantages like minimal sample preparation and high spatial resolution using a microscope.

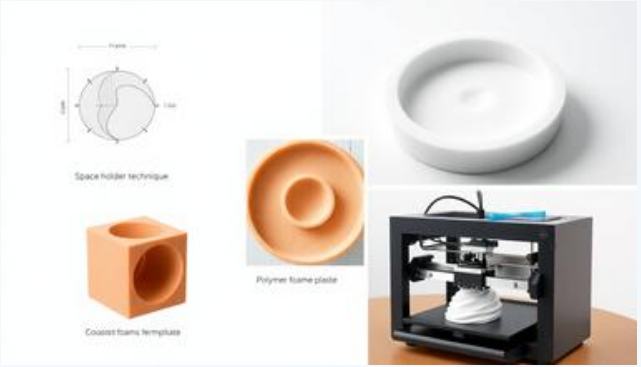
Ceramic Physical Form Matters

Physical Form: A Crucial Influence

Beyond chemical composition, the physical form of manufactured bone graft substitute ceramics is highly influential.

- Properties: Affects mechanical properties, cell infiltration, vascularization, and overall tissue integration.
- Production: HA, TCP, and BCP ceramics are produced using typical ceramic approaches, optimizing powder properties (particle size, surface area) and sintering conditions (compaction pressure, temperature, atmosphere).

Macroporous Ceramic Fabrication

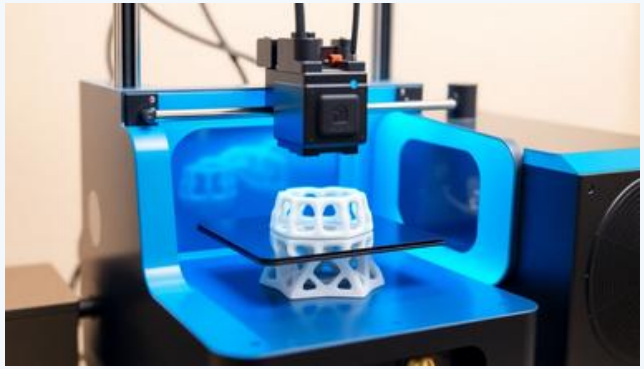


Production of Macroporous Ceramics

Due to relatively poor mechanical properties of dense monolithic calcium phosphate ceramics, their applications are limited.

- Natural Sources: Converted coral and bovine bone (relies on sintering/densification to produce macroporous structure, 100-1000 µm pores).
- Synthetic Methods:
- Space holder: Polymer spheres burn out to create pores.
- Polymer foam templates: Ceramic slurry coats foam, foam removed by heat.

Additive Manufacturing for Bioceramics



3D Printing: Precision Design for Scaffolds

Three-dimensional (3D) printing methods provide a significant amount of design control not available with other techniques.

- Feasibility: Enables the creation of individualized patient-specific scaffolds with complex architectures.
- Control: Precise control over pore size, shape, and interconnectivity.
- Scalability: Currently, scalable additive manufacturing for large volumes may be limited to more simple architectures.

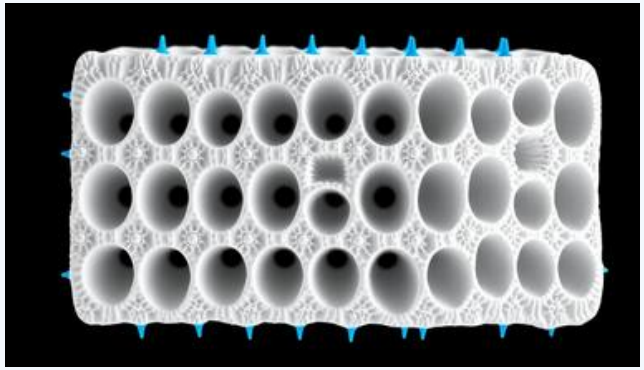
Pore Structure for Osseointegration

Pore Characteristics and Bone Ingrowth

The characteristics of the porosity are crucial for effective bone regeneration.

- Key characteristics: Pore size, pore size distribution, total porosity, and pore interconnectivity.
- Typical macroporous bone graft substitutes: Resemble cancellous bone-like foam architectures, with 50%-90% total porosity and macropore sizes of 100-1000 μm, and high interconnectivity.
- Significance: Directly affect bone ingrowth and integration.

Sintering for Scaffold Strength

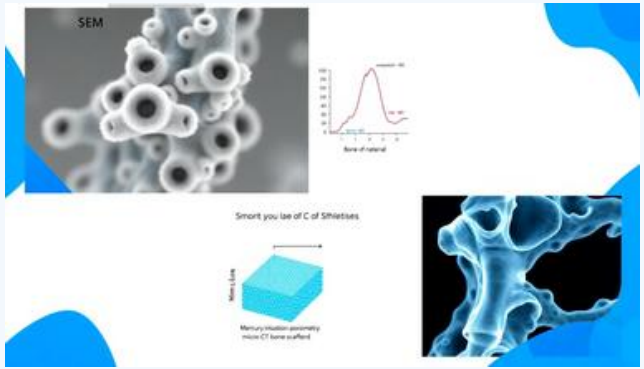


Structural Support: Densification of Struts

In macroporous calcium phosphate materials, the calcium phosphate particles form the struts or the 'skeleton' of the material.

- Purpose: To improve the scaffolds' resistance to crushing or damage, these struts need to undergo densification/sintering.
- Optimization: Powder properties and sintering parameters are optimized to achieve sufficient mechanical integrity for load-bearing applications or handling.

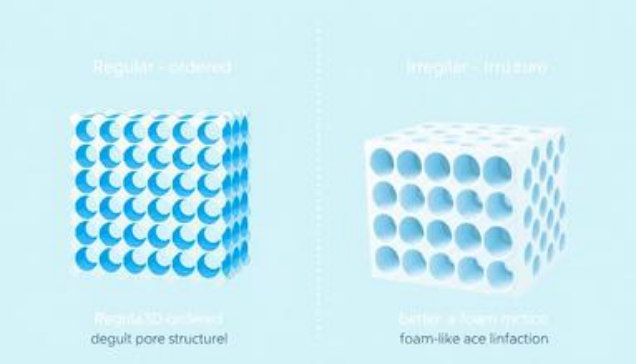
Pore Architecture Characterization



Characterizing Pore Structure: Advanced Techniques

- Scanning Electron Microscopy (SEM): Used to study pore shape/structure from material surfaces or 2D sections.
- Mercury Intrusion Porosimetry: Quantifies pore size distribution and indicates interconnectivity/presence of trapped pores.
- Microcomputed Tomography (µCT): Non-destructive method for quantifying macroporosity and, with small pixel sizes, microporosity. Provides 3D information.

Pore Design for Cell Behavior



Optimal Pore Morphology for Bone Regeneration

For effective bone regeneration, the morphology and degree of interconnectivity of pores can be more critical than just pore size.

- Large Pores: Essential for blood (carrying cells) flow into the scaffold, space for 3D growth of immature bone, and crucially, population by blood vessels (vascularization).
- Example: Bone ingrowth was more rapid in foam scaffolds than 3D-printed scaffolds with similar interconnection sizes, attributed to bone progenitor cells preferring the concave niche of foam pores.

Marketed CaP Graft Products

Commercial CaP Bone Graft Substitutes (Table 1.3.4.5)

A large number of synthetic bone graft substitutes have been approved for clinical use.

- NanoBone Granulate (Artoss): Nanocrystalline HA and silica gel matrix (granules).
- Chronos Granules (Synthes): β-TCP (macroporous granules).

- Actifuse ABX (Baxter): (Silicated) HA (macroporous granules in poloxamer hydrogel)

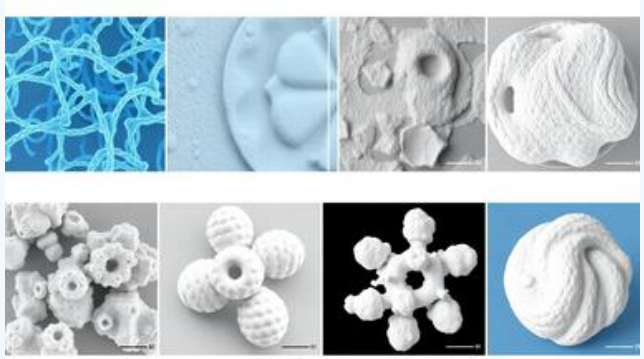
Evidence Gap in Graft Efficacy

Clinical Efficacy Data: A Persistent Challenge

Despite numerous approved products, clinical data supporting the efficacy of specific synthetic bone graft substitutes is limited.

- Limited studies: Lack of large-scale, well-designed clinical trials.
- Broad range of fusion techniques/approaches: Makes direct comparisons difficult.
- Comparison with Autograft: Some studies compare synthetic grafts to autograft (clinical gold standard), but more data is needed for strong conclusions.

SEM of Graft Microstructures



Visualizing Bone Graft Substitutes

Scanning Electron Microscopy (SEM) images reveal the diverse microstructures of commercial synthetic and natural bone graft substitutes.

- Show differences in sintered grain structures and microporosity.
- Illustrate variations across different products and source materials (e.g., synthetic vs. bovine bone derived).

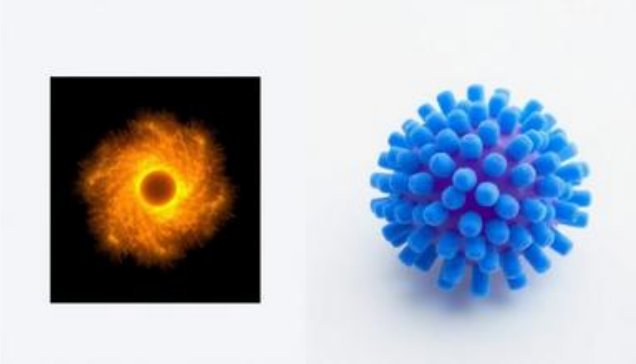
Graft Delivery and Formulation

Enhancing Handling: Granules and Carriers

Calcium phosphate bone graft substitutes typically consist of macro- and/or microporous granules (0.4-2 mm size).

- Handling: Granules are often mixed with saline, blood, or bone marrow aspirate (BMA) to improve handling.
- Biological Factors: This mixing can also introduce biological factors from blood or BMA.
- Carriers: Most products use hydrogel, anhydrous polymeric, or collagen (or gelatin) scaffolds to improve intraoperative handling, placement, and shaping.

Actifuse ABX: Porosity Revealed



Actifuse ABX: A Case Study in Porosity

Actifuse ABX (Baxter, UK) is a silicon-substituted synthetic HA available as foamed granules (~3 mm).

- Microcomputed Tomography (µCT) Imaging: Reveals its pore network and quantifies open pore architecture.
- Key Feature: Possesses a modal interconnect size of 120 µm, important for its efficacy in bone regeneration.
- Importance: Demonstrates how advanced imaging helps understand structure-function relationships in biomaterials.

CaP Cements: Injectable Bone Fillers

Calcium Phosphate Cements: In Situ Setting

Calcium phosphate bone cements involve mixing specific calcium phosphate phases with an aqueous solution.

- Process: Forms a paste that undergoes a chemical dissolution and reprecipitation reaction.
- Outcome: Leads to interlocking/entanglement of new crystals of the product phase, producing a set and hardened mass.
- Analogy: Similar to calcium silicate construction cements.

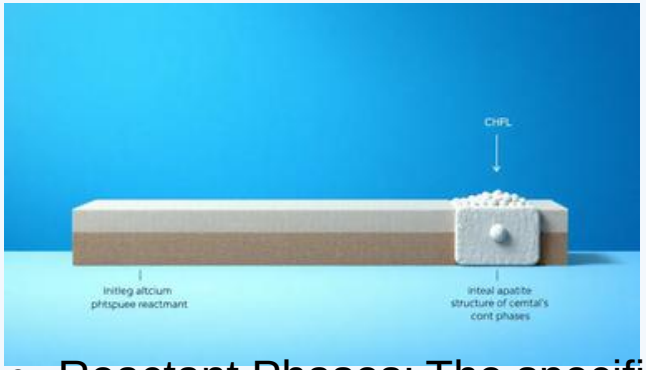
Benefits of CaP Bone Cements

Advantages of CaP Cements

Calcium phosphate cements offer unique advantages over typical ceramics for filling bone defects:

- Injectability: Can be precisely injected into complex defects.
- Mechanical Properties: Creates a hardened mass with compressive strength similar to cancellous bone.
- Drug Delivery: Allows for the incorporation of drugs or biomolecules (e.g., antibiotics) into the aqueous phase for localized release.

Forming Apatite Cements

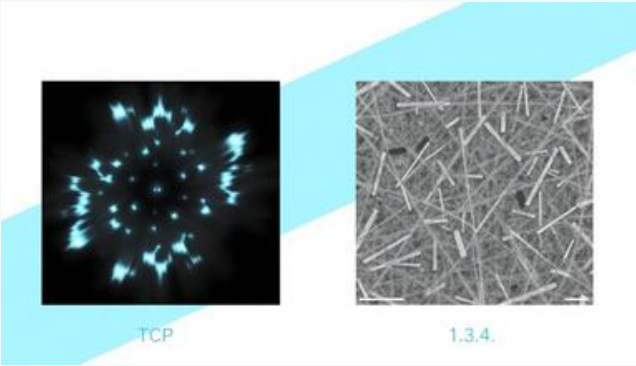


Apatite-Forming CaP Cements

The final product of a calcium phosphate bone cement reaction is often an apatite phase (typically Ca-deficient apatite, CDA).

- Reactant Phases: The specific product phase depends on the chosen reactant phases.
  - Early Clinical Formulation (1980s): Mixtures of tetracalcium phosphate and dicalcium phosphate anhydrous (DCPA) or dihydrate (DCPD) formed apatite.
- Alternative: α-TCP and DCPA, with small amounts of precipitated HA or calcium carbonate additives, have also led to clinically used cements.

Comparative CaP Cement Reactivity



Cement Reactivity: α-TCP vs. β-TCP

The choice of calcium phosphate reactant significantly impacts cement setting and properties.

- α-TCP Cement: Shows almost complete conversion to a Ca-deficient apatite (CDA) product phase within 7 days, with associated entanglement of apatite crystals.
- β-TCP Cement: Exhibits minimal reactivity under similar conditions, demonstrating the importance of phase selection.
- Parameter Effects: Particle size, surface area, liquid/powder ratio, and aqueous solution composition also influence paste/hardened cement properties.

Brushite Cements: Resorbable Options

Brushite Cements: Gradual Resorption

An alternative class of CaP cements, brushite cements, typically form from a combination of β-TCP and monocalcium phosphate monohydrate with an aqueous phase.

- Mechanism: Dissolution of reactant phases and precipitation of brushite crystals.
- Key Property: The brushite product phase is inherently unstable at physiological pH.
- Benefit: Undergoes gradual dissolution, allowing it to be replaced by new bone over time, making it useful for remodeling.

Bioglass: Pioneering Bone Integration

Bioglass and Bioactive Glass: A Breakthrough in Bone Bonding

Bioglass, specifically 45S5 Bioglass, was the first material demonstrated to directly bond with bone rather than being encapsulated by fibrous tissue.

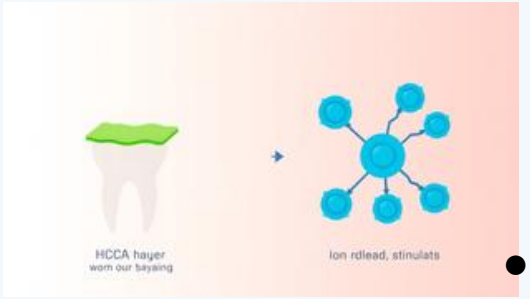
- Developed by Larry Hench.

- Discovery: Launched the entire field of bioactive ceramics.
- Impact: Revolutionized approaches to bone repair and regenerative medicine.

Bioglass: Two-Fold Bioactivity

Bioglass Bioactivity: Dual Mechanism

Bioglass degrades through dissolution in solution, exhibiting two primary modes of bioactivity for bone repair:



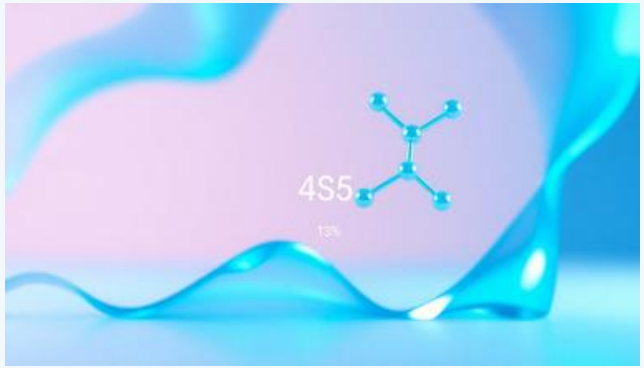
1. Bone Bonding

- Forms a hydroxycarbonate apatite (HCA) layer on its surface following dissolution and precipitation.
- This HCA layer integrates with collagen fibrils of the host bone, creating a strong bond.

2. Osteogenic Property

- Dissolution products (soluble silica and calcium ions) directly stimulate bone cells.
- Promotes bone cell proliferation and differentiation, leading to enhanced bone formation.

45S5 Bioglass: Chemical Formula



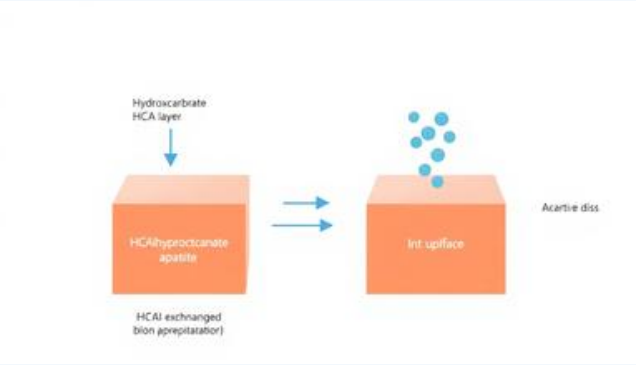
Composition of 45S5 Bioglass

The original Bioglass, termed 45S5 Bioglass, has a specific composition designed for its unique bioactivity:

- SiO_2: 46.1 mol%
- Na_2O: 24.4 mol%
- CaO: 26.9 mol%
- P_2O_5: 2.6 mol%

- This precise balance of oxides enables the rapid ion exchange and HCA formation crucial for its bone-bonding properties.

HCA Layer Formation Process

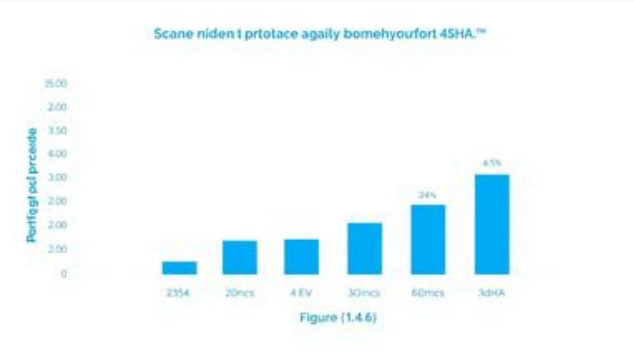


Mechanism of HCA Layer Formation

The formation of the HCA layer on the Bioglass surface is a solution-mediated process:

- Cation Exchange: Cations (Na^+, Ca^{2+}) in the glass exchange with protons (H^+) from blood/solution.
- Silica-rich Layer: This leaves a silica-rich layer and Si-OH bonds on the glass surface. The low connectivity allows for continuous ion transport.
- CaP Deposition: Increased local concentrations of Ca and P from blood, combined with a pH rise at the glass surface, promote amorphous calcium phosphate deposition.

Bioglass Outperforms sHA

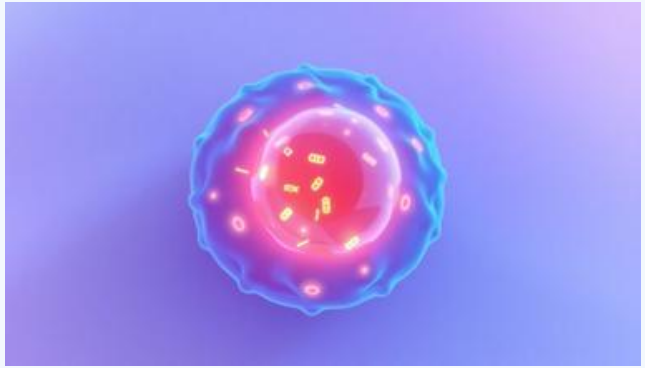


Bioglass vs. sHA: Superior Bone Regeneration

In vivo comparative studies have demonstrated the superior performance of Bioglass compared to synthetic hydroxyapatite (sHA).

- Rate and Quality: Bioglass produces more rapid and higher quality bone regeneration than sHA.
- Quantified Difference: One study showed 17 times more bone in defects filled with Bioglass after a week, and twice as much bone after 24 weeks, compared to sHA.
- This highlights the potent osteogenic capabilities of Bioglass dissolution products.

Bioglass: Genetic Stimulation of Bone



Osteostimulation: Genetic-Level Impact

In vitro studies revealed that Bioglass dissolution products can directly stimulate bone cells at the genetic level.

- Mechanism: Soluble silica and calcium ions from dissolution upregulate seven families of genes supporting osteogenesis within 48 hours.
- Effect: Induces transcription and secretion of extracellular matrix components, which mineralize without additional supplements.
- Dose-Dependent: Optimal gene expression observed at specific concentrations of soluble silica (~20 µg/mL) and calcium ions (60-90 µg/mL).

NovaBone: Widespread Clinical Use

Commercial Bioglass Granules: NovaBone

The original 45S5 Bioglass composition has been widely commercialized, impacting millions of patients.

- Reach: Used in over 1.5 million patients worldwide.
- Product Name: Marketed under the trade name NovaBone as a particulate synthetic bone graft.
- Applications: Primarily for repairing bone defects in orthopedics and maxillofacial

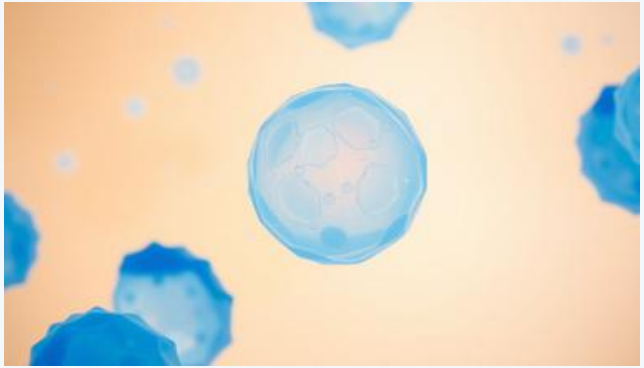
PerioGlas: Dental Bone Regeneration

PerioGlas: Pioneering Dental Applications

While NovaBone particulate reached the market later, PerioGlas was the first particulate Bioglass product launched in 1993.

- Application: Synthetic bone graft for repairing pockets in the jaw bone resulting from periodontal disease.
- Usage: Typically applied by mixing with saline solution.
- Clinical Success: Clinical studies showed bone pockets treated with PerioGlas were ~70% filled with new bone, compared to ~35% for controls (e.g., bovine bone mineral).
- Advanced Use: Also used with polymeric membranes in guided tissue regeneration (GTR).

Biogran: Targeted Periodontal Repair



Biogran: Refined 45S5 for Periodontal Regeneration

Biogran (Biomet 3i) is another 45S5 glass particulate graft, with a narrow particle size range (300-350 µm), used in periodontal regeneration.

- In Vivo Degradation: HCA layer forms, then particles hollow out within 4 weeks due to phagocytes entering through cracks in the HCA shell to break down the glass core.

- Performance: Clinical trials showed Biogran outperformed synthetic HA in jaw bone pockets, demonstrating its effective bioactivity and remodeling.

Expanding Bioactive Glass Portfolio

Beyond 45S5: Other Bioactive Glass Compositions

The 45S5 Bioglass composition is not the only glass composition capable of bioactivity.

- Composition Map: Predicts regions where a glass composition will bond with bone.
- Example: S53P4 (53.8 mol% SiO_2, 21.8 mol% CaO, 22.7 mol% Na_2O, 1.7 mol% P_2O_5) is another synthetic bone graft, marketed as BonAlive.

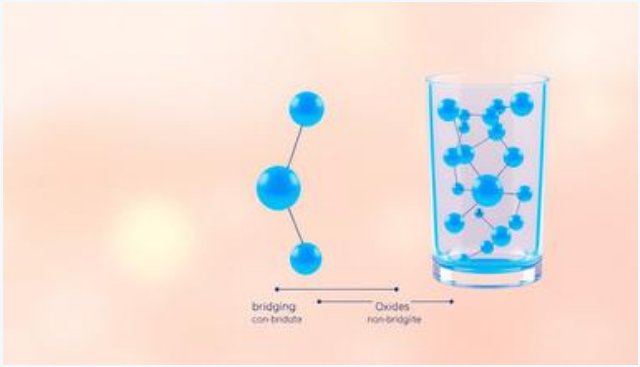
BonAlive: Unique Clinical Profile

BonAlive (S53P4): Antimicrobial and Long-Term Results

BonAlive, with its S53P4 composition, presents unique properties and clinical outcomes.

- Particle Size: Has a larger particle size range (1-4 mm) compared to 45S5.
- Antimicrobial Properties: In vitro studies suggest it may have antimicrobial properties, with clinical reports indicating effectiveness against chronic osteomyelitis.
- Long-Term Presence: Clinical studies (e.g., benign bone tumors) showed thicker cortical bone, but some glass particles remained even after 14 years.

Predicting Bioactivity: Network Connectivity



Network Connectivity and Bioactivity

Network connectivity (NC') is a method for predicting the bioactivity of bioactive glasses based on their nominal composition.

- Equation: $NC' = [4(M_x) - 2(M_2{}^1O + M^{77}O) + 6(M_{o205})] / M_x$
- M_x: molar fraction of network oxide (e.g., SiO_2).
- $M_2{}^1O$, $M^{77}O$: molar fractions of mono- and divalent modifier oxides (e.g., Na_2O, CaO).
- Assumptions: Glass is homogeneous, bridging oxygen bonds are replaced by nonbridging oxygen, and atom roles (former/modifier) are defined.

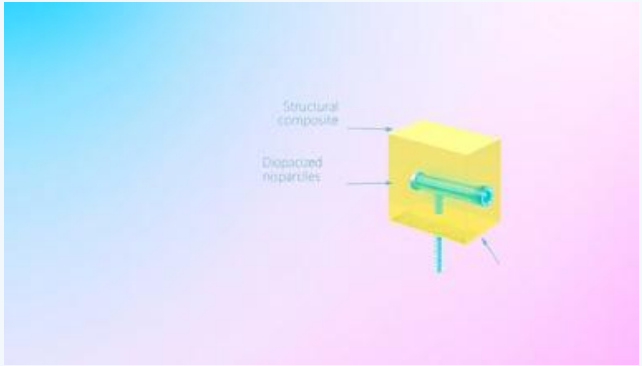
Bioactive Glass Formulations

Bioactive Glass Composites and Putties

Bioactive glasses are increasingly integrated into composites and putties for enhanced clinical utility.

- Forms: NovaBone, GlassBone, and BonAlive are available in bioresorbable putty form.
- Composition: Consist of a carrier matrix (e.g., PEG and glycerin) containing the glass particles.
- Benefit: Aims to provide clinicians with easier delivery methods and improved handling.
- Combinations: Common bone graft devices combine bioactive glass with natural polymeric matrices (e.g., Vitoss Bioactive Bone Graft, NanoFuse) to partially mimic natural bone, often improving outcomes over DBM alone.

Bioactive Glass in Load-Bearing Composites

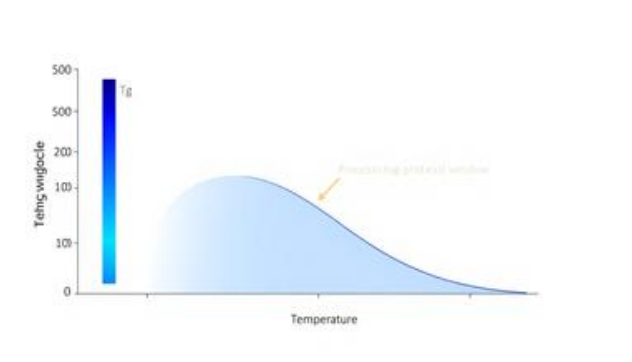


Structural Composites with Bioactive Glass

For applications requiring load-bearing capacity and cyclic loads, bioactive glasses are incorporated into structural composites.

- Example: LockActiv screw (CE marked 2015) for anterior cruciate ligament reconstruction.
- Composition: Poly(L-lactide)-co-poly(D,L)lactide polymer matrix containing 45S5 Bioglass particles.
- Challenge: Much of the bioactive glass particles can be embedded within the polymer, which may reduce their overall bioactivity by limiting exposure to the physiological environment.

Porous Bioactive Glass Manufacturing Hurdles



Challenges in Porous Bioactive Glasses

While porous sHA has been clinically successful, creating porous constructs from 45S5 and S53P4 Bioglass compositions while maintaining their amorphous glass structure is challenging.

- Issue: Small difference between their glass transition temperatures (T_e) and crystallization onset temperatures ($T_{1xx8xxxəx}$).
- Problem: Heating above T_e for sintering risks reaching $T_{1xxxxxxəx}$, causing crystallization.
- Consequence: Crystallization reduces bioactivity and can lead to instability.

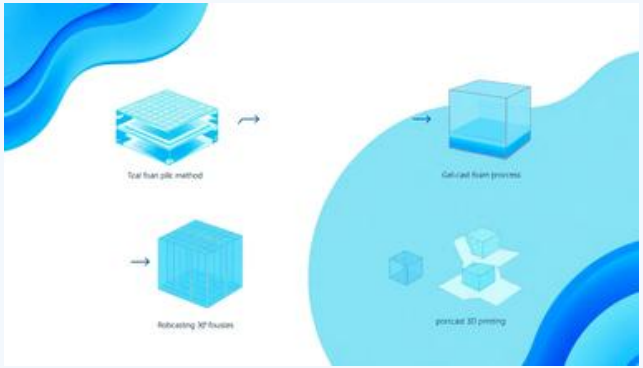
Designing Processable Bioactive Glasses

Novel Compositions for Porous Bioactive Glass Scaffolds

To address the challenges of making porous bioactive glasses, new compositions have been designed.

- Focus: Increased sintering thermal processing window, allowing thermal processing post-melt quenching.
- Examples:
- 13-93 glass (e.g., 54.6 mol% SiO_2, 22.4 mol% CaO): Excellent processing window, high network connectivity (2.58).
- ICIE16 glass (e.g., 49.46 mol% SiO_2, 36.6 mol% CaO): Designed to have network connectivity close to 45S5 (2.13).

Porous Bioactive Glass Production Methods

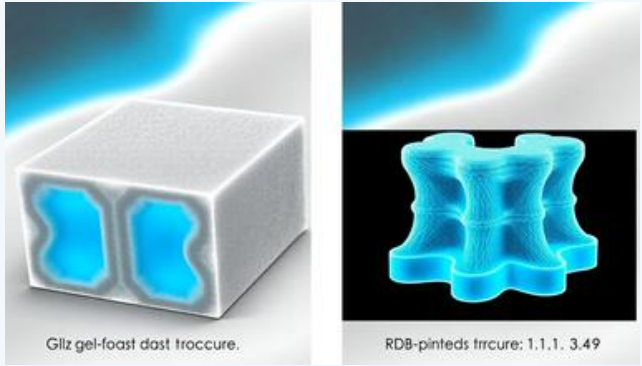


Manufacturing Porous Bioactive Glasses

Three common processes are used for making porous glasses:

- Foam Replica (Reticulation): Uses a sacrificial polyurethane foam template. Glass particle slurry coats foam, which is burned out during sintering. Can result in hollow struts, reducing compressive strength.
- Direct Foaming (Gel-Cast Foaming): Direct foaming of a glass particle slurry with a surfactant. Stabilizes air bubbles, rapid gelation solidifies slurry, forming pores. Example: ICIE16 glass foam scaffolds (79% porosity, 1.9 MPa compressive strength).

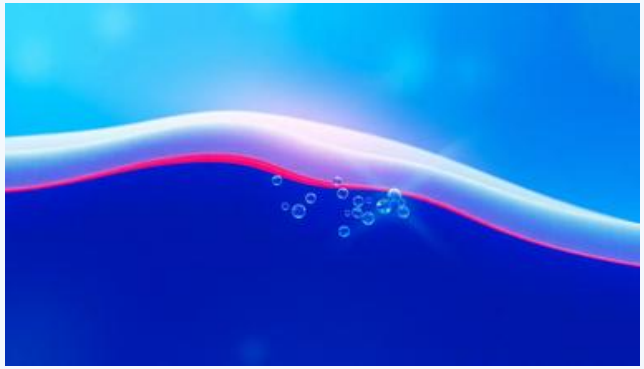
SEM of Bioactive Glass Scaffolds



Visualizing Porous Bioactive Glass Scaffolds

- Scanning Electron Microscopy (SEM) images provide insight into the intricate structures of porous bioactive glass scaffolds.
- Demonstrates the different pore architectures achieved through various manufacturing techniques.
- Examples: Gel-cast foam scaffolds (more irregular, interconnected pores) and Robocast 3D printed scaffolds (highly ordered, grid-like channels).

Bioactive Glass for Wound Care



Bioactive Glass in Wound Healing

Bioactive glass extends its utility beyond bone repair, showing promise in wound healing applications.

- Benefit: Amorphous glass can release various ions with potential therapeutic benefits as it biodegrades.
- Controlled Release: Delivery of ions is sustained and controlled by the degradation rate of the glass, which can be tailored.
- FDA Approval: Borate-based bioactive glasses (e.g., MIRRAGEN, ETS Woundcare) are FDA approved for healing chronic wounds like diabetic venous ulcers.

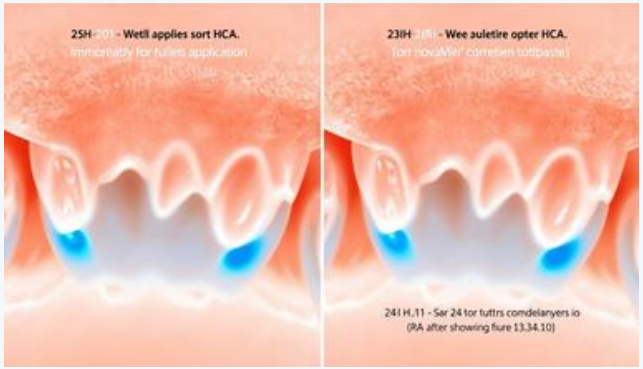
Bioactive Glass in Oral Care

Bioactive Glass in Toothpaste: Daily Impact

One of the largest commercial applications of a bioactive material is in consumer healthcare, specifically toothpaste.

- Similarity to Bone: Enamel and dentine share similarities with bone, containing HCA mineral and collagen.
- Hypersensitivity: Addresses dentine hypersensitivity, caused by exposed dentine microtubules leading to the pulp cavity and nerves.
- Product Example: Fine 45S5 Bioglass particulate (~18 µm), termed NovaMin (owned by GlaxoSmithKline), is used in toothpaste.

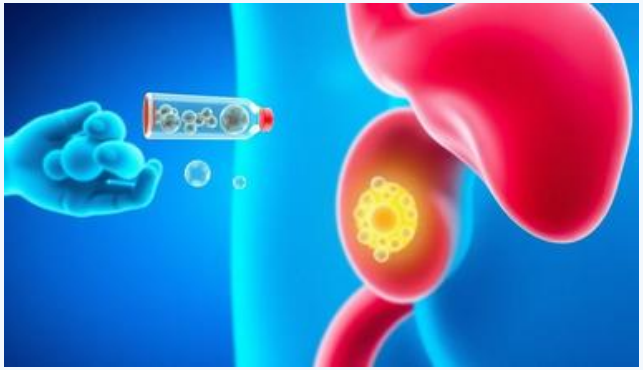
Oral Bioactive Glass: Function



Bioactive Glass in Toothpaste: Mechanism and Advanced Formulations

- Mechanism: NovaMin releases calcium and phosphate species during glass dissolution, which then form HCA on the dentine surface.
- Result: Rapid surface coverage by HCA, effectively sealing the tubules and reducing sensitivity.
- Advanced Formulations: BioMinF (BioMin Technologies Ltd.) is a fluoride-releasing bioactive glass that stimulates fluorapatite formation, which is more resistant to acid attack than HCA.

Bioactive Glass in Oncology

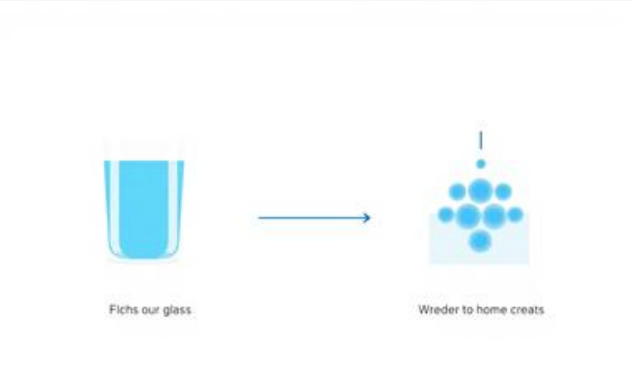


Glasses for Cancer Therapy

Insoluble glass microspheres are employed as microinjectable delivery systems for in situ cancer treatment.

- Product: TheraSphere (BTG) contains ^{90}Y isotopes within the glass composition, making them radioactive.
- Delivery: Travel to tumor sites via blood, lodge in tissue.
- Mechanism: Deliver a localized dose of radiotherapy from inside the tissue, minimizing damage to surrounding healthy tissues.

Glass-Ceramics: Fabrication Process



Glass-Ceramics: From Glass to Polycrystalline

Glass-ceramics are materials that begin as a glass and are transformed into a polycrystalline ceramic.

- Initial Step: Melt quenching to form a glass object, allowing for complex compositions and shaping.
- Nucleation: Glass is heated to 500-700°C to produce a high concentration of nuclei.
- Crystal Growth: Temperature is then raised to 600-900°C to promote crystal growth from the nuclei, often achieving up to 100% crystallization.

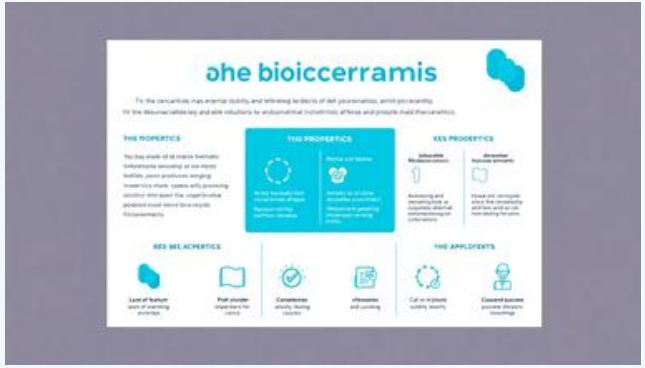
Glass-Ceramics in Dentistry

Applications of Glass-Ceramics

Due to their unique properties, glass-ceramics are widely used in specialized medical fields.

- Dental Restorations: Commonly used for inlays, onlays, crowns, and multiunit bridges.
- Aesthetic Appeal: High strength combined with the ability to closely mimic the color and aesthetics of natural teeth.
- Durability: Provide durable and biocompatible solutions for dental applications.

Bioceramics: Key Takeaways



Summary of Bioceramics

Bioceramics comprise ceramics, glasses, and glass-ceramics, serving diverse biomedical applications.

- Types: Can be nearly inert (e.g., Alumina, Zirconia) or bioactive/biodegradable (e.g., Calcium Phosphates, Bioglass).
- Inert Uses: Valued for hardness, wear resistance, and degradation resistance.
- Bioactive Uses: Excellent as bone graft substitutes; some (Bioglass) directly bond to bone.

Hydroxyapatite: Bone's Mineral Counterpart

Introduction to Hydroxyapatite (HA)

Hydroxyapatite (HA, HAp) is a stoichiometric calcium phosphate phase with the composition $Ca_{10}(PO_4)_6(OH)_2$.

- Importance: High interest in biomedicine due to its chemical similarity to the calcium phosphate apatite phase found in bone and tooth mineral.

- Nonstoichiometric Variants: Its chemistry allows for a range of nonstoichiometric compositions to also be described as apatite phases.

HA: Hexagonal and Monoclinic Forms

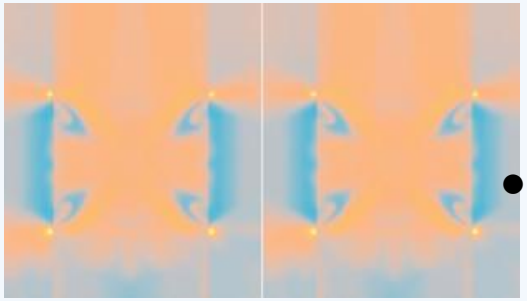
Crystal Structure of Hydroxyapatite

- Commonly reported as having a hexagonal crystal structure, space group $P6_3/m$.
- Typical unit cell parameters: a = 9.422 Å, c = 6.883 Å.
- Also reported as having a monoclinic crystal structure, space group $P2_1/c$.

- Difference: Ascribed to whether the hydroxyl groups exist in an ordered (monoclinic) or disordered (hexagonal) crystal lattice, related to preparation conditions.

HA: Synthetic vs. Biological Diffraction

Crystalline HA vs. Bone Mineral Apatite



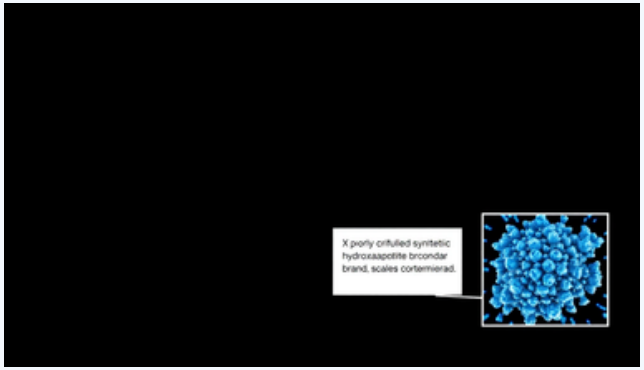
Crystalline HA

- Typically refers to HA heated to >~800°C, forming a ceramic.
- Produces X-ray diffraction (XRD) pattern with narrow, distinct diffraction peaks (Figure 1.3.4A.2A).
- Analogous to naturally occurring mineral forms.

Bone Mineral Apatite

- XRD pattern has very broad diffraction peaks (Figure 1.3.4A.2B).
- Due to very small crystallite size (nanoscale), crystal imperfections, or lattice strain.
- Crystallites are nanoparticles (mean ~32nm c-axis, ~5nm thick).

Replicating Bone Mineral Structure



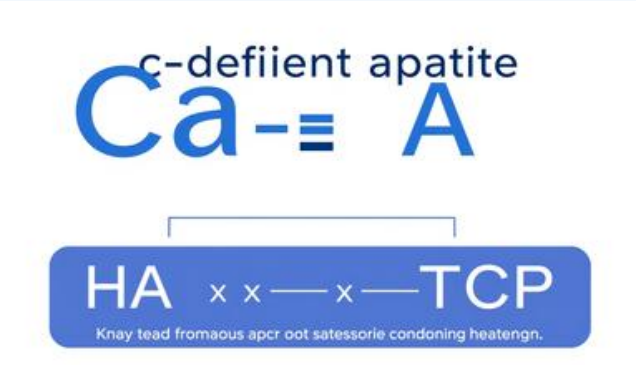
Synthetic Bone-Like Apatites

Bone mineral apatite is not amorphous; despite broad peaks, structural order exists within nanocrystals.

- Mimicry: Aqueous-based synthesis methods can produce nanocrystals of apatite compositions (including stoichiometric HA) with similar size scales and XRD patterns to bone mineral apatite (Figure 1.3.4A.2C).

- Thermal Conversion: Heating these synthetic nanocrystals above ~800°C results in crystal growth and an XRD pattern characteristic of 'crystalline HA'.

Ca-Deficient Apatite: Structure & Fate



Ca-Deficient Apatite (CDA)

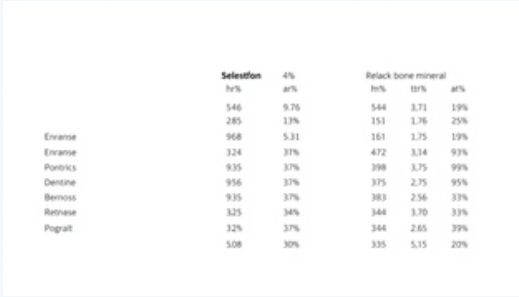
A more general description of apatite compositions produced by aqueous methods is Ca-deficient apatite (CDA):

- Formula: $Ca_{1018xxxə}(PO_4)_{618xxxə}(HPO_4)_{xxxə}(OH)_{218xxxə}$, where $0 \leq x \leq 1$.
- XRD: Produces an XRD pattern largely indistinguishable from stoichiometric HA (x=0).
- Heating Effects: Heating CDA above ~800°C results in the formation of HA and tricalcium phosphate (TCP). The relative proportions depend on the 'x' value; for x=1, only TCP forms above ~740°C.

Elemental Differences in Apatites

Differences in Ion Composition: Bone vs. Synthetic HA

A major distinction between natural bone mineral apatite and synthetic HA is the presence of various substituting ions and vacancies in bone mineral.



	Selestfon	4%		Relack bone mineral		
	hr%	ar%		ht%	ttr%	at%
	546	9.76		544	3,71	19%
	285	13%		151	1,76	25%
Envanse	968	5.31		161	1,75	19%
Envanse	324	31%		472	3,14	93%
Pontrics	935	37%		398	3,75	99%
Dentine	956	37%		375	2,75	95%
Bemoss	935	37%		383	2.56	33%
Retnase	325	34%		344	3,70	33%
Pogralt	32%	37%		344	2.65	39%
	508	30%		335	5,15	20%

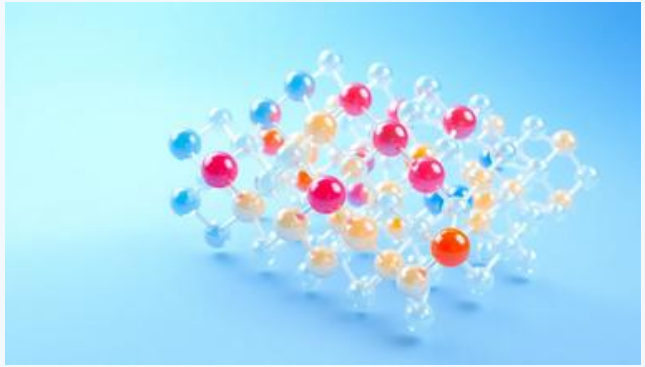
Substitutions in Bone Mineral

- Calcium (Ca) sites: Replaced by sodium (Na^+), magnesium (Mg^{2+}), or strontium (Sr^{2+}).

Table 1.3.4A.1: Comparative Chemical Composition

- Enamel (wt%): Ca 37.1, P 18.2, Na 0.5, Mg 0.45, CO_3 2.4
- Dentine (wt%): Ca

Tailoring HA for Bioactivity



Ion Substitutions for Enhanced Biological Response
The knowledge of ion substitutions in natural bone mineral has led researchers to synthesize HA with various ion modifications.

- Purpose: To better understand biological apatites and, more recently, to test if these substitutions lead to improved biological responses.
  - Common Ions: Sodium (Na), Magnesium (Mg), Strontium (Sr), Carbonate (CO_3), Fluoride (F), Chloride (Cl), Potassium (K), Lithium (Li), Barium (Ba), Silicate (Si), Copper (Cu), Cobalt (Co), Silver (Ag), and Zinc (Zn).
- Benefits: Some ions exhibit osteogenic (bone-forming), angiogenic (blood vessel-forming), or antibacterial properties.

HA Synthesis Routes

Synthesis Methods for HA Ceramics: Overview

The choice of HA synthesis method depends on the final application and required production scale.

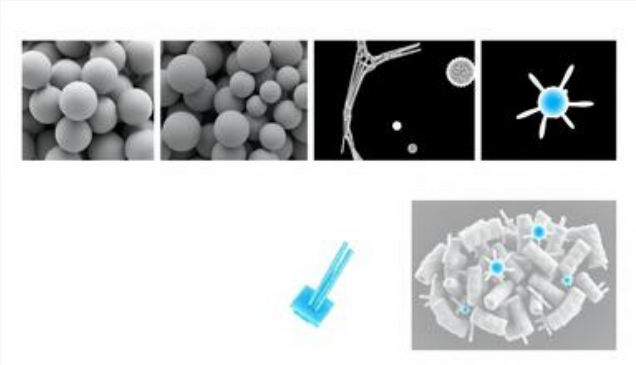
Natural Sources

- Coral-derived HA: Coral acts as template and reactant in hydrothermal reactions.
- Bovine cancellous bone: Thermal/chemical conversion to deproteinated inorganic bone (ASTM F1581-08).

Synthetic Approaches

- Solid-state synthesis: Traditional, good stoichiometry control, but high temp and low surface area.
- Aqueous precipitation: Most widely used, precise control, scalable for high surface area.

HA Nanomaterials: Synthesis and Applications

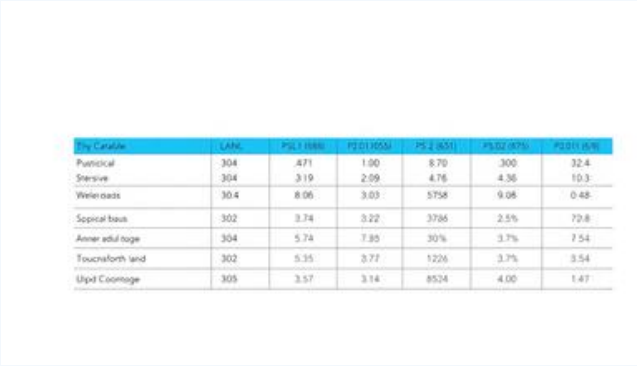


Advanced HA Synthesis and Nanomaterials

Beyond traditional methods, various advanced techniques enable precise control over HA properties and morphology.

- Methods: Sol-gel, biomimetic, hydrolysis, microwave, mechanochemical, sonochemical, emulsion, hydrothermal, combustion, pyrolysis.
- Nanoparticle Morphology: These methods can produce diverse nanoscale morphologies: spherical, nanoneedles, nanorods, nanowires, nanowhiskers, nanosheets, hollow nanospheres, nanotubes, nanobelts, whiskers.
- New Applications: HA nanoparticles are explored for drug delivery, gene delivery, cell delivery in tissue engineering, hyperthermia therapy, and in vivo imaging.

HA Characterization: Physiochemicals



Punctical	304	471	1.00	8.70	300	32.4
Stersive	304	319	2.09	4.76	4.36	10.3
Weiercoads	30.4	8.06	3.03	5758	9.08	0.48
Soppical baus	302	3.74	3.22	3786	2.5%	72.8
Anner adul toge	304	5.74	7.85	30%	3.7%	7.54
Toucrisforth land	302	5.35	3.77	1226	3.7%	3.54
Uipd Coomoge	305	3.57	3.14	8524	4.00	1.47

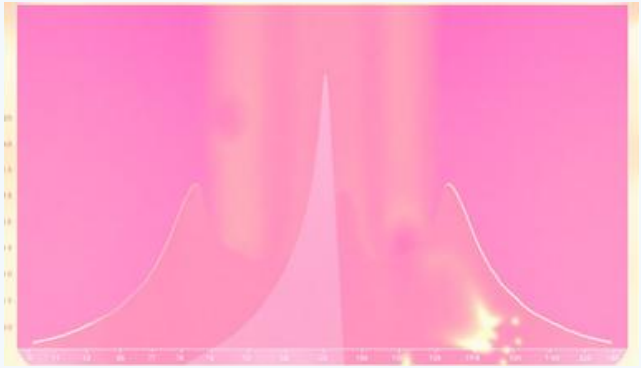
Characterization of HA Ceramics: Physicochemical Properties

Comprehensive characterization ensures the quality and suitability of HA ceramics for medical applications.

- Standards: Guided by ASTM F1185-03 (2014) and NIST standard reference materials.

- Key Variables (Table 1.3.4A.2): Chemical composition (Ca/P ratio, ion substitutions), phase composition (β-TCP, CaO, $CaCO_3$), density/porosity, pore size/interconnectivity, grain size, physical form (granule, block, putty, coating, etc.), and additives.

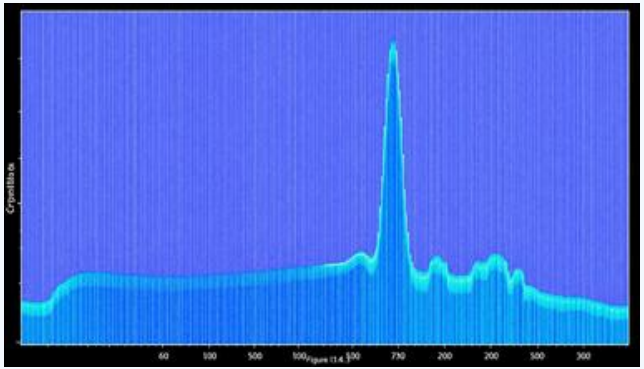
XRD for HA Analysis



HA Characterization: X-ray Diffraction

- Phase Composition & Purity: Identifies crystalline phases (e.g., HA, β-TCP) and amorphous content.
- Crystallite Size: Determines the size of the individual crystallites, crucial for mechanical and biological properties.
- Unit Cell Parameters: Provides precise measurements of the crystal lattice dimensions, sensitive to ion substitutions.
- Identification: Uses Powder Diffraction Files (PDFs) as 'fingerprints' for phase identification.

Spectroscopic Analysis of HA

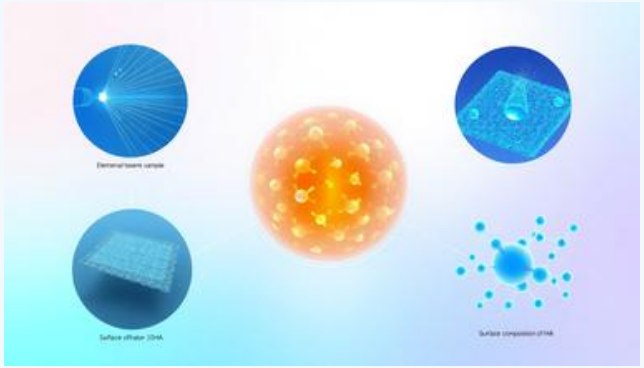


HA Characterization: Infrared & Raman Spectroscopy

FTIR and Raman spectroscopy offer complementary insights into HA's chemical structure.

- Vibrations: Phosphate and hydroxyl groups show characteristic vibrations (Table 1.3.4A.3).
- Substitutions: Identifies presence of other ions, especially carbonate (A-type vs. B-type substitution).
- Crystallinity: Assessed from phosphate vibrations (550-600 cm^{-1}).

Elemental and Surface HA Characterization



HA Characterization: Chemical & Surface Analysis

- Chemical Composition: Ca/P molar ratio and trace elements (Na, Mg, K, Sr, Si, As, Hg, Pb, Cd) using XRF and ICP-OES.

- Solid-State NMR: Provides information on local atomic structure (e.g., ^{43}Ca, ^{31}P, ^{1}H NMR) and ion substitutions (^{13}C, ^{29}Si NMR).
- Surface Analysis: X-ray Photoelectron Spectroscopy (XPS) and Time-of-Flight Secondary Ion Mass Spectrometry (TOF-SIMS) for surface composition and correlation with bulk.

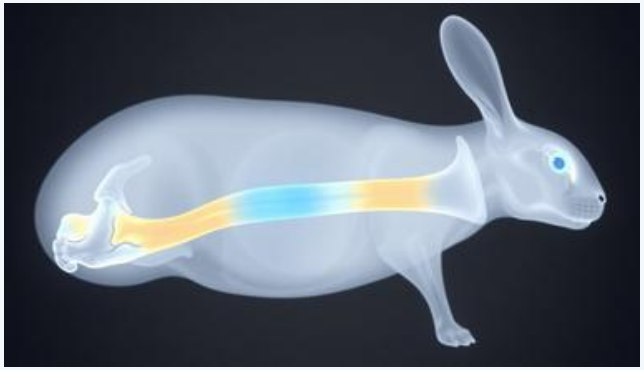
In Vitro HA Biocompatibility

HA Characterization: In Vitro Biological Response

HA ceramics are well-established for their biocompatibility, osteoconductivity, and bioactivity.

- Evaluation: Typically assessed by cell culture studies (e.g., mesenchymal stem cells, osteoblasts, osteoclasts, endothelial cells, macrophages) and apatite layer formation when immersed in simulated body fluid (SBF).
- Standards: Follows established ISO protocols (10993-5, 10993-6, 23317) and ASTM standards (F2721-09, F3207-17).

In Vivo HA Evaluation

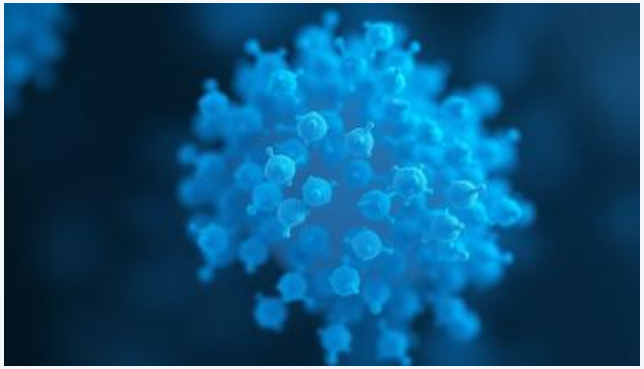


HA Characterization: In Vivo Performance

In vivo evaluation is crucial for assessing HA's performance in living systems.

- Models: Used in models for repairing critical size bone defects, spinal fusion, and assessing osteoinductivity.
- Osteoinductivity: Some HA-based bone graft substitutes exhibit osteoinductive properties, forming bone when implanted in non-osseous sites (e.g., intramuscular or subcutaneous defects).
- Mechanisms: Osteoinductive mechanisms are complex and may involve inflammatory response, localized Ca/P concentrations, or growth factor capture.

Nanoscale HA: Response & Risk



HA Nanomaterials: Inflammation and Safety

The development of HA nanomaterials has spurred interest in their specific in vitro and in vivo responses.

- Agglomeration: Nanoparticles often agglomerate to form larger secondary particles, impacting their biological interaction.
- Applications: Used in drug delivery and gene delivery, requiring functionalization for improved dispersion and cell membrane crossing.
- Inflammatory Response: Studies show higher acute inflammation for certain morphologies (e.g., needle-shaped particles) compared to spherical nanoparticles.

Diverse Forms of HA in Clinic

Clinical Use of Hydroxyapatite Ceramics: Forms

HA is utilized in various forms to suit different medical applications.

- Ceramic (solid mass, typically sintered >1100°C).
- Coating on biologically inert materials (metals, polymers).
- Nanocrystals (drug/gene delivery).
- Granules (porous or dense, 200 µm to 5 mm).
- Granules within a putty (polymeric carrier).
- Granules within a collagen matrix.
- Injectable paste or slurry (small particles dispersed in a carrier).
- Cement (in situ setting).

HA Coatings in Joint Replacement

Clinical Use: HA Coatings on Implants

- Primary Application: Most closely associated with orthopedic hip and knee implants, and dental tooth root implants.

- Fixation: Provides an alternative method of fixation to polymeric bone cements, promoting biological integration.
- Variability: Clinical outcomes are influenced by variables in the plasma-spraying process and HA powder used.
- Systematic Reviews: For uncemented porous titanium-coated femoral hip prostheses, no clear benefit of HA coating on Harris hip score or radiographic/clinical success was found in one review.

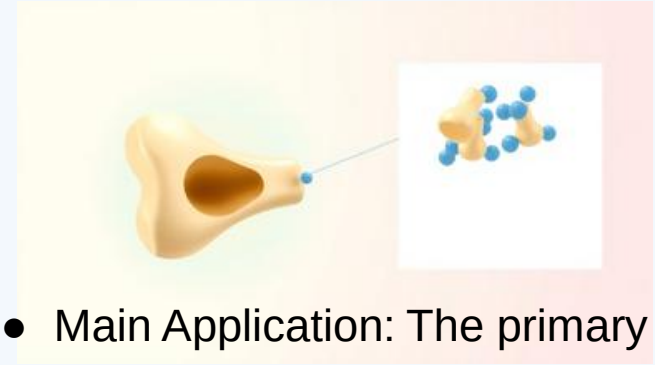
HA Coatings for Dental Implants

Clinical Use: HA-Coated Dental Implants

HA-coated dental implants have shown specific performance characteristics in long-term clinical use.

- Early Fixation: Good early fixation of the implants.
- Long-Term Survivorship: However, the survivorship of HA-coated implants has been observed to be inferior after longer periods compared to non-coated or plasma-sprayed titanium implants.
- Example: 8-year survivorship of titanium plasma-sprayed dental implants was 92.7% vs. 77.8% for HA-coated implants in one study.

HA: Bone Grafting Alternative



Clinical Use: HA as Synthetic Bone Graft Substitutes

- Main Application: The primary use of HA and other calcium phosphate ceramics (TCP or BCP) is as synthetic bone graft substitutes.
- Alternative to Autograft: Serve as an alternative to autograft bone for filling bone defects
- Form: Typically porous granules or blocks, often combined within a polymeric carrier or dispersed in a collagen foam strip.
- Function: The porous structure encourages bone ingrowth and integration; materials can act as carriers for growth factors, antibiotics, BMA, or platelet-rich plasma.

HA Grafts: Unmet Clinical Data Needs

Clinical Efficacy of HA Bone Grafts: The Evidence Gap

Despite a large number of FDA-approved synthetic bone graft substitutes containing HA, clinical trial data remains limited to support specific products.

- Product Variability: Many products have different permutations of chemical, physical, and compositional features, making it challenging to identify which parameters affect outcomes.
- Lack of Strong Evidence: Systematic reviews highlight the scarcity of high-quality clinical evidence (e.g., randomized controlled trials) comparing these materials to established alternatives like autografts.
- Future Need: Addressing this lack of high-level clinical efficacy data is crucial for translating biomaterial science into improved clinical treatments.

Structural Ceramics: Medical Importance

Introduction to Structural Ceramic Oxides

Structural ceramics are materials of significant importance in medical applications due to their robust mechanical properties.

- Characteristics: Strong, hard, and desirable for load-bearing and structural support.
- Key Examples: Articulating surfaces for hip and knee joints (femoral heads, acetabular cups), dental implants.
- Other Uses: Electrical feedthroughs, internal support structures, enclosures for devices like cochlear implants and pacemakers.

Benefits of Structural Ceramics

Advantages of Structural Ceramic Oxides

- High strength and hardness: Withstand significant mechanical stress.
- Good electrical insulation: Essential for electronic implants.
- Low solubility: Stable in the body environment.
- Good biocompatibility: Well-tolerated by biological tissues.
- RF transparency: Allows communication and battery charging for implanted devices.
- Extremely high degrees of surface smoothness: Ideal for articulating applications, reducing wear.

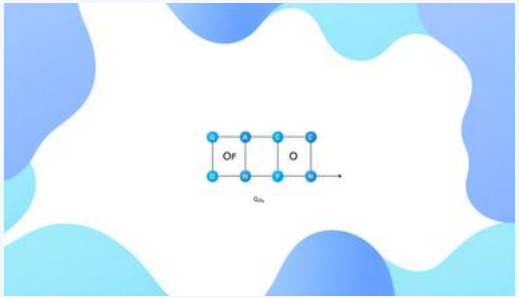
Structural Ceramics: Challenges

Trade-offs and Considerations for Structural Ceramics

Despite their advantages, structural ceramics also present challenges:

- High Young's Modulus: Compared to bones, their high stiffness can lead to stress shielding.
- Stress Shielding: This phenomenon reduces the load on the bone, which can be detrimental to bone healing and repair over time.
- Brittleness: Ceramics are generally brittle and susceptible to catastrophic failure from cracks, a key design consideration.

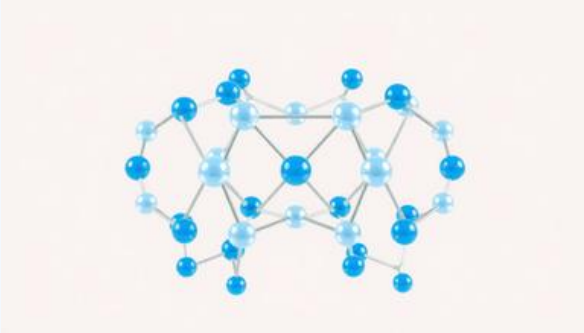
Fundamentals of Oxide Ceramics



Structural Ceramic Oxides: Core Principles

- Composition: Physically nonmetallic and chemically inorganic.
- Origin: Derived from commonly mined materials like silica sand (SiO_2), bauxite ($Al(OH)_3$), and zircon sands ($ZrSiO_4$).
- Bonding: Tend to have iono-covalent bond structures.
- Structure: Can form three-dimensional amorphous (glassy) as well as lattice (crystalline) structures.
- Lattice: Based on an oxygen anion lattice structure with metal cations (e.20.g., Al, Zr, Si) in interstitial locations.
- Properties: Vary significantly with full chemical makeup and thermal processing (sintering).

Alumina: Structure and Properties



Aluminum Oxide (Alumina, Al_2O_3)

Alumina (Al_2O_3) is also known as corundum and sapphire (gemological forms).

- First Ceramic: Historically, alumina was the first ceramic widely used for medical applications.
- Hardness: Extremely hard (Mohs hardness of 9, just below diamond).
- Crystal Structure: Crystallographically classified as rhombohedral, based on a hexagonal close-packed structure of oxygen anions.
- Atomic Arrangement: Aluminum cations sit in two-thirds of the octahedral interstitial sites.
- Repeat Unit: Takes six oxygen layers to create the rhombohedral repeat unit, forming the complex crystalline structure.

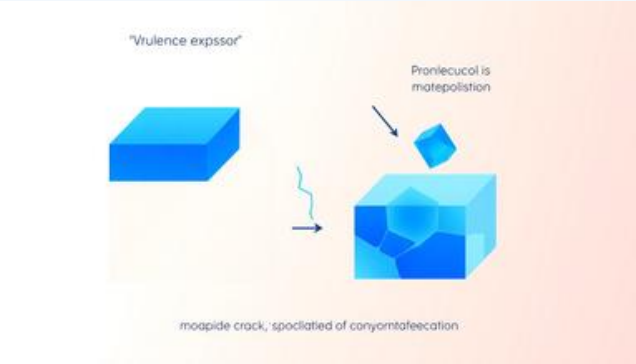
Zirconia: Phases and Transitions

Zirconia (ZrO_2): Polymorphism and Transformations

Zirconia (ZrO_2) is a more complex material known for its various crystal phases.

- Origin: Derived from zircon sands.
- Crystal Structure: Oxygen anions are arranged in a square pattern, not hexagonally close-packed.
- Polymorphs: Exhibits three primary crystal phases with specific transition temperatures:
- Cubic phase (stable at ~2750°C down to 2370°C)
- Tetragonal phase (stable from 2370°C down to 1170°C)
- Monoclinic phase (stable below 1170°C and at room temperature)

Zirconia: Phase Transformation Issues

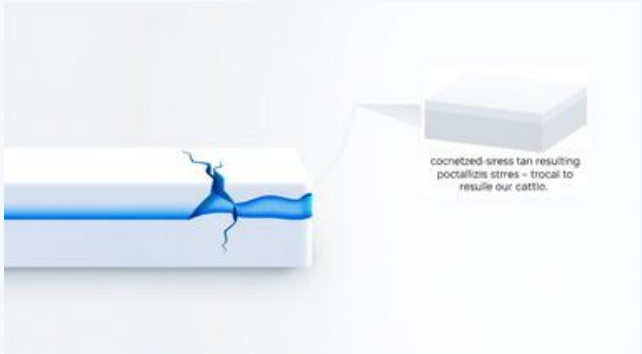


Zirconia: Volume Changes and Challenges

Phase transformations in zirconia are accompanied by significant volume changes, posing manufacturing challenges.

- Cubic to Tetragonal: ~0.18% decrease in volume.
- Tetragonal to Monoclinic: A relatively large ~4.4% increase in volume.
- Problem: This large volume change can destroy the microcrystalline structure during cooling, leading to broken or defective parts if not controlled.
- Historical Use: Limited until control over these transformations was achieved.

Zirconia Toughening Mechanisms

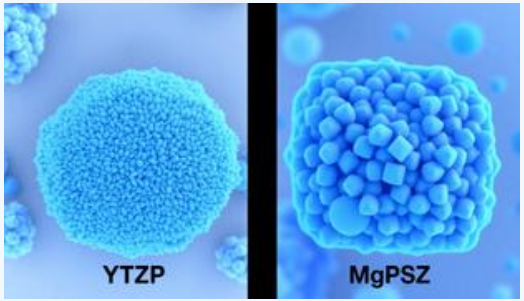


Yttria and Magnesia-Stabilized Zirconias

To harness zirconia's potential, chemical stabilization is used to control its phase transformations.

- Stabilization: Dopants like yttria (Y_2O_3) or magnesia (MgO) stabilize specific polymorphs (e.g., cubic, tetragonal) beyond their pure temperature ranges.
- Metastable Tetragonal Phase: Appropriate dopants and thermal processing create a metastable tetragonal phase, which is key to toughness.
- Toughening Mechanism: Stress (e.g., from a crack) can induce a diffusionless martensitic transformation from metastable tetragonal to monoclinic.

Stabilized Zirconia Types



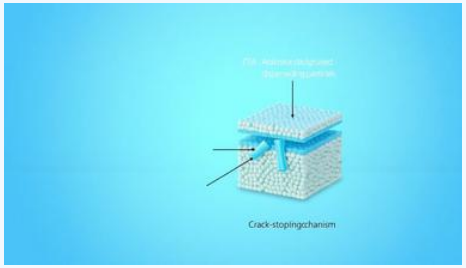
Yttria Tetragonal Zirconia Polycrystalline (YTZP)

- Microstructure: Entirely composed of small tetragonal zirconia crystals.
- Toughening: Crack propagation causes tetragonal crystals in the crack front zone to transform martensitically to monoclinic, creating compressive stress.
- Challenge: Sensitivity to water-initiated degradation (FDA 'do not steam resterilize' warning, 1997), mitigated by chemistry and grain size optimization.

Magnesia Partially Stabilized Zirconia (MgPSZ)

- Microstructure: Mostly large cubic zirconia crystals.
- Toughening: Contains transformable tetragonal 'seeds' embedded within the larger cubic crystals.
- Mechanism: When a crack front approaches, these seeds transform, creating compressive stress to toughen the material.

ZTA: A Synergistic Composite



Zirconia-Toughened Alumina (ZTA)

ZTA is a ceramic matrix composite that combines the best features of alumina and zirconia.

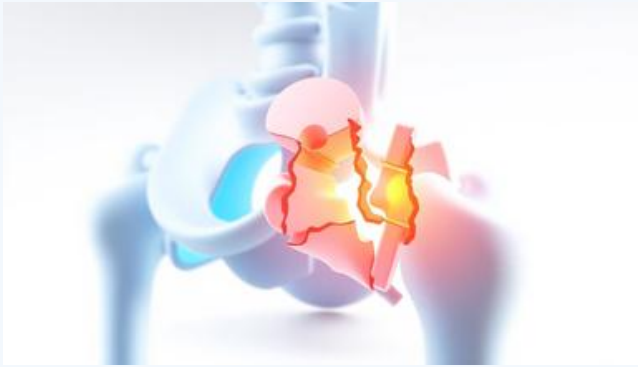
- Composition: Alumina matrix with added zirconia.
- Benefit: Maintains much of the hardness of alumina while incorporating the toughness of zirconia.
- Mechanism: Zirconia modifies the alumina by creating a compressive stress region (via transformation) if a crack propagates through the region.
- Current ZTAs: Toughened with YTZP and sometimes further by strontium (promotes platelet-like alumina growth) and chromium (imparts pink color, originally to improve hardness after softer zirconia addition).

Alumina: Early Success in Orthopedics

History: Alumina's Early Role

- First Material: Alumina was the earliest and most heavily researched ceramic for medical devices.
- Early Commercial Use: Since the 1930s (e.g., as an insulator for spark plugs).
- Hip Implants (1970s): Pioneered by Boutin for hip implants, replacing metal femoral ends that suffered from wear (generating 'particle disease' from CoCr grinding polyethylene).
- Performance: A highly polished alumina femoral head basically doubled the life of total hip replacement (THR) implants by reducing wear rates from ~0.2 mm/year to <0.1 mm/year.

Alumina: Fragility and Solutions



Alumina: Brittleness and Challenges

- Major Problem: Alumina's inherent brittleness. Once a crack forms, it's difficult to stop, leading to catastrophic failure of devices.
- Failure Rates (1990s): Could be as high as 0.5% for ceramic hip heads.
- Mitigation: Improved manufacturing processes and the use of 'proof-testing' tools reduced failure rates to an acceptable 0.01%.
- Hard-on-Hard Systems: Attempting to use alumina for acetabular cups (hard-on-hard) led to high wear in early designs due to unforgiving rigidity. Modern designs have addressed this.

Zirconia: A Tougher Alternative

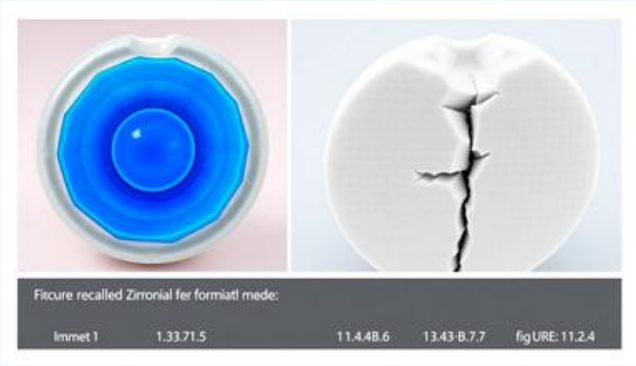
History: The Rise of Zirconia

- The 'Ceramic Steel': Zirconia was seen as a solution to alumina's brittleness, termed 'ceramic steel' due to its toughness.

- Overcoming Phase Transformation: Additives like MgO were found to stabilize the cubic phase. Research in the 1960s allowed for the creation of a metastable tetragonal phase, crucial for toughening.

- Flaw Tolerance: This metastable material is more flaw tolerant; when a crack propagates, the material transforms martensitically, creating a compressive layer that slows the crack.

Zirconia: The 2001 Implant Crisis



The Zirconia Crisis: Manufacturing and Failure

- Manufacturing Sensitivity: Stabilized zirconias are more nuanced to manufacture than alumina.

- YTZP Degradation: YTZP specifically had a problem with water-initiated degradation (water replaces bonds, destabilizes). This led to an FDA 'do not steam resterilize' warning in 1997, later mitigated by chemistry and grain size adjustments.

- 2001 Recall (St. Gobain Prozyr): A major recall occurred due to manufacturing changes (batch to belt furnace, environmental temperature variables).

Biolox Delta: ZTA's Success Story

History: The Emergence of Biolox Delta (ZTA)

- Innovation Driver: The zirconia failures created an opportunity for a new material. CeramTec, a major alumina manufacturer, innovated.
- Biolox Delta: Introduced in the early 2000s, this material was an alumina toughened with zirconia.
- Composition: Further enhanced with chromium (imparting pink color, originally for hardness) and strontium (promoting alumina growth in hexagonal platelets).
- Strategic Timing: Its introduction coincided fortuitously with the zirconia failures, providing a material that was neither pure alumina nor pure zirconia, but a robust combination.

Structural Ceramics: Core Attributes

General Properties of Structural Ceramics

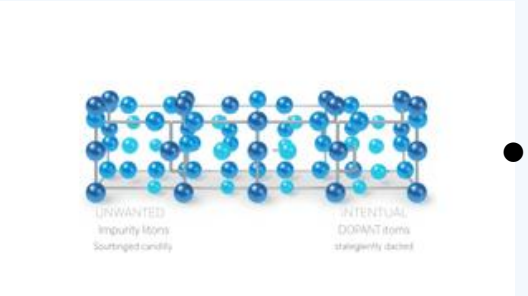
Structural ceramics are integral to medical devices due to their superior mechanical and physical properties.

- Attributes: Very hard, very strong, insoluble, and can be manufactured with an extremely smooth surface.
- Impact: Gained significant popularity in orthopedic implants (mostly hips), drastically reducing failure due to wear of articulating surfaces.
- Electrical Properties: Excellent electrical insulators, making them ideal for electrical feedthroughs in electronic packages (e.g., pacemakers).
- RF Transparency: Relatively transparent to RF frequencies, allowing for containers for electronics and batteries, facilitating communication and charging of implanted devices.

Ceramic Composition: Impurities & Dopants

Impurity vs. Dopant: The Role of Composition

The composition of ceramics is never perfectly pure, with intentional and unintentional additions impacting properties.



Impurities

- Elements naturally present in the raw materials, different from the primary material.
- Their level and type must be carefully controlled as they can significantly affect manufacturing and final properties.

Dopants

- Elements intentionally added to the material to modify or enhance its desired properties.
- Examples: MgO in alumina sintering, Y_2O_3 in zirconia for toughening, Cr and Sr in ZTA.

Alumina Grades: Property Spectrum

Manstissures	Protectuves	Table 1.3.4.B1	Thermal codulam		Manufactures	Mobsimepal ser: —	
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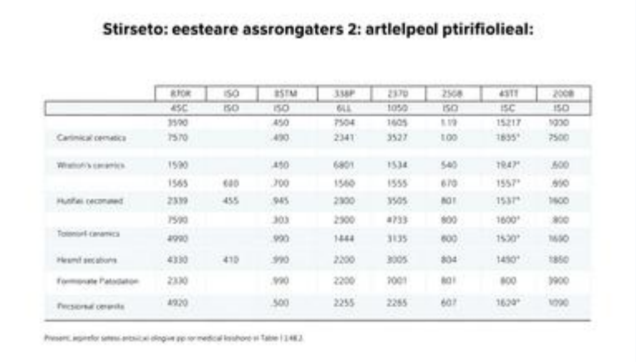
Compeemcal	Dentsity	223030	134,040	15,00	1.85	137	205
Flextal steegth	Ackoyve	120070	265,000	2,370	-	—	2100
Fenedacy	Acdsity	113038	104,206	15.38	1.7	12205	25,000
	Enclayves	113008					

Properties of Alumina Grades (Table 1.3.4B.1)

Different grades of alumina vary in purity and consequently in their properties, affecting their suitability for specific medical applications.

- Alumina Content: Ranges from 99 wt% to 99.9 wt%.
- Density: Typically 3.8 to 3.92 g/mL.
- Flexural Strength: Increases with purity, from 310 MPa to 400 MPa.
- Elastic Modulus: Generally high, around 360-386 GPa.
- Thermal Conductivity: Varies slightly between 29-34 W/(m°K).
- These variations allow manufacturers (e.g., Kyocera, CoorsTek) to tailor materials for specific requirements.

Medical Ceramic Standards Overview



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	45C	ISO	ISO	6LL	1050	ISO	ISC	ISO
	3590		.450	7504	1605	1.19	15217	1030
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	1565	680	.700	1560	1555	670	1557*	.690
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	7590		.303	2300	4733	800	1600*	.800
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Hesmf secabons	4330	410	.990	2200	3005	804	1490*	1850
Formorate Patodation	2330		.990	2200	7001	801	800	3900
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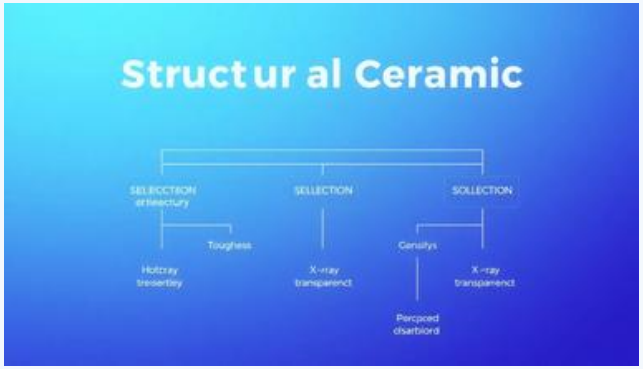
Present: aspirefor satess antsical olegive pp or medical losshore in Table 1.3.48.2

Property Standards for Medical Implants (Table 1.3.4B.2)

Medical-grade alumina, zirconia, and ZTA adhere to international specifications (ASTM and ISO) which define minimum allowable values.

- Density (g/cm^3): Alumina ≥3.90, YTZP ≥6.00, Biolox delta 4.36.
- Strength (4 point bend) (MPa): Alumina ≥250, YTZP ≥800, ZTA Type X ≥1000.
- Weibull Modulus: ≥8 for most, Biolox delta 13 (higher indicates greater reliability).
- Young's Modulus (GPa): Alumina ≥370, YTZP ≥200, ZTA ≥320.

Ceramic Selection Criteria



Choosing the Right Structural Ceramic

The selection between alumina, zirconia, and ZTA depends on specific design priorities.

- Alumina: Hard, strong, but very flaw sensitive (prone to catastrophic failure). Preferred for lower density (~3 g/mL vs. ~6 g/mL for zirconia) and X-ray translucency.
- Zirconia or ZTA: Preferred when toughness is paramount, as they are more resistant to crack propagation.
- All three: Make good, strong, inert, electrically insulative, and RF transparent materials.

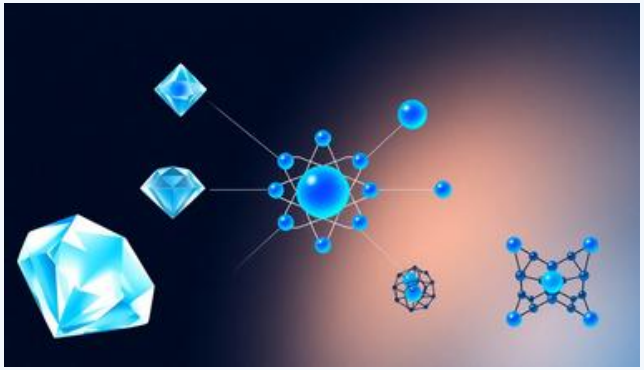
Carbon Biomaterials: A Historical View

Introduction to Carbon Biomaterials

The biocompatibility of carbon has been recognized since ancient times, with manmade permanent tattoos using pulverized charcoal.

- Modern Era: In the late 1960s, a pyrolytic form of carbon was discovered to have remarkable blood compatibility and structural properties for artificial heart valves.
- Versatility: Since then, various forms of carbon have been investigated for medical devices.
- Applications: Drug delivery, phototherapy, imaging, biosensors, antimicrobial therapy, cardiovascular, orthopedic, dental, neurological, ophthalmological applications, catheters, and guidewires.

Carbon's Versatility in Biomaterials



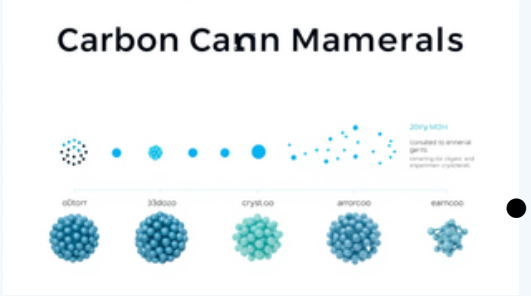
Carbon Biomaterials: Fundamental Properties

Carbon atoms (6 electrons, $1s^2\ 2s^2\ 2p^2$) possess unique properties and high plasticity, allowing them to form diverse structures.

- Covalent Bonding: Can form strong covalent bonds with other carbon atoms or other elements.
  - Structural Diversity: This enables the formation of complex carbon materials with distinct and remarkable properties (e.g., diamond, graphite, fullerenes, graphene).
  - Importance: These properties are key to their broad utility as biomaterials.

Carbon Biomaterials: Key Characteristics (Part 1)

Characterizing Carbon Biomaterials: Key Dimensions



1. Dimension

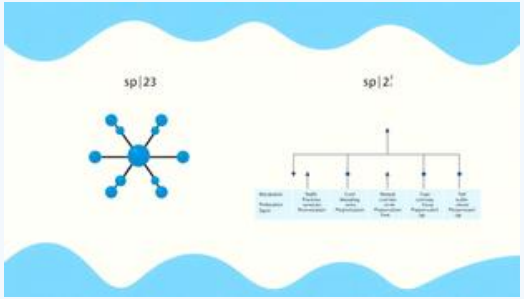
- Materials: All dimensions nanometric (e.g., nanodiamonds, fullerene, graphene quantum dots, carbon dots).
- 3D Materials: Three dimensions out of nanometric range (e.g., diamond, pyrolytic carbon, diamond-like carbon, carbon fibers, graphite).

2. Crystallinity

- Entirely Crystalline: Highly ordered atomic structure (e.g., diamond, graphite).
- Entirely Amorphous: Lacks long-range order (e.g., pyrolytic carbon, diamond-like carbon, carbon dots).

Carbon Biomaterials: Key Characteristics (Part 2)

Characterizing Carbon Biomaterials: Hybridization



3. Carbon Atom Hybridization State

- sp^2 Hybridized Carbons: Characterized by planar structures and delocalized pi-electrons (e.g., graphite, graphene).
- sp^3 Hybridized Carbons: Characterized by tetrahedral bonding (e.g., diamond).

Organization (Fig. 1.3.5.2)

- Visualizes common carbon biomaterials based on their dimension, crystallinity, and hybridization state.
- Provides a framework for understanding the diverse properties of carbon materials used in medicine.

Diamond & DLC: Hardness and Biocompatibility

Diamond and Diamond-Like Carbon (DLC)

Diamond

- Nature: A 3D material with a fully crystalline form of carbon.
- Hardness: Its crystalline structure and strong chemical bonds make diamond the hardest known material.
  - Hybridization: Composed predominantly of sp^3 hybridized atoms.
  - Structure: Each carbon atom is linked to four other carbon atoms arranged tetrahedrally.

Diamond-Like Carbon (DLC)

- Nature: Amorphous carbon material that possesses some of the unique properties of natural diamond.
- Hybridization: Contains a mixture of sp^2 and sp^3 hybridized carbon bonds.
- Properties: Offers high hardness, low friction, chemical inertness, and good biocompatibility.

Pyrolytic Carbon: Hemocompatibility

Pyrolytic carbon is an amorphous form of carbon produced by the pyrolysis of hydrocarbons.

- Structure: Typically consists of small, randomly oriented graphite crystallites.
- Properties: Known for excellent blood compatibility (hemocompatibility), good strength, and wear resistance.
- Primary Application: Widely used in cardiovascular implants, notably for artificial heart valve leaflets and housings.
- Advantages: Its smooth surface and resistance to thrombus formation are critical for long-term implant success in blood-contacting environments.

Carbon Composites in Medicine

Carbon Fibers and Carbon-Carbon Composites

Carbon fibers offer high strength-to-weight ratios and are used in composites.

- Carbon Fibers: Strong, lightweight filaments, often used to reinforce polymer or ceramic matrices.
- Carbon-Carbon (C-C) Composites: Consist of carbon fibers embedded in a carbon matrix. High strength, fracture toughness, and fatigue resistance.

- Biomedical Use: Orthopedic implants (e.g., bone plates, spinal cages) and prosthetics where high mechanical performance and radiolucency are desired.