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Water-Response Materials in the Medical Field

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Abstract. Water-response materials (WRMs) are intelligent materials that shift shape, swell, or disintegrate with water. Biocompatibility facilitates use in medicine. At present, in biomedical fields such as bone defect repair and artificial muscle, traditional materials still face significant challenges in terms of biocompatibility, functional adaptability and minimally invasive implantation. The paper is a summary of WRMs' principles, categories, and preparation procedures, with an emphasis on the treatment of bone defects and the artificial muscle. The problems involving response stability, functions, and the limitations of scalability are discussed. The direction for the future is a move toward precision, multi-response synergy, and merging with 4D printing. WRMs are capable of breaking through the limitations of ordinary alloys, increasing biological compatibility, and decreasing the necessity for follow-up surgery, and consequently promoting the further development of minimally invasive medicine. This study systematically reviews the design principles and application frontiers of water-responsive materials, providing crucial theoretical basis and material selection for the development of the next generation of intelligent medical devices.

Keywords: Water-responsive materials; Biomedical use; Hydrogel; 4D printing; Repair.

1. Introduction

Water-response materials (WRMs) are responsive to water or biological fluids and alter properties and shape reversibly. The result is novel benefits under wet physiological conditions, prompting an increase in medical applications for tissue engineering and drug delivery [1]. They, without the use of external energy, are capable of matching geometry and mechanical properties in real time, and that is what adds more value to the field, particularly for applications in orthopedics, regenerative medicine, and oncology.

Water-sensitive scaffolds for repairing bones disintegrate with the infiltration of fluids, conforming to cavities to facilitate the formation of new bones. For example, a silk fibroin-magnesium system expands within 5 minutes after implantation, blending with host bone to facilitate healing [2]. In artificial muscles, a bilayer of polyurethane shape memory polymer and pH-responsive hydrogel uses water and acidity to achieve a reversible contraction strain of 35% at 0.3 Hz, mimicking natural muscle efficiency [3]. In cancer treatment, materials that exploit tumor microenvironment properties can trigger localized drug release, reducing myocardial toxicity by 70% compared to traditional chemotherapy [4].

Medical-grade WRMs should fulfill three stringent requirements: non-immunogenicity, degradability, and mechanical compatibility. Natural polymers cross-linked with chromium (III) ions amplified from 5 to 120 MPa the compressive modules, retaining above 95% cell viability, to form high-strength, absorbable implants [5]. Surgical workflows demand that the material response rate to 37 °C bodily fluids be programmable and highly suitable for minimal invasive implantation. Recently, water-trained polymers are capable of securing, for 8 weeks, a transient shape and, at body temperature, regenerating the native shape within 10 seconds, satisfying the requirement for "single positioning, immediate fixation" [6].

This paper studies the classification, preparation, and medical applications, specifically in bone defect repair and artificial muscles, of water-response materials. Its research objectives are to analyze the application principles, showcase practical cases, identify current challenges, and forecast future development trends of WRMs in the medical field.

2. Types of Water-Response Materials and Hydrogel Preparation

2.1. Concept and Core Mechanism of Water-Response Materials

Water-sensitive materials are shape memory polymers that are tailored to be sensitive to water, moisture, or biological fluids. Such stimulations give rise to the restoration of the structure with the help of polymer-water interactions, facilitating the activation of predefined functions, for example, shape memory, swelling, or degradation, without the incorporation of an external energy source, making these materials highly versatile for in-vivo medical procedures [7].

2.2. Page Numbers

WRMs are classified by response mechanism into: Swelling Type (e.g., hydrogels that expand with water), Degradation Type (e.g., polyesters hydrolyzing in fluids), and Shape Memory Type (e.g., polycaprolactone that regains shape with water). By material source, they fall into: Natural Polymer-based (e.g., collagen, chitosan) for biocompatibility; Synthetic Polymer-based (e.g., poly(N-isopropylacrylamide), polylactic acid) for controllability; and Composite-based (e.g., nano-hydroxyapatite/hydrogel) for bioactivity and strength. Spider-silk mimicking polypeptides (natural) and PVA/SA composite hydrogels (synthetic) show exceptional performance [8] [9].

2.3. Hydrogels as Mainstream WRMs: Diversified Preparation Techniques

Patterning strategies such as photolithography and soft lithography design microscopic tissue repairing structures. Microfluidics fabricates micro-scale hydrogel microspheres for localized drug delivery. Molding and freeze-drying tailor macro-porous scaffolds that replicate bone porosity. Electrospinning fabricates nanofiber membranes for skin and tendon tissue engineering. A combination of 4D printing with water-responsive elements enables "post-printing transformation." For stents with minimal invasion, a pre-printed stent expands to a preset form with fluid contact after implantation, reducing the complexity of surgery. Gradient hydrogel scaffolds can be fabricated through in-situ injection and freeze-drying to replicate bone gradients for facilitating regeneration [10-12].

Table 1. Comparison of Characteristics of Four Types of Water-Response Material Preparation Technologies.

Preparation Technology	Advantages	Disadvantages/Challenges	Main Applications
4D Printing	Precise structure, customizable	Material viscosity, humidity affect precision	Complex stents, artificial organs
Electrospinning	High surface area, mimics ECM	Low yield, relatively simple structures	Skin, tendon repair
Microfluidics	Uniform size, monodisperse	Complex equipment, limited throughput	Drug delivery microspheres
Freeze-drying	High porosity, open structure	Time-consuming process, potentially low strength	Tissue engineering scaffolds

3. Application of Water-Response Materials in Bone Defect Treatment

3.1. Performance of WRMs in Bone Defect Treatment Influenced by Three Key Factors

The comprehensive requirements for WRMs in bone defect repair are primarily reflected in three aspects. First, hydrophilicity is crucial; only by achieving surface wetting within seconds in a water or blood environment can the material promptly initiate its shape memory or expansion mechanism to conform to the irregular defect walls. Second, the implant must maintain mechanical continuity

until bone tissue regeneration is complete; thus, its degradation rate needs to synchronize with the three-to-six-month maturation cycle of new bone – absorption that is too fast leads to premature loss of support, while absorption that is too slow hinders osteon ingrowth, potentially forming fibrous isolation. Third, to withstand masticatory or movement loads without collapsing, the material's compressive strength in the wet state must cover the range from cancellous to cortical bone (2–100 MPa). A recently reported rapid water-response composite system from Xi'an Jiaotong University, with a room-temperature tensile modulus exceeding 1.5 GPa and tensile strength surpassing 100 MPa in simulated body fluid, provides a feasible demonstration of coupling these performance requirements [10].

3.2. Composite Hydrogels Predominate as Common Materials in This Field

Current carriers for bone defect repair predominantly appear as composite hydrogels. Their design strategy involves integrating multiple osteogenic signals onto a natural polymer backbone. A chitosan or gelatin network first ensures cell affinity and low inflammatory response in the wet state. Subsequently, incorporated nano-hydroxyapatite crystals, chemically similar to bone mineral, can form a bone-like apatite layer at the interface, accelerating osteoblast adhesion. To further shorten the bone formation period, researchers often immobilize Bone Morphogenetic Protein-2 (BMP-2) within the network via electrostatic or covalent bonds, enabling its sustained release upon bodily fluid stimulation and inducing mesenchymal stem cell differentiation towards the osteogenic lineage. Concurrently, divalent cations like magnesium and zinc ions are introduced into crosslinking points; they form reversible hydrated coordination with polymer chains, granting shape memory capability, while also activating integrin and Wnt/β-catenin pathways to enhance osteogenic gene expression. Building on this, degradable medical magnesium alloys (e.g., Mg-Ca, Mg-Zn systems) are often dispersed within the gel as microfibers or particles. Its degradation releases Mg^{2+} ions, maintaining weak alkalinity and rising alkaline phosphatase activity. It also enhances the osteoconductivity and elasticity of polymatrix and hydroxyapatite to create a responsive microenvironment [11].

Magnesium (Mg) is an essential element for bone health and disease, as it participates in physiological processes like bone tissue formation, bone metabolism, and bone mineral crystallization [12]. However, the rapid degradation of Mg and its alloys in vivo and the subsequent hydrogen gas release are pressing issues for researchers. In contrast, magnesium oxide (MgO), as the oxide of Mg, neither degrades rapidly nor produces hydrogen gas in vivo, thus serving as a source of Mg^{2+} in bone tissue materials. After implantation of SF/MgO scaffolds, Mg^{2+} is slowly released as the MgO particles degrade, regulating the function of migrating cells and promoting the expression of related osteogenic genes; ultimately, critical-sized bone defects are repaired in situ [13].

3.3. Core Requirements: "Precise Adaptation" and "Dynamic Support"

4D printing forms personalized scaffolds from patient CT images for asymmetrical bone holes following the removal of tumors. The scaffold conforms to the defect and enlarges with fluid induction following implantation, first supporting and later breaking down as bone tissue develops. Gradient scaffolds duplicate inherent bone characteristics, promoting cell differentiation through fiber alignment and pore architecture design [12].

3.4. Significant Outcomes from Practical Application Cases

Mao Zhinan et al. 4D printed chitosan/nano-hydroxyapatite hydrogel to achieve regular. After implanting into a 15 mm rabbit radial defect, the material underwent pre-programmed contraction upon bodily fluid stimulation, reducing porosity from 65% to 45%. This stabilized the mechanical environment and concentrated endogenous growth factors. At 8 weeks, the new bone formation rate reached 75%, significantly higher than the 52% observed with traditional ceramic scaffolds, confirming that water-responsive contraction can actively optimize the regenerative space [3].

Scientists encapsulated autologous bone marrow mesenchymal stem cells in a shape memory polymer mesh. The scaffold restored shape under exposure to body fluids, releasing cells onto defect sides. In

a rat 8 mm calvarial defect model, persistent cortical bone bridging happened at the midsection within 12 weeks, with the mechanical strength up to 82% that of normal bone, attaining functional regeneration. Recently, a 3D-printed scaffold encapsulating roxadustat with GelMA/hydroxyapatite/polydopamine utilized near-infrared light to produce gentle hyperthermia (42 °C, 5 min), releasing the HIF-PHD inhibitor. The result favored a "vessels first, bone later" sequence under early angiogenesis and osteogenesis coupling. In a model for critical rat bone defects, the whole healing happened within 8 weeks, with the volumetric fraction for the newly constructed bone reaching 64%, indicating that introducing WRMs and drug delivery can profoundly accelerate complex defect regeneration [11].

4. Application of Water-Response Materials in Artificial Muscles

4.1. Significant Advantages and Demand for Artificial Muscles in the Medical Field

Differently from conventional motors, synthetic muscles emulate the human muscular compliancy to minimize tissue damage and achieve stable activation under wet conditions. Artificial muscles are applied to limb reconstructions (e.g., finger support), gastrointestinal reinforcement (e.g., stent devices), and bladder support, treating movement disorders and organ malfunction [14].

4.2. Materials and Technologies for Artificial Muscles Revolve Around Water-Response Characteristics

The matrix for current water-response artificial muscles commonly employs high water-absorbent resins, such as sodium polyacrylate grafted with polyethylene glycol, or shape memory polymers that combine elasticity with programmability. Their core actuation mechanism is "swelling-shrinkage" coupling. By constructing a bilayer structure of hydrophilic/hydrophobic layers within a film or fiber, the material generates asymmetric volume expansion upon water ingress, thereby outputting reversible bending or linear stress. To further enhance work density, researchers have introduced electrospinning, co-axially spinning polyurethane shape memory segments and pH-responsive hydrogel segments into parallel fiber bundles that mimic the striated arrangement of skeletal muscle. This allows the fibers to contract synchronously in a moist environment, with measured contraction stress reaching 0.5–2 MPa, on the same order of magnitude as the active tension of human skeletal muscle. In a typical example, a bilayer composite strip of polyurethane shape memory polymer and pH-responsive hydrogel was programmed into a temporary spiral shape in 60 °C hot water. When placed in simulated body fluid at 37 °C and pH 6.5, water molecules rapidly penetrate the hydrophilic layer, and polymer chains relaxed and accelerated by H^+ catalysis. The strip completed a flattening-reverse coiling cycle within 15 seconds, with an average angular velocity as high as 25.71°/min, providing a high-frequency, large-stroke actuation prototype for micro biomimetic joints and flexible grippers [3].

4.3. Huge Application Potential of Water-Response Artificial Muscles

In limb rehabilitation, research teams are weaving bilayer water-response fibers into exoskeletal cuffs. The wearer only needs to spray a small amount of saline or utilize their own sweat to trigger a circumferential contraction of 0.8 MPa within 10 seconds, providing 20 N·m of assistive torque for elbow and knee joints. The entire device weighs less than 300g, far lighter than traditional motor-driven rigid exoskeletons. For internal therapy, a capsule-shaped "drug delivery pump" with a diameter of 2mm has been validated in the mouse intestine: its shell is made of pH-swelling hydrogel, which contracts instantly upon reaching the ileum due to the higher pH of the fluid, squeezing the inner chamber to achieve timed and quantized insulin release, reducing blood glucose fluctuations by 65% over 24 hours. If combined with flexible neural electrode arrays, a "nerve-muscle" closed-loop system could be constructed in the future, allowing spinal cord injury patients to directly regulate the contraction frequency and amplitude of implanted artificial muscles through intention, enabling precise gait reconstruction. Concurrently, microscopic mechanisms – such as spider silk undergoing

supercontraction upon water content change and mussel byssus self-healing upon seawater stimulation – provide new biomimetic paradigms for the macroscopic layered structure, fiber arrangement, interface toughening, and repairable design of artificial muscles [15].

5. Challenges Currently Faced by Water-Response Materials

After long-term immersion in bodily fluids, materials are prone to decreased swelling rates and attenuated mechanical strength (e.g., some hydrogels experience a 40% reduction in elastic modulus after 3 months). The actuation precision and lifespan of water-response intelligent actuators also need improvement under repeated stimulation [16].

Most materials only achieve a single water-response function (e.g., shape memory OR drug release), making it difficult to meet the integrated need for "repair + monitoring + treatment." Although polyurethane/SMP/pH-responsive hydrogel composites have achieved dual-function synergy, true multifunctional integration still requires breakthroughs [17].

The printing accuracy of 4D-printed water-response scaffolds is still constrained by both material viscosity and environmental humidity: high-viscosity gels are prone to shear-thinning at the nozzle, causing line width fluctuations of ±15%, while a mere 5% variation in workshop humidity can lead to a 7% drift in crosslinking density, ultimately resulting in a 10° difference in shape recovery angle between batches. Although biomimetic interfacial hydrogels can undergo sol-gel transition within 3 seconds under blue light irradiation, enabling "printing while setting," for centimeter-scale porous scaffolds, the shrinkage stress induced by interlayer temperature differences causes buckling of cantilever structures. Currently, continuous printing heights exceeding 20mm lead to collapse, with a qualified yield for scaled production below 60% [6].

On the other hand, although medical magnesium alloys can release osteogenic ions, their degradation byproduct Mg^{2+} can increase erythrocyte osmotic fragility when local concentration exceeds 10 $mmol \cdot L^{-1}$, and $Mg(OH)_2$ microcrystals might block renal tubules. The longest follow-up in existing large animal studies is only 26 weeks, insufficient to cover the complete cycle of human bone remodeling. Therefore, degradation rates and the long-term accumulation risks of byproducts still require validation through larger sample sizes and longer-term clinical trials to establish safety thresholds [11].

6. Future Development Trends of Water-Response Materials

6.1. Intelligent Precision and Multi-Response Synergy as Core Directions

Intelligent precision and multi-response synergy have become central axes for the advancement of WRMs. Biomimetic design is evolving from macroscopic imitation to molecular topological control: using genetic engineering to recombinant spider silk polypeptides allows precise adjustment of β-sheet content to 35%, enabling the material to exhibit 8% reversible supercontraction upon water absorption. Supplementing this with a "water training" process – applying 5 MPa pre-stress to the sample under constant humidity cycles to induce the formation of oriented nanocrystalline regions – ultimately allows the same material to achieve a dry-state modulus of 2 GPa and a wet-state modulus of 50 MPa, realizing broad-frequency dynamic tunability of mechanical and response behaviors [18][19].

6.2. Deep Integration with 4D Printing Technology to Break Application Limits

Deep integration with 4D printing is breaking through the two-dimensional ceiling of "structure-property." For organ-level repair, gradient artificial bone 4D printing technology is drawing on the "temperature-phase transition" parameter control experience from shape memory alloys in new energy devices. It dynamically adjusts the hydroxyapatite volume fraction (5%–40%) along the printing path to form an integrated "bone-cartilage" scaffold with a continuous mechanical transition

from 0.3 GPa to 15 GPa. Implanted into rabbit femoral defects, it achieved complete integration with the subchondral bone within 16 weeks, providing a replicable engineering paradigm for the "printing-response-regeneration" closed-loop system [12][13].

7. Conclusion

WRMs provide key benefits for medical use through their water-activated adaptability, surpassing traditional materials' limitations. Despite advances in material variety and applications, challenges in stability, functionality, and manufacturing remain. The future focuses on creating intelligent, multi-responsive WRMs with 4D printing to enhance precision and minimally invasive medical technologies.

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