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Biomaterial Advances in Medicalfield

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Abstract: *Biomaterials for medical applications have broadly been exploited since long time and subsequently increased their utility in health-care industry that is growing rapidly due to chronic diseases, traumatic accidents, surgical reconstructions, and other health-care problems. Over the time, an extensive research has been done on biomaterials that have shown an imperative role in medical field, especially tissue engineering, drug delivery applications and wound healing. In this review article, recent advances in biomaterials developed to favor drug delivery and tissue repair are presented.*

Key words*: Biomaterials, drug delivery system, wound healing*

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I. Introduction

Biomaterials are at the forefront of important advances in health sciences. Given the aging population and the growing number of chronic illnesses, which represent major challenges for the public health sector, the demand for more sophisticated medical products is expected to increase in the coming years, hence there is need for ongoing research into state-of-the-art technology. Biomaterials offer a wide range of opportunities to address these issues. As their name indicates, biomaterials are the result of a synergy linking several disciplines, notably material sciences and biology, as well as a number of new techniques in biomechanics, biophysics and biochemistry.

Biomaterial is defined as "materials of synthetic as well as of natural origin in contact with tissue, blood, and biological fluids, and intended for use for prosthetic, diagnostic, therapeutic, and storage applications without adversely affecting the living organism and its components"[1] and "any substance (other than drugs) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ, or function of the body"[2]

Biomaterials can be composed of metal and metal alloys (stainless steel, titanium, etc.), ceramics (alumina, phosphate, etc.), polymers (functional or resorbable) or naturally sourced materials (biological tissues, chitin, cellulose, etc.). First and foremost, a biomaterial must be biocompatible—it should not elicit an adverse response from the body, and vice versa. Additionally, it should be nontoxic and non-carcinogenic. These requirements eliminate many engineering materials that are available. Next, the biomaterial should possess adequate physical and mechanical properties to serve as augmentation or replacement of body tissues. For practical use, a biomaterial should be amenable to being formed or machined into different forms.[3]

Use of biomaterials in medical field

The primary use of biomaterials is to replace hard or soft tissues that have become damaged or destroyed through some pathological process.

The different materials or devices that are used include sutures, needles, catheters, artificial tissue, etc. Biomaterials have been developed in the few decades, which are used as an organ in a living system or to function along with the living tissues. The different biomaterials that are used mainly are metallic, ceramic, polymeric, and composite biomaterials.[4] Each material has their diverse property that helps them to survive in the particular applications.

Table No. 1

S.No.	Problem Area	Examples	Biomaterials
1	Replacement of diseased or damaged part	Artificial hip joint, kidney dialysis machine	PolyethylenePolymethylmethacrylate,Alumina , Zirconia
2	Assist in healing	Sutures, bone plates, and screws	Polypropylene, Polyvinylchloride, 316L stainless steel, CP-Ti, Ti-Al-V, Ti-Al-Nb, Ti- 13Nb-13Zr, Ti-

			Mo-Zr-F, Ni-Ti
3	Improve function	Cardiac pacemaker, intraocular lens	Polymethylmethacrylate Polyethylenterephthalate CP-Ti, Ti-Al-V, Ti-Al-Nb, Ti- 13Nb-13Zr, Ti-Mo-Zr-F , Polyurethane, Acetal
4	Correct functional abnormality	Cardiac pacemaker	Polyethylenterephthalate CP-Ti, Ti-Al-V, Ti-Al-Nb, Ti- 13Nb-13Zr, Ti-Mo-Zr-F Polyurethane, Acetal
5	Correct cosmetic problem	Augmentation mammoplasty	Silicone gel Poly acrylamide hydrogel
6	Aid to diagnosis	Probes and catheters	Polyamide Polyvinylchloride Polyurethane
7	Aid to treatment	Catheters, drains, drug delivery system	Polyvinylchloride, Polyethylene, Polyamide, Polyurethane,Polyesters, Hydrogel

Table No. 2.Biomaterials in Organs

S.No.	Organ	Examples	Biomaterials
1	Heart	Cardiac pacemaker, artificial heart valve, total artificial heart, blood vessels	Polypropylene Polyethylenterephthalate Polytetrafluoroethylene CP-Ti, Ti-Al-V, Ti-Al-Nb, Ti- 13Nb-13Zr, Ti-Mo-Zr-F, Polyurethane, Acetal
2	Lung	Oxygenator machine	Polypropylene
3	Eye	Contact lens, intraocular lens	Polymethylmethacrylate
4	Ear	Artificial stapes, cochlea implant	Polydimethyl siloxane Silicone,Platinum,Titanium
5	Bone	Bone plate, intramedullary rod	316L stainless steel CP-Ti, Ti-Al-V, Ti-Al-Nb, Ti- 13Nb-13Zr, Ti-Mo-Zr-F, Ni-Ti
6	Kidney	Catheters, stent, Kidney dialysis machine	Polyvinylchloride, Polyethylene Polymethylmethacrylate Polytetrafluoroethylene Polyamide 316L stainless steel Polyurethane
7	Bladder	Catheter and stent	Polyvinylchloride, Polyethylene Polytetrafluoroethylene Polyamide 316L stainless steel Ni-Ti, Polyurethane

Table No. 3 Biomaterials in Body System

S.No.	System	Examples	Biomaterials
1	Skeletal	Bone plate, total joint replacements	Polyethylene 316L stainless steel CP-Ti, Ti-Al-V, Ti-Al-Nb, Ti- 13Nb-13Zr, Ti-Mo-Zr-F, Ni-Ti,Alumina, Zirconia
2	Muscular	Sutures, muscle stimulator	Polypropylene Polyamide Polyethylenterephthalate
3	Nervous	Hydrocephalus drain, cardiac pacemaker, nerve stimulator	Polyethylenterephthalate, Acetal
4	Endocrine	Microencapsulated pancreatic islet cells	Poly-l-Lysine (PLL) Poly-l-Ornithine (PLO)
5	Reproductive	Augmentation mammoplasty, other cosmetic replacements	Collagen-C6S Matriderm

Recent Advances

1) Reactive oxygen species responsive nano-platforms as smart drug delivery systems

Nanoplatforms have the potential to directly access the target area and achieve a site-specific drug delivery. During the last 50 years, nanoparticles with different compositions, sizes, surface charges and targeting ligands have been investigated as carriers for drug delivery.[5]Smart nanomaterials responsive to the reactive oxygen species (ROS) concentrate in the inflamed areas, can be formulate into nanoplatforms to selectively release the active compounds, avoiding unspecific drug delivery to healthy tissues and limiting systemic absorption. In vitro & in vivo studies have been conducted to find out the ability of nanoplatforms to achieve a site-specific drug delivery directly in the intestinal mucosa.Recent developments of ROS-responsive nanoplatforms include combination with other materials to obtain multi-responsive systems and modifications/derivatization to increase the interactions with biological tissues, cell uptake and targeting.

Nanoparticles with small size (below 200 nm) accumulate in the areas of intestinal diseases compared to the healthy GI tissues as a consequence of the compromised barrier function and increased particle uptake by macrophages. Nano-sized drug carriers could also display a prolonged intestinal transit time due to increased adhesion to the thick mucus layer.[5] Nanomedicine, compared to conventional drugs, may also protect the payload from destabilization or hydrolysis, improving the bioavailability and increasing drug release/retention at diseased sites.[6]

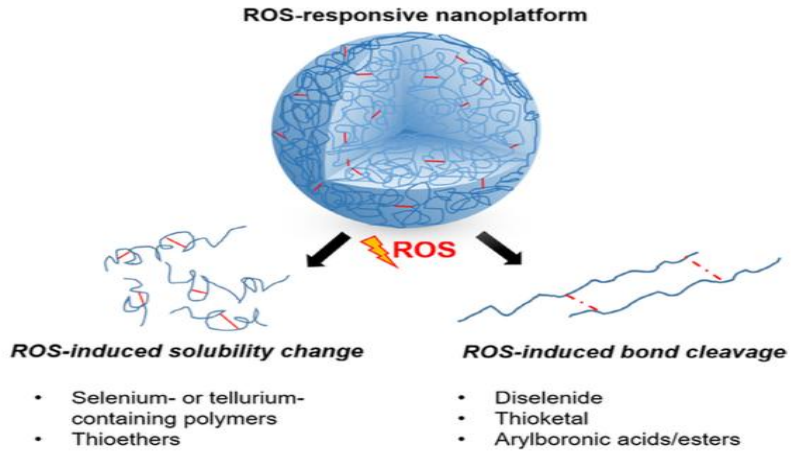

Fig I Schematicillustrationof the possible behavior of ROS-responsive nanoplatforms in the presence of ROS. Polymer chains are indicated as **blue lines**; chemical bonds of the polymer are represented as **red segments**[6]

Progress in polymer chemistry has led to the development of several novel ROS-responsive biomaterials in the last few years, which have provided specific sensitivity toward H2O2 as a therapeutic approach for oxidation-sensitive systems.[7]Wilson et al.[8] developed a new poly-(1,- 4-phenyleneacetone dimethylene thioketal) (PPADT) ROS-sensitive polymer for targeting inflamed intestinal tissues that were stable in acidic, basic and protease-abundant environments analogous to the GI tract. Using PPADT, they formulated ROS-responsive nanoparticles (TKNs) via an oil-in-water single-emulsion procedure. TKNs degraded when reaching the site of intestinal inflammation via thioketal linkages, thus localizing the release of the payload to inflamed intestinal tissue.

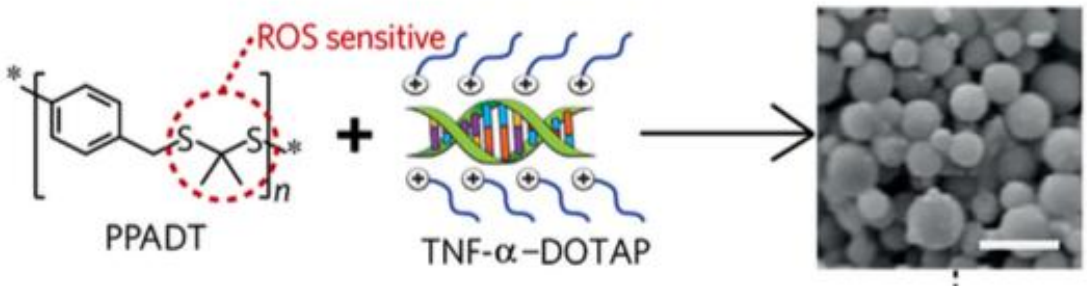

Fig II

PPADT 3 is a new polymer composed of ROS-sensitive thioketal linkages (circled dashed). TNF- α–TKNs were prepared by first precomplexing TNF-α–siRNA with the cationic lipid DOTAP. Next, these TNF-α–DOTAP complexes were added to an organic solution containing PPADT. The scanning electron micrograph shows TNF-α–TKNs (scale bar represents 1.5 μm).

Zhang et al.[9] also developed a nano system based on Tempol (Tpl selected as a SOD-mimetic drug) loaded in a biocompatible ß-cyclodextrin-derived material (OxbCD).This nanomedicine (Tpl/OxbCD NP), prepared by a nanoprecipitation/self-assembly method, is stable in the GI tract and can target inflammatory sites by releasing the payload in the presence of non-physiologically high ROS levels.

2) Collagen based biomaterials for wound healing

Collagen by virtue of its ubiquity, low immunogenicity, and ability to be molded into strong, bio-compatible scaffolds plays a leading role in wound care. Moreover, collagen-based materials are adroitly at the interface of natural and synthetic macromolecules.

Collagen is important in related area of wound caredue to their ability of controlled-release of bioactive molecules. Complementary to the use of heterogeneous collagen composites, the development and use of collagen mimetic peptides as a potent system for targeted delivery of therapeutic molecules to the wound site, can expedite progress in the field of wound healing and tissue regeneration.

Collagen films have been used in wound healing and tissue engineering, primarily as a barrier. Films of 0.1–0.5 mm thickness can be cast from collagen solutions and air dried in a manner similar to ophthalmological shields. As an added advantage, films made from biodegradable materials like telopeptide-free reconstituted collagen demonstrate a slow release of encapsulated drugs. The loaded films afford easy sterilization and become pliable after hydration, without compromise to their mechanical strength. Biodegradable collagen membranes can be scaffolds for viable fibroblasts. A blend of collagen and another polymer, such as an atelocollagen matrix, added on the surface of poly- urethane films promotes the attachment and proliferation of fibroblasts, supports their growth, and enhances long-term survival. In addition, recombinant type I collagen from Pichia pastoris yeast has been used to formulate films for tissue engineering and guided tissue regeneration after dental surgery.[10]

3) pH-Responsive Polymers

Many tissues, fluids, and organelles within the human body contain different pH values. To improve the efficacy and precision of therapeutic molecules involves the design of polymeric drug delivery systems that can respond to specific pHs. As a general strategy to create pH-sensitive materials, it is common to incorporate chemical functional groups that can be protonated or deprotonated within polymeric matrices.

One specific area where pH-responsive materials have improved therapeutic targeting is in the treatment of tumors. The tumor microenvironment often exists at a lower pH (≈5.7) than its surroundings (≈6.8–7) due to localized acidosis.[11] Given this difference, multifunctional acid sensitive nano- composites have been explored for the controlled release of anticancer drugs.[12]Importantly, these materials were also functionalized with folic acid, improving the targeting of these materials to overexpressed folic acid receptors on the cancer cell surface. Moreover, a similar concept has been employed for materials incorporating acid-sensitive diamino-ketal cross links, and drug-laden versions of these materials have demonstrated increased cellular uptake relative to that observed for the free drug alone.[13] Finally, acid responsive poly(ethylene glycol) derivatives have also been designed for the controlled release of therapeutics using hydrazine chemistry, and tumor targeting with pH-responsive materials continues to be an area of interest to the drug delivery community.

4) Hydrolysis and Enzymatically Responsive Polymers

Hydrolysis-sensitive polymeric materials have also been designed, synthesized, and implemented in vivo for drug delivery purposes.TheGliadel wafer is one example product on the market that demonstrates the power of hydrolysis-sensitive materials for drug delivery.[14]Consisting of the chemotherapeutic Carmustine impregnated within a poly- anhydride material, the Gliadel wafer can be implanted into brain tumors for the controlled release of a chemotherapeutic to malignant gliomas. Of note, the Gliadel wafer improves the 6-month survival rate of patients diagnosed with glioblastoma multiforme.

5) Temperature-Responsive Polymers

Temperature-sensitive polymers can also be used for drug delivery purposes.[15]The human body resides at a temperature of 37 °C; by contrast, ambient temperature is ≈25 °C. To take advantage of this difference, polymer systems that flow at room temperature but gel at body temperature have been developed—these materials are predominantly used for local delivery applications, capitalizing on the sol-gel transition of specific polymers. Many base materials have been used for temperature responsive polymer development including poloxamers, poly (*N*-alkyl acrylamides), poly (*N*- vinyl caprolactams), cellulose, xyloglucan, and chitosan. Of note, the material properties of thermoresponsive polymers can be modulated by employing one or more of several different strategies.[16] These strategies include varying the ratio of monomers, end-group modifications, and postpolymerization modifications. Each of these strategies has afforded temperature-responsive polymers for varied biomaterials applications

6) Magnetic-Responsive Polymers

This concept has been extended to designing systems to release compounds to specific organs by pairing therapeutic treatment with drug-loaded polymers and magnetic resonance imaging (MRI) techniques. The examples include: i) the systematic release of dopamine from alginates impregnated with magnetic beads; ii) targeted plasmid delivery to the lung using chitosan nanoparticles; and iii) insulin delivery, among others.[17] The combination of two or more environmental responses in a single material can be highly advantageous. For example, if one were to include magnetic particles within a polymer that was designed to degrade in highly acidic conditions, then one could use MRI imaging to pinpoint the exact location that the drug was delivered upon dispersion of the particles within, for instance, the stomach. An added benefit to incorporating magnetic material within a delivery nanoparticle is that it can double as a retrieval method. Having a magnetic system allows for the material to be more easily removed, especially in a self-circulating system

7) Electrically Responsive Polymers

Electrically responsive polymers represent yet another class of tunable materials for biomaterials applications. The human body is replete with electrical stimuli; for example, neurons transmit information via electrical signals.[18] To directly inter- face with these cell populations and for other forms of orthogonal drug delivery in the body, different classes of electrically responsive polymers have been developed. From a chemical standpoint, electrically responsive materials tend to be highly conjugated aromatic systems.[19]Polypyrrole, for example, has been used extensively as a base material for electronic applications and the biocompatibility of polypyrrole nanoparticles has been studied in mice.[20] To date, electrically responsive polymers have been used for an array of biomaterials applications including controlled drug release, and have also been used in tandem with temperature responsive systems to form dual responsive materials, among others.[21]

8) Ceramic and Composite Scaffolds Fabricated Using 3D Printing

Scaffolds for tissue engineering (TE) were fabricated using 3D printing with wide range of biomaterials. These biomaterials have diversity in their chemical, mechanical, and biological properties.Ceramics are the class of biomaterials that include metals and inorganic salts of calcium and phosphate. These biomaterials find immense potential in bone and dental TE because of their osteoconductive and osteoinductive nature. Commonly-used ceramic biomaterials include β-tricalcium phosphate (β-TCP), α-tricalcium phosphate (α-TCP), hydroxy apatite (HA), bi-phasic calcium phosphate (BCP—a mixture of β-TCP and HA), calcium sulfate (CS), calcium phosphate cement (CPC), and titanium. These ceramics are often brittle in nature and are, hence, added with polymers. Biomaterials that have ceramics and polymers are categorized as composites. Commonly-added polymers include chitosan, polycaprolactone (PCL), poly lactic acid (PLA), poly L-lactide-glycolic acid (PLGA), and poly ethylene glycol diacrylate (PEGDA)

In the quest to formulate composites that have mechanical properties similar to bone, materials such as zirconium oxide, graphene, silica, and bioglass were introduced into the scaffold composition. 3D printed scaffolds using strontium, hardystonite, gahnite, HPMC, and sodium polyacrylate was shown to have compressive strength similar to bone of 110 MPa and the scaffolds were 34% porous. These scaffolds have very large potential in bone tissue engineering because of the high mechanical properties and their ability to promote vascularization.[22]

9) Polyamidoamine dendrimers-based gene vectors

Polyamidoamine (PAMAM) dendrimers have become the most utilized dendrimer-based vectors for gene transfer due to ease of synthesis and commercial availability. Commonly, PAMAM dendrimers possess generation-dependent properties. Low generation PAMAM dendrimers, such as G0-G3 exhibit poor gene transfection efficiencies and less cytotoxicities, while high generation, such as G4–G8 show better gene transfection efficiencies but certain cytotoxicities. As the same with PLL and PEI polymers, various alterations to the pristine PAMAM dendrimer structure have been tested to improve the transfection efficiency and reduce cytotoxicity.[23]

10) Bioactive glass functionalized chondroitin sulfate hydrogel

Blood vessels play an important role in bone defect repair and growth, and a critical challenge of bone defect repair is the promotion of blood vessel formation. Most of the current methods promote vascularization by adding specific growth factors, which are costly and easy to inactivate. The novel covalently cross-linked aminated bioactive glass nanoparticle-chondroitin sulfate methacrylate (ABGN-CSMA) organic-inorganic composite hydrogel has angiogenic properties. The amino groups of the ABGNs form covalent bonds with the carboxyl groups on CSMA. Surface amination modification of BGNs not only improved the dispersion of BGNs in CSMA but also significantly improved the mechanical properties of the composite hydrogel. The largest storage modulus (1200 Pa), the largest loss modulus (560 Pa) and the strongest resistance to deformation of the

hydrogel are seen at 10% concentration of ABGNs. Simultaneously, the local pH stability and sustained ion release of the composite hydrogel are conducive to cell adhesion, proliferation. ABGN-CSMA hydrogel was more beneficial to promote osteogenesis and angiogenesis than pure CSMA hydrogel and this organic-inorganic compound hydrogel has the potential to be used for large segment bone defects repair.[24]

II. Conclusion

Biomaterials have been developed in a wide range mainly based on its properties and biomedical applications. It has made a great impact in various medical applications. Numerous biomaterials have been developed with better performance in bio medicalfield.Various recent advancements are still under research which require more clinical applications and long term follow up, can opening a new platform in medical field.

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