Biomaterials and therapeutic applications

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Abstract. A number of organic and inorganic, synthetic or natural derived materials have been classified as not harmful for the human body and are appropriate for medical applications. These materials are usually named biomaterials since they are suitable for introduction into living human tissues of prosthesis, as well as for drug delivery, diagnosis, therapies, tissue regeneration and many other clinical applications. Recently, nanomaterials and bioabsorbable polymers have greatly enlarged the fields of application of biomaterials attracting much more the attention of the biomedical community. In this review paper I am going to discuss the most recent advances in the use of magnetic nanoparticles and biodegradable materials as new biomedical tools.

1. Introduction

The family of biomaterials is huge. Nevertheless new materials are under investigation (1; 4). Currently, biomaterials can be subdivided based on their physicochemical nature. Materials presently used in biomedicine can be: metallic, ceramic, polymeric, composite and biodegradable polymers (3) (Table 1).

| Table 1. List of some biomaterials currently used in biomedicine. |
|---------------------------------------------------------------|
| **Metallci** | Vanadium (V), iron (Fe), chromium (Cr), cobalt (Co), nickel (Ni), titanium (Ti), tantalum (Ta), niobium (Nb), molybdenum (Mo), and tungsten (W) |
| **Ceramic** | Alumina, zirconia, silicone nitrides, carbons, glass ceramics, dense hydroxypatites, calcium phosphates and calcium aluminates |
| **Polymeric** | Polyvinylchloride, Polyethylene, Polypropylene, Polymethylmetacrylate, Polystyrene, Polyethyleneterephthalate, Polytetrafluoroethylene and Polyamide |
| **Composite (4)** | Combination of two or more materials e.g.: bisphenol-A-glycidyldimethacrylate (Bis-GMA); triethylenglycoldimethacrylate (TEGDMA) |
| **Biodegradable polymers and materials** | Polyhydroxyalkanoates, polyhydroxyvalerate, polyhydroxyhexanoate, Polylactic, Polybutylene succinate , polycaprolactone , Polyanhdyrides, Polyvinyl alcohol. Collagen, Elastin, Albumin, Fibrin, Polysaccharides |

Modern biomedicine offers a variety of implantable medical devices able to improve the quality of life since they restore or implement body functions. They range from bone prosthesis (5) to devices for
continuous glucose monitors (6), brain-stimulating electrodes (7), coagulation sensors (8) and drug delivery systems (9). Biomaterials are also used for diagnosis, therapies (10), tissue regeneration (11) and biomedical research (12; 13). Many of the challenges in producing new medical devices and biocompatible materials are focused on the mitigation of the host foreign-body response, which encapsulates the implant in a fibrotic membrane. In fact, immediately after biomaterial implantation, a normal process of tissue inflammation becomes prolonged and aberrant, producing after several weeks a distinct, avascular, collagenous sheath around the implant (14). The ultimate effect of this body’s response is to isolate and neutralize the implanted material with inevitable chronic inflammation. Modifications of material’s surface as well as geometry, porosity and mechanical properties are often executed in order to diminish cellular response. These modifications can be easily achieved by coating biomaterials’ surface with polysaccharides, polyacrylamide, poly(vinyl alcohol), poly(N-vinyl-2-pyrrolidone) and polyethylene glycol (PEG) (15) or by functionalization (16). Another strategy has been to design implants that release anti-inflammatory drugs. These devices can reduce foreign-body cellular response at the implant sites, but only until the drug is released (17). Furthermore, for many applications such as angioplasty stent implantation are now available bioabsorbable materials that allow to restore proper tissue function and in parallel reduce chronic inflammation thanks to the body’s self-absorption (18). This paper will present and discuss clinical purposes and issues related to the use of magnetic nanoparticles and biodegradable materials.

2. Magnetic nanoparticles

2.1. Nanoparticles definition and properties
Nanoparticles are particles with a size between about 1 and 100 nm that show properties that are not found in bulk samples of the same material (19). As other biomaterials, nanoparticles can be fabricated from organic and inorganic matter. Specifically, magnetic nanoparticles are synthesized from a variety of metallic atoms combined eventually with oxygen including iron oxides, such as Fe₃O₄ and γ-Fe₂O₃, spinel-type ferromagnets such as MgFe₂O₄, MnFe₂O₄, and CoFe₂O₄, alloys such as CoPt₃ and FePt as well as pure metals such as Fe and Co (20). Successful application of such magnetic nanoparticles in biomedicine is highly dependent on the stability and behaviour of the particles under specific parameters such as those found in the body tissues and fluids. An important and critical feature is that a single magnetic domain must show magnetization only in response to applied magnetic fields. This characteristic, named superparamagnetism, makes magnetic nanoparticles very attractive for biomedical applications because the risk of forming agglomerates is very low in the absence of magnetic fields.

2.2. Body’s response to magnetic nanoparticles
As mentioned in the introduction, following the implantation of biomaterials in the human body an inflammatory response is expected.Particles and superparamagnetic nanoparticles are not exempt by this response and since their surface-to-volume ratio is particularly high, for such kind of biomaterials the body’s response may be exacerbate with respect to prosthesis or other implants. In fact, independently by the size, naked magnetic nanoparticles will react with biological fluids (blood, plasma, interstitial fluid) immediately. One of the first events is the opsonization of each single particles. Opsonin are specialized circulating proteins belonging to the immune system able to mark, by covering them, foreign materials and microbes in order to facilitate the phagocytosis (a process that eliminates from the human body foreign organisms and tiny parts) (21). A similar process is expected to happen also in vitro when magnetic nanoparticles as well as other nanomaterials are in contact with the culture medium, which is rich of organic molecules (proteins, sugars, vitamins etc.). In this case the phenomenon is known as corona formation (also called crowing formation and is often used as synonymous of opsonization) and is due to the reactivity of nanoparticles surface (e.g. z-potential) (21). Finally, it is important to mention that also the size of the magnetic nanoparticles is critical for a proper biomedical performance. Particles smaller than 10 nm are removed from blood and eliminate with urine because kidneys are not able to hold such small particles; whereas particles bigger than 200
nm are trapped by the liver and also in this case they are removed by the blood pretty soon. In both cases the blood half-life of nanoparticles that are not in that range is a few minutes (21).

2.3 Biomedical application of magnetic nanoparticles

Nowadays plenty biomedical and biotechnological applications have been reported for magnetic nanoparticles. They are suitable for imaging and drug delivery (22), gene therapy and gene delivery (23), isolation and purification of DNA and RNA (24); isolation and purification of proteins (25), hyperthermia and magnetomechanical cell disruption for cancer therapies (26; 27), cell immobilization for bioscience research (28); stem cell therapies for tissue regeneration (29). In spite of these already existing applications, investigation on magnetic nanoparticles is expanding rapidly thanks to the easy manipulation performed using a magnetic field. This characteristic makes these carriers, amongst others, a desirable option for use in biomedical and process engineering applications.

3. Biodegradable materials

3.1. Biodegradable polymers definition and properties

A biodegradable material can be absorbed by the body following hydrolytic or enzymatic degradation that ultimate in its erosion. They can be both synthetically and biologically derived (natural). In table 1 are reported some examples of biodegradable polymers (30). Important characteristics of biodegradable materials are: 1) material should not evoke a sustained inflammatory response; 2) degradation products should be non-toxic; 3) material should have acceptable shelf life; 4) material should be with appropriate mechanical properties.

3.2. Body’s response to nanoparticles

Though a biological response is expected to take place after biodegradable materials implantation, it should not evolve in chronic inflammation because the implant undergoes degradation avoiding in this way long-term biocompatibility issues. Furthermore, material bioengineering offers the possibility to design biodegradable polymers embedded with specific anti-inflammatory drugs that reduce the immune response and improve long-term clinical outcomes (31). Hydrolytically degradable polymers present functional groups susceptible to hydrolysis that include esters, orthoesters, anhydrides, carbonates, amides, urethanes, ureas, etc (32). Enzymatic degradation is executed within the body via enzymes and act mainly on protein biodegradable implants. These enzymes can digest specific molecules, such as collagenases for collagen, or act in a more aspecific way such as metalloproteinases. In both cases the biomaterial is split in the corresponding amino acids (30).

3.3. Biomedical application of biodegradable materials

Biodegradable platform materials are required for three-dimensional structures, tissue engineering and remodelling, regenerative medicine, controlled drug delivery and bionanotechnology. Three-dimensional scaffold have been used, for example, to generate in vitro cartilage tissue from stem cell that potentially can be implanted in the human body (33). Zartner and colleagues showed an elegant application of biodegradable material for tissue remodeling by using such kind of martial to restore the functionality of pulmonary artery (18). Moreover, another example of the utility of bioabsorbable fabrics that at the same time can release drug came again from angioplasty. It has been demonstrated that biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis with good clinical outcomes (31). As for nanoparticles, research on biodegradable materials is expanding rapidly and new products are continuously studied. It has been estimated that almost all permanent biostable/biocompatible devices used for therapeutic applications will be replaced by biodegradable devices since offers better clinical performance and quality of life.

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