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IR and Visible Light-Activated Antimicrobial Properties and Biosafety Issues of New Polymeric Hybrid Hydrogels Containing Non-Stoichiometric Metal Oxides Nanoparticles

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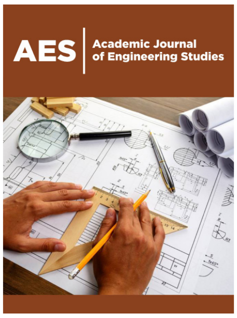

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Abstract

This opinion and perspective paper deals with the potential properties and clinical applications of new ceramic-polymeric hybrids hydrogels for tissue engineering containing non-stoichiometric metal oxides WO3-x, SiO2-x, and TiO2-x nano-fillers presenting strong photo-absorption at visible and infrared light wavelengths. The hybrid bioactive hydrogels are potential candidates as bone tissue engineering materials with photo-induced antimicrobial activity. The improved photo-activity derives from the oxygen gap in the crystalline structure that produces a strong Local Surface Plasma Resonance (LSPR) generating Reactive Oxygen Species (ROS) that damage the microbial agent's membrane components. However, in tissue engineering, these biological effects could also extend to neighboring eukaryotic cells, raising the question concerning the biosafety of these new materials. Further studies are needed to establish a complete risk assessment of the presence of bioactive nanoparticles since they directly affect cellular singling and damage DNA, causing mutations. Biosafety issues of these new materials arise from genetic and epigenetic effects. Cell growth ability, apoptosis, free radicals' generation, and DNA damage are crucial parameters to be controlled in order to promote the use of these new materials. The development of materials with IR and light-induced antimicrobial properties represents an important advancement for the reliability of orthopaedic implants characterised by high bone-implant contact surfaces. Multi-drug-resistant bacteria and viruses' contamination could be partially hindered by photoactive coating hydrogels that self-inhibit the proliferation and spreading of these pathogens.

Keywords: Epigenetic effects; Biosafety issues; Antimicrobial; Osseointegration; Contamination

Abbreviations: LSPR: Local Surface Plasma Resonance; ROS: Reactive Oxygen Species; NIR: Near-Infrared; AM: Additive Manufacturing; EFSA: European Food Safety Authority

Introduction

The emergence of multi-drug-resistant bacteria, or superbugs, is a global issue for prosthetic biomaterials since they could be colonized by antibiotic-resistant pathogens sustaining the spread of infections. New research aimed at developing biomaterials that could prevent or control bacterial colonization is the current effort in this area [1-10]. The current paper is coherent with what is set by the new Horizon Europe (Global Challenges and European Industrial Competitiveness) and Agenda 2030 (goal 3-Ensure healthy lives and promote well-being for all ages). In particular, the research investigates the optimal combination of the material, manufacturing process, and surface modification to give birth to a new generation of coating materials characterised by reduced post-surgical complications. The development of anti-bacterial surfaces is entirely related to these topics since a decrease in infections is beneficial not only for the patient but also for the health system, leading to minor costs of hospitalization and revision procedures. The most common method to produce 'antimicrobial materials' is adding an active agent, such as silver ions, quaternary ammonium salts, phenols, and antibiotics, to the polymer as an additive [4-6]. These additives (most of them are biocides capable of killing all living organisms) are slowly leached into the surrounding environment killing the microorganisms, and can only be effective when leached. However, there are biosafety concerns of the use of materials impregnated with a leaching antibacterial agent, including contamination of the environment and short durations of antimicrobial action due to rapid leaching at the beginning of use (the so-called "burst effect" that involves an initially too high concentration of the released agent). Several alternative approaches have been used to make non-leaching biocidal materials to overwhelm these problems [7-14]. The development of nano-materials with biocidal and antiviral traits provided several benefits to counter the surface and airborne contamination [4-6,15-20]. The already commonly used inorganic nanoparticles with biocide properties are pure metals such as silver, gold, iron, aluminium, cadmium, cobalt, zinc, and copper, as well as UV photo exited metal-oxides comprising $TiO2$, $FeO2$, $Fe3O4$, $SiO2$, $CeO2$, $WO3$, and $ZnO2$ [15-20]. However, some concerns for use in biomedical applications were raised since they are activated under UV radiation. UV photo-excited nanoparticles induce the generation of pairs of electrons and holes, which react with water and oxygen to yield Reactive Oxygen Species (ROS) that have been proven to damage microbial membrane, triggering controlled cellular processes. Nonstoichiometric metal oxide nanomaterials such as $WO3{-}x$, $SiO2{-}x$, or $TiO2\text{-}x$ have recently shown efficient photo-activation even in visible and Near-Infrared (NIR) light frequencies. The oxygen defects in the structure induce strong Local Surface Plasma Resonance (LSPR) and strong photo-absorption in a broad wavelength range of the NIR region [20]. It appears, hence, that there are several opportunities to create advanced intelligent materials that can kill bacteria without harming other higher organisms. This could be a critical distinction as biosafety regulatory issues and clinical impacts are considered. The European Food Safety Authority (EFSA), responsible for assessing health risks related to food for human and animal consumption, has issued scientific opinions on emerging risks of nanostructured materials [21].

Discussion

The long-term success of an orthopaedic implant largely depends on the extent of its osseointegration in the surrounding bone. In recent decades, there have been several attempts to develop porous metal structures and coatings to maximize bone ingrowth on prosthesis surfaces. Innovative Additive Manufacturing (AM) technologies, which are based upon building components by adding layers of material rather than by removing material from a raw shape, can provide a breakthrough solution to overcome the significant limitations of the existing technologies and enhance the performance of porous scaffolds significantly. This article reviews the latest developments in EBM technology applied to prepare highly biocompatible porous materials such as Trabecular Titanium and the production of orthopaedic prostheses with enhanced characteristics. While Additive Manufacturing (AM) technologies continuously improve orthopedic implants' shape and mechanical performance, few solutions have optimised new bone growth and osseointegration without sacrificing device performance. Our perspective study falls in the new Horizon Europe program (Pillar 2 cluster 1, Health, "Tackling diseases and reducing disease burden: identifying new prevention, diagnostics, vaccines, therapies, alternatives to antibiotics"). The new materials have the potential to accelerate the transition to a novel, improved implant device production, exploiting the potentiality of innovative manufacturing technologies and treatments [22,23]. In particular, to develop novel coating technologies for maxillofacial and orthopaedic implants to enhance implant osseointegration and prevent early and late bacterial infections. By considering data on orthopaedic implants failure and occurrence of associated infections (revisions close to 10% of the primary operations; loss of 6 15% within ten years after implantation; periprosthetic infection occurrence in 1-2% of all primary implant surgeries, 8% for revision surgeries), it is immediately apparent that the research outcome not only could represent an up-and-coming market but will also be able to improve the patients' life-quality drastically. It should also be considered that the highest cost is nowadays on the hospital stay and surgery: the time the patient spends in the hospital can be primarily reduced by the adoption of implants with improved osseointegration and antibacterial performance, especially in surgery where the part has to be partially or reconstructed (examples: pelvis, mandible, cheekbone). At the same time, these characteristics will drastically reduce hospitalisation time. A prosthesis or fixation device designed to include both osseointegration and antibacterial/ bioactive properties will reduce the possibility of failure (aiming at reducing at less than 5% within ten years after implantation) and the cost for the secondary actions.

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