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Molecular Interactions in Scaffolds for Bone Tissue Engineering: Why a Fundamental Approach is Needed

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Abbreviations: SGBR: Scaffold-Guided Bone Regeneration

Introduction

Aliphatic polyesters are a versatile class of polymers with tunable physico-chemical properties, compatible with additive manufacturing, thereby enabling the conception of scaffolds for biomedical applications. Notably, polymeric. scaffolds reinforced with ceramic bioactive particles have attracted attention in the last decades in scaffold-guided bone regeneration (SGBR). These composite materials exhibit enhanced properties compared to pure polymers. Biocompatibility or osteointegration are improved because of the chemical composition of the ceramic particles that resemble natural bone [1-3]. The mechanical performance of the composite can also be improved depending on the size of the particles within the matrix [4-7], but only for low ceramic contents until recently [6, 8-11].

Recent advances in ceramic particle homogeneity and dispersion during extrusion-based additive manufacturing have prevented particle agglomeration and allowed fabricating high-quality composite constructs with ceramic contents that approach that of natural bone [12-14]. In physiological conditions (37°C in a hydrated environment), water becomes an essential component of the system by adding water-ceramic and water-polymer interactions, especially plasticization. In such hydrated material, the investigation of mechanisms occurring at the molecular scale, especially those at the polymer-ceramic interfaces, is a fundamental approach necessary to predict the mechanical behavior at the macroscale. Surprisingly, there is a lack of studies in literature that have adopted a material science's point of view to depict the complex interplay of water molecules, polymeric chains and ceramic particles. Even worse, the mechanical behavior of these composite materials in physiological conditions, although essential in a biomedical context, is not systematically investigated.

The complex interplay at the molecular scale in hydrated composites

The parameters affecting the polymeric structure are traditionally studied separately. The complexity of the interplay of interactions at the molecular scale arises from the combination of the effects (Figure 1) [15]. For instance, material science has demonstrated that the incorporation of a ceramic phase into the polymeric matrix modifies stress transfer in the vicinity of particles [16], reduces the mobility of the chains [17], and changes the crystallinity [4, 11].Or, in hydrated polymers, water molecules break the hydrogen bonds bridging the polymeric chains and create their own bonds with the chains or with other water molecules. After the complete rearrangement of the hydrogen bonds network, called water plasticization, different phases of water coexist [15,18]. Mechanistically, the polymeric chains

gain more mobility, which affects the thermal and mechanical properties at the macroscale [15,19,20]. Further exposure to water leads to the breakage of stronger types of bonds, the chemical bonds in the polymeric chains, a degradation mechanism called hydrolysis [21].

Although there is an abundant literature on plasticization or the role of ceramic particles in polymer, the combination of the two effects appears unpredictable given the cascade of mechanisms that results: ceramic particles promote the diffusion of water in the composite and accelerate plasticization [22,23]; the polymeric matrix swells, which redistributes the stress [24]; the crystalline regions of the polymer, where chains are ordered, limits the diffusion of water, but crystallites are dissolved from amorphous regions [25]; ceramic dissolution and hydrogen bonds disruption result in a loss of the stress transfer at hydrated polymer–ceramic interfaces [26, 27]; finally, water adhering to polymeric and ceramic binding sites has also been reported [28], which opens the way toward the development of water-mediated interfaces [29], or interfacial strength governed by hydration repulsion or hydrophobic attraction [30].

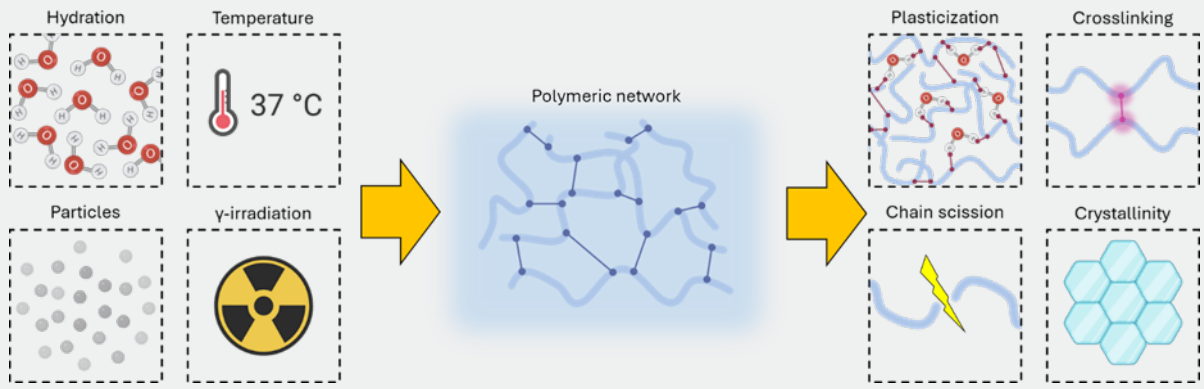

Figure 1: Hydration, temperature, ceramic particles or irradiation have an impact on the structural organization of polymers at the molecular scale. When their effects are combined, a cascade of mechanisms, including plasticization, cross-linking, chain scission, or changes in crystallinity, occurs. This complex interplay complexifies the prediction of the macroscale properties, such as the mechanical and thermal properties. The elucidation of these phenomena remains, however, essential in the context of SGBR.

Furthermore, the effect of γ-irradiation, commonly used in the sterilization of biomedical implants [31], can be responsible for chain scission or cross-linking, depending on the irradiation dose [32-35]. These structural changes therefore affect the mobility of the polymeric chain and so the crystallinity, which further complexifies the interactions with ceramic particles or water molecules [14,36]. Temperature in physiological conditions can also be critical for aliphatic polyesters with a glass transition temperature just above 37°C, like poly-lactic acid. At physiological temperature, polymeric chains gain mobility and ease the penetration of water [37], thereby leading to additional plasticization and hyperelasticity [14,15]. The elucidation of the interplay at the molecular, and sub-molecular scale must be taken seriously to develop materials with adequate properties in physiological conditions. Current and new characterizations techniques are essential tools to extend our understanding in this field.

New Characterization Techniques for a Fundamental Approach

Studies on the physico-chemical characterizations of scaffolds for SGBR have traditionally focused on macroscopic characteristics, such as mechanical testing or degradation rate for instance, and microscopic features, with microstructure imaging or element and chemical bond identification for instance. A new fundamental approach would consist in probing matter at the sub-molecular scale. Nuclear magnetic resonance, wide frequency range spectroscopy or non-linear optics already enable, the measurement of the strength of the hydrogen bonds [38], the detection of the different states of water [39], the observation of the interactions of water with hydrophobic polymers [40], or the evaluation of the distances between the water molecules and the polymeric chains [41].

However, the revolution in this approach resides in the emergence of new technologies, such as ultrashort infrared laser pulses, that enable novel characterization techniques that examine matter at sub-femtosecond timescales. For instance, X-ray free-electron lasers, vacuum ultraviolet free-electron lasers, or ultrafast two-dimensional infra-red spectroscopy can examine the electronic structures of water molecules [42], the reorientation dynamics of individual molecules within water structures [43] or decipher water hydration structure, like in undecamer water rings $H_2O)_{11}$ [44]. With the continuous improvement of computational performances, molecular dynamics simulations could bridge the gap between molecular dynamics and quantum mechanics [45]. Such techniques could reveal unique observations and change our understanding of the molecular interactions in hydrated composites.

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