

Degradable particulate composite reinforced with nanofibres for biomedical applications

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Received 1 July 2008; received in revised form 27 October 2008; accepted 25 November 2008
Available online 10 December 2008

Abstract

Nanofibre-based structures and their composites are increasingly being studied for many biomedical applications, including tissue engineering scaffolds. These materials enable architectures resembling the extracellular matrix to be obtained. The search for optimized supports and carriers of cells is still a major challenge for the tissue engineering field. The main purpose of this work is to develop a novel composite structure that combines microparticles and nanofibres in reinforced polymeric microfibres. This innovative combination of materials is obtained by melting extrusion of a particulate composite reinforced with chitosan nanofibre meshes (0.05 wt.%) produced by the electrospinning technique. The reinforced microfibres were analysed by scanning electron microscopy and showed a considerable alignment of the chitosan nanofibres along the longitudinal main axis of the microfibre composite structure. The tensile mechanical properties revealed that the introduction of the nanofibre reinforcement in the particulate microfibre composite increased the tensile modulus by up to 70%. The various structures were subjected to swelling and degradation tests immersed in an isotonic saline solution at 37 °C. The presence of chitosan nanofibres in the particulate microfibres enhances the water uptake by up to 24%. The combination of good mechanical properties and enhanced degradability of the developed structures is believed to have great potential for various biomedical applications, including three-dimensional fibre mesh scaffolds to be applied in the field of bone tissue engineering.
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Keywords: Biodegradable materials; Biomaterials; Nanofibres; Polymeric composite; Tissue engineering

1. Introduction

The extracellular matrix (ECM) of connective tissues is a biological example of a fibrous structure based in collagen fibrils reinforced by other fibrous structures such as glycosaminoglycans and polysaccharides. Collagen fibre, being the primary structural element of the ECM of many tissues, provides a target for the design of new fibrous

structures intended for tissue engineering scaffolding. Type I collagen molecules assemble into triple helix collagen fibrils which are long filamentous structures organized to form collagen fibrils and hierarchically aligned in overlapped bundles (each fibril may have more than 700 individual collagen protein strands) [1]. The precise spatial organization of collagen structures in vivo determines the properties of the tissues, such as the tensile strength. In the case of bone, entire collagen triple helices lie in a parallel staggered array to ensure continuity to its structure. Bone is an outstanding structural tissue and a true nanocomposite reinforced by the HAP crystals. It is a complex and highly specialized connective tissue that constitutes the skeleton of the vertebrates [2]. Structurally, bone is organized and assembled in various levels of hierarchical

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units elegantly designed at several length scales, nano to macro, to ensure its multiple functions. The structure of bone inspired the authors to develop the ternary composites proposed in the present paper.

Generally, the collagen fibrils in bone are 50–500 nm in diameter and can be hundreds of micrometres long. In native tissues, these fibrils are further assembled into larger collagen bundles that may be several micrometres in diameter and millimetres to centimetres in length [3]. The anisotropic fibril architecture of natural ECM has important implications on the cell behaviour [4]. These collagen assemblies are characterized by high stiffness and tensile strength, which imparts resistance to compression, tensile and shear loads to the tissues [5]. It is therefore advantageous to engineer tissues consisting of organized fibres to exploit these physiological and mechanical cues [6].

One of the most important requirements for a nanofibre-reinforced composite is that the external stresses applied are efficiently transferred to the nanofibres, allowing them to take a disproportionate share of the load. If the interface properties are adequate and the fibre distribution is homogeneous, the shear stresses developing at the interface of each nanofibre will support the stress applied to the composite [7]. An efficient composite requires that the nanofibres be uniformly dispersed as isolated nanofibres and individually coated with the polymer that constitutes the continuous matrix of the composite [8]. Good dispersion also allows for a more uniform stress distribution and minimizes the appearance of stress-concentration points. A random orientation of fibrous composites results in lower efficiency of reinforcement than does perfect alignment, but perfect alignment generates anisotropy in the mechanical properties. The alignment is necessary when maximization of the strength and modulus are needed in particular directions [9].

Electrospinning has been explored as an efficient process for obtaining nanofibres with diameters in the submicrometre range [10]. The interesting properties of electrospun fibres include increased surface-area-to-volume ratio as a consequence of the diameter, and the high interconnectivity and porosity of the nanofibre meshes at the micrometre length scale [11]. Another inherent feature of the electrospun nanofibres is their ability to mimic the ECM of a variety of tissues, which can create a more favourable microenvironment for the cells [12]. Thus, their use in tissue/organ repair and regeneration as biocompatible and biodegradable medical implant devices has been suggested by many authors [13–15]. The nanoscale size of the biodegradable fibres may also offer advantages in inducing a specific kinetics of degradation. Different nanofibrous structures have already been produced by this technology using a number of both natural and synthetic polymers, such as collagen [16], chitosan [17], silk fibroin [12] and polycaprolactone [18] or polylactides [19]. An important disadvantage of collagen, gelatine, keratin and elastin is their animal origin, remaining a concern in relation to immunogenicity and disease transmission [20]. The present

work uses biomaterials from a marine source as an alternative. Chitin is a biopolymer found in nature and is derived mainly from the exoskeletons of crustaceans, insects and molluscs, and the cell wall of micro-organisms. Chitin is a glucose-based polysaccharide. Chitosan is an alkaline deacetylated derivative of chitin. This material is a polysaccharide and shares some structural similarities with glycosaminoglycans. Chitosan is non-cytotoxic, biodegradable and reported as potentially biocompatible [21].

Composite materials using synthetic and natural-based materials are increasingly proposed for biomedical applications [22–24]. The chronic inflammatory responses and cytotoxicity of some synthetic polymers are reduced or eliminated by the composition with natural polymers. Natural polymers such as chitosan [25], collagen [6], soy [20], alginate [26], silk [12] or starch [27] have already been proposed in many biomedical applications. The biological environment is prepared to recognize these biopolymers and to interact with them metabolically. Another attractive feature of natural polymers is their ability to be cleaved by naturally occurring enzymes, facilitating degradation by physiological mechanisms [28].

Synthetic biodegradable polymers are already used extensively in the biomaterials field including biodegradable aliphatic polyesters, such as poly(lactic acid), poly(glycolic acid) or poly(caprolactone) and its copolymers. Most synthetic polymers are degraded via hydrolysis. The polyester bonds of synthetic polymers are hydrolysed in non-toxic natural metabolites and are eliminated from the body by the normal physiological processes [29]. Therefore, composite materials using synthetic and natural-based polymer materials are increasingly being developed and designed to improve not only the physical and chemical properties but also to improve biological performance [22,24]. The basis of the composite material in the present work is a microparticulate composite of chitosan microparticles dispersed in poly(butylene succinate) (PBS). This biodegradable material has already been shown to have excellent biological performance both *in vitro* and *in vivo* for bone and for cartilage tissue engineering applications [30–33] and tested in various three-dimensional (3D) morphologies. The nanofibres used to reinforce this composite are intended to improve some properties but to preserve the good biological performance already shown.

The aliphatic polyester PBS presents a hydrophobic character. However, the chitosan structure is rich in polar groups (–OH and –NH₂). Therefore, its presence in the composite resulted in a significant increase in the hydrophilicity [32]. The microparticulate composites (with particles of chitosan) have thus enhanced the hydrophilic properties, thus resulting in a higher variation in mass and tensile modulus, as was confirmed after degradation tests [34]. The kinetics of loss of tensile modulus after degradation can be modulated by the introduction of nanofibres in the particulate composite. The fibrous reinforcement provides additional elastic modulus but also enhances the surface-area-to-volume ratio, facilitating access of water to the

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