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Biocompatibility and chemical reaction kinetics of injectable, settable polyurethane/allograft bone biocomposites

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ABSTRACT

Injectable and settable bone grafts offer significant advantages over pre-formed implants due to their ability to be administered using minimally invasive techniques and to conform to the shape of the defect. However, injectable biomaterials present biocompatibility challenges due to the potential toxicity and ultimate fate of reactive components that are not incorporated in the final cured product. In this study the effects of stoichiometry and triethylenediamine (TEDA) catalyst concentration on the reactivity, injectability, and biocompatibility of two component lysine-derived polyurethane (PUR) biocomposites were investigated. Rate constants were measured for the reactions of water (a blowing agent resulting in the generation of pores), polyester triol, dipropylene glycol (DPG), and allograft bone particles with the isocyanate-terminated prepolymer using an in situ attenuated total reflection Fourier transform infrared spectroscopy technique. Based on the measured rate constants, a kinetic model predicting the conversion of each component with time was developed. Despite the fact that TEDA is a well-known urethane gelling catalyst, it was found to preferentially catalyze the blowing reaction with water relative to the gelling reactions by a ratio >17:1. Thus the kinetic model predicted that the prepolymer and water proceeded to full conversion, while the conversions of polyester triol and DPG were <70% after 24 h, which was consistent with leaching experiments showing that only non-cytotoxic polyester triol and DPG were released from the reactive PUR at early time points. The PUR biocomposite supported cellular infiltration and remodeling in femoral condyle defects in rabbits at 8 weeks, and there was no evidence of an adverse inflammatory response induced by unreacted components from the biocomposite or degradation products from the cured polymer. Taken together, these data underscore the utility of the kinetic model in predicting the biocompatibility of reactive biomaterials.

1. Introduction

Injectable biomaterials offer significant advantages over pre-formed implants or autologous grafts, in part due to their ability to be administered using minimally invasive techniques and conform to defects with a complex geometry. In the treatment of bone defects injectable biomaterials are of interest for a number of clinical indications, including filling of contained defects where the structural bone is intact, as well as defects in trabecular bone at non-weight-bearing sites [1].

Since their discovery in 1982 [2] calcium phosphate cements (CPCs) have been successfully introduced into clinical use due to their ease of use, osteoconductivity, and fast setting times [3–6]. However, their poor shear and fatigue properties can lead to brittle fracture when CPCs are subject to physiologically relevant dynamic loads [7,8]. Hydroxyapatite (HA) cements have been combined with hydrogels (e.g. dextran [9] or sodium hyaluronate [10]) to form osteoconductive injectable bone void fillers (BVFs). Other BVFs for metaphyseal bone defects include non-setting allograft pastes [11], which are typically delivered using viscous carriers such as hyaluronic acid or glycerol [12]. While injectable pastes promote bone healing, they do not set in situ, resulting in weak mechanical properties.

Two component lysine-derived reactive polyurethanes (PURs) have been investigated as injectable BVFs and cements, and have been shown to elicit a mild and transient inflammatory response

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