Acta Biomaterialia 6 (2010) 820–829

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

# Porous bioactive diopside ($CaMgSi_2O_6$) ceramic microspheres for drug delivery

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ARTICLE INFO

*Article history:*
Received 13 June 2009
Received in revised form 22 September 2009
Accepted 28 September 2009
Available online 1 October 2009

*Keywords:*
DP microspheres
Porosity
PLGA modification
Drug release

ABSTRACT

Ideal bioceramic microspheres for bone regeneration need to be bioactive and degradable, but at the same time possess a controlled drug-release ability. The main disadvantage of the currently available microspheres is their failure to combine these properties. The aim of this study is to develop bioactive ceramic microspheres with optimal properties for use in bone-tissue regeneration. In this study, we utilize diopside ($CaMgSi_2O_6$, DP) with proven excellent bioactivity and degradation ability to develop microspheres by controlling their porosity and size, and further modify their surface with polymer to enhance and control their drug-loading/release ability. The phase composition, surface and inner microstructure, and porosity of DP microspheres were tested. Results indicate that carbon powders as porogens with various contents determined the porosity of the porous DP microspheres. The drug-loading and release ability of dexamethazone (DEX) from porous DP microspheres was regulated by their porosity and size. Poly(lactide-*co*-glycolide) modification forms a film on the surface of DP microspheres and resulted in an enhanced DEX-loading and release ability of the microspheres. Results presented here indicate that the developed DP microspheres have the potential to be used as bioactive filling materials for bone-tissue regeneration.



## 1. Introduction

Significant attention is focused on the use of microspheres as carriers for proteins and drugs. The main advantage of microspheres, compared to the more traditional macroporous block scaffolds, is that microspheres possess not only better drug-delivery properties, but also the ability to fill the bone defects with irregular and complex shapes and sizes [1]. The interstitial space between the particles of the microspheres is crucial for effective and functional bone regeneration [2–4] as they allow for both bone and vascular ingrowths.

Current available microspheres are made of ceramics, polymers or their composites. Polymers microspheres, such as poly(lactide-*co*-glycolide) (PLGA) and poly(hydroxybutyrate-polyhydroxyvalerate) (PHBV), are resorbable but their bioactivity is compromised [5,6]. On the other hand, ceramic microspheres, such as hydroxyaptite (HAp) ceramics, are bioactive, but they lack the controlled porosity, which to some extent influences the controlled drug release [7–10]. Although nano-sized microspheres have been developed for drug delivery, their small sizes compromise their use in cell-based therapy for bone-tissue engineering [11–13]. Their nano-sizes result in an inadequate interstitial space for tissue and vascular ingrowth and are also too small to carry the bone-forming cells. It is therefore important to develop new bioactive larger-size microspheres (hundreds of micrometers) with controlled drug-delivery properties and improved degradation rate.

Diopside ($CaMgSi_2O_6$, DP) ceramics possess excellent in vitro apatite-formation ability, in vivo bioactivity and degradability [14–17], and improved mechanical strength compared to hydroxyapatite [16]. In the current study, we explored the use of bioactive DP as microspheres for drug delivery and as filler materials for bone-tissue regeneration.

It is known that the porosity and surface properties of microspheres may influence their drug-delivery properties [18–20]. Carbon powders, as porogens, have been used to prepare porous alumina ceramic bulk [21]. In the present study we used carbon powders as porogens in the preparation of porous DP ceramic microspheres to obtain various porosities by controlling the porogen contents. We previously showed that polymer modification of $CaSiO_3$ ceramic scaffolds can form a layer of polymer film (3 μm thick) on the surface of scaffold walls [22]. We propose that the polymer modification of DP microspheres will also form a polymer film and this layer of film may further control drug release. Therefore, the aim of this study is to develop DP microspheres with combined bioactivity, degradability and controlled drug delivery for bone-tissue regeneration through controlling the spheres' porosity, size and through their surface modification with polymers.

## 2. Materials and methods

### 2.1. Preparation of porous diopside ceramic microspheres

DP powders were synthesized by the coprecipitation process using tetraethyl orthosilicate ($(C_2H_5O)_4Si$, TEOS), magnesium

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doi:10.1016/j.actbio.2009.09.025

nitrate hexahydrate ($Mg(NO_3)_2{\cdot}6H_2O$) and calcium nitrate tetrahydrate ($Ca(NO_3)_2{\cdot}4H_2O$) as raw materials according to our previous publication [14].

Porous DP microspheres were prepared using alginate cross-linking with $CaCl_2$ solutions in combination with the porogen of carbon powders with a size of 10 μm (Barnett Chemicals, USA). Steps include mixing DP powders (<60 μm) and different contents of carbon powders (the mass ratio of carbon/(DP + carbon): 0%, 20%, 40% and 60%) with 3wt.% sodium alginate water solution to obtain a uniform and well-dispersed slurry (the concentration of

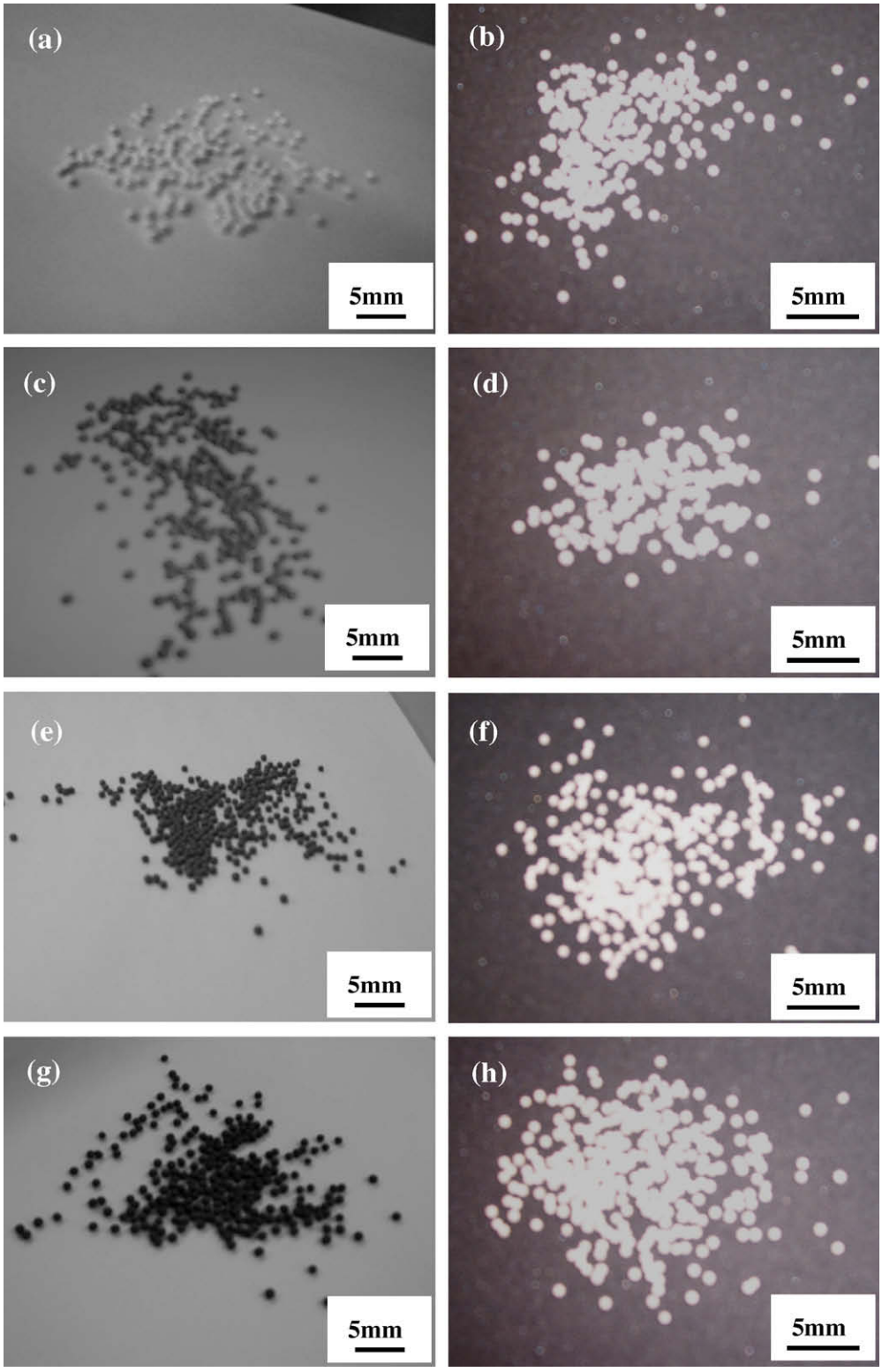


**Fig. 1.** Optical microscopy of diopsode (DP) microspheres with different carbon contents before sintering (a, c, e and g) and after sintering (b, d, f and h): (a) and (b) no carbon; (c) and (d) 20% carbon; (e) and (f) 40% carbon; (g) and (h) 60% carbon. The size of spheres before and after sintering is about 1000 μm and 800 μm, respectively.

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