Fabrication of Porous Substrates: A Review of Processes Using Pore Forming Agents in the Biomaterial Field

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ABSTRACT: This paper is a review of solid and casting manufacturing processes able to create porous materials, mainly in the biomaterial field. The considered methods are based on pore forming agents that are removed either by heating or by dissolution. All techniques lead to products presenting pores with amount, size, and shape are close to those of the initial pore formers. Porosities up to 90% with pores ranging from 1 to 2000 μm are reported. Major differences concern macrointerconnections that are more frequently obtained using foams, or porogens which undergo a melting stage during firing. Casting methods combined with solid free form fabrication are promising for the design of porous network through the manufacturing of 3D scaffolds corresponding to the desired porosity. J Pharm Sci 97:1135–1154, 2008

Keywords: pore former; porosity; texture; compaction; casting; foaming; bioceramics; biomaterials; powder technology; processing

INTRODUCTION

Porous materials, especially porous ceramics, are of significant interest in many fields due to their wide range of applications at all length scales, ranging from filtration membranes[1] and catalyst supports[2,3] to biomaterials such as scaffolds for bone ingrowth[4–6] or drug delivery system.[7–13] Porous systems are also used as piezoelectric materials,[14,15] as thermally or acoustically insulating bulk materials or coating layers.[16] Constraints vary according to the different cases. Whatever the application, there is an obligation to find a compromise between porosity and sufficient mechanical strength.

Moreover, porous system technology presents an interesting interdisciplinary challenge for drug release, involving the pharmaceutical, chemical and material engineering, biomaterials, and medical communities.[17] In the case of biomaterials loaded with therapeutic agents, controlled porosity allows their liberation on a targeted site by a slow, local, continuous, and controlled flux (over days, months or years). This release is linked to microporosity which consists in pores with size less than 10 μm in diameter. This microporosity allows the ions produced during degradation of bioactive ceramics to diffuse out of the implant[18] but also the slow release of included drug.[19] Flux of a substance through a layer is dependent both on the characteristics of the drug substances, that is, diffusivity, concentration gradient, solubility, and on the microstructure of the porous product, that is, pore size distribution[20] and tortuosity.

In the bioceramic field, it is expected to use ceramic implants with an additional larger

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porosity, called macroporosity, promoting integration with biological tissues, especially bone ingrowth.[18,19,21–30] The occurrence of these processes is affected by macropore size and ratio, as well as morphology.[31–33] As indicated by Hulbert et al.,[34] macropores of at least 100 μm in diameter are needed to host the cellular and extracellular components of bone and blood vessels and those greater than 200 μm in diameter are expected to be effective in osteoconduction.

Moreover, most studies suggest that pores have to be interconnected. The interconnections are the pathway between pores that favor cellular and vascular penetration and ensure bone ingrowth inside pores. *In vitro*, the minimal necessary interconnection size is 20 μm, but the most favorable one for cell penetration is over 40 μm.[32] *In vivo*, an interconnection size of over 20 μm allows cell penetration and chondroid tissues formation inside macropores. However, an interconnection size of over 50 μm can assure mineralized bone formation. Interconnections act only as pathways, thus pore size has to be larger than interconnection size.[32] Interconnection pathways have generally a size ranging from 10 to 100 μm and consequently are sometimes called mesoporosity.[35]

To impart macroporosity to ceramic bodies, various methods are known to be used. Most of them are based on admixing templates called porogens or pore forming agents, whatever the manufacturing process (Fig. 1). This porogen can be either a foreign combustible organic material that burns away during firing or heating, leaving free spaces and voids in the resulting body[36] or a soluble additive that leaves pores by dissolution.

TYPE OF PROCESS	**Casting processes** *Cement* *Slurry*		**Solid processes** *Compaction* *Extrusion*
METHOD	**Direct** *Without sintering (cement)*		**Indirect** *With sintering*
NATURE OF POROGEN	**Gaseous**	**Liquid**	**Solid** *Dispersed powder* *3D skeleton*
REMOVAL OF POROGEN	**Heating** *Sublimation* *Evaporation* *Melting* *Calcination*		**Dissolution** *During process* *In situ*

Figure 1. Macroporous materials: manufacturing processes using porogens.

The first method allows to produce an interconnected pore system when polymer fibers or a mixture of porogens are used.[15,35,37–39] The salt-leaching method does not require firing, but it usually leads to closed pores that are only connected by small-diameter connecting channels.[37] Standard manufacturing methods involving either dispersed porogens or bubbles do not allow a precise control of pore size, shape, and spatial distribution.[40] Furthermore, connectivity obtained with such structures is poor in comparison to the volume of the pores[41] and finally, these drawbacks lead to low mechanical strength.[40]

Several processes are developed to manufacture porous ceramics with various pore characteristics. They include, as summarized in Figure 1, solid (dry) processes which are essentially compaction and extrusion techniques and casting (wet) processes which consist in molding a slurry (dispersion of ceramic powder into a liquid) or a cement paste. In that last case, no further sintering step is required for cohesion acquisition and is then considered as a direct method. The slurry techniques allow the fabrication of intricate shaped-bodies with controlled microstructure, especially in the case of replication method.[42–44]

This paper, summarizes the different methods to create porosity in the biomaterial field mainly bioceramics and calcium phosphate cements. The considered processes are all based on pore forming agents and they will be presented according to the way they are removed, either by heating (sublimation, evaporation, melting, and calcination) or dissolution (during process or *in situ*). This review does not consider porous materials obtained from processes such as solvent evaporation, phase separation, coacervation, encapsulation, and spray-drying methods. Fabrication of porous ceramics through conversion of coral skeleton (replamineform process) or natural bone[45] as well as electrophoretic deposition technique[46] are not on the scope of this review as they do not require addition of porogen to create high porosity. This paper only relates to the methods able to create porosity, on the micrometer range, that, from 1 to 1000 μm, by a solid way or by a casting method.

This review is divided into two parts relative to the way of elimination of the pore forming agent. The first part concerns the elimination by heating whereas the second one considers the elimination by dissolution. Each part distinguishes solid and casting manufacturing processes.