Ultrahigh Drug Loading and Release from Biodegradable Porous Silicon Aerocrystals

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ABSTRACT SUMMARY

Biodegradable porous silicon (pSi) is under assessment for the controlled release of both proteins and poorly-soluble API formulations. Super-critical drying of ultrahigh porosity (90%) porous silicon is shown here to preserve much higher mesopore volumes (up to 4mL/g) and surface areas (up to 600m^2/g) than achievable with standard air drying. The payloads and physical state of the model drug (S) (+) ibuprofen, as loaded within a super-critically dried porous silicon carrier matrix, were quantified and assessed using TGA, DSC, cross-sectional EDX, XRD, Raman mapping and FT-IR. In-vitro biodegradability was assessed using molybdenum blue assay and drug release using RP-HPLC. Entrapped drug payloads as high as 70%w/w have been achieved, substantially higher than values reported for other mesoporous materials. The entrapped (S) (+) ibuprofen showed faster release than bulk (S) (+) ibuprofen.

INTRODUCTION

It is estimated that 40% of new drug compounds may be regarded as poorly-soluble, with that percentage even higher for certain therapeutic classes[1]. Controlled release systems have gained increased recognition as an alternative way to deliver APIs falling under Class II of the classification system (low aqueous solubility or high intestinal permeability)[2].

Non-polymeric biodegradable matrix systems have an advantage over reservoir systems in the avoidance of dose dumping of the API; moreover, polymeric encapsulants are not required to control the release of the active drug. One key function of any controlled drug delivery system should be the capability to carry a high payload of the API. A second is to control the release of the loaded API in a desired way by enhancing the dissolution behaviour. Several therapeutically active APIs have been loaded in mesoporous materials[3,4] out of which Class II drugs have been studied most, mainly because their dissolution can be improved by mesoporous carriers. Payloads as high as 50% w/w have been reported for mesoporous carriers[4]. In this study, we report the development of a novel super-critically dried form of biodegradable porous silicon, an 'aerocrystal'[5]. With high surface area and high pore volume, such an aerocrystal has the ability to carry high drug payloads whilst offering nano-entrapment of poorly-soluble drugs, such as (S) (+) ibuprofen.

EXPERIMENTAL METHODS

Porous silicon layers were prepared on silicon wafers (p-type, 5-20 mΩcm resistivity) by anodisation[6] and electrochemically detached from the substrate. Super-critical drying of the layers (using a Quorum Technologies Ltd K850 dryer) was carried out with carbon dioxide. After drying, the hydrophobic sample was rendered hydrophilic by thermal oxidation in a 1% O_2 (in N_2) gas mixture at 600^{0}C for 16hr. Pore characteristics of the resulting aerocrystals were determined by gas adsorption/desorption analysis. Biodegradability was assessed in-vitro over 15 days under sink conditions with tris buffer, pH 7.4 and 37^{0}C.

A melt loading technique was used for both flakes and powders. To the molten mass of (S) (+) ibuprofen at 80^{0}C, the aerocrystal was added under stirring to ensure a homogeneous mixture. The loaded co-formulation was then gently ground in a mortar and pestle to separate agglomerated particles. Studies were conducted on both hydrophobic as-anodised aerocrystal flakes (TGA, DSC, EDX, MB assay) and hydrophilic aerocrystal powders (TGA, DSC, XRD, FTIR, Raman, HPLC).

RESULTS AND DISCUSSION

From the gas adsorption/desorption isotherms, the surface area, pore volume, and average pore diameter of the main sample used for release profiling were calculated to be, respectively: 587m^2/g, 3.837mL/g and 26.1nm before oxidation and 421m^2/g, 2.277mL/g and 21.5nm after oxidation.

The total loading of (S) (+) ibuprofen in this sample was found to be 74.6% by TGA. DSC was used to distinguish between the melting endotherm

of (S) (+) ibuprofen inside the pores and on the surface.

SEM imaging and EDX analysis, in cross-section, was carried out after cleaving another loaded oxidized porous silicon layer ($573m^2/g$, 4.011mL/g, 28nm before oxidation and $415m^2/g$, 2.691mL/g, 26nm after oxidation); by revealing a freshly-exposed surface (Figure 1a), it is possible to detect the presence and distribution of elemental carbon, expected from, and after loading, (S) (+) ibuprofen; a uniform distribution can be seen through (Figure 1b) the layer at the points sampled shown in Figure 1a.

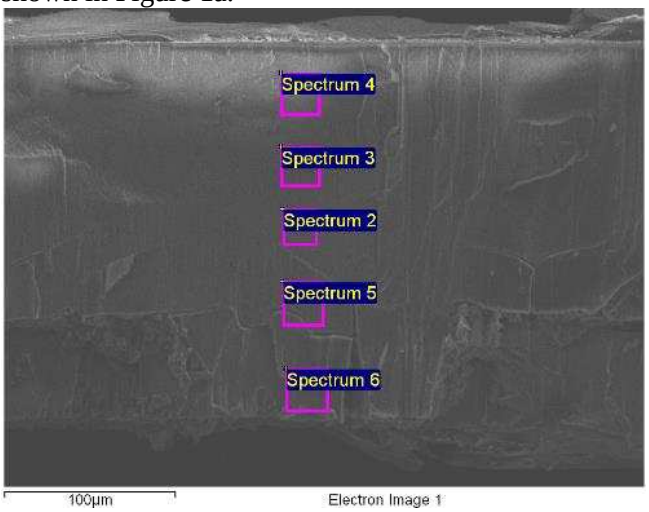

Figure 1a. Cross-sectional SEM image of a loaded pSi flake (sampling points for EDX shown).

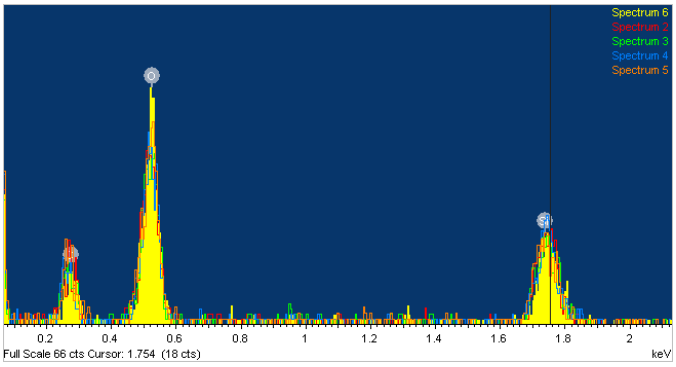

Figure 1b. Cross-sectional EDX spectra showing 'C' and 'O' after loading with Ibuprofen (peaks normalised to that of Si, shown for comparison).

Unloaded aerocrystal flakes biodegraded into silicic acid in-vitro with much faster kinetics than air-dried controls. This was consistent with the higher pore volumes and surface areas attained via supercritical drying. The release profile of aerocrystal loaded Ibuprofen microparticles is compared to bulk Ibuprofen microparticles in Figure 2. A significant improvement in dissolution rate was observed as a result of mesopore entrapment.

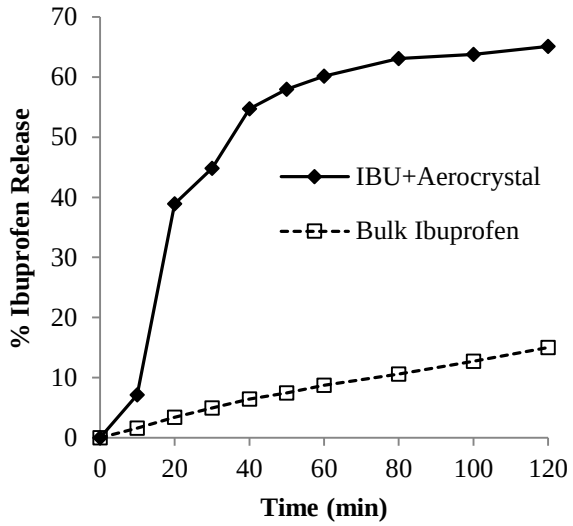

Figure 2. Release profile comparing (S) (+) ibuprofen loaded aerocrystal and bulk (S) (+) ibuprofen; USP type II, 50rpm, Phosphate buffer (pH 7.2), 37 ± 1^0C, sampling volume 2mL.

For such aerocrystal matrices, the maximum payload of small molecule drugs scales with pore volume and drug density within the mesopores. An even higher payload of 85±2%w/w has been achieved from preliminary melt loading studies with triclosan, an antibacterial, and our highest pore volume material (Figure 1a).

CONCLUSION

The ability of silicon-based aerocrystals to carry very high drug payloads and to be loaded by simple techniques has been demonstrated for the first time.

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