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Sol-gel processing of drug delivery materials and release kinetics

F. DE GAETANO, L. AMBROSIO*, M. G. RAUCCI, A. MAROTTA, M. CATAURO
Department of Materials and Productions Engineering, University of Naples "Federico II", Piazzale Tecchio, 80125 Naples, Italy
E-mail: catauro@unina.it

Silica, calcium (5 mol%) silicate and silica/polycaprolactone hybrid inorganic/organic amorphous materials, all mixed with sodium ampicillin, a broad-spectrum antibiotic, have been synthesized by sol-gel method. The amorphous nature of the gels was ascertained by X-ray diffraction analysis. Release kinetics in a simulate body fluid (SBF) have been subsequently investigated. The amount of sodium ampicillin released has been detected by UV-Vis spectroscopy and SEM. The release kinetics seems to occur in more than one stage. Finally FTIR measurements and SEM micrograph showed the formation of a hydroxyapatite layer on the surface of the samples soaked in SBF. All data showed that these materials could be used as drug delivery bioactive systems.

1. Introduction

Controlled, localized drug release offers several advantages over other delivery options. Plasma concentrations of drugs administered via injection, inhalation or ingestion, methods which can require repeated and relatively greater dosing and patient compliance, reflect the typical kinetics of an inefficient bolus delivery. Controlled local release system provide the desired constant drug concentrations at the delivery site, lower systemic drug levels and a reduced potential for deleterious side effects.

The benefits of such systems make them the ideal choice for the delivery of heparin as an inhibitor of smooth muscle cell proliferation in cardiovascular applications. These include localized delivery of the drug to a particular part of the body, assurance of treatment continuity in the nocturnal phase, drug stability, reduced need for follow-up care and optimized drug absorption.

Ampicillin is a β-lactam antibiotic that is active against both gram-positive and gram-negative bacteria and is widely used for the treatment of infections [1]. Most drugs can be administrated by a variety of routes, broadly defined as local and systemic [2].

As the systemic use of antibiotics may cause several side effects (sensitivity, resistant strains, superinfections) the local administration of antibiotics has received considerable attention [3].

Periodontitis is associated with bacterial inflections of a chronic nature, which lead to ongoing destruction of the periodontium and affect the outcome of the therapy [4]. The effective use of antibacterial agent for treatment of periodontal diseases requires an adequate drug concentration at the site of action, and a means of maintaining that level for a long enough period to allow the agent act [5]. Placing ampicillin directly into silica, $CaO\text{-}SiO_2$ and SiO_2/PCL hybrid, which are used as biomedical materials, leads the local antibiotic administration to prevent and treat bone infection in orthopaedic surgery [6]. The use of ceramic materials as carriers for drug release has been also extensively reported in the literature for many biomedical applications [6, 7]. However, there have been only a few studies about filling bone materials showing simultaneously controlled drug release and bioactive behaviour [8]. Actually, it seems to be a very attractive idea to look for materials that could release an antibiotic in a local and controlled way while showing bioactive properties [9–11]. These materials would prevent infections and also would ensure the bone integration and regeneration.

The aim of this work is the study of the antibiotic release kinetics from amorphous bioactive materials containing sodium ampicillin that have been synthesized by sol-gel method.

2. Experimental

Silica (SiO_2), calcium (5 mol%) silicate (Si/Ca) and silica/polycaprolactone hybrid inorganic/organic (Si/PCL) [12] amorphous materials, all mixed with sodium ampicillin (Sigma-Aldrich), a broad-spectrum antibiotic, were prepared by means of sol-gel process. The precursors were analytical reagent grade

**Present address*: Institute of Composite and Biomedical Materials CNR, Interdisciplinary Research Centre in Biomaterials (CRIB), University of Naples "Federico II", Piazzale Tecchio 80, 80125 Naples, Italy.

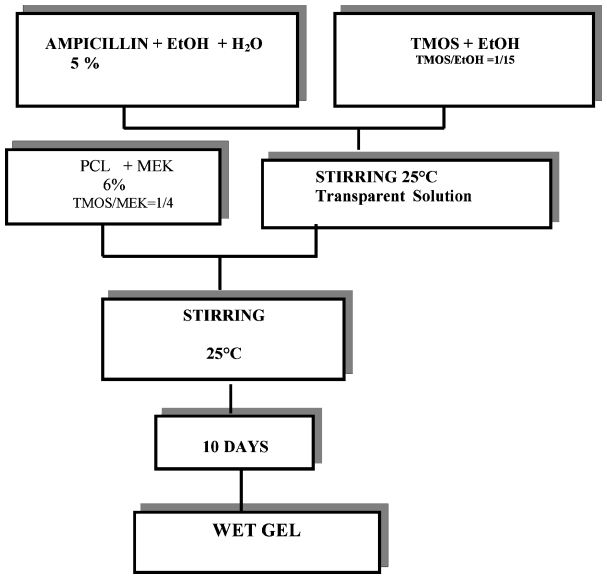

Figure 1 Flow chart of hybrid synthesis with ampicillin incorporated.

tetramethyl orthosilicate (TMOS) (Sigma-Aldrich), calcium nitrate (Sigma-Aldrich) and polycaprolactone (PCL $M_w = 65000$). Fig. 1 shows the flow chart of the Si/PCL gel synthesis. The flow charts of the other two synthesized gels are similar.

Measurements of ampicillin release from the studied materials were carried out on samples soaked in a simulated body fluid (SBF) with ion concentrations, as reported elsewhere [13], nearly equal to those of the human blood plasma. During soaking the temperature was kept fixed at 37 °C. The amount of sodium ampicillin released was detected by means of UV-VIS spectroscopy (Cary-3 varian). In order to establish the relationship between the UV absorbance of sodium ampicillin, at 230 nm, and the concentration of the sodium ampicillin solution, a calibration curve was drawn for standard solutions ranging from 0.010 to 1.0 mg of sodium ampicillin/ml, Fig. 2. All standard solutions were prepared with distilled water. Gel glass powders, with grains of diameter 90 μm $\leq d \leq$ 125 μm were soaked in a SBF using a solid/solution ratio 0.25 g/50 ml, for different times, 7, 14 and 21 days.

In order to verify their bioactivity, powers (170 + 230 mesh) of the reacted samples were then submitted to IR spectroscopy for ascertaining the ability to form an apatite layer. Fourier transform infrared (FTIR) transmittance spectra, using a Mattson 5020 system, were recorded in the 400–1200 cm^{-1} on KBr palletized disks containing 2 mg of sample and 200 mg KBr.

An electron microscope equipped with an energy dispersive analytical system (EDS) Cambridge model S-240 was used in order to verify the morphology of the apatite deposition and to make a qualitative elemental analysis.

3. Results and discussion

After gelation the gels were dried by air and small glassy pieces were obtained, Fig. 3. The X-ray diffraction pattern, Fig. 4, of the dried Si/PCL gel exhibits, as well those of the other investigated gels, broad humps characteristic of the amorphous nature of the dried gels.

Kinetics measurements of ampicillin release from the studied materials were carried out in 20.0 ml SBF solution at 37 °C. At regular intervals 1.00 ml of solution was extracted from SBF solution and analysed at 230 nm for ampicillin quantification.

The calibration curve (Fig. 2) followed the Lambert and Beer's law:

$$A = \varepsilon l C$$

where A is the absorbance and C the concentration, ε is a proportionality constant (known as absorptivity and l is the path length which is constant) [14].

Ampicillin release profiles from SiO_2, Ca/Si and Si/PCL glasses are reported in Figs. 5–7. It was observed that ampicillin release from SiO_2 is complete in 400 min, while ampicillin release from Ca/Si and Si/PCL levels off more quickly, about in 250 min. The presence of polymer, polycaprolactone, as well the presence of Ca^{++} ions, significantly increases the release rate of the active ingredient. The increase in the release rate could be ascribed to a change in the network structure which results in an increase in the amount of water inside the matrix that may favour drug release.

The biphasic release observed in all cases suggests that the initial phase of release be thought to occur mainly by dissolution and diffusion of the drug entrapped close to or at the surface of the samples. The second and slower phase release was thought to involve the diffusion of drug entrapped within the inner part of

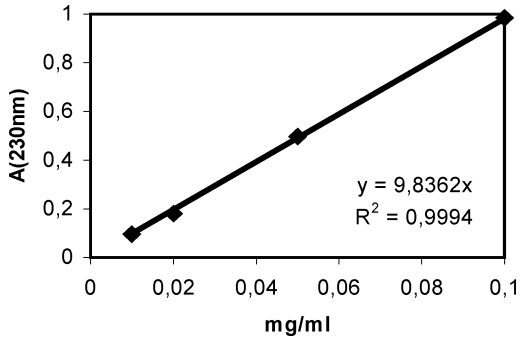

Figure 2 Calibration curve UV absorbance of sodium ampicillin.

Figure 3 Si/PCL hybrid with ampicillin incorporated after drying in air.

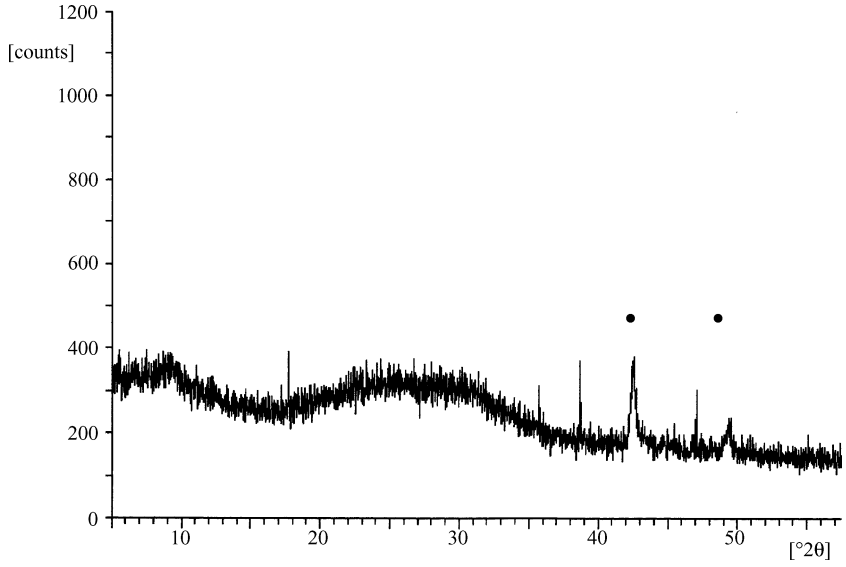

Figure 4 X-ray diffraction pattern of Si/PCL shows amorphous nature of samples, (●) holder.

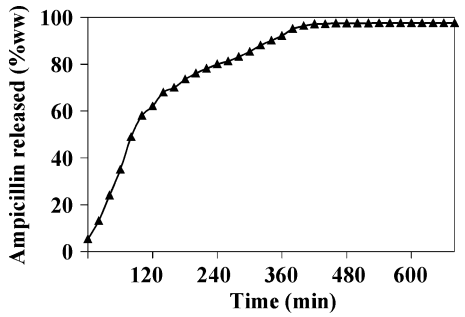

Figure 5 Time-dependent drug release plot for SiO_2 at 37 °C in SBF solution.

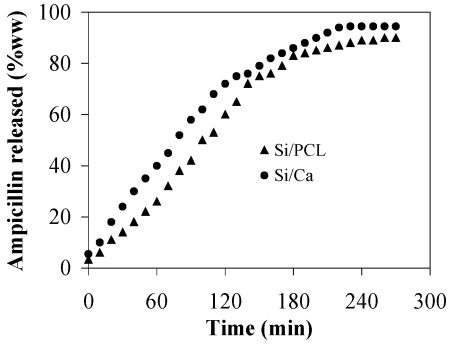

Figure 6 Time-dependent drug release plot for Si/Ca and Si/PCL at 37 °C in SBF solution.

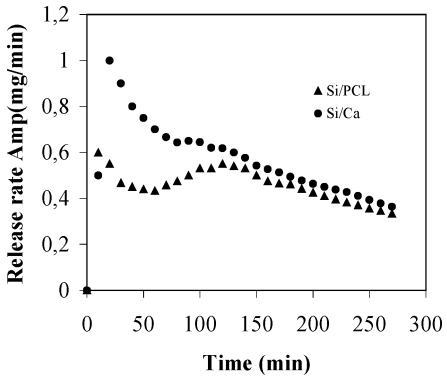

Figure 7 Time-dependent of drug release rate plot for Si/Ca and Si/PCL at 37 °C in SBF solution.

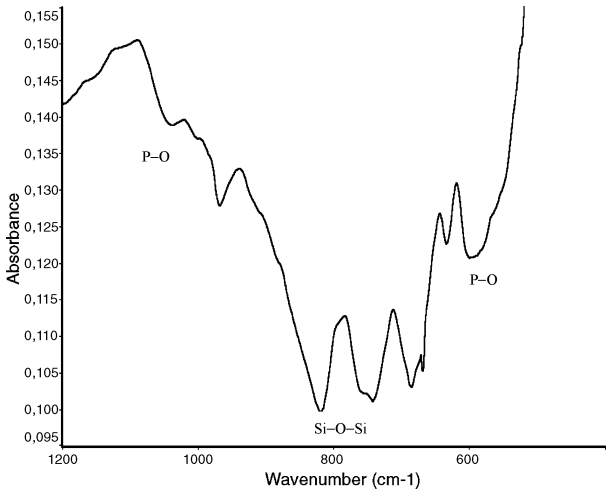

Figure 8 FTIR spectra of Si/PCL soaked in SBF for 14 days.

silica clusters. An interesting observation is the general presence of a lag period, which is indicative of the need for solvent penetration into the structure.

The FTIR spectra of Si/PCL samples after soaking 14 days in SBF for antibiotic release tests are reported in Fig. 8. These spectra evidence the formation of a hydroxyapatite layer given by the appearance of the 1160 and 1035 cm^{-1} bands, usually assigned to the P─O stretching [15], and of the 610 cm^{-1} band, usually assigned to P─O bending mode [15]. The splitting of the 610 cm^{-1} band into two others at 640 and 600 cm^{-1} can be attributed to formation of crystalline hydroxyapatite [16]. Finally, the band at 800 cm^{-1} can be assigned to the Si─O─Si band vibration between two adjacent tetrahedra characteristic of silica gel [15]. This supports the hypothesis that a surface layer of silica gel forms as supposed in the mechanism proposed in the literature for hydroxyapatite deposition [17]. The same behavior was observed in the other two investigated materials.

Moreover an evaluation of the morphology of the apatite deposition and a qualitative elemental analysis

were carried out by electron microscopy observations. In Figs. 8(a), 9(a) and 10(a) the SEM micrograph of SiO_2, Ca/Si and Si/PCL respectively samples soaked in SBF for 14 days. The characteristic apatite globular crystals are clearly visible. As it can be seen, the

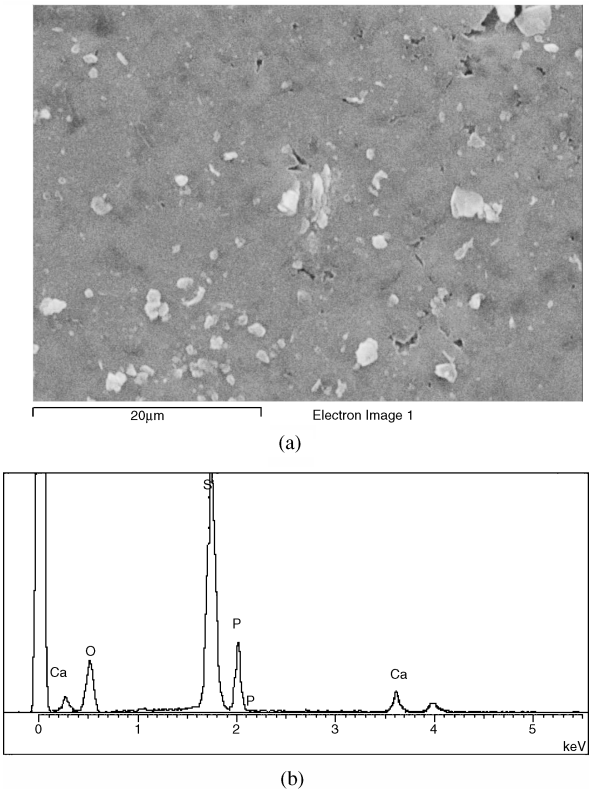

Figure 9 SEM micrograph (a) and EDS (b) of SiO_2 soaked 14 days in SBF.

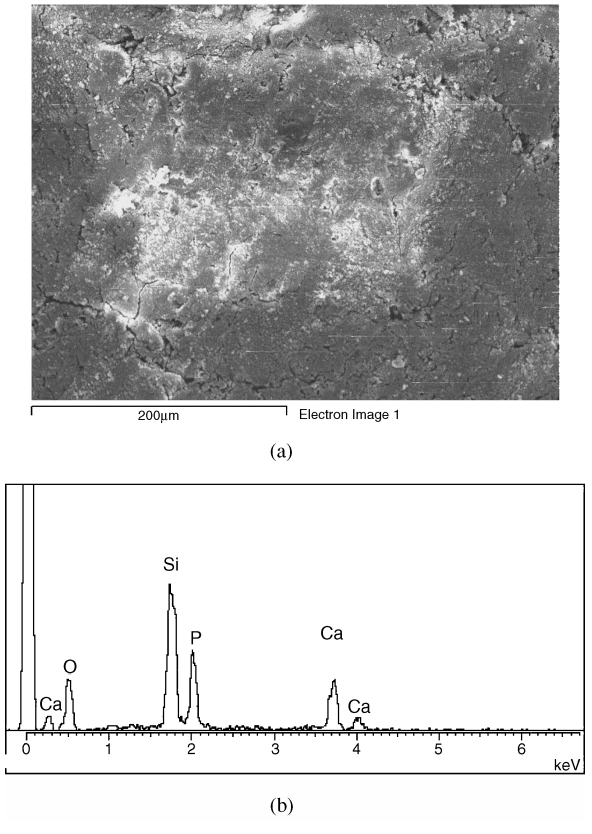

Figure 10 SEM micrograph (a) and EDS (b) of Si/Ca soaked 14 days in SBF.

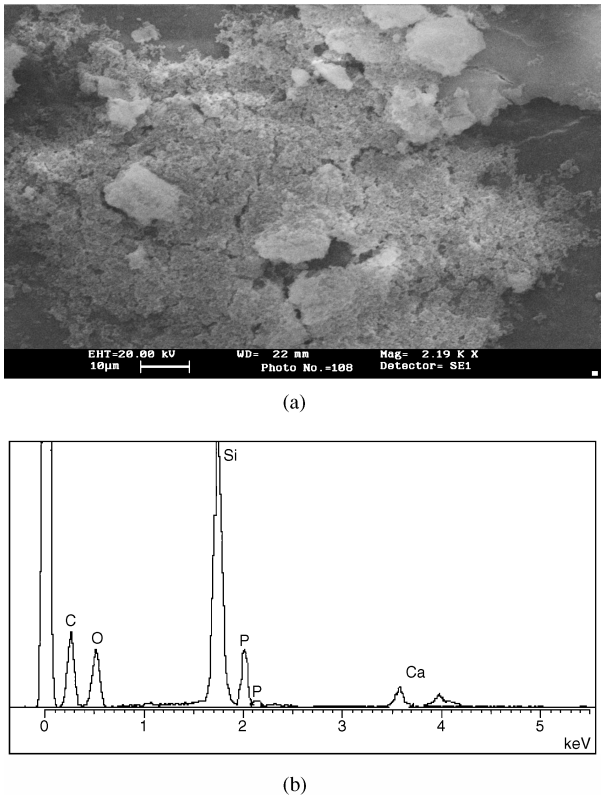

Figure 11 SEM micrograph (a) and EDS (b) of Si/PCL soaked 14 days in SBF.

EDS reported in Figs. 8(b), 9(b) and 10(b) confirm that the surface layer observed in the SEM micrographs is composed of calcium phosphate.

4. Conclusions

From the experimental results the following conclusions can be drawn:

(a) Amorphous materials containing ampicillin, suitable to be used as biomaterials, have been synthesized by sol-gel method

(b) The investigated materials supply high doses of the antibiotic during the first hours when soaked in SBF. Thereafter, a slower drug release occurs.

(c) A hydroxyapatite layer grows on the sample surfaces when they are in contact with SBF. The presence of ampicillin does not inhibit the bioactive behaviour of the studied materials.

Acknowledgments

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