

Nanohybrids for controlled antibiotic release in topical applications

L. Tamaro^a, U. Costantino^b, A. Bolognese^c, G. Sammartino^d, G. Marenzi^d,
A. Calignano^e, S. Tetè^{f,*}, F. Mastrangelo^f, L. Califano^d, V. Vittoria^a

^a Department of Chemical and Food Engineering, University of Salerno, via Don Melillo, 84084 Fisciano (Sa), Italy

^b Centro di Eccellenza Materiali Innovativi Nanostrutturati (CEMIN), Department of Chemistry, University of Perugia, via Elce di Sotto 10, 06123 Perugia, Italy

^c Department of Organic Chemistry and Biochemistry, University of 'Federico II', via Cynthia 6, 80126 Napoli, Italy

^d Department of Oral and Maxillofacial Sciences, University of 'Federico II', via S. Pansini 5, 80131 Napoli, Italy

^e Department of Experimental Pharmacology, University of 'Federico II', via D. Montesano 49, 80131 Napoli, Italy

^f Department of Oral Sciences, University 'G. D'Annunzio', via dei Vestini 31, 66100 Chieti, Italy

Received 6 October 2006; accepted 28 November 2006

Abstract

New polymeric composite materials containing a nanohybrid to be used for the controlled release of an antibiotic molecule, chloramphenicol succinate, have been formulated, prepared and characterised. The nanohybrid consists of a layered double hydroxide of Mg–Al hydrotalcite-type, in which the nitrate anions present in the host galleries were replaced with chloramphenicol succinate anions (CFS⁻) by a simple ion-exchange reaction. Different amounts of the hybrid material were incorporated in polycaprolactone and processed as films of 0.15 mm thickness. The composite materials were analysed by X-ray diffractometry and thermogravimetry and their mechanical properties were determined. They showed properties even better than those of the pristine polymer. The release process of the antibiotic molecules was found to be very interesting and promising for tuneable drug delivery. It consists of two stages: an initial stage of a very rapid burst, in which a small fraction of drug is released; and a second stage that is much slower, extending for a longer and longer time. This behaviour is profoundly different and much slower than that of a sample in which the antibiotic molecule is directly incorporated into the polymeric matrix. The parameters influencing drug release have been individuated and discussed.

© 2007 Elsevier B.V. and the International Society of Chemotherapy. All rights reserved.

Keywords: Nanohybrid; Polycaprolactone; Drug release; Antibiotic molecules; Hydrotalcites

1. Introduction

Delivery of drugs by new technologies is a highly topical challenge of polymer chemistry. So far, numerous products either on the market or in development are being produced and studied to obtain precise and tuneable control of molecular release. These controlled release drug delivery technologies have not only revitalised old pharmaceuticals but have also been directed toward newer biopharmaceuticals produced by genetic research [1–4].

Polymers have played a major role in the development of controlled release systems; as matter of a fact, the early polymeric drug delivery systems incorporated commercially available polymers [5–8]. Successively extensive research efforts aimed to improve both the polymers and the processes, as well as to apply them to the controlled release of a wide variety of pharmaceuticals or more general 'active' products. However, with the continued development of controlled-release technology, the need has arisen for materials with more specific drug delivery properties [9–12]. These materials include new biodegradable polymers, polymers with both hydrophilic and hydrophobic characteristics, and hydrogels that respond to temperature or pH variations. In addition, methods to overcome some of the barriers associated with current drug delivery are necessary. The possibility of reduc-

* Corresponding author. Tel.: +39 0871 355 4095; fax: +39 0871 355 4095.

E-mail addresses: tete@unich.it (S. Tetè),

filibertomastrangelo@hotmail.com (F. Mastrangelo).

ing, or even eliminating, oral administration of possibly dangerous drugs (such as anti-inflammatories, antibiotics, etc.) using new biocompatible polymers in which drugs are directly incorporated is currently under investigation. In the medical field, in particular in surgery, it may be of great clinical utility to be able to modulate the activation of tissue repair and the regeneration processes, which are at the base of the healing process. In this context, some surgical devices (e.g. sutures, membranes, osteosynthesis plaques) made of reabsorbable materials able to favour the completion of the various reparatory phases and that do not necessitate further surgical intervention for their removal are extremely useful. It is an advantage to load these devices with active pharmacological substances. In fact, the possibility of local diffusion of a drug through biocompatible and reabsorbable matrixes offers the advantage of a drastic reduction of the systemically administered dose and, as a consequence, of related side effects. A limit of these systems is the reduced capacity of guaranteeing an adequate and slow local release of the drug. A more remarkable innovation in this field is currently coming from nanoscience and nanotechnologies, which are opening new opportunities for producing materials with surprisingly unusual properties. The possibility of manipulating at atomic or molecular level induces structures with unique characteristics and completely new functionalities to be used not only as structural materials but also as smart structures for many fields such as drug delivery. Innovative composites can be obtained by employing a suitable nanoscale or other fine-scale architecture to control the structural organisation and, as a consequence, the physical and mechanical properties of the material [13]. Nanoscale reinforcement has found widespread interest in the macromolecular field, since polymer properties are remarkably improved compared with virgin polymer or conventional microcomposites. On the other hand, a wide range of additives, including biologically active molecules, can be immobilised on the inorganic lamellae with ionic bonds. They can be successively released by exchange reactions with ions present in the solutions they are put in contact with. Recently, a novel therapeutic delivery system based on magnesium–aluminium-layered double hydroxides (LDHs) was proposed [14]. LDHs consist of layers of magnesium hydroxide, with aluminium isomorphically substituted to give the layers a net positive charge. This charge is balanced by interlayer hydrated anions, resulting in a multilayer of alternating host layers and gallery ions [15]. Using an ion-exchange reaction, many novel complexes may be synthesised, and indeed anti-inflammatories, antibiotics, plant growth regulators and others have been incorporated into LDHs, obtaining nanohybrids that can slowly release the active molecules [16,17]. We incorporated these nanohybrids containing an anti-inflammatory molecule into a biodegradable polycaprolactone and obtained a much slower release than with the molecule directly incorporated into the polymer [18].

In the present paper, we present the preparation, structural and physical characterisation, and drug release profiles of

new nanohybrid composites, obtained by fixing an antibiotic drug, chloramphenicol succinate (CFS) (4-[2-(2,2-dichloroacetyl)amino-3-hydroxy-3-(4-nitrophenyl)-propoxy]-4-oxo-butanoic acid), with ionic bonds into a lamellar inorganic compound and incorporating the obtained hybrid material into a polymeric matrix, polycaprolactone. Previous papers have reported the intercalation of an anti-inflammatory drug into HTlc, via an ion-exchange procedure, obtaining nanohybrids with high drug loading [19,20], or by reconstruction or co-precipitation methods [21] obtaining compounds with low loading. In our case, a high-loading HTlc–CFS complex has been prepared and dispersed into the biodegradable polymer to obtain systems characterised by excellent mechanical properties and very slow drug release. The polymeric matrix is a polyester, polycaprolactone, which has the advantage of adding biodegradability and biocompatibility to the traditional properties and therefore can be tailored for biomedical applications in many fields [22–24].

This paper is a part of a wider investigation aimed at correlating the active molecule loading, the thickness of the sample and the processing conditions with the release behaviour. A complete picture of the interrelationship between the different parameters will allow the samples to be tailored for specific applications.

2. Materials and methods

2.1. Materials

A well crystallised and characterised Mg–Al hydrotalcite-like compound with the formula $[\text{Mg}_{0.65}\text{Al}_{0.35}(\text{OH})_2](\text{CFS})_{0.26}(\text{NO}_3)_{0.09} \times 1 \text{ H}_2\text{O}$ (hereafter referred to as HTlc–CFS) was obtained by $\text{NO}_3^-/\text{chloramphenicol succinate anion (CFS}^-)$ exchange reaction as previously reported [18].

Poly(ϵ -caprolactone) (PCL) ($M_n = 80\,000$ Da), chloramphenicol succinate sodium salt (CFS–Na) and tetrahydrofuran (THF) were used as received from the manufacturer (Sigma-Aldrich, Milan, Italy).

2.2. Preparation of the nanohybrid

2.2.1. Preparation of composites by solvent casting of HTlc–CFS and PCL solution

A THF suspension (30 mL) containing 100 mg of HTlc–CFS was stirred for 3 h at room temperature. Then, 1 g of high-molecular-weight PCL was added and the mixture was stirred for 3 h at room temperature. The solvent was then slowly evaporated in a Petri dish, obtaining a PCL sample with 10% HTlc–CFS. Using the same procedure, two more samples were obtained, containing 5% and 20% HTlc–CFS.

Hereafter, the samples will be named as PCL–HCFS $_n$, where n is the amount of HTlc–CFS present in the composite.

2.2.2. Preparation of composite by solvent casting of CFS-Na and PCL solution

A THF suspension (30 mL) of 60 mg CFS-Na was stirred for 3 h at room temperature. Then, 1 g of high-molecular-weight PCL was added and the mixture was stirred for a further 3 h at room temperature. The solvent was then slowly evaporated in a Petri dish.

Hereafter, the sample will be referred to as PCL–CFSNa6.

2.3. Film preparation

Films were obtained by moulding the previous samples, dried in vacuo, in a Carver Laboratory Press between two Teflon sheets at a temperature of 70 °C and rapidly quenching them in an ice water-bath. No cracks or imperfections were visible on the surface of the films, implying that incorporation of the nanohybrid did not interfere with the formation of homogeneous films.

2.4. Methods of investigation

Thermogravimetric analysis (TGA) was carried out in an air atmosphere with a Mettler TC-10 thermobalance from room temperature to 800 °C at a heating rate of 20 °C/min. Degradation temperatures, T_d , are evaluated as the midpoint of the degradation step.

X-ray powder diffraction measurements were performed with a Bruker diffractometer (equipped with a continuous scan attachment and a proportional counter) with Ni-filtered Cu K α radiation ($\lambda = 1.54050 \text{ \AA}$).

The mechanical properties of the samples were evaluated from the stress–strain curves obtained using a dynamometric apparatus INSTRON 4301. The experiments were conducted at room temperature with a deformation rate of 2 mm/min. Dumbbell-shaped samples with initial length of 10 mm, width of 5 mm and thickness of 150 μm were investigated. Elastic moduli were derived from the linear part of the stress–strain curves, giving to the sample a deformation of 0.1%.

Ultraviolet (UV) spectroscopy, set at a wavelength of $\lambda = 278 \text{ nm}$, was used to quantify the amount of CFS released into the solution in each time interval. A calibration curve was used to determine the molar extinction coefficient in the investigated concentration range. Measurements were made in triplicate and the values were averaged. A circular sample of each PCL–HCFS n sample, with a surface of 1 cm diameter, was cut from the film of thickness 150 μm and placed into 100 mL of physiological saline solution at room temperature and kept in the dark. After specific intervals, 1 mL of solution was removed and replaced with 1 mL of fresh solution to maintain a constant volume of release medium. No hydrolytic degradation of PCL occurred in the time that the release measurements were performed and therefore the active molecule release is not due to polymer degradation and erosion but only to diffusive movement into the matrix.

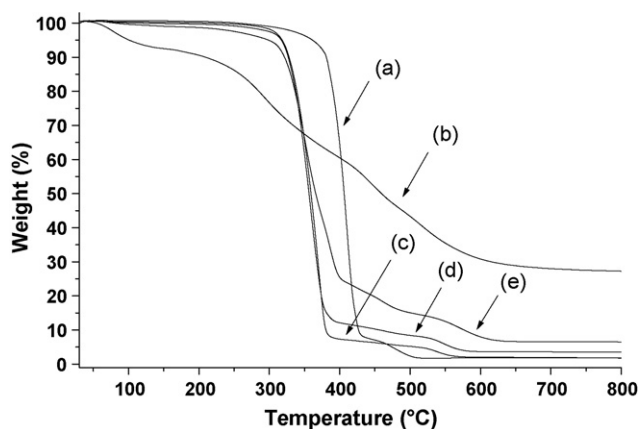


Fig. 1. Thermogravimetric analysis (thermograms) of (a) PCL; (b) HTlc–CFS; (c) PCL–HCFS5; (d) PCL–HCFS10; and (e) PCL–HCFS20, where the number represents the amount of HTlc–CFS present in the composite. Heating rate 20 °C/min in air flow. PCL, poly(ϵ -caprolactone).

3. Results

3.1. Thermogravimetric analysis

All the samples were analysed by TGA to determine the degradation temperatures and to confirm the content of the inorganic component in the nanohybrid materials after thermal decomposition of the organic part in air up to 800 °C [21].

Fig. 1 shows the TGA curves of the samples. The thermogravimetric curve of PCL (Fig. 1a) displays one main degradation step with a T_d midpoint value of 402 °C. It can be seen that the shapes of the curves are very similar for both neat PCL and the composites, although the degradation temperatures for the samples PCL–HCFS5, PCL–HCFS10, PCL–HCFS20 are 44 °C, 47 °C and 40 °C lower, respectively, than that of pure PCL. This behaviour is due to the presence of nanohybrid HTlc–CFS in the samples, which degrade at a lower temperature than PCL. The T_d midpoint value of HTlc–CFS is 374 °C.

Considering the stoichiometric relations between HTlc and CFS in the formula: $[\text{Mg}_{0.65}\text{Al}_{0.35}(\text{OH})_2](\text{CFS})_{0.26}(\text{NO}_3)_{0.09} \times 1 \text{ H}_2\text{O}$, the amount of CFS is 57.0% of the total hybrid weight. In Table 1 we report the amount of CFS in each sample.

Table 1
Concentration of the hybrid HTlc–CFS, concentration of the antibiotic molecule CFS and the theoretical quantity of drug that can be released (mg^t CFS) for all the samples

Sample	% HTlc-CFS	% CFS	mg^t CFS
PCL–HCFS5	5	2.85	0.97
PCL–HCFS10	10	5.70	2.05
PCL–HCFS20	20	11.40	5.05
PCL–CFSNa6	0	6	2.55

CFS, chloramphenicol succinate.

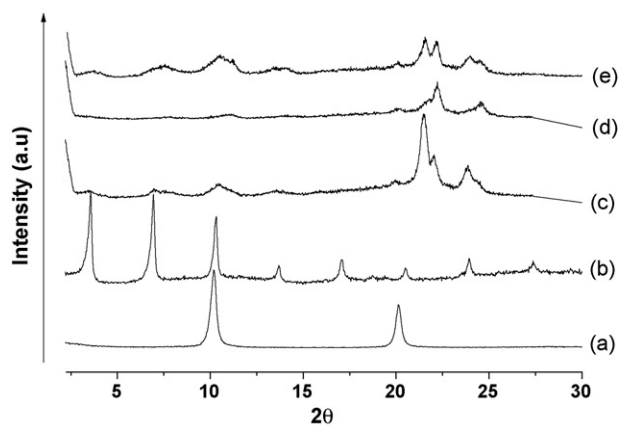


Fig. 2. X-ray diffractograms of (a) HTlc-NO₃; (b) HTlc-CFS; (c) PCL-HCFS5; (d) PCL-HCFS10; and (e) PCL-HCFS20, where the number represents the amount of HTlc-CFS present in the composite. PCL, poly(ϵ -caprolactone).

3.2. X-ray powder diffraction measurements

X-ray analysis was used to study the effect of the intercalation of CFS into the interlayer region of HTlc and to investigate the dispersion degree of the nanohybrid into the polymer.

Fig. 2 shows, in the 2–30° interval of 2θ , the X-ray diffractograms of the pristine hydrotalcite in the nitrate form, HTlc-NO₃ (Fig. 2a), the nanohybrid HTlc-CFS (Fig. 2b) and the composites PCL-HCFS5, PCL-HCFS10 and PCL-HCFS20 (Fig. 2c–e). The X-ray diffractogram of the starting HTlc-NO₃ (Fig. 2a) shows an intense peak at $2\theta=10.2^\circ$, which corresponds to the 003 basal plane of 0.87 nm. Exchange of nitrate ions with the organic anion of the drug CFS gives rise to expansion of the d-spacing. We observe that the first peak of HTlc-CFS is located at $2\theta=3.57^\circ$, corresponding to a basal spacing of 2.47 nm. This increase accounts for the intercalation of CFS anions that have substituted the nitrate anions inside the galleries. The second and third peaks of HTlc-CFS (Fig. 2b) correspond to the higher harmonics of the interlayer distance. All the peaks are sharp, indicating an ordered accommodation of the drug anions within the interlayer regions.

The pattern of the composites PCL-HCFS5 (Fig. 2c), PCL-HCFS10 (Fig. 2d) and PCL-HCFS20 (Fig. 2e) shows that the HTlc-CFS is present in the polymer in a much less ordered arrangement. Indeed, PCL-HCFS5 (Fig. 2c) and

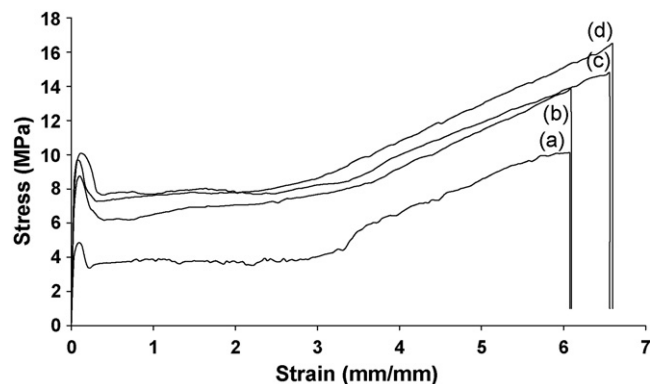


Fig. 3. Stress–strain plots of (a) PCL; (b) PCL-HCFS5; (c) PCL-HCFS10; and (d) PCL-HCFS20, where the number represents the amount of HTlc-CFS present in the composite. PCL, poly(ϵ -caprolactone).

PCL-HCFS20 (Fig. 2e) show very broad peaks of the inorganic component at 2θ values of ca. 3.5° , 7.0° and 10.4° , whereas PCL-HCFS10 (Fig. 2d) does not show any peak, indicating a possible exfoliation of the inorganic lamellae.

The PCL of the composites is crystalline and shows the usual peaks of its structure at $2\theta=21.3^\circ$ and 23.7° , although of different intensity [25].

3.3. Mechanical properties

In Fig. 3 we show the engineering stress–strain curves for PCL (Fig. 3a), PCL-HCFS5 (Fig. 3b), PCL-HCFS10 (Fig. 3c) and PCL-HCFS20 (Fig. 3d). The drawing curve of sample PCL (Fig. 3a) is conventional, with upper and lower yield points describing the neck formation and subsequent transformation into an oriented structure. The neck propagation, after the yield drop, ends before 300%; afterwards, a steeper increase of the stress and the breaking point at ca. 600% are observable. The composites samples (Fig. 3b–d) show a much more pronounced and sharper yield and post-yield drop than the initial sample. Fracture of the composite materials occurs at higher deformation than the pure polymer.

An improvement of all the mechanical parameters can be observed (see Table 2).

As matter of fact, all the composites show a consistently higher elastic modulus in addition to a higher yield and breaking stress.

Table 2

Mechanical properties evaluated from the stress–strain curves for all samples

Sample	σ_y (MPa)	ϵ_y (%)	σ_b (MPa)	ϵ_b (%)	Elastic modulus (MPa)
PCL	4.858	9.818	10.085	607.7	220
PCL-HCFS5	8.757	9.825	13.834	609.2	305
PCL-HCFS10	10.065	13.521	14.789	656.2	315
PCL-HCFS20	9.648	9.918	16.482	659.7	390

σ_y , stress at the yield point; ϵ_y , deformation at the yield point; σ_b , stress at the breaking point; ϵ_b , deformation at the breaking point; PCL, poly(ϵ -caprolactone).

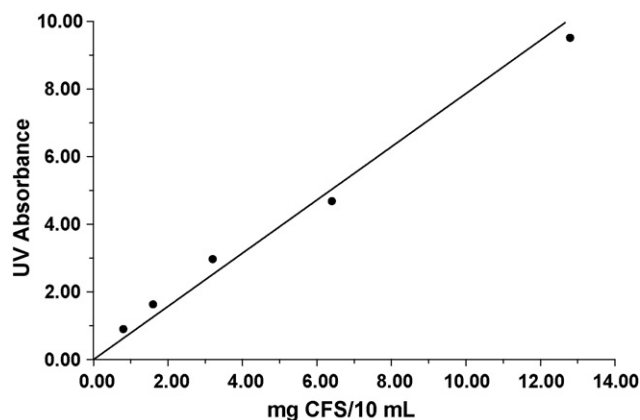


Fig. 4. Calibration curve of chloramphenicol succinate (CFS) in physiological saline solution.

3.4. Chloramphenicol succinate release

The calibration curve of CFS in physiological saline solution is shown in Fig. 4. The UV absorbance at $\lambda = 278$ nm is reported as a function of CFS concentration (mg/10 mL) in the range of interest for release from the polymeric matrix. We can observe that the dependence of the absorbance on the concentration is linear in the investigated range, and only at the highest concentration was a slightly lower value measured, indicating an initial deviation from linearity.

The release of CFS from PCL–HCFS5, PCL–HCFS10 and PCL–HCFS20 is presented in Fig. 5. It is worth recalling that the CFS content is 57.0% of the total HTlc–CFS, and therefore the samples contain 2.85%, 5.70% and 11.4% of drug, respectively (see Table 1). Depending on the sample weight, the theoretical quantity of drug that can be released is also reported in Table 1.

In Fig. 5, the sample with CFS directly dispersed into the polymer (PCL–CFSNa6), with a concentration of 6%, is also compared with PCL–HCFS10.

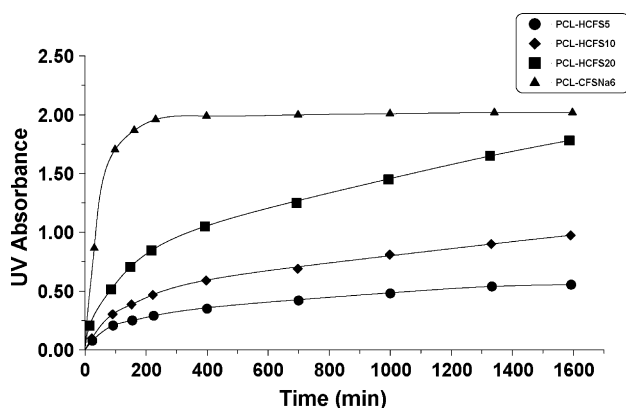


Fig. 5. Ultraviolet (UV) absorbance at $\lambda = 278$ nm, reported as a function of time (min) for samples PCL–CFSNa6 and PCL–HCFS5, PCL–HCFS10 and PCL–HCFS20, where the number represents the amount of HTlc–CFS present in the composite.

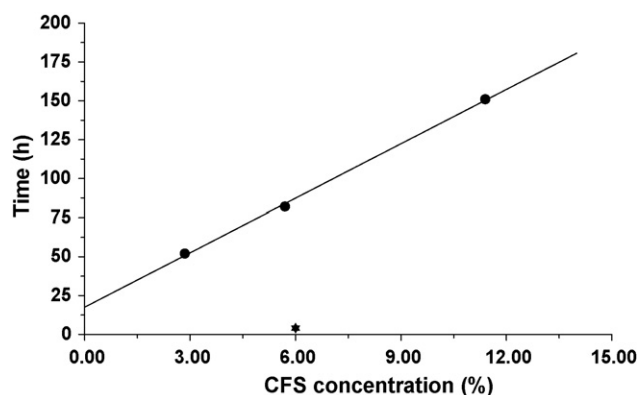


Fig. 6. Time for complete release of chloramphenicol succinate (CFS) reported as a function of concentration.

We observe that the three samples containing the CFS drug in the nanohybrid show the same qualitative release behaviour. The typical time-dependent profile of each sample shows fast release in the early period, followed by a reduced release. The first stage lasts ca. 100 min and is completed in an increasing time with increased drug loading in the sample. In the sample with the highest drug concentration (11.4%), the first stage extends up to 200 min, whereas ca. 100 min are needed for the sample with the lowest concentration of CFS (2.85%). In the second stage, after the rapid burst of a fraction of CFS, drug release increases linearly with time, with the slope increasing with the increase in drug concentration (see Fig. 5), as already reported in the case of diclofenac [18].

The release behaviour of sample PCL–CFSNa6, containing the drug directly incorporated into the polymeric matrix, is very different. It is linear with time up to 100 min and afterwards reaches the value corresponding to complete release of the incorporated quantity (see Table 1). The drug is quickly released, with linear kinetics with time, and reaches the equilibrium value after 250 min. The corresponding sample, PCL–HCFS10, containing approximately the same quantity of drug anchored to the HTlc layers, has released only 30% of the theoretical quantity after 250 min. Assuming a linear release with time, up to complete drug release, we can calculate the time needed for complete release in each sample containing the drug anchored in the nanohybrid. In Fig. 6, we report the time needed for complete release as a function of the concentration of CFS. We observe that the total release time is linearly dependent on the nanohybrid loaded in the polymer, and it is much higher than the time needed for complete release of the drug directly incorporated into the polymer, represented by the star in Fig. 6.

It is worth noting that the different dispersion of the inorganic sample, in terms of distortion of the structure or delamination, as shown by the X-rays, appears not to have a strong influence on the release time. Indeed, Fig. 6 shows a good linear correlation, in spite of different dispersion of the inorganic lamellae in the different samples. The release is strongly dependent on the ionic force of the outside solution, the diffusion of anions inside and outside the sample fol-

lowing water diffusion, and the sample thickness. All these parameters must be investigated in further studies to derive a complete picture of the release behaviour. This will allow the parameters to be changed, obtaining tuneable drug delivery.

4. Discussion and conclusions

We have formulated, prepared and characterised new polymeric composite materials containing a nanohybrid to be used for controlled molecular delivery of an antibiotic molecule, CFS [1–4]. Different amounts of the hybrid material were incorporated in PCL, a biocompatible and biodegradable polyester mainly applied in biomedical applications [22–24,26].

The mechanical properties of the composite material were investigated and showed that the samples display very good properties, better than the pure polymer. However, the most interesting property for biomedical topical applications is the release behaviour. As a matter of fact, in our films the release of antibiotic molecules, anchored on the lamellae of an inorganic compound, was found to be very interesting and promising for tuneable drug delivery.

Release consists of two stages: (i) an initial very rapid burst, for which the time to be completed is dependent on the hybrid concentration in the polymeric matrix; and (ii) a second stage that is much slower, extending for a longer and longer time, also depending on the hybrid concentration. We suggest that the first stage is due to exchange of CFS ions anchored to the inorganic lamellae on the surface of the sample. Therefore, the amount of antibiotic molecules and the time to complete this stage can be varied by varying the composition, the ionic force of the outside solution, and the surface area. At variance, the CFS anions anchored to the inorganic lamellae inside the film are released from the sample in the second stage. They can be removed not only by exchange reactions but also by diffusion of anions and counter-anions that must be exchanged. Moreover, the fraction of drug released in the first burst from the surface depends on the sample thickness, which determines a different surface/volume ratio. In this paper, we used a thickness of 150 μm and a comparison with different values is in progress. In conclusion, the release can be tuned in many ways (as ionic force of the outside solution, concentration of the drug inside the inorganic lamellae, concentration of the inorganic component into the polymeric matrix, thickness and form of the sample, type of polymeric matrix) in order to obtain the best results for different local applications. Indeed, control of the flogistic mediators involved in tissue reparation of the oral cavity is able to improve both the recovery and the post-operative course. Employment of pharmacologically-loaded delivery systems allows a reduction or avoidance of systemic delivery of antibiotics, anti-inflammatory drugs and pain killers [27,28]. Moreover, by reducing the systemic concentration of the drugs, it is possible to limit their side effects. This is especially helpful in the case of patients with con-

comitant diabetes, hepatopathy, nephropathy, cardiopathy or haemorrhagic diathesis.

Acknowledgment

We thank the MIUR (PRIN project 2004 and PRISMA project entitled 'Nanobioibridi a matrice polimerica per il rilascio controllato di molecole attive') for financial support.

References

- [1] Jain NK, editor. Controlled and novel drug delivery. New Delhi, India: CBS Publisher; 1997. p. 1.
- [2] Chasin M, Langer R, editors. Biodegradable polymers as drug delivery systems. New York: Marcel Dekker; 1990. p. 9.
- [3] Langer R. New methods of drug delivery. *Science* 1990;249:1527–33.
- [4] Pitt CG. Poly- ϵ -caprolactone and its copolymers. In: Chasin M, Langer R, editors. Biodegradable polymers as drug delivery systems. New York: Marcel Dekker; 1990. p. 71.
- [5] Sinha VR, Bansal K, Kanshik R, Kumria R, Trehan A. Poly ϵ -caprolactone microspheres and nanospheres: an overview. *Int J Pharm* 2004;278:1–23.
- [6] Ravi Kumar MNV, Kumar N. Polymeric controlled drug-delivery systems: perspective issues and opportunities. *Drug Dev Ind Pharm* 2001;27:1–30.
- [7] Sinha VR, Trehan A. Biodegradable microspheres for protein delivery. *J Control Release* 2003;90:261–80.
- [8] Van de Velde K, Kiekens P. Biopolymers: overview of several properties and consequences on their applications. *Polym Test* 2002;21:433–42.
- [9] Gander B, Meinel L, Walter E, Merkle HP. Polymers as platform for drug delivery: reviewing our current portfolio on PLGA microsphere. *Chimia* 2001;55:212–7.
- [10] Lu Y, Chen SC. Micro and nano-fabrication of biodegradable polymers for drug delivery. *Adv Drug Deliv Rev* 2004;56:1621–33.
- [11] Hunfrey S, Metha S, Seaber A, Parker V. Pharmacokinetics of a degradable drug delivery system in bone. *Clin Orthop Relat Res* 1998;349:218–24.
- [12] Giavaresi G, Tschon M, Borsari V, et al. New polymers for drug delivery systems in orthopaedics: in vivo biocompatibility evaluation. *Biomed Pharmacother* 2004;58:411–7.
- [13] Cypes SH, Saltzman WM, Giannelis EP. Organosilicate-polymer drug delivery systems: controlled release and enhanced mechanical properties. *J Control Release* 2003;90:163–9.
- [14] Vittoria V, Marenzi G, Bolognese A, et al. Sistema di rilascio controllato di sostanze farmacologicamente attive, processo di preparazione e impieghi in campo medico. *Ns Rif.:6698PTIT. DOM:RM2005A000393*. 2005.
- [15] Rives V, editor. Layered double hydroxides: present and future. New York: Nova Science Publishers, Inc.; 2001.
- [16] Costantino U, Nocchetti M. Layered double hydroxides and their intercalation compounds in photochemistry and medicinal chemistry. In: Rives V, editor. Layered double hydroxides: present and future. New York: Nova Science Publishers, Inc.; 2001. p. 383.
- [17] Khan AI, Lei L, Norquist AJ, O'Hare D. Intercalation and controlled release of pharmaceutically active compounds from a layered double hydroxide. *Chem Commun (Camb)* 2001;22:2342–3.
- [18] Sammartino G, Marenzi G, Tammaro L, et al. Anti-inflammatory drug incorporation into polymeric nano-hybrids for local controlled release. *Int J Immunopathol Pharmacol* 2006;19:53–8.

- [19] Ambrogi V, Fardella G, Grandolini G, Perioli L, Tiralti MC. Intercalation compounds of hydrotalcite-like anionic clays with anti-inflammatory agents, II: uptake of diclofenac for a controlled release formulation. *AAPS PharmSciTech* 2002;3:E26.
- [20] Dupin J-C, Martinez H, Cuimon C, Dumitru E, Fechete I. Intercalation compounds of Mg–Al layered double hydroxides with diclofenac: different methods of preparation and physico-chemical characterization. *Appl Clay Sci* 2004;27:95–106.
- [21] Costantino U, Marmottini F, Nocchetti M, Vivani R. New synthetic route to hydrotalcite-like compounds: characterization and properties of the obtained materials. *Eur J Inorg Chem* 1998;1:1439–46.
- [22] Gorrasi G, Tortora M, Vittoria V, Chiellini E, Galli G. Transport and mechanical properties of blends of poly(ϵ -caprolactone) and a modified montmorillonite. *J Polym Sci B Polym Phys* 2002;40:1118–24.
- [23] Gorrasi G, Tortora M, Vittoria V, Pollet E, Alexandre M, Dubois Ph. Physical properties of poly(ϵ -caprolactone) layered silicate nanocomposites prepared by controlled grafting polymerization. *J Polym Sci B Polym Phys* 2004;42:1466–75.
- [24] Tammaro L, Tortora M, Vittoria V, Costantino U, Marmottini F. Methods of preparation of novel composites of poly(ϵ -caprolactone) and a modified Mg/Al hydrotalcite. *J Polym Sci A Polym Chem* 2005;43:2281–90.
- [25] Hu H, Dorset DL. Crystal structure of polycaprolactone. *Macromolecules* 1990;23:4604–7.
- [26] Vert M, Fejigen J, Albetsson AC, Scott G, Chiellini E. *Biodegradable polymers and plastics*. London, UK: Royal Society of London; 1992.
- [27] Uchegbu IF, Florence AT. Adverse drug events related to dosage forms and delivery systems. *Drug Saf* 1996;14:39–67.
- [28] Sam T. Optimising the therapeutic trinity of active ingredient, delivery system and functional packaging. *J Control Release* 2003;87:153–7.