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Note

Oxaliplatin loaded PLAGA microspheres: design of specific release profiles

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Abstract

Oxaliplatin loaded PLAGA microspheres have been prepared by solvent extraction process. Parameters affecting the release kinetics in vitro have been studied in order to design specific release profiles suitable for direct intra-tumoral injection. By varying the nature and the relative proportions of different polymers we managed to prepare microspheres with good encapsulation efficiency (75–90%) and four different release profiles: zero order kinetics (type II) and the classical sigmoïd release profile with three different sizes of plateau and burst. These results, if correlated with in vivo activity, are promising to enhance effectiveness of local tumor treatment. © 2002 Elsevier Science B.V. All rights reserved.

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Oxaliplatin (L-OHP) (oxalato(trans-l,1,2-diaminocyclohexane) platinum(II) is a third generation of Pt anti-tumor compound and it is now approved as first-line chemotherapy in combination with 5-fluorouracil for the treatment of advanced colorectal cancer in several major European countries. Despite its better tolerability in comparison to other Pt compounds, like cisplatin and carboplatin, oxaliplatin displays a few side effects (acute dysesthesias, cumulative peripheral distal neurotoxicity) limiting the range of usable doses. To reduce the systemic effects of oxaliplatin, it is possible to encapsulate the drug in a polymer matrix. The resulting PLAGA microspheres can be injected around the tumor. After some preformulation work, we have been able to control the release and the burst of the L-OHP by varying several parameters, such as the nature and quantity of the polymers used or the drug loading.

We used PLAGA polymers RG503, RG502 (Mw 40 000, Mw 10 000, B.I. Chimie, France) and PLA oligomer (Mw 2000 Phusis, France). The L-OHP was a kind gift from Debiopharm S.A., Switzerland. The microspheres were prepared by a solvent extraction process using ethyl acetate as

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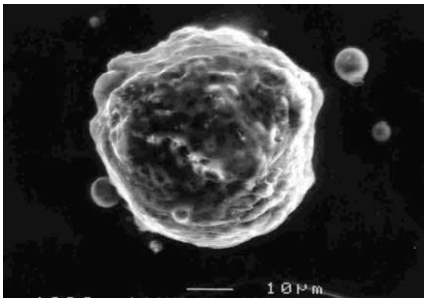
the polymer solvent (Sah, 1997). The resulting encapsulation rate was determined by measuring the Pt content of the aliquots by ICP-MS (Gamelin et al., 1997) after total destruction of the matrix. The release kinetics was determined by putting a precisely weighed amount of L-OHP (sink conditions) in 1 l PBS buffer (pH 7.4) maintained at 37 °C with light stirring (100 rpm). At specific times, 1 ml samples were taken through a 2 μm filter and the Pt content was determined. To determine the mean kinetic profile of the sample, each release experiment was made in triplicate.

The microparticles were characterized by Scanning Electron Microscopy (SEM) JEOL 6301F field emission microscope (JEOL-France, Paris). For the study of external morphology, the microparticles were deposited on an adhesive paper and covered by a fine layer carbon (10 nm) with a MED 020 (Baltec, Balzers, Lichtenstein). Examinations were done with a tension at 11 kV. For each field, two micrographs were taken. A first image (obtained with the secondary emitted electrons—SEEM) provided precise morphological aspects of the microspheres. A second one (obtained with the backscattered emission mode—BSEM) allowed a clear imaging of the L-OHP crystals around and inside the microspheres.

The encapsulation rate ranged from 10 to 35% (encapsulation efficiency 75–90%), and the size of the microspheres averaged 60 ± 25 μm.

The drug loading acts upon three characteristics of the kinetic profile (Fig. 1). High drug loadings generate an important burst effect, the fading of the plateau and accelerate the average speed of the L-OHP release in the buffer. The increase of the quantity of the L-OHP near the microspheres surface explains the raising of the burst effect (pictures 1 and 2), the burst effect can also be explained by the presence of a few non-encapsulated L-OHP crystals as shown on picture 3. If the drug loading is greater than 25%, a percolation mechanism (Deyme et al., 1992) sets up and leads to the fading of the plateau, in that case the release of the L-OHP is less dependent of the polymer's nature. Although, for low drugs loading, the polymer used has an important effect on the release profile. High molecular weights and high PLA content polymers lead to a slower release and a longer plateau. As previously described, adding increasing quantity of low molecular weight oligomers (Geze et al., 1999) allowed us to shorten or to eliminate the plateau (Fig. 2). Incorporating fast degrading polymers in the matrix contribute to generate pores where the water infiltrates and dissolves L-OHP crystals, which will then diffuse out. This diffusion is helped by the structure of the polymer matrix, which looks like a sponge (picture 4)[1].

(1)



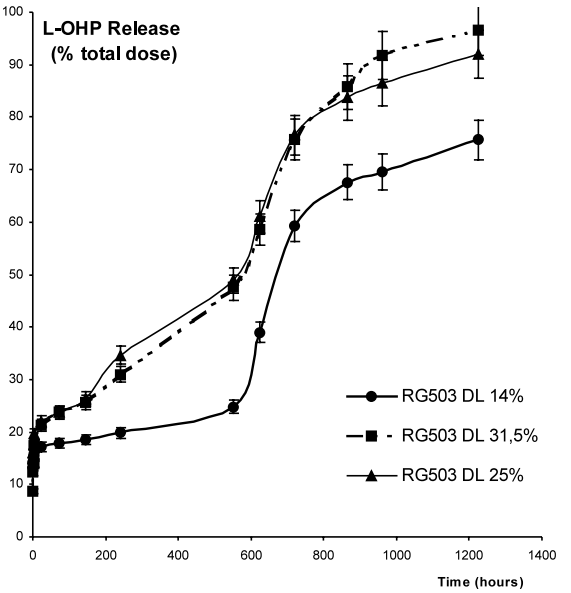


Fig. 1. In vitro release kinetics of L-OHP loaded PLAGA 50/50 microspheres. Influence of the drug loading (DL) on the release kinetic profile.

[1] Pictures 1–4: SEM of L-OHP loaded microspheres. Batch with 31.5% drug loading, SEEM (1) and BSEM (2, 3). Batch with 34% drug loading SEEM (4). BSEM allowed a clear imaging of the L-OHP crystals (in white) around and inside the microspheres, these observations are used to explain some particular characteristics of the release kinetic profile (see text).

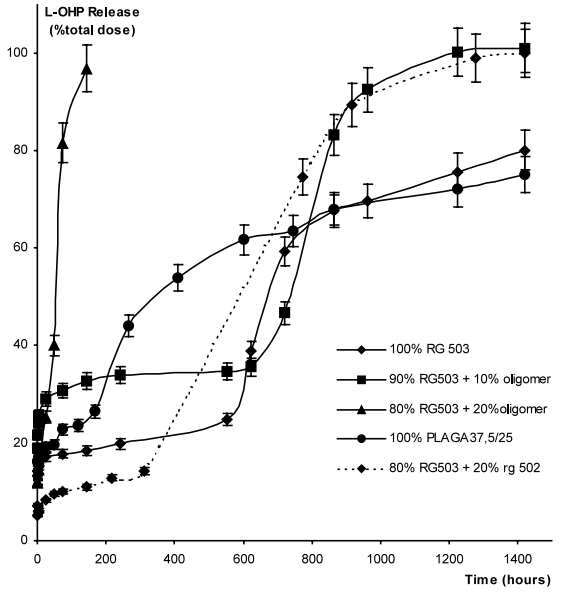
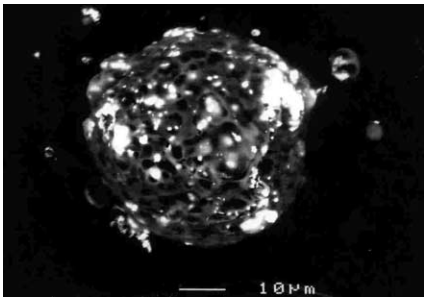
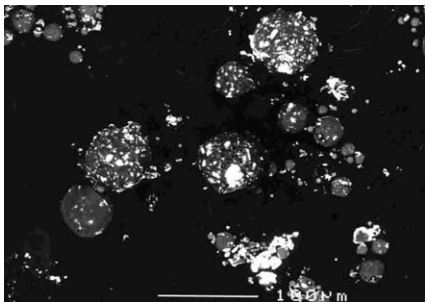


Fig. 2. In vitro release kinetics of L-OHP loaded microspheres. Influence of the core material on the release kinetic profile. Each sample has a drug loading ranging from 14 to 16%.

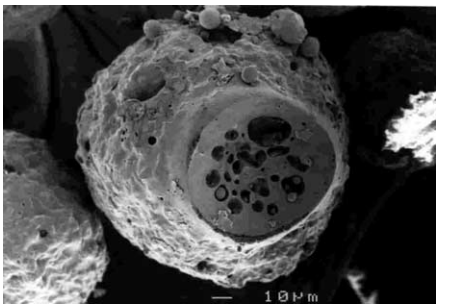
(2)



(3)



(4)



The previous results allowed us to modulate the release by using medium loaded particles (20%) and different blends of polymers (Fig. 3). The release profile is in conformity with either a continuous infusion or an injection every 2 weeks. These results show that Type II microspheres have a zero order release kinetics imitating a continuous infusion following a bolus dose (20% total dose). Previous unpublished studies from our laboratory have demonstrated the interest of that type of profile for microspheres intra-tumoral injections. Other types of microspheres imitate two bolus doses with a 10-day interval of very low infusion rate (the plateau on the curve). The importance of the 'first dose' (i.e. the burst effect) as compared to the 'second dose' (i.e. curve take

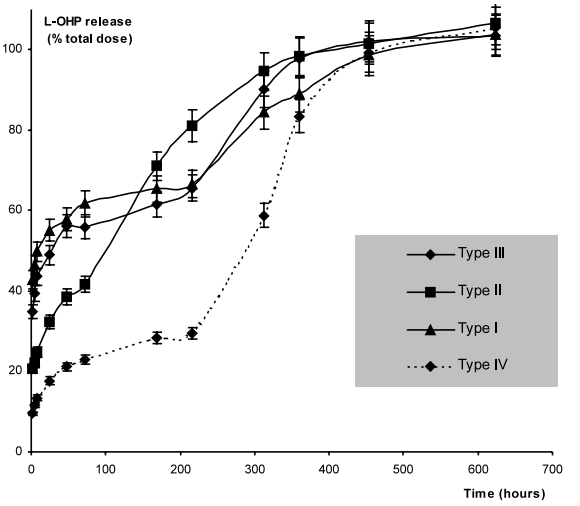


Fig. 3. In vitro release kinetics of L-OHP loaded microspheres. Type I RG503 100%, loading 28.5%; Type II PLA oligomer 10% RG 503 90%, loading 21.5%; Type III RG502 20%, RG503 80%, loading 26%; Type IV as Type III with 16% loading.

off after the plateau) can be adjusted by the drug loading. The duration of the plateau can be modulated by the drug loading and the percentage of low Mw PLAGA used. These results need to be correlated with in vivo activity.

By using variable blends of different polymers, we managed to control the L-OHP release profile and to mimic a continuous infusion or an injection every 2 weeks. This is promising for enhancing the effectiveness and efficiency of local tumor treatment.

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