MALDI-TOF MS IMAGING OF CONTROLLED RELEASE IMPLANTS

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INTRODUCTION

Lipid implants offer a great potential for the controlled release of fragile drugs (e.g. proteins), avoiding drops in micro-pH (as associated with PLGA). However, yet little is known on the underlying drug release mechanisms and the inner structure of the systems as well as on changes thereof upon exposure to the release medium. MALDI-TOF MS (Matrix-Assisted Laser Desorption/Ionization Time-Of-Flight Mass Spectroscopy) imaging provides an interesting opportunity to get novel insight into the spatial and temporal distributions of the compounds of advanced drug delivery systems [1,2].
The aim of this study was to apply MALDI-TOF MS imaging to lipid implants prepared by extrusion at room temperature before and after exposure to phosphate buffer.

EXPERIMENTAL METHODS

Glyceryl tristearate and theophylline were wetted with aqueous Poloxamer 407 solution and extruded with a piston extruder to obtain strings, which were cut into cylinders. Drug release was measured in phosphate buffer pH 7.4 at 37 °C (80 rpm). MS images were obtained using an AutoFlex speed LRF MALDI-TOF mass spectrometer (Bruker), equipped with a Smartbeam II laser (repetition rate = 1000 Hz). Positive mass spectra were acquired in the 0–1000 m/z range. The mass spectrometer was operated in the reflectron mode and the mass spectrum obtained for each position corresponds to the averaged mass spectra of 500 consecutive laser shots at the same location (image raster step = 50 µm). Cross-sections were obtained using a Leica cryostat CM3050S.

RESULTS AND DISCUSSION

The following analytical solution of Fick's second law of diffusion was used to quantify theophylline release from the lipid implants [3]:

$$\frac{M_t}{M_\infty} = 1 - \frac{32}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{q_n^2} \cdot exp\left(-\frac{q_n^2}{R^2} \cdot D \cdot t \right) \cdot$$

$$\sum_{p=0}^{\infty} \frac{1}{(2 \cdot p + 1)^2} \cdot exp\left(-\frac{(2 \cdot p + 1)^2 \cdot \pi^2}{H^2} \cdot D \cdot t \right)$$

where M_t and M_∞, represent the absolute cumulative amounts of drug released at time t, and infinite time, respectively; q_n are the roots of the Bessel function of the first kind of zero order $[J_0(q_n)=0]$, R and H denote the radius and height of the cylinder, and D represents either the diffusion coefficient of the drug or of water.

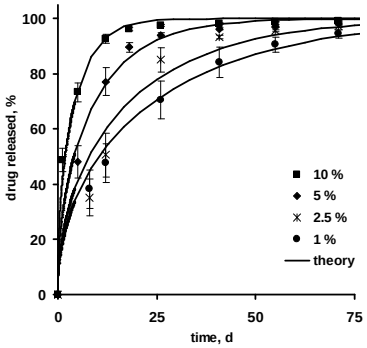

Fig. 1: *Effects of the initial drug loading (indicated in the diagram) on theophylline release from glyceryl tristearate-based implants in phosphate buffer pH 7.4 (symbols: experimental results; curves: theory).*

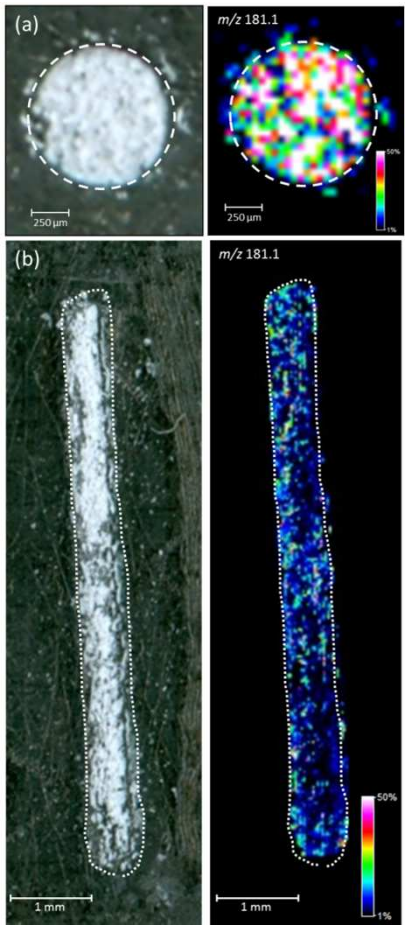

Fig. 2: *Optical (left) and MALDI-TOF MS images (right) of lipid implants (loaded with 5 % theophylline) before exposure to the release medium: radial (a) and longitudinal (b) cross-sections.*

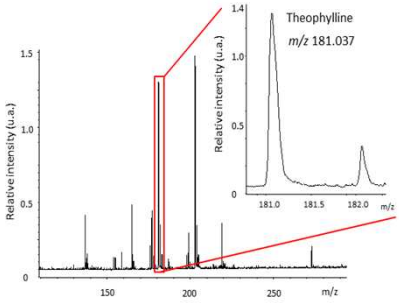

Fig. 3: *MALDI-TOF Mass spectrum related to one x,y position in molecular image (Fig. 2b) showing theophylline ion specie (m/z 181.037).*

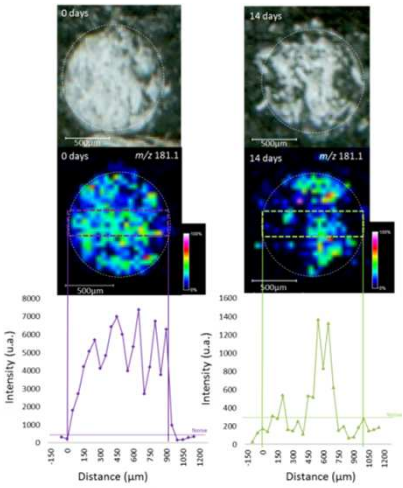

Fig. 4: *Optical and MALDI-TOF MS images of lipid implants (initially loaded with 2.5 % theophylline) at 0 and 14 days of exposure to phosphate buffer pH 7.4: radial cross-sections. Graphic representations of theophylline average intensity obtained in the diameter region of the implants (300µm x 1000µm).*

CONCLUSIONS

MALDI-TOF MS imaging and mathematical modelling can offer interesting new insight into inner structure of advanced drug delivery systems and changes thereof upon exposure to the release medium.

REFERENCES

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