Preferential Partition of Paclitaxel in PEG /PLGA blends and its release visualized by coherent anti-Stokes Raman scattering microscopy

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Introduction Poly(ethylene glycol) (PEG) has been added to a poly (lactide-co-glycolic acid) (PLGA) matrix to provide elasticity to a PLGA-based drug carrier that may need to stand repetitive mechanical movements, such as in drug-eluting stents. The addition of PEG resulted in modulated release profiles of a drug. However, the mechanism of drug release from the PEG-added matrix was not clearly understood. Drug distribution in PEG/PLGA blends and its effects on release profiles have not been examined. The effects of PEG addition on paclitaxel (PTX) distribution and its release from the PEG/PLGA films were examined via 3D molecular imaging using coherent anti-Stokes Raman scattering (CARS) microscopy. CARS allows imaging of drug molecules in their native forms without any fluorophore labeling.

Methods: ***CARS Microscopy.*** Two Ti:sapphire lasers (Coherent Inc, Mira900) were tightly synchronized to generate the 2.5-ps pump and Stokes beams at frequency ω_p and ω_s respectively ($\omega_p > \omega_s$). The two excitation beams were collinearly combined and were directed into a laser scanning microscope (Olympus Inc, FV300/IX70). CARS is a four-wave-mixing process in which a signal field at $\omega_{as}=2\omega_p-\omega_s$ is generated. The signal is enhanced when $\omega_p-\omega_s$ is tuned to the vibrational frequency of a Raman band, thus providing chemical selectivity.

Film preparation. Films were prepared by spray coating of a PEG/PLGA/PTX mixture in THF/toluene with the 4:1 ratio. The PTX concentration was maintained at 15 wt% of the total polymer.

Results and Discussion: A PEG20wt%/PLGA film with or without 15wt% PTX was characterized using X ray diffraction analysis. PEG crystalline phase existed without the drug, while PEG crystalline phase was reduced when the drug is loaded in the film, indicating that PEG interacts with drug. This interaction between PEG and PTX may affect the release profile since PEG will dissolve fast in aqueous release media. Release study of PEG20wt%/PLGA and PLGA film loaded with 15wt% PTX was performed to examine the effect of PEG addition on drug release. As PEG was added, PTX release was accelerated during the initial stage, as compared with that from the PLGA matrix without PEG. After the initial stage, cumulated PTX release became lower than that from PLGA matrix without PEG (Fig. 1b). The results suggested that PEG addition accelerated PTX release.

To visualize morphological changes of PEG dissolution and PTX distribution using CARS, the best Raman shifts to image PTX, PEG, and PLGA needed to be determined from the spectra. The CARS spectra at 2900 cm^{-1} are shown in Fig. 2-a. A peak and a dip for PTX from aromatic CH stretching were determined at 3060 and 3090 cm^{-1}, respectively. The image of PTX was constructed using the signal difference between 3060 and 3090 cm^{-1} to remove the nonresonant background. The images of the PEG and PLGA were taken at 2890 cm^{-1} for CH_2 and 2940 cm^{-1} for CH_3 stretching vibration, respectively.

PTX distribution before and after release was visualized for PEG20wt%/PLGA/15wt% PTX. The morphology of PEG demonstrated that the PEG phase was separated in the PLGA matrix, forming domains (Fig. 2b). PTX was preferentially distributed in the PEG phase over PLGA matrix, coincident with PEG domain (Fig. 2c). This PTX preferential partition in PEG phase supported the attractive interaction between PEG and PTX, corresponding to XRD analysis. The PTX release was visualized by CARS for 1 h. PEG was dissolved creating a pore in the PLGA matrix (Fig. 2d) and PTX locally partitioned in the PEG phase before release was redistributed, showing that circles around pores were generated by PEG dissolution (Fig. 2e). From the visualization of the PTX release, PEG dissolution promoted PTX diffusion while PTX diffusion was limited in hydrophobic PLGA matrix.

Conclusion: Initial release resulting from the PEG addition in PEG/PLGA film, as well as PTX redistribution during the release was visualized by CARS microscopy, providing an imaging tool to investigate drug distribution and release behavior in situ from a solid state polymer matrix.

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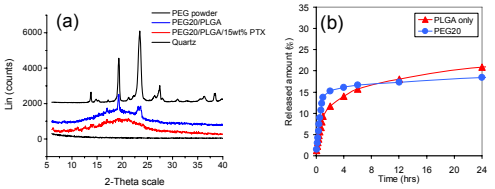

Fig. 1. (a) X-ray diffraction spectra (b) Release profiles from PEG20wt.%/PLGA/15wt% PTX

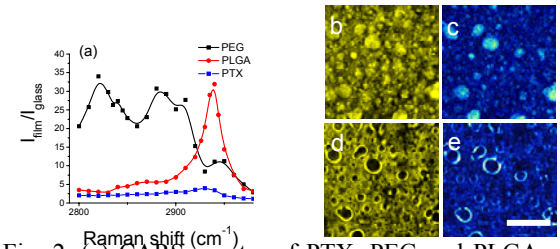

Fig. 2. (a) CARS spectra of PTX, PEG and PLGA at 2800 cm^{-1} region. (b) and (c) Before release, (d) and (e) After release, (b) and (d) XY image of PEG taken at 2940 cm^{-1} (c) and (e) XY image of PTX difference signal between 3060 and 3090 cm^{-1}. Bar presents 10 μm.