UNDERSTANDING OF FLUOROURACIL NANOPARTICLES SONOCHEMICAL FORMATION FOR ITS CONTROLLED DELIVERY FROM POLYMERIC SURFACES

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Introduction

The advancement in biomaterial design and engineering has led to the rapid development of novel polymeric materials with increasing complexity and functions. Controlled drug delivery systems (DDS), which are aimed to deliver drugs at predetermined rates and predefined periods, have attracted increasing attention. The main aspects which have to be considered while designing the system for regional drug delivery are the choice of drug molecules, which are suitable for the targeted tissue and the method of its anchoring to the medical device surfaces. Too weak binding results in burst effect and fast release of the therapeutic agent, while too strong one limits or even block the elution and as a result the therapeutic effect.

The direct insertion of bioactive molecules into the surface of the biomedical device is a promising strategy. Among several methods, which can be used to fabricate drug delivery systems, sonochemistry has proved to be a very effective technique, particularly for polymeric surfaces. The principles are based on the ultrasonic irradiation of water-soluble antibiotic which leads to the formation of nanoparticles (NPs). When the irradiation is performed in the solution over the polymeric surface, the antibiotic NPs are subsequently embedded into the exposed surface in a one-step process. This strategy allows for obtaining a composite NPs/polymer with prolonged drug release from the surface.

The formation of NPs increases the activity and bioavailability of the drugs, moreover, the tissue penetration by the drug can be significantly improved. The detailed understanding of the sonochemical formation of nanoparticles is still insufficient. Hence, in this work we propose the application of Molecular Dynamics simulations (MD) to give insights in the sonochemical formation of nanoparticles. Therefore, we investigated experimentally and by molecular dynamics simulations the first steps of fluorouracil nanoparticles formation via the sonochemical method.

Materials and Methods

Fluorouracil nanoparticles were formed and deposited on the oxygen plasma modified polymers (parylene C) using a homogenizer (Sonics Vibracell CV18) with a frequency of 20 kHz, amplitude 35%, and time 4 min. The size of the sonochemically formed fluorouracil NPs was determined using the LM10 Nanosight instrument (Malvern Instruments Ltd) equipped with a sCMOS camera (Hamamatsu Photonics, Hamamatsu, Japan) and a 450 nm blue laser. Data were processed with NTA software version 3.1 Build 3.1.45. The developed system was thoroughly characterized in terms of particle size (NTA, TEM), surface (ATR-IR), and drug release kinetics (UV-Vis).

Atomistic molecular dynamics simulations were performed to investigate the early stages of fluorouracil nanoparticles formation. The atomistic MD simulations were carried out in an NVT ensemble using GROMACS 5.1.x software and the parameters for fluorouracil molecule were taken from the Amber03 force field.

Drug release studies of the parylene C with sonochemically embedded fluorouracil nanoparticles were performed in phosphate buffered saline solution (PBS) at 37°C.

Results and Discussion

The developed system was thoroughly characterized, before and after embedment, by spectroscopic and microscopic methods. It was revealed that the optimization of the applied ultrasound conditions resulted in the formation of nanoparticles (80-100 nm, FIG. 1A), while the molecular structure of the drug was preserved (confirmed by the FTIR spectra). The experiments reveled the possibility of embedding NPs into polymeric surface with the use of ultrasounds. In parallel using MD simulations the mechanism of fluorouracil nanoparticles nucleation was investigated. The aggregation of drug molecules at the bubble interface, which can be considered as and an early-stage of NPs formation, is shown in FIG. 1B. MD simulations provided valuable information concerning the fluorouracil solution composition (water/alcohol) for the effective formation of nanoparticles.

Drug elution studies were performed to determine stability of the fluorouracil NPs deposited on the polymeric surface.

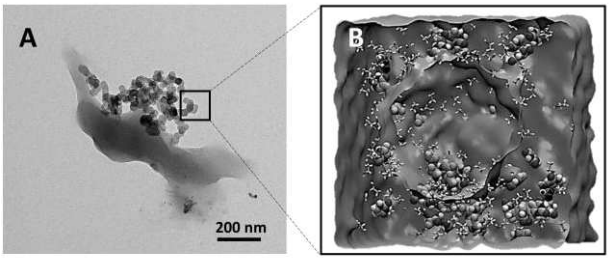

FIG. 1. TEM image of sonochemically created fluorouracil nanoparticles deposited on holey carbon mesh (A). MD simulation snapshot of fluorouracil aggregation at the bubble-solvent boundary (B).

Conclusions

Sonochemical synthesis is a powerful method for the production of nanostructured materials made of biologically active substances. The apparent benefits of the proposed sonochemical approach such as short preparation time, direct drug accessibility, lack of chemical wastes are pointed out. The molecular dynamics simulations provide the insights into the formation of drug nanoparticles and support the design of the synthesis protocol by adjusting the composition of the native solution.

References

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