Modeling of Drug Release Kinetics from Porous Ceramic Disks

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Statement of Purpose

The two primary mechanisms that govern the drug release from a porous bioceramic are the dissolution of the drug from the outer most surface and the diffusion of the drug molecules from the inner pores to the outside solution. The goal of the present research work is to develop and validate computational models to understand the role of dissolution and diffusion mechanisms in drug release from porous α-cristoblaite. The selection of α- cristoblaite which is inert material eliminates the effect of erosion of the carrier on the release kinetics. The effects of porosity characteristics on drug binding and release are analyzed.

Materials and Methods

α- Cristobalite particles (90-150 mm) were mixed with 0% (Cris0), 15% (Cris15) and 50% (Cris50) polyethylene glycol (PEG), pressed uniaxially at 283 MPa and then heated at 100 C/1h, 350 C/24 h, 900 C/1h and 1100C/12h to make porous disks. Porosity characteristics were measured by mercury porosimetry and BET. The disks (n =4) were immersed in 8 mg/ml Vancomycin (Vanc) in PBS for 4h or 24 h. The concentration of Vanc in the solution was measured before and after immersion and the amount of drug bound on the disks were calculated. The disks were immersed in 2 ml PBS solution and 1 ml is removed at each time point (1, 4, 8, 12, 24, 48, 120, 168 and 360h) and refreshed with equivalent amount of PBS. The concentration of the drug in the removed solution was measured by HPLC. Drug binding and release data were analyzed statistically using Student t-test; ($p<0.05$) is considered statistically significant.

Mathematical modeling

Since the samples are cylindrical, the drug was assumed to be released uniformly in the angular direction. Consequently, one-dimensional and two-dimensional axisymmetric finite element models were sufficient to study drug release from the Cristobalite samples. The finite element models were built using the commercial software ABAQUS [1]. The initial burst phase and the subsequent diffusion-dominated phase were modeled by considering both the disk and the aqueous solution. The drug diffusion/dissolution problem was modeled by treating the problem as a transient heat conduction problem with appropriately defined material properties and interpreting the temperature as drug concentration. The mass transfer coefficient for the initial dissolution phase and the diffusion coefficient for the Cristobalite samples were determined for the three porosities using the finite element results in combination with the experiments. The experimental data and the numerical data used to obtain these coefficients are shown in Figure 1 where the cumulative drug release From Cris50 is plotted against time.
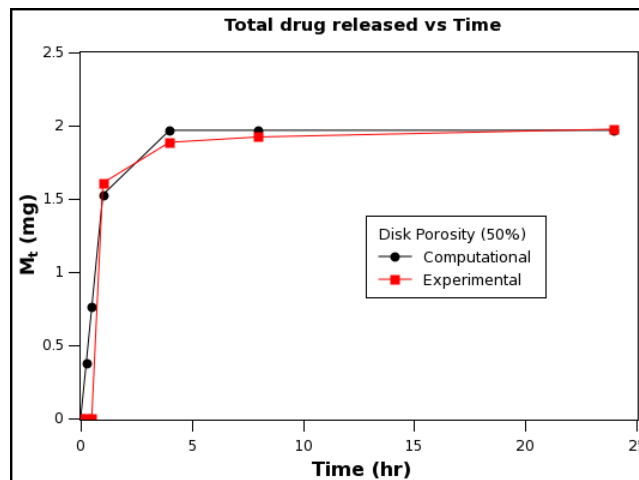

Figure 1: Total drug released as a function of time for a disk with porosity 70%.

Results

Porosity measurements showed that disks with 0, 15 and 50% PEG acquired porosity % of 58.60, 59.28 and 72.06. Comparable surface area for all samples was noticed. However, for Cris0, Cris15 and Cris50 the pores in the size range 3nm to 0.99 mm contributed 41.93, 43.33 and 23.27 % of the total pore volume respectively. In conjunction with the differences in the percent of pore volume contributed by the nano pores, the rate of release of Vanc increased in the order Cris15 < Cris0 < Cris50. For Cris50, the mass transfer coefficient for the initial phase of drug dissolution in PBS was found to be 5×10^{-7} cm/s. The diffusion coefficient for the Cristobalite matrix was found to be 5×10^{-10} cm^2/s.

Conclusion

The higher percentage (32%) of drug released from Cris50 in the burst stage is consistent with the significantly higher percent surface area (73%) contributed by the micro size pores. The high contribution of the nanopores to the total surface area of Cris0 and Cris15 have resulted in a lower rate of drug release during the diffusion dependent sustained release stage. The low value of the diffusion coefficient indicates that the diffusion of drug through the porous ceramic matrix is very slow and that initial burst release is predominantly due to the dissolution process. This is also evident from the experimental curve in Figure 1 which shows that the majority of the drug released is in the initial (burst) phase. Further experimental work is being carried out to validate the values for the diffusion and mass transfer coefficients.

References.

1. ABAQUS v6.13, Dassault Systems Simulia, Rhode Island, MA, US.