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Mathematical modelling of controlled drug release from eroding matrices

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ABSTRACT

During these years there has been a great interest in the development of implantable polymeric drug delivery systems which have increased their performances moving from simple pills to programmable devices. The first devices that have been developed were characterized by immediate and uncontrolled release so that it may happen that the drug concentration approaches toxic levels and subsequently falls down below the therapeutic level needed. Mathematical modelling of the phenomena involved in the release of the drug from the devices into the arterial wall can be useful.

The drug transport inside a pharmaceutical systems involves multiple steps due to different physical and chemical phenomena. The main process that we want to take into account are the diffusion, the dissolution and the erosion of the matrix where the drug has been embedded. Usually the drug inside the matrix has the form of micro-nano crystals and has no possibility to diffuse thought the matrix. Upon a contact with the fluid (plasma) the matrix starts to swell and the dissolution takes place, thus the dissolved drug can easily diffuse through the matrix network. To complete the description the erosion of the matrix due to chemical and physical reasons can be considered. In our study a surface erosion that affect only the outer parts of the matrix was modelled [1].

When dealing with modelling phenomena of this type the different characteristic times have to be taken into account. Dissolution proceeds very rapidly compared to diffusion and erosion mechanisms. In our mathematic framework we assume that the initial load of the drug embedded in the matrix is much larger than its solubility and we model the dissolution as a reformulation of the Noyes-Whitney equation [2]. The models is further improved considering the erosion of the matrix with an additional differential equation that describe the erosion front as a variable depending on the concentration gradient of the dissolved drug. The problem is modelled by a system of partial differential equation in a boundary moving setting..

The model described above is used to characterize the release of the drug from an erodible matrix and has been coupled with a model of drug transport into the arterial

wall. The transport in the tissue is governed by the advection-diffusion equation where the convection terms is due to the plasma filtration inside the arterial wall. Moreover the effect of binding of the drug with particular sites into the tissue is taken into account. On the numerical side the challenge was to employ a numerical technique able to capture the different kinetics of the release inside the matrix and the tissue in an accurate manner. In fact the process that take place in the matrix is very rapid compared to the diffusion of the drug inside the wall. A domain decomposition technique was employed and the characteristic time of the diffusion in the two different media has been taken into account by the adoption of a double time step technique.

We simulate the drug release from a single planar matrix with different set of parameters to emphasize the role of the different phenomena involved in the release. In Fig.1 the solution in terms of drug concentration released is shown. The effect of relative position of the stent struts is investigated.

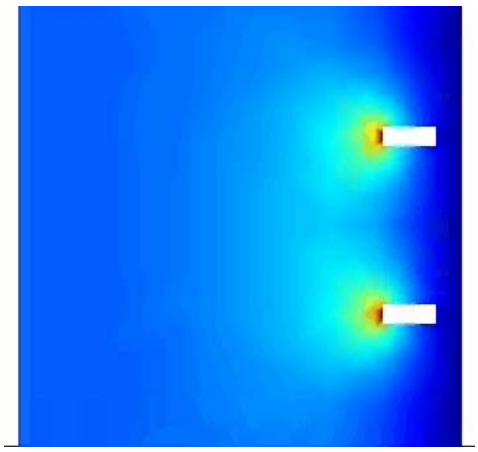

Fig.1

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