EXPERIMENTAL STUDY OF DRUG RELEASE SYSTEM BASED ON ELECTROSPUN NANOFIBRES

Paweł Nakielski, Tomasz Kowalczyk, Tomasz A. Kowalewski

Institute of Fundamental Technological Research, Polish Academy of Sciences, IPPT PAN, 02-106 Warsaw

Summary The paper contains our attempts to estimate diffusion parameters of nanofibers actually applied as protective mats for neurosurgery. Measurements of concentration profiles of fluorophore released from stained nanofibres are performed. The two release systems are investigated: solid nanofibres and core-shell nanofibres with targeted drug simulator encapsulated inside nanofibres. The gathered information allows us to estimate parameters necessary for controlling drug release profiles.

Nanofibres produced by electrospinning of biologically active substances became attractive material for encapsulating living cells, bacteria, and drugs for targeted therapy. Here, we aim to use nanofibre matrices as neurosurgery protective membranes and drug carriers. Proper administration of drugs requires precise control of the diffusion process during the time of release of days or even weeks. Construction of such system is a tedious experimental task. To avoid hundreds of tests it is aimed to build a numerical model including essential information about composition, process conditions, and fibres geometry necessary to construct suitable polymer matrices for dedicated drug delivery systems.

Dye release from a single nanofibre

Even though the release kinetics were studied experimentally for a number of substances, the physicochemical mechanisms of drug release have not been fully elucidated. Hence, we commence our study with a simple geometry of single nanofibre spanned in a cuvette filled with selected liquid (Fig. 1). Spatial and temporal variation of the fluorescent light intensity is measured using a CCD camera and spectrophotometer. It allows to evaluate variation of concentration profiles and access diffusion parameters for selected configurations and compositions of liquids/polymers.

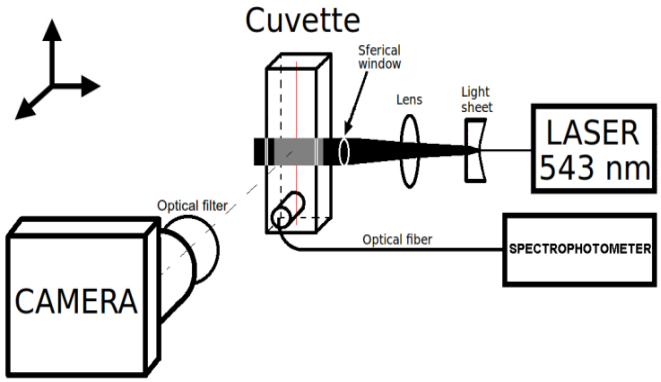

Figure 1. Experimental setup. Laser with excitation wavelength λ = 532 nm, light–sheet optics, disposable cuvette with single fibre spanned along the central axis, CCD camera, optical filter 600 nm ± 15 nm and spectrophotometer.

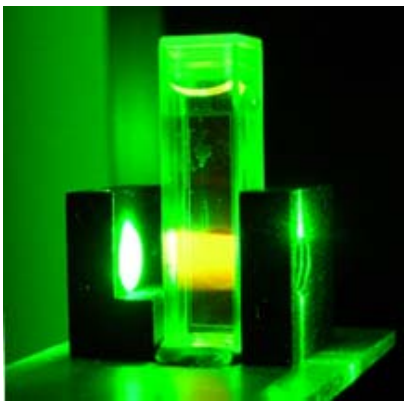

Figure 2. Laser beam in the cuvette during the experiment.

Synthetic nanofibres of poly (ε-caprolactone) blended with rhodamine B were produced in the electrospinning process. For the single fibre experiments rotating disk was used as a collector. Two methods of loading nanofibres with dye were investigated: simple fibre with uniformly distributed dye and core-shell nanofibre with encapsulated dye.

Figure 3 presents concentration profiles of released dye (coloured markers) obtained at several time steps for uniform nanofibre. They are compared with analytical solutions obtained for infinite cylinder with constant surface concentration. Evidently this simple model is far from physical reality. Beside molecular complications of the diffusion process it is necessary to include variation of internal and external diffusion in time and space.

Figure 4 demonstrates different behaviour of the release characteristics obtained for the core-shell nanofibre. The sigmoid behaviour of the concentration profiles at higher concentrations can be explained as the effect delayed diffusion through the shield of already washed out core. The apparent diffusion constant changes by two orders of magnitude giving perspectives for constructing delayed drug release system.

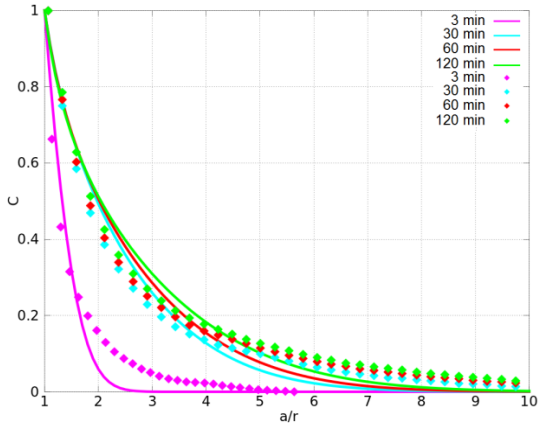

Figure 3. Dimensionless concentration – distance profile for uniform nanofibre. The measured concentration profiles (points) fitted by the analytical model (lines). Apparent diffusion coefficient is D = 1.3e-9 m^2/s.

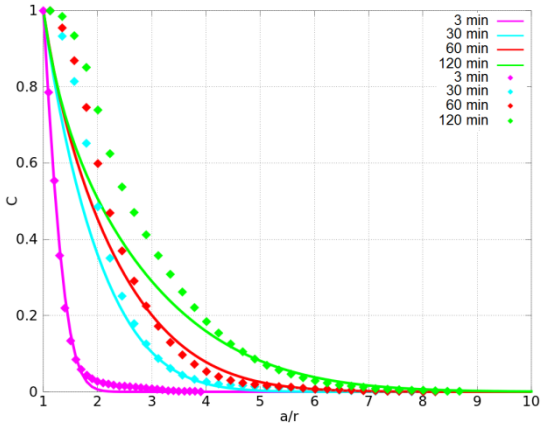

Figure 4. Dimensionless concentration – distance profiles for core-shell nanofibre. The measured data (points) and the fitted analytical model (lines). Apparent diffusion coefficient is D = 0.6e-11 m^2/s.

Dye release from a polymer matrix

Recently our electrospun nanofibreous mats (Fig. 5) appeared to be affordable to prevent excessive cicatrisation after neurosurgical procedures (patent pending, 2011). Additional functionality of these mats is tested for controlled administration of the drugs. This should help to avoid brain neurodegeneration frequently present after traumatic injury. Various factors have a significant effect on the release profile of a drug substance. Comparing with a single nanofibre the diffusion from mats strongly depends on their structure and porosity. This nonlinear behaviour of the release process is additionally biased by environmental changes. In the case of drug release in the brain, due to the frequent exchange of cerebrospinal fluid, it is important to study the drug release both in a static way, as well as dynamic. Figure 6 presents an example of *in vitro* release profile of alpha tocopherol in micelle solution for two cases: blue markers – mixing of supernatant during drug release, black markers – release of drug without mixing.

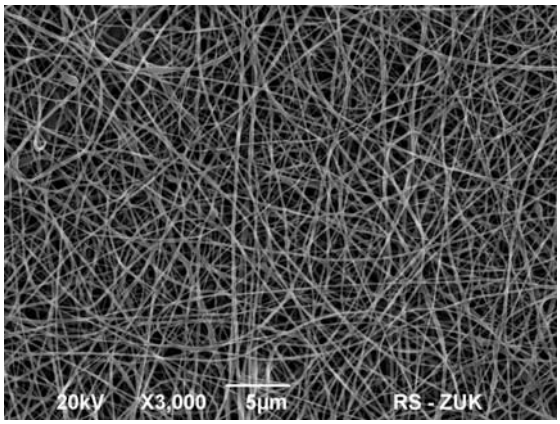

Figure 5. SEM micrograph of 9% wt. PLC nanofibers mat used for drug release experiments. Mean nanofibers size 247 ± 63nm, porosity measured by ImageJ 74%.

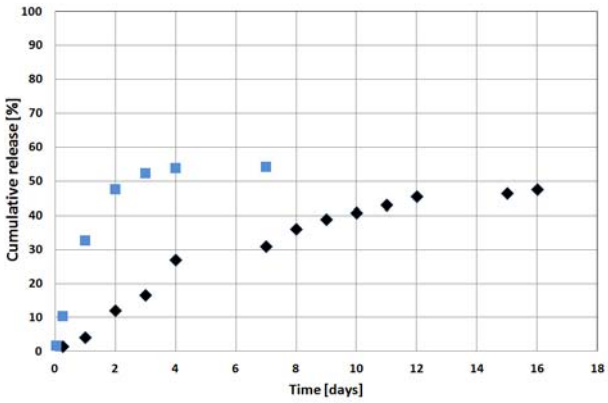

Figure 6. Cumulative release of alpha tocopherol 12 wt% from 9 wt% PLC nanofibre mat. Blue markers - – mixing of supernatant during drug release, black markers – release of drug without mixing.

The construction of the targeted drug release mats is supported by single nanofibre studies. The data obtained for individual nanofibres are related with drug release measurements from nanofibreous mats. The intention of our present research is to find parameters which allow for optimization of drug release process, so that the administered dose allows for the maintenance of drug levels in the desired therapeutic window, while not causing any systematic damage.

Acknowledgments. This research is supported by Ministry of Science and Higher Education, NCBiR grant no. R13008110. The first author has been supported with a scholarship from the European Social Fund, Human Capital Operational Programme.