ABSTRACT

Charles University, Faculty of Pharmacy in Hradec Králové
Department of Pharmaceutical Technology
Candidate **Mgr. Pavel Berka**
Supervisor **Doc. RNDr. Pavel Doležal, CSc.**
Title of Doctoral Thesis **Biopharmaceutical aspects of macromolecular carriers for systemic sublingual drug delivery**

The primary aim of this work was to experimentally verify the hypothesis on sublingual permeation of macromolecules as drug carriers. Literature data about the sublingual route of drug administration and methods of sublingual and buccal membrane processing for in vitro experiments were reviewed for this purpose. The task to design and verify a new methodology of processing and preservation of sublingual membranes suitable for permeation experiments resulted from this literature review.

The new methodology of the “flash freezing” membranes uses the prepared membranes with complete epithelial composition, including the lamina propria and part of the fibrous substrate. Rapid membrane freezing with liquid nitrogen (-180 °C) was performed without cryoprotectants to avoid affecting membrane permeability, with only preliminary fixation of protein structures with sodium azide. For comparison, membranes were also frozen by conventional slow freezing to -20 °C and declared as “frozen” membranes.

Neither “fresh” nor “flash frozen” membranes showed signs of damage under microscopic examination, even after subsequent four weeks storage in a conventional freezer at -20 °C. Impedance and in vitro permeability of caffeine as small water-soluble molecule was used for initial evaluation of barrier properties of such treated membranes. The apparent permeation coefficient Papp values for caffeine, obtained on the “fresh”, conventionally “frozen” (-20 °C) and “flash frozen” (-180 °C) membranes did not show any difference. However, impedance and microscopic techniques have shown significant structural deterioration in conventionally “frozen” membranes.

FITC-labelled dextrans of different molecular weights (FD4, FD20, FD40, and FD70) were used to substantially verify the integrity and in vitro permeability of the sublingual membranes. Again, the measured data confirmed similar barrier properties of the “fresh” and “flash frozen” membranes and their usability for permeation experiments. Unfortunately, these experiments have shown that dextrans are not suitable drug carriers for the sublingual route of administration since they have passed through the membrane very slowly.

Therefore, we tried another macromolecular model carrier - albumin. Nanofiber strips containing FITC-labelled albumin were prepared by electrospinning. The question was whether albumin would be released from the nanofibers and would be capable of further permeation. It turned out that nanofiber albumin can handle both steps at a demonstrably higher level than from a solution of the same initial albumin concentration. In the form of a nanofibrous formulation, albumin can be protected from saliva dilution and subsequent swallowing after sublingual administration under real in vivo conditions. Accordingly, the actual permeation of albumin from nanofiber preparation will be much higher than that of albumin from a solution of similar composition. Thus, albumin in the nanofibrous formulation can become a suitable carrier for small drug molecules for non-invasive systemic sublingual administration.

Keywords: sublingual drug administration, nanofibers, albumin, dextrans