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Macro- and microstructural tracking of ageing-related changes of papaverine hydrochloride-loaded electrospun nanofibrous buccal sheets

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ABSTRACT

Electrospun papaverine hydrochloride-loaded nanofibrous sheets consist of hydroxypropyl cellulose/poly(vinyl alcohol) composite were prepared for buccal administration for cerebral ischemia. The nanofibrous drug delivery system was subjected to accelerated stability test for four weeks in order to scrutinize the solid state changes relating to the stress induced (40 ± 2 °C/75 ± 5% relative humidity) physical ageing. Micro- and macrostructural alterations were detected using scanning electron microscopy (SEM), Raman spectroscopy, Fourier transform infrared spectroscopy (FTIR) and positron annihilation lifetime spectroscopy (PALS). Significant changes were revealed at both supramolecular and macroscopic levels. Microscopic morphology uncovered major morphological transitions. Subtle variations of Raman and FTIR spectra indicated that the local chemical environment of papaverine was altered suggesting a partial phase transition of the active. Discrete o-Ps lifetimes and lifetime-distributions unveiled a two-step ageing process of the drug carrier. In addition to the tracking of the glassy-to-rubbery transition of the fiber forming polymers, the Raman spectroscopy enabled monitoring the kinetics of the phase transition observed.

1. Introduction

The opium alkaloid papaverine exerts a non-specific direct relaxant effect on smooth muscles, including the dilatation of blood vessels [1]. These pharmacodynamic properties make it a potential candidate for the treatment of cerebral ischaemia, but its unpleasant physicochemical and biopharmaceutical properties (such as slight water solubility, poor peroral bioavailability, high pharmacokinetic intra- and interindividual variability) restrict the *per os* administration [2,3]. These unfavourable features can be addressed with the combination of a nanofibrous and a buccal formulation. The former targets the solubility related issues, whilst the latter aims at the concerns associated with first pass metabolism and the consequential oral bioavailability. The rapid onset of effect and the reduced inter-and intraindividual varieties are also representing the favourable expectations of this formulation [4,5].

In our previous study, hydroxypropyl cellulose (HPC)- and polyvinyl alcohol (PVA) based papaverine hydrochloride loaded nanofibrous sheets were prepared for buccal application. During the preformulation study the ratio of the two polymer was varied (HPC:PVA = 5:5, 6:4, 7:3, 8:2, 9:1) and the total polymer concentration was kept constantly at 15% (w/w). HPC:PVA 6:4 composite mass ratio resulted the best fiber forming characteristics [6], so in the following, only this sample ratio was examined. Fourier transform infrared (FTIR) measurements suggested that the drug went through a solid state phase transition (presumably crystalline-amorphous transition) as a result of the electrospinning process. Although, amorphous form represent an effective means of dissolution enhancement, the thermodynamically metastable nature of such systems is a real headache for researchers [7]. High enthalpy of amorphous materials is considered as the main reason for spontaneous transition into a lower enthalpy correspondent crystalline form. Such transitions can be efficiently tracked by volume- and enthalpy relaxation measurements [8,9]. The amorphous polymers might undergo physical ageing, which can be accompanied with

Abbreviations: FTIR spectroscopy, Fourier transform infrared spectroscopy; HPC, hydroxypropyl cellulose; o-Ps, ortho-positronium; PVA, poly(vinyl alcohol); PALS, positron annihilation lifetime spectroscopy; SEM, scanning electronmicroscopy.

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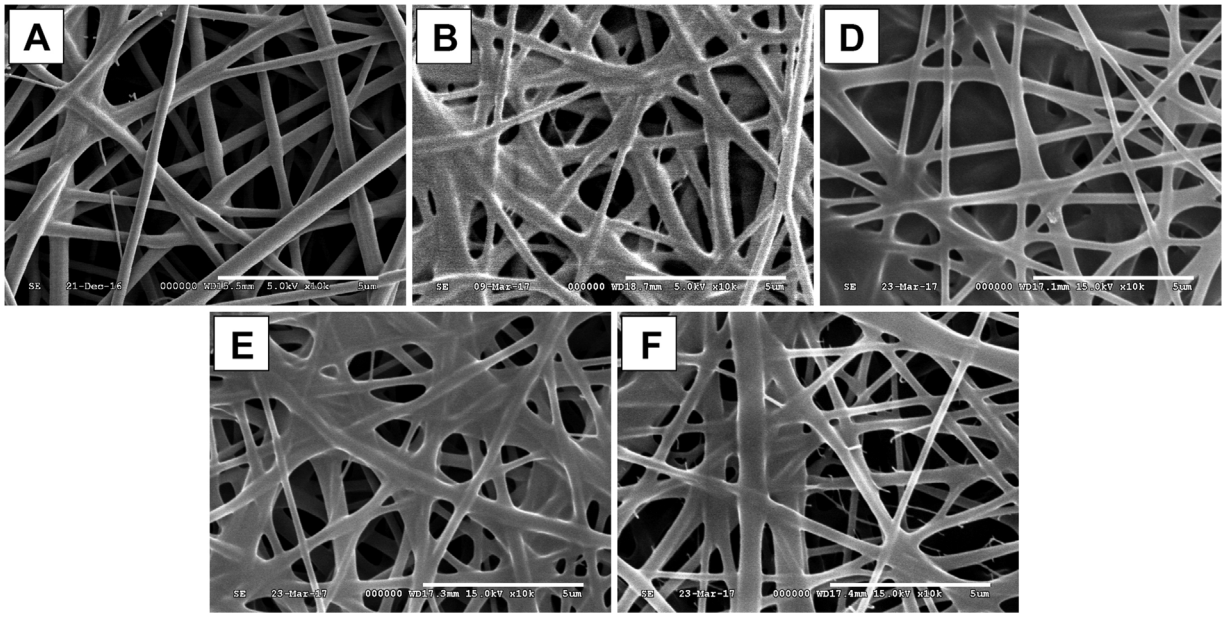

Fig. 1. SEM morphology of the freshly prepared (A) and the stored samples (week 1(B), week 2 (C), week 3 (D), week 4 (E)).

supramolecular changes in the polymers. The moisture- and CO_2 absorption from the surrounding air is one of the possible explanations for this phenomenon [10,11]. It has been well documented that solid dispersions possess higher physical stability than that of the raw amorphous material itself. The possibilities for the formation of drug-polymer interactions (e.g hydrogen-bond formation) decrease the recrystallization tendency of amorphous actives [12].

The supramolecular structure and the solid state characteristics of a polymeric drug delivery system influence the drug release characteristics, which have a major impact on peroral bioavailability. The monitoring of the solid state stability and the supramolecular changes of the amorphous drug loaded polymer-based nanofibrous system is of special interest, since these are crucial factors from the point of long term stability [13].

The different types of solid state characterization methods can be classified in three groups: imaging techniques (e.g. scanning electron microscopy (SEM) and atomic force microscopy (AFM)), macrostructural (e.g. FTIR spectroscopy, Raman spectroscopy, differential scanning calorimetry (DSC) and power X-ray diffraction (PXRD)) and microstructural (e.g. positron lifetime spectroscopy (PALS), solid-state nuclear magnetic resonance (ssNMR)) characterization methods [13]. The ssNMR is very sensitive to molecular conformation in solid-state systems, but with this technique the free volumes remain invisible [14–18]. PALS is a sensitive method to determine size distribution of free volume holes through *ortho*-positronium (o-Ps) lifetime distributions, which is in strong correlation with the physical ageing of the polymers [10,19–21].

The aim of the present study was to monitor the supramolecular changes of the papaverine-HCl-loaded hydroxypropyl cellulose-poly(vinyl alcohol) nanofibrous system, through positronium lifetime distribution and tracking the physical stability of the delivery system with FTIR and Raman spectroscopy in the course of the four weeks long storage under stress condition.

2. Materials and methods

2.1. Materials

For the fiber forming process hydroxypropyl cellulose (Klucel EXF Pharm, Ashland, USA; Mw ~80000; the moles of substitution = 3.8), poly(vinyl alcohol) (18–88 Ph. Eur., Merck, Darmstadt, Germany) and polysorbate 20 (Ph. Eur., Molar chemicals, Hungary) were used. The active pharmaceutical ingredient was papaverine hydrochloride (Ph. Eur.).

2.2. Fiber preparation

Papaverine-HCl containing gel of 15% (w/w) total polymer concentration and HPC: PVA 6:4 mass ratio, was prepared by the addition of the necessary amount of HPC, PVA and 30 mg/g papaverine-HCl aqueous stock solution (according to [6]) applying gentle heat and magnetic stirring. The gel was then transferred into a plastic syringe equipped with a metallic needle (1.2 mm inner diameter). In our previously published paper the effect of the applied voltage and the needle to collector distance on the fibers morphology was studied. The applied voltage was examined in three levels: 20, 25 and 30 kV. The needle to collector distance was 5, 10 and 15 cm. The best fiber characteristics were achieved in case of 15 cm distance and better fiber characteristic was found with the increasing voltage.

So that, for the electrospinning process the voltage was set to 30 kV. The distance between the spinneret and the collector was 15 cm. The fibers were collected on aluminum foil in the course of the 45 min spinning duration.

2.3. Storage conditions

The accelerated stability test was done based on the standard protocol to follow the quality changes of the product and determine recommended storage conditions. The nanofibrous samples were stored in closed containers at $40 \pm 2\,^{\circ}C$ and $75 \pm 5\%$ relative humidity for four weeks.

2.4. Scanning electron microscopic analysis (SEM)

The morphology changes of the nanofibrous systems were followed with scanning electron microscope (SEM). SEM studies were performed by a Hitachi S-4300 instrument equipped with a Bruker energy dispersive X-ray spectroscope (Hitachi Science Systems, Ltd., Japan). The surfaces of samples were covered by a sputtered