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Supramolecular Structure and Stability of Nanofibrous Drug Delivery Systems

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1. Introduction

A significant proportion of new drug candidates possesses poor solubility and/or membrane permeability. Several promising techniques have been developed to overcome these disadvantageous properties, including different fiber formation methods. The electrospinning and high-speed rotary spinning are the most commonly used spinning techniques for fiber formation. The fiber properties (high specific surface area, porosity, the possibility of controlling the crystalline-amorphous phase transitions of the loaded drugs) enhance the dissolution rate and apparent solubility of actives and thus their rate and extent of absorption. The hydrophilic polymer-based drug-loaded nanofibrous orally dissolving webs are promising candidates for rapid drug release, which is due to the advantageous morphological and physical-chemical features of the system. They are also capable of controlled drug delivery over time for local or systemic drug administration. The solubility of the polymer, the fiber diameter and the fiber structure are the primary parameters affecting drug release. In the case of small molecules, developments focus mostly on overcoming the unfavourable physicochemical feature of the active agents (1). However, the physical and chemical stability of these systems has not yet been thoroughly investigated and thus poses a challenge in their development. Since the stability of these systems is a crucial issue, its sensitive and non-destructive tracking could be of great practical relevance in the prediction of their applicability.

2. Materials and methods

Most of the selected Active Pharmaceutical Ingredients (APIs) belong to BCS II. The applied fiber-forming polymers were the followings:

Poly(vinyl alcohol) (PVA) (18–88 Ph. Eur., Merck, Darmstadt, Germany), hydroxypropyl cellulose (HPC, KlucelEXF Pharm, Ashland, USA; Mw ~80000), poly(vinylpyrrolidone) (PVP, Kollidon 90 F, Mw ~1000000–1500000, BASF, Ludwigshafen, Germany). The combination of state-of-art morphology (SEM, AFM imaging) and solid-state characterisation methods (ssNMR, PALS, FTIR spectroscopy, XRD, DSC) were applied to obtain information about the supramolecular changes in the course of storage. ***Figure 1*** illustrates the nuclear chemistry background of PALS technique. This non-invasive nuclear probing technique was applied for the tracking of the free volume changes of polymer-drug composite fibers as a function of storage time based on the variation of the ortho-positronium (o-Ps) lifetime values.

3. Results

Table 1 summarizes the changes of functionality-related characteristics of various nanofibrous systems after storage, which were tracked by the

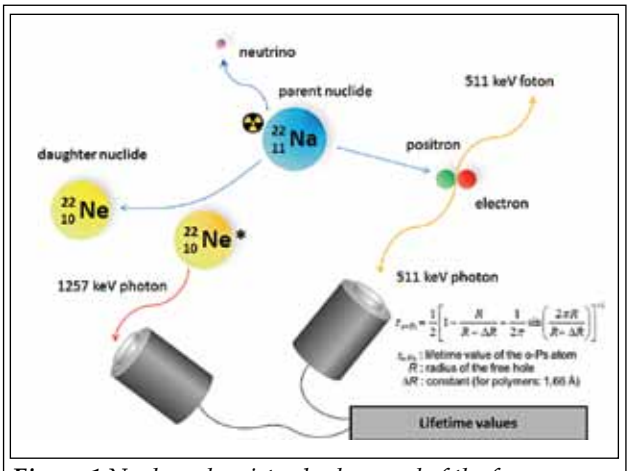

Figure 1 *Nuclear chemistry background of the free volume determination by Positron Annihilation Lifetime Spectroscopy*

Table 1 *Stability tracking of various fibrous systems*

API	Fiber-forming polymer	Significant o-Ps lifetime changes after storage	Influenced stability-indicating property
carvedilol (2)	HPC	+	amorphous-crystalline ratio of API
metoclopramide (3)	PVA	+	fiber morphology
nebivolol hydrochloride (4)	PVA	+	amorphous-crystalline ratio of API
papaverine hydrochloride (5)	HPC/ PVA	+	fiber morphology, amorphous-crystalline ratio of API
living bacteria (6)	PVA	+	viability of *S. maltophilia*

changes of the discrete o-Ps lifetimes and lifetime-distributions. The stress conditions initiated simultaneous polymer carrier and active solid-state transitions, which can be distinguished.

4. Conclusions

The sensitive PALS technique enabled effective means for the detection and the prediction of possible supramolecular interactions based on the free volume changes initiated by stress conditions during storage. Since most of these interactions involve secondary bonds, thus their rearrangements modify the size and distribution of free volume holes.

The applied experimental setup represents a useful approach to track the effect of storage either on the polymeric carrier or on the solid-state changes of the active, which significantly modify the functionality-related characteristics of the delivery system.

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