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Preparation and comparison of spray dried and electrospun bioresorbable drug delivery systems

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ABSTRACT

Two continuous processes, the spray drying method, producing microparticles in presence of hot gas flow, and the electrospinning technology, producing continuous polymer nanofibers at low temperature under high electric fields, were investigated and compared the first time. Both techniques were used to prepare slow release caffeine (as a model of rapidly water-soluble drug) using water-insoluble, biocompatible and bioresorbable PLGA and PLA as polymeric matrix. The structural characterization of the obtained samples was performed using SEM, XRD, DSC and at-line Raman mapping, while in vitro dissolution was detected by UV spectrophotometer. We found that the release profile of a highly water soluble drug can be adjusted to the requirements through the investigated continuous technologies. Solid molecular dispersion of caffeine at colloidal level could be prepared in PLA matrix using electrostatic spinning. Furthermore the continuous nonwoven structure of ultrafine fibers, produced this way, allows easer handling than that of independent fine particle's. On the other hand continuous production of drug loaded microspheres with slightly less performance can be performed with the conventional technology of spray drying which is well known in the pharmaceutical industry.

1. Introduction

The control of drug release poses great challenges for the pharmaceutical industry regardless of poor or high solubility of the active pharmaceutical ingredient (API) in water. In the case of highly water-soluble active drugs, which are otherwise rapidly eliminated from the body, the requirement is to find the appropriate technology and excipients to achieve smooth and sustained drug release. The methods assigned for this purpose should be gentle and productive enough allowing efficient manufacturing on industrial scale. Although both the well-known spray drying (SD) and the recently introduced electrospinning (ES) techniques have been already used for forming controlled release formulations [1–5], these were, surprisingly, not yet tested with the same formulation comparing their capability.

Several investigations have revealed the suitability of SD for producing bioresorbable drug delivery systems in a continuous manner [6–8], providing the amorphous form of the APIs (in most cases). More recently, similar reports have appeared regarding ES [9–11]. The high tendency for amorphization in the cases of ES and SD is ascribed to

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the fast evaporation of the solvent [12], which results in amorphous solid dispersion or solution of the drug in the polymer matrix [9]. Amorphous state of a drug promotes its dissolution advantageously comparing to the crystalline state if it is stabilized by the surrounding polymer phase. It is a disadvantage, however, that the SD technique requires elevated temperature that can damage thermally unstable compounds [13].

In order to achieve controlled release of drugs of high water solubility with these techniques, the selected polymer matrices must not be (or just very slowly) soluble in water allowing smooth release of drug. Poly(lactic acid) (PLA) and poly(lactide-co-glycolide) (PLGA) are such bioresorbable and thermoplastic water-insoluble polymers (approved by all the relevant authorities for use in human subjects). These biocompatible polymers have been employed as suture materials [8], inter-body cages [14], scaffolds for tissue engineering [15], and biodegradable drug delivery systems [16] with sustained drug release [17]. Both PLA and PLGA matrices are frequently applied to achieve sustained drug release, but a so-called "burst effect" is experienced in many cases [18,19]. Significant initial burst release can result in such a high drug concentration in the blood that means significant risk to the patient's health. Furthermore, early depletion of the drug in these cases is a further disadvantage regarding the intended long-term release. Currently, burst release values between 10% and 80%, depending on the encapsulated drug load, are commonly seen in publications as well as in marketed products [20].

The objective of this study was to prepare sustained-release caffeine (as a model of water-soluble API) by spray drying and electrospinning and evaluate the capabilities of these methods for amorphization and controlled release by solid-phase analytical methods and in vitro dissolution tests.

2. Experimental

2.1. Materials

The poly(lactide-co-glycolide) (PLGA) block copolymer used in this work was PURASORB® PDLG 5004, M_w = 40,000, inherent viscosity of 0.4 dl/g (25 °C), it contains 50% D,L-lactide. Polylactic acid homopolymer was PURASORB® PL 24 (PLA, D isomer < 5%) (both obtained from PURAC; Netherlands). Caffeine was purchased from Sigma–Aldrich Chemie GmbH (Germany). Dichloromethane (CH_2Cl_2); chloroform ($CHCl_3$) and N, N-dimethylformamide (DMF) was obtained from Reanal Private Ltd. (Hungary) (see Fig. 1).

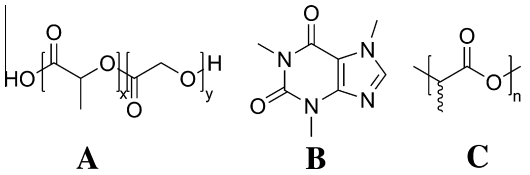

Fig. 1. Structures of the used drug and polymers in this study: PLGA (A); caffeine (B); PLA (C).

2.2. Spray drying and electrospinning processes

Microspheres with and without caffeine were prepared using spray drying method. For this purpose, PLGA of 5% (w/v) and PLA of 1% (w/v) concentrations, respectively, were dissolved in CH_2Cl_2 and caffeine was added in different concentrations (0–100 w/w%) to the solution of the polymers. The code and concentration of samples prepared are given in Table 1. Spray-drying was performed with a Pro-Cep-T 4M8-TriX spray dryer (ProCept, Belgium) using a 0.4 mm two-fluid nozzle. The process parameters were as follows: atomization air pressure 1 bar; inlet air temperature 40 °C; outlet air temperature 38 °C; pump control 2.24 mL/min; airflow 0.8 m^3 min^{-1}.

Electrospun fibers were prepared using and 4, 6 and 10 (w/w%) PLA solution in $CHCl_3$:DMF = 6:1 co-solvent system to which 0, 10, 20 or 50 (w/w)% caffeine was added. All electrospinning experiments were performed at room temperature (24 ± 2 °C) assembling the fibers on aluminum foil affixed to the collector. To perform electrospinning, an infusion pump (Aitecs SEP-10S Plus syringe pump, Lithuania) and constant voltage ranging from 20 to 30 kV were applied provided by a direct current power supplier (NT-35 High Voltage DC Supply MA2000, Hungary). The distance between the collector and the spinneret (with 0.4 mm internal diameter) was 23 cm and the solutions were fed with 0.13 mL/min rate.

The yields were determined based on outcome of the solid product related to the solid starting materials.

2.3. At-line Raman spectrometry and mapping

At line measurements were performed using a LabRAM 300 micro-Raman spectrometer manufactured by Jobin Yvon Horiba (France) and equipped with a fiber optic coupled probe, using a 400 mW, 785 nm laser source and an air cooled CCD detector. The instrument is described

Table 1
The composition of spray dried microparticles and electrospun samples.

Sample code	Caffeine (w/w%)	PLA (w/w%)	PLGA (w/w%)	Yield (%)
SD_PLA80	80	20	–	79
SD_PLA50	50	50	–	74
SD_PLA20	20	80	–	54
SD_PLA10	10	90	–	54
SD_PLA5	5	95	–	72
SD_PLA	0	100	–	76
SD_CAF	100	–	–	65
SD_PLGA80	80	–	20	69
SD_PLGA60	60	–	40	72
SD_PLGA50	50	–	50	76
SD_PLGA40	40	–	60	62
SD_PLGA30	30	–	70	67
SD_PLGA25	25	–	75	68
SD_PLGA20	20	–	80	63
SD_PLGA10	10	–	90	48
SD_PLGA5	5	–	95	35
SD_PLGA	0	–	100	46
ES_PLA50	50	50	–	97
ES_PLA20	20	80	–	95
ES_PLA10	10	90	–	95
ES_PLA	0	100	–	94