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Direct fractionation of spray-dried polymeric microparticles by inertial impaction

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ABSTRACT

The current study describes a convenient method for a direct size classification of spray-dried powders, which is of general interest for diverse applications in drug delivery. Accordingly, the time-consuming "trial-and-error" approach to identify critical formulation and process parameters influencing the final product specifications is replaced by a final fractionation step of the dried particles by inertial impaction.
When employing the "original" vibrational spray-dryer (i.e., Nano Spray-Dryer B-90, Büchi) it was evident that both the liquid feed characteristics (e.g., concentration of dissolved solids) and process parameters (e.g., nozzle type and spray-rate) significantly affected the particle size and size distribution of generated sildenafil-loaded poly(lactide-*co*-glycolide) microparticles (particle size: ~4–~11 μm; particle size distribution (*span*): ~1.3–~2.2). The said formulations showed prolonged in vitro drug release properties with mean dissolution times (MDTs) ranging between ~4 and ~14 h. By contrast, replacing the electrostatic particle collector of the vibrational spray-dryer by a Next Generation Impactor enabled a direct size classification of spray-dried microparticles according to their aerodynamic behavior. Formulations collected from the individual impactor stages exhibited a defined particle size (i.e., stages I, II, III and IV with 7.8, 4.5, 3.0 and 2.1 μm, respectively) and were significantly narrowly distributed (*span*: ≤1.2) than the non-fractionated controls. Likewise, fractionated formulations were characterized by a sustained sildenafil in vitro release behavior (MDT: ~1.5–~7 h).
Overall, regardless of the primary particle size and size distribution of spray-dried powders, desired size characteristics can be achieved by a terminal size classification by inertial impaction. Hence, the described approach provides spray-dried products meeting the specific requirements of the intended application (e.g., prolonged drug delivery to the lungs).

1. Introduction

Spray-drying is utilized in many relevant branches such as the pharmaceutical industry with the aim to stabilize sensitive materials (e.g., proteins) [1] and/or generate powders with specific properties (e.g., controlled release of an encapsulated drug) [2]. The main advantages of spray-drying comprise the continuous, one-step nature and scalability of this process and the high flexibility to manipulate the particle size and morphology of the generated product [3,4].

Latest innovations in device design provided spray-dryers (e.g., Nano Spray-Dryer B-90, Büchi) employing piezoelectric-actuated metal apertures and electrostatic precipitators for an efficient droplet generation and particle collection [5,6]. The said instrument revealed potential for the fabrication of beneficial particulate drug carriers enabling a more specialized therapy of diseases [7–13]. A limitation of "original" vibrational spray-drying is related to the numerous parameters influencing the properties of the final product [7,13–21], causing time-consuming investigations in order to prepare specified formulations meeting the requirements for the intended application [3,4]. Moreover, analysis of recent reports accented rather "heterogeneous" particle sizes and size distributions of obtained powder formulations [7–11,13,15–22].

However, defined drug carrier properties are of significant concern for diverse applications in the biomedical field. As an example, the size of particles administered to the respiratory tract via the inhalative route should be ideally between 2 and 4 μm to guarantee an efficient deposition within the deep lungs [23]. Larger particles (>5 μm) would impact in the upper airways (leading to potential side effects), while smaller ones (<1 μm) would be exhaled (lack of drug action) [24]. Furthermore, the release rate of an encapsulated drug is a function (beside other factors) of the particle size, where smaller particles generally showed faster drug release [25].

To overcome the drawback of vibrational spray-drying, the current study proposed a direct size classification of spray-dried powders allowing for a more systematic manufacture of defined drug-loaded

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polymeric microparticles (MPs). Firstly, formulation and process parameters with significant impact on the properties of the spray-dried product were identified under application of the "original" B-90 set-up. Thereafter, the electrostatic particle collector was replaced by an impactor in order to fractionate the dried particles according to their inertial behavior. Obtained MPs were analyzed by means of laser diffraction and scanning electron microscopy (SEM). Finally, the controlled release characteristics of "heterogeneous" and "homogeneous" MP samples were followed by monitoring their in vitro drug release profiles.

2. Materials and methods

2.1. Materials

Poly(lactide-*co*-glycolide) (PLGA), Resomer® RG502H was acquired from Boehringer Ingelheim (Ingelheim, Germany). Sildenafil (free base) was obtained from bioKEMIX (Nienburg, Germany). All other chemicals and solvents were of analytical grade.

2.2. Preparation and characterization of polymer solutions

PLGA and sildenafil (10 wt.% per polymer mass) were dissolved together in acetone (total solid content: 10, 20, 50, 70 and 100 mg/ml) for ~12 h, followed by a filtration step (5.0 μm; Cameo 30 N syringe filters, GE Water & Process Technologies, Ratingen, Germany). Polymer solutions were characterized for the kinematic viscosity (Ubbelohde capillary (Type 0c ($k = 0.003121\ mm^2/s^2$)); Schott, Mainz, Germany), density (oscillating density meter; DMA 4100 M, Anton Paar, Graz, Austria) and surface tension (Wilhelmy plate; K11-Mk3, Krüss, Hamburg, Germany) at 25.0 ± 0.1 °C.

2.3. Preparation of sildenafil-loaded PLGA-MPs

Spray-drying (Nano Spray-Dryer B-90, Büchi, Flawil, Switzerland) was employed for polymeric MP preparation [8,17,22]. Briefly, polymer solutions were atomized using spray-dryer nozzles with nominal orifice diameters of 4.0, 5.5 and 7.0 μm. The process parameters were as follows: inlet temperature = 45 °C, outlet temperature = 25–30 °C, drying gas flow rate = 100 l/min (N_2/CO_2), and relative spray-rate = 25–100% (with 100% representing a nozzle frequency of 60 kHz). The collected formulations were subjected to vacuum (72 h, ~0.05 mbar; Beta I, Christ, Osterode, Germany) and then stored in a sealed desiccator at 4 °C until further analysis.

The total throughput of the feed solution was determined volumetrically for each spray-drying experiment. The resulting difference in volume was used to calculate the feed solution throughput rate in ml/h.

2.4. Fractionation of sildenafil-loaded PLGA-MPs

The electrostatic particle collector implemented inside the B-90 spray-dryer was replaced by a Next Generation Impactor (NGI; Copley Scientific, Therwil, Switzerland) in order to directly fractionate the dried product from the drying gas according to the aerodynamic behavior of the generated MPs [26]. Therefore, the NGI was assembled and operated according to the specifications described in the United States Pharmacopeia XXXI ("*Physical Tests*/‹601› Aerosols", pages: 209–229). Briefly, the NGI equipped with the pre-separator was connected to a critical flow controller (TPK, Copley Scientific, Therwil, Switzerland) and a vacuum pump (HCP5, Copley Scientific, Therwil, Switzerland). The flow rate, measured at the inlet of the pre-separator (DFM2000, Copley Scientific, Therwil, Switzerland), was adjusted to 60 l/min (±5%). Thus, the cut-off diameters ($d_{cut\text{-}off}$) of stages I–IV of the NGI amounted to 8.1, 4.5, 2.8 and 1.7 μm, respectively [27,28]. The pre-separator was filled with ~15 ml of distilled water to capture particles with aerodynamic diameters (d_{ae}) of >12.8 μm.

Sildenafil-containing PLGA solution (total solid concentration: 50 mg/ml (10 wt.% of drug per polymer mass)) was processed (orifice diameter: 4.0 μm; spray-rate: 100%) as described above. The spray-drying procedure was continued for ~20–30 min to ensure adequate quantities of sample on stages I–IV of the NGI. Collected powder deposits were handled as described above until further analysis.

2.5. Characterization of sildenafil-loaded PLGA-MPs

The median geometric diameter of spray-dried MPs (d_p, based on the volume distribution) was determined by laser diffraction using a Mastersizer X (Malvern Instruments, Herrenberg, Germany). Samples were dispersed in filtrated, double-distilled water (B. Braun, Melsungen, Germany), containing 0.1 wt.% of polysorbate 80 (Sigma-Aldrich, Steinheim, Germany), using brief ultrasound (SONOREX DIGITEC, BANDELIN, Berlin, Germany). Aliquots were then placed in a stirred cuvette until a laser obscuration of >10% was achieved. The obtained diffraction patterns were analyzed in Mie mode (real part of the refractive index of water and MPs were set to 1.33 and 1.59, respectively). The size distribution (i.e., *span*) was calculated from the laser diffraction values as follows

$$span = (d_{90\%} - d_{10\%})/d_{50\%} \quad (1)$$

with d_n as the diameter at the percentile n of the cumulative distribution.

The morphology of spray-dried MPs (deposited on silica wafers) was visualized by SEM. Samples were sputter-coated with a gold layer (in an argon atmosphere at ~0.3 mPa; Sputter Coater S-150, Edwards, Kniese & Co. Hochvakuum, Marburg, Germany) before imaging and observed using a scanning electron microscope (S-510, Hitachi, Tokyo, Japan) at an accelerating voltage of 25 kV.

The true density of spray-dried sildenafil-loaded PLGA-MPs was determined by helium pycnometry (Ultrapycnometer 1000 T, Quantachrome, Odelzhausen, Germany) at 25.0 ± 0.1 °C. Prior to the analysis, samples were dried in vacuum (72 h, ~0.05 mbar) and about 0.5 g of powder was then used for the measurements. The true density of MPs amounted to 1.46 ± 0.01 g/cm^3 (mean ± SD, $n = 4$) [22].

To determine the sildenafil content of the spray-dried formulations, MPs were dissolved in acetonitrile (a common solvent for PLGA and sildenafil). Sildenafil concentrations were quantified by UV/Vis spectroscopy. The drug incorporation efficiency is reported in terms of drug content [wt.%], which was calculated according to the following equation

$$\text{drug content}[\text{wt.}\%] = (\text{mass of drug in MPs}/\text{mass of MPs}) \cdot 100. \quad (2)$$

The actual sildenafil content of the diverse spray-dried MP formulations ranged between 8.7 ± 1.3 wt.% and 11.3 ± 0.5 wt.% (mean ± SD, $n = 4$).

2.6. In vitro drug release studies

The in vitro drug release was carried out in phosphate-buffered saline (pH 7.4) supplemented with 0.1 wt.% sodium dodecyl sulfate (SERVA, Heidelberg, Germany). Spray-dried sildenafil-loaded PLGA-MPs (1 mg, theoretical drug content: 10 wt.%) were dispersed in the release medium (2 ml) by brief sonication. Incubation occurred at 37 °C with shaking. Samples were taken at predetermined time points and centrifuged (Centrifuge 5418, Eppendorf, Hamburg, Germany) prior to determining the cumulative release of sildenafil by UV/Vis-spectroscopy. No loss or degradation of sildenafil was observed during incubation time [17,22,29,30]. The cumulative amount of sildenafil released was calculated by the following equation

$$\text{cumulative amount of drug released}[\%] = M_t/M_\infty \cdot 100 \quad (3)$$