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# Polymeric controlled release inhalable powder produced by vibrational spray-drying: One-step preparation and *in vitro* lung deposition

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ABSTRACT

Innovative polymeric controlled release inhalable dry powders containing dexamethasone were developed for the treatment of pulmonary diseases. Powders were prepared in one step by vibrational atomization spray-drying using an organic solution containing dexamethasone, poly(ε-caprolactone) and a surfactant. The characteristics of the powders were monitored considering the drug content, morphological features, mean particle size, drug-polymer-surfactant compatibility and physical state. *In vitro* dexamethasone release was studied applying the dialysis bag method. The dose uniformity of the powders, their aerodynamic properties and the *in vitro* lung deposition were evaluated using a Dosage Unit Sampling Apparatus and Andersen Cascade Impactor. The powders had a high yield (65–80%), drug content between 170 and 880 mg·g$^{-1}$ and high encapsulation rate (93–97%). All formulations had spherical particles with a rough surface and the primary mean particle size was around 1.00 μm. The formulation prepared with the lowest amount of polymer led to a more symmetric primary particle size distribution and an efficient deagglomeration behavior. The powders exhibited dexamethasone crystallinity and no interaction between the drug and other excipients was evidenced. Dexamethasone release from the powders followed the biexponential model. The lowest drug:polymer ratio led to the best controlled release of the drug. Furthermore, the powders showed dose uniformity close to 100%, a mass median aerodynamic diameter lower than 5 μm and fine particle fraction between 59% and 62%. These polymeric particles (as powders) can be recommended as a platform for the production of new controlled release systems for pulmonary administration.



## 1. Introduction

Vibrational atomization spray-drying is a technique used for the preparation of spherical small-size particles from aqueous or organic solutions. It produces powders in high yields [1–3] with low water content [4,5]. Beck-Broichsitter and co-workers demonstrated the application of this technique to dry engineered polymeric nanoparticles [6]. This recent technique involves some interesting novel technologies: vibrational atomization by the piezoelectric process generating the vibration of the mesh spray, laminar drying air flow to dry the droplets and an effective electrostatic particle collector [7].

This novel spray-drying technique was recently applied to produce inhalable powders [6,8–10]. The pulmonary route is considered to be non-invasive, where drugs can be delivered for local and systemic effects [11,12]. The respiratory tract is a region that has been targeted over recent years for the development of micro- and nanoparticles as drug delivery systems due to their potential to increase and sustain the local drug concentration [11,13,14]. However, to the best of our knowledge, there is only one report describing the preparation of polymeric drug delivery systems by vibrational spray-drying for pulmonary application. Polymeric particles containing sildenafil were produced from organic poly(D,L-lactide-co-glycolide) (PLGA) solutions [6]. These formulations control the drug release rate. Their suitability for pulmonary administration was demonstrated by the particle redispersion in aqueous medium and subsequent nebulization. In the same study, the authors reported the feasibility of using vibrational spray-drying to obtain dry engineered polymeric nanoparticles [6] obtaining composite particles. These composites were produced from aqueous sildenafil-loaded PLGA nanosuspensions and their pulmonary administration was only suggested, after their blend with lactose, as carrier particles.

Recently, it has been demonstrated that dexamethasone is able to reduce *in vitro* the inflammation response in a model of cystic fibrosis bronchial epithelial cells [15] and regulate *in vivo* the expression of inflammatory factors in the lung [16]. Dexamethasone is a synthetic glucocorticoid used as an anti-inflammatory medicine to treat acute and chronic inflammation [17]. The preparation of particles containing dexamethasone by vibrational spray-drying was previously described [5,18,19], however none of these reports intended to deliver the developed systems to the lungs.

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In this scenario, the aim of this study was to produce innovative polymeric inhalable powders containing dexamethasone using a one-step method, applying the vibrational spray-drying technique. Formulations containing different drug:polymer ratio were prepared to evaluate the influence of this factor on the mean particle size, deagglomeration behavior, controlled drug release profile and *in vitro* lung deposition.

## 2. Materials and methods

### 2.1. Materials

Poly(ε-caprolactone) (PCL, average $M_n$ 80,000, pellets) and sodium deoxycholate were purchased from Sigma-Aldrich (São Paulo, Brazil). Dexamethasone was kindly donated by Multilab Industry of Pharmaceutical Products Ltda (São Jerônimo, Brazil). Acetone and acetonitrile were supplied by F. Maia Indústria e Comércio (São Paulo, Brazil) and Tedia (Rio de Janeiro, Brazil), respectively. All chemicals were of pharmaceutical grade. Acetone and acetonitrile were of analytical and high performance liquid chromatographic grade, respectively.

### 2.2. Preparation of dexamethasone solutions and spray-dried powders (SPs)

Firstly, dexamethasone, PCL and sodium deoxycholate, as the surfactant, were dissolved in acetone:water (20:1, v/v) solutions at different drug:polymer: surfactant ratios (S1, S2 and S3; Table 1) under magnetic stirring at 40 °C to produce a clear solution. In addition, a solution without polymer was also prepared at the highest solid content (S4; Table 1). Acetone:water mixture was chosen as the organic solution due to the dexamethasone solubility in this mixture as well as the low viscosity of acetone, which makes quicker the passage of drug solution through the vibrational membrane, and consequently reducing the processing time [5]. The proportion of surfactant in the particles was kept constant at a ratio of 10:1 (w/w, drug and polymer/surfactant), according to our previous report showing the assembly of submicron drug particles under these proportions [5]. However, in the present study we changed the surfactant to sodium deoxycholate, taking into account its cationic characteristic and its wide use in pharmaceutical formulations for different administration routes, including the pulmonary. The presence of ionic surfactants improves the process yield [5]. Each solution (42 mL) was fed into the Nano Spray Dryer Advanced Model B90® (Büchi, Switzerland), linked to a cooling unit for overall drying. Powder formulations were called SP1, SP2, SP3 and SP4, corresponding to S1, S2, S3 and S4, respectively. The drying process was performed applying the following conditions: inlet temperature of 55 °C, outlet temperature of 34 °C, head temperature of 63 °C, air flow of 110 $L \cdot min^{-1}$, spray mesh with 4.0 μm aperture size, pump mode number 2, spray rate of 100% and 37 mbar of pressure. An Inter Loop B-295 (Büchi, Switzerland) was used to maintain the residual oxygen level below 4%. This cooling unit prevents the formation of an explosive gas mixture and inert nitrogen gas was used. Formulations were collected from the collecting electrode with a spatula. Three independent batches were produced for each formulation (SP1 to SP4).

**Table 1**
Quali-quantitative composition of the feed solutions (n = 3).

| Solution | Dexamethasone % (w/v) | Poly(ε-caprolactone) % (w/v) | Sodium deoxycholate % (w/v) |
|---|---|---|---|
| S1 | 0.10 | 0.10 | 0.02 |
| S2 | 0.10 | 0.20 | 0.03 |
| S3 | 0.10 | 0.40 | 0.05 |
| S4 | 0.50 | – | 0.05 |

### 2.3. Yield, moisture content, drug content and encapsulation rate

The yield was calculated from the quotient between the powder mass obtained after drying and the solid mass present in the starting solution multiplied by 100 (to be expressed in percentage terms). Karl Fischer titration (Mettler Toledo 37, Columbus, USA) was used to measure the residual moisture content of the SP (also expressed in percentage terms). The dexamethasone content of the SP was assayed by a LC method [20]. The liquid chromatography system (Shimadzu, Kyoto, Japan) was equipped with a model LC-20AT pump, an SPD-M20AV detector, a DGU-20A5 degasser, a SIL-20A auto-sampler, a CBM-20A system controller and a C18 column (150 mm × 4.6 mm, 5 μm particle size, 110 Å pore diameter, Discovery®, Supelco Analytical, Sigma-Aldrich, Brazil). The mobile phase consisted of acetonitrile/water (45:55, v/v) at an isocratic flow rate of 1 $mL \cdot min^{-1}$. UV detection was carried out at 240 nm and the injection volume was 100 μL (total run: 5 min). The method was linear ($r = 0.9997$) in the range of 0.1–3.0 $\mu g \cdot mL^{-1}$, precise (RSD < 2%), accurate (97.92–101.31%) and specific. For the drug assay, the SPs were dissolved in acetonitrile, sonicated for 1 h, diluted in mobile phase and filtered through a hydrophilic membrane (0.45 μm, Millipore®). The dexamethasone content was expressed in $mg \cdot g^{-1}$ (milligram of the drug per gram of SP). The drug encapsulation rate (%) in the SP was calculated using the following Eq. (1):

$$\text{Encapsulation rate} = \frac{\text{amount of drug determined in SP}}{\text{initial drug amount}} \times 100. \quad (1)$$

### 2.4. Morphological and mean particle diameter analysis

The shape and surface analysis was carried out by scanning electron microscopy (SEM) (JEOL JSM-6060, Japan) at the *Centro de Microscopia Eletrônica* — UFRGS (Porto Alegre, Brazil). The microscope was operated under high vacuum conditions with an accelerating 10 kV voltage, at different magnifications. Each powder was placed on aluminum stubs containing adhesive tape and then coated with gold. The mean primary particle diameter and symmetry of particle size distribution were analyzed using the Software ImageJ (version 1.45s, National Institute of Health, USA) [5].

In order to observe whether deagglomeration of the primary particles occurs at the dispersing pressures, the mean diameter expressed as the number ($d_{0.1}$, $d_{0.5}$ and $d_{0.9}$) of the powders was also measured by laser diffraction using a Mastersizer 2000® equipped with a Scirocco dry disperser (Malvern Instruments, Worcestershire, UK) [21]. The polydispersity was given by the span index, according to Eq. (2):

$$\text{Span} = \frac{d_{0.9} - d_{0.1}}{d_{0.5}} \quad (2)$$

where $d_{0.9}$, $d_{0.5}$ and $d_{0.1}$ are the particle diameters determined respectively at the 90th, 50th and 10th percentile of undersize particles [22].

### 2.5. Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD) and differential scanning calorimetry (DSC) analysis

Infrared spectra were recorded on a spectrophotometer (PerkinElmer FT-IR, Spectrum BX, UK) to investigate the drug-polymer-surfactant compatibility. The dexamethasone, PCL, sodium deoxycholate, their physical mixtures and SPs were analyzed at room temperature and the transmission mode spectra within a range of 4000–600 $cm^{-1}$ were used. The crystallinity of the SPs was analyzed using XRD (Siemens, D5000 model, Munich, Germany), Cu anode and operating at 40 kV and 25 mA. The samples were examined from 2° to 72° 2$\theta$ with a scanning rate of 0.02° 2$\theta$ for 1 s. The thermal analysis of the pure raw materials, their physical mixtures and all SPs was performed using DSC (TA