Development of Budesonide NanoCluster Dry Powder Aerosols: Formulation and Stability

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ABSTRACT: The physical and chemical stability of dry powder aerosol formulations is an essential component in the development of an inhaled therapeutic. The pharmaceutical processing methods and storage conditions are primary determinants of the stability of a dry powder inhaler (DPI) formulation. Wet milling was used to produce budesonide NanoClusters (NCs), which are agglomerates of drug nanoparticles (~300 nm) with a mean aerodynamic diameter between 1 and 3 μm, capable of deep lung penetration. In this study, the reproducibility of NC processing and performance was established. The physical stability of a selected budesonide NC formulation was investigated using industry standard dose content uniformity and cascade impaction techniques. The chemical stability of the lead formulation was also determined as a function of processing parameters and storage conditions. This study confirms the reproducibility and robust stability of NC powders as a novel means to turn drug particles into high-performance aerosols. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:3445–3455, 2012

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INTRODUCTION

Previously, wet milling was demonstrated as an effective method to produce agglomerates of budesonide nanoparticles. These "NanoCluster" (NC) formulations with customizable aerodynamic sizes exhibited superior flowability and dispersion properties. In this work, we focus our attention on the reproducibility of the manufacturing process and the effect of storage conditions on the physical stability and aerosol dispersion profiles on the budesonide NC formulations.

Formulation development of dry powders for inhalation is particularly challenging. The limited number of excipients[1]; patient demographics and disease state[2,3]; flow rate; and environmental factors such as humidity and storage temperature would lead to the variability of the delivered dose. Consequently, a reproducible therapeutic effect can be difficult to attain.[4] Moreover, manufacturing process and the storage conditions affect the physical and chemical stability of a dry powder formulation, which would further have a profound effect on the aerosol performance of a formulation.[5]

The chemical and physical stability of the dry powder formulation is affected by several factors. They include (1) the crystallinity and polymorphism of the therapeutic molecule,[5,6] (2) interactive forces within the formulation components,[7] (3) moisture content and hygroscopicity of the formulation,[8,9] (4) particle size and surface morphology,[10–12] and (5) the chemistry of the excipients and carrier particles.[13–15] Storage conditions such as relative humidity (RH) and temperature also play a significant role in formulation stability as they affect the crystallinity, polymorphism, or chemical degradation of the therapeutic molecule of the formulation. This would in turn influence the dispersion profile of the formulation.[5,7,16] In order to develop a robust dry powder inhaler (DPI)

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formulation, it is essential to characterize the effect of manufacturing process and the storage conditions on the aerosol performance and the chemical integrity of the formulation.

MATERIALS AND METHODS

Materials

Budesonide (lot# 40188-01008M) was obtained from Sicor de Mexico, Lerma, Mexico. Methanol, ethanol, and acetonitrile were purchased through Fisher Scientific, Fair Lawn, New Jersey. Double-distilled water was used throughout the study, provided by an EASYpure® RODI (Model# D13321; Barnstead International, Dubuque, Iowa).

Budesonide NC Formulation

The wet-milled budesonide NC suspensions were fabricated using a Netzsch MiniCer Media Mill (NETZSCH Fine Particle Technology, LLC, Exton, Pennsylvania). Briefly, 5 g of the drug powder was milled in 300 mL of pure water for 10 h under an agitation speed of 2772 rpm using YTZ® grinding media (0.2 mm; Tosoh Corporation, Tokyo, Japan), as reported previously. After milling, the suspension was collected in 20 mL antistatic vials, frozen using liquid nitrogen, and lyophilized for approximately 36 h at a temperature of −72°C and under vacuum of approximately 150 mTorr (VirTis Feezemobile-12XL; The VirTis Company, Gardiner, New York). Lyophilized NC powder was stored under desiccant at room temperature for further use.

Batch Reproducibility

There batches of budesonide NCs were prepared under the same optimized process condition and characterized.

Particle Size Measurement of NC Suspensions

The particle size of three different NC batches was measured at different time intervals during the milling process using dynamic light scattering (ZetaPALS; Brookhaven Instruments Corporation, Holtsville, New York). Nanoparticle size was determined as follows: 0.5 mL of the milled suspension was diluted to 10 mL with water and sonicated with a microtip probe sonicator for 30 s using an amplitude of 20% (Sonic Dismembrator; Fisher Scientific, Pittsburgh, Pennsylvania).

Particle Imaging by Scanning Electron Microscopy

The reproducibility of the formulation process from batch to batch was also confirmed using a LEO 1550 field-emission scanning electron microscope (Carl Zeiss NTSC, LLC, Peabody, Maine) and compared with the drug as received. Prior to imaging, the samples were sputter coated with gold for 3 min.

Powder Flow Characteristics

The tap density of budesonide NC dry powder was estimated for different batches by a micro-tap test approach and compared with the drug as received.[17,18] The powder was placed into pre-weighed micro-centrifuge tubes, and the tubes were weighed again to determine the mass of powder. The tube was then tapped 20 times on the laboratory bench to compress the powder. The volume of the powder was approximated by comparing the height of the compressed powder with that of the volume of water in an identical pre-weighed micro-centrifuge tube. The tube containing the water was then weighed to determine the volume of water (assuming a density of 1 g/cm^3). The powder density was calculated by dividing the mass of powder by the volume of water.

Aerosolization of Budesonide NC Dry Powders

Dose Unit Sampling Apparatus

Dose content uniformity testing, also known as uniformity of delivered dose, is mandatory for all inhaled products to confirm consistency from batch to batch and across the product lifetime. The delivered dose is the amount of the drug emitted from the device and hence available to the user.[19,20,21] The emitted dose (ED) uniformity for the NCs and the drug as received, jet-milled budesonide, was determined from the DPI (Plastiape Monodose® inhaler RS01 Model 7, Plasticape, Milan, Italy) using the dose uniformity sampling apparatus (DUSA). All tests were carried out under controlled conditions (21 ± 2°C, 50 ± 5% RH) in triplicate. The sampling apparatus was assembled in a horizontal position with the loaded inhaler in an appropriate mouthpiece adapter to ensure an airtight seal. The airflow rate was set at 90 L/min for 2.6 s (4 L inhalation volume), and two 47 mm glass fiber filters were used in the sampling apparatus to prevent any structural tear of the filter. The dry powder to be tested was filled into capsules [hydroxypropylmethyl cellulose (HPMC) type, size 3, generously provided from Capsugel®, Peapack, New Jersey] in a dose of 3.0 ± 0.5 mg. The capsule was punctured and the contents were drawn from the DPI into the collection tube of the DUSA. Methanol containing mometasone as an internal standard (25 μg/mL) was used as extracting solvent. Using this solvent, the drug was extracted from the sample collection tube and filter support base. The filters were placed in a Petri dish containing the extracting solvent and rocked for 20 min at a speed rating of 13 and tilt rating of 10. Appropriate sample dilutions were performed prior to testing by high pressure liquid chromatography (HPLC).