Supporting Inhalation Drug-Device Combination Product Quality Using 3D Printing Technology

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DISCLAIMER

This abstract reflects the views of the authors and should not be construed to represent the Food and Drug Administration's views or policies.

SUMMARY

One of the important factors influencing drug deposition in the lung by metered dose inhalers (MDIs) is the design of device components. In this study, a solution-type beclomethasone dipropionate MDI was used to compare the aerosol performance of actuators taken from three commercially available, FDA-approved MDI products to actuators made in-house by three-dimensional (3D) printing. Variables evaluated included spray orifice dimensions, surface roughness, and aerosol properties such as spray pattern and aerodynamic particle size. In at least one case, the 3D printed actuator performed similarly to the commercial actuator on which its design was based, suggesting that printed models may be useful to identify critical quality attributes in orally inhaled drug products (OIDPs). When properly validated, data generated using 3D printed inhalation device components has the potential to provide supporting information for the scientific review of Nnew drug applications (NDAs) and abbreviated new drug applications (ANDAs) for OIDPs submitted to the Agency.

INTRODUCTION

In April 2018, FDA issued a revised draft guidance, metered dose inhaler (MDI) and dry powder inhaler (DPI) products – quality considerations [1]. In this draft guidance, the material properties and dimensions of the device constituent part are included as critical quality attributes (CQAs) to MDI products, and considered important factors that may affect product safety and performance. One of the important factors influencing drug deposition in the lung by MDIs is the design of device components, e.g., the actuator [2, 3]. The recent advancement of 3D printing technology has enabled inhaler device manufacturers [4] to print customized inhaler device constituent parts for different objectives, for example, low volume product production or rapid prototyping. To ensure consistent quality of 3D printed inhalation drug delivery systems, the effect of process parameters of 3D printing on product performance needs to be evaluated.

In this study, three commercially available, FDA-approved MDI products were surveyed. 3D printed MDI actuators were made in-house based on the design of one commercial MDI product and evaluated by 3D imaging to investigate the effects of variables (including the dimensions of spray nozzle orifice, surface roughness, and actuator internal structure) on product quality. Furthermore, both the commercial and 3D printed actuators, each combined with a marketed MDI drug canister, were evaluated for their in vitro drug release performance in terms of spray pattern, particle size distribution, and emitted dose [3-5]. The purpose of the study is to identify potential risk areas in using 3D printing technologies to produce innovator and generic MDI products. The results from this work could potentially impact the FDA's current thinking on MDI device recommendations for new and generic MDI products from the product quality and performance perspective.

METHODS

In collaboration with the FDA's core facility of Additive Manufacturing of Medical Products (AMMP) at Center for Devices and Radiological Health, scientists in the FDA's Office of Testing and Research (OTR) developed 3D actuator models of the commercially available, FDA-approved MDI devices where orifice diameter and nozzle design were precisely controlled. The 3D models of actuators were then used as blueprints for 3D printing. With the 3D actuator models, there are also potentials to make variations in the critical actuator parameters, such as orifice diameter and surface roughness, as well as its process conditions.

A Form 2 Stereolithography (SLA) 3D printer (Formlabs Inc., Somerville, MA) with grey and clear photoreactive liquid resin material was used to build inhaler actuators. The SLA 3D printing technology produces 3D parts layer-by-layer using photopolymerization, during which a 405 nm violet laser (250 mW, 140 μm laser spot size, FWHM) was used to crosslink chains of molecules to form polymers. Build volume of the printer was 145 mm × 145 mm × 175 mm. In this study, the 3D actuators were printed in both vertical and horizontal orientations, with layer thickness of 25 μm. Post-processing, including rinsing by isopropyl alcohol (IPA) and post-curing by 405 nm LED lights, was conducted to ensure high quality finishing of the print surfaces.

Combined with a marketed MDI drug canister (120 metered actuations, 40 mcg dose of beclomethasone dipropionate in 50 microliters of solution formulation per actuation), the 3D printed actuators were characterized for their performance attributes including spray pattern, emitted dose, and aerodynamic particle size distribution. The results were further evaluated by confocal and conventional microscopy to understand the impact of 3D printing material and process parameters on the quality and performance of MDI products.

RESULTS AND DISCUSSION

The 3D printed MDI actuator nozzle part by SLA printing technology with the 3D models is shown in Figure 1. *In situ* characterization (spray pattern and spray velocity, not shown) is effective in 3D printing validation and quality evaluation, in addition to performance testing of inhalation drug-device combination products [3, 5]. The spray pattern results at 3 cm distance from the 3D printed nozzle were compared with those from commercial MDI products (Table 1). The 3D printed actuators produced spray patterns with a mean ellipticity of 1.067, while the three commercial MDIs resulted in mean ellipticities that ranged from 1.038 to 1.078. The elliptical ratio of the spray pattern was therefore used as rapid screening for the initial evaluation of actuator nozzle printing quality.

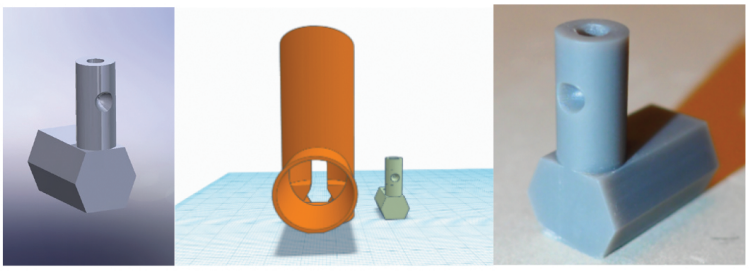

Figure 1. 3D inhaler model (left and middle) and 3D printed nozzle part (right).

Table 1.

Spray pattern measurements for three commercial MDI products and 1 MDI product with a 3D printed actuator printed by clear resin.

Inhaler	Ellipticity	SD (n = 3)	Dmin (mm)	SD (n = 3)	Dmax (mm)	SD (n = 3)
MDI 1	1.040	0.010	11.7	0.3	12.2	0.3
MDI 2	1.038	0.013	21.7	0.3	22.5	0.2
MDI 3	1.078	0.011	20.2	0.9	21.8	0.8
3D Printed	1.067	0.035	19.5	0.7	20.8	0.6

The printing quality of the nozzles was further inspected using 3D laser confocal microscope (Figure 2). 3D printed MDI actuator achieved structure and surface quality comparable with one commercial MDI (MDI 2) in terms of nozzle dimensions and line/surface roughness. Nozzle diameters for the actuator in the commercial MDI 2 and the 3D printed actuator (grey material, vertical orientation) are 257 μm and 267 μm, respectively. The line roughness (Ra) of three actuators in commercial MDI products ranged from 0.91 to 2.08 μm, compared to 2.37 μm for the 3D printed actuator. The surface roughness measurements of actuators in three commercial MDI products ranged from 1.53 to 2.94 μm, compared to 3.44 μm for 3D printed actuator.

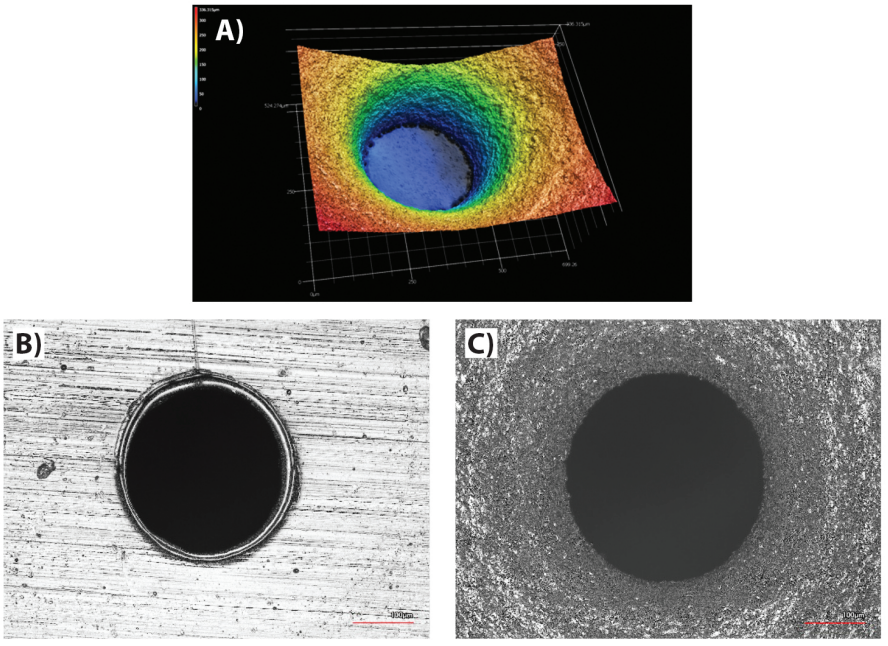

Figure 2. A) 3D confocal image of 3D printed MDI nozzle. Comparison of B) commercial (MDI 2) and C) 3D printed (grey, vertical) nozzles.

In vitro performance testing in terms of particle size distribution and emitted dose (Figure 3 and Table 2) for 3D printed actuators and actuators of commercial product MDI 2 showed a close similarity in cumulative particle size distribution profile. This indicates the potential device comparability achieved by the 3D printing technology used in this work.

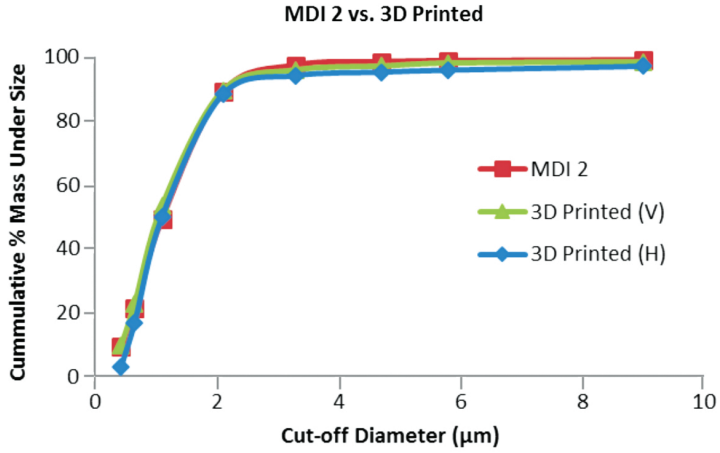

Figure 3. Cumulative particle size distribution of one commercial MDI product (MDI 2) and two MDIs using 3D printed actuators with different printing orientations (V = vertical, H = horizontal).

Table 2.

Fine particle fraction (FPF, < 5 μm emitted dose) and particle size distribution for one commercial MDI (MDI 2) and two MDIs using 3D printed actuators (V = vertical, H = horizontal printing orientations).

	Fine Particle Fraction (%)	Particle Size Distribution MMAD (um)	GSD
MDI 2	71.6	1.1	1.7
3D Printed (V)	69.7	1.0	1.7
3D Printed (H)	60.7	1.1	1.7

CONCLUSION

3D printing allows assessment on a range of device constituent parts that would be impractical with conventional molding to discover which design elements are critical design attributes of MDI components such as the actuator. However, the 3D printing process requires evaluation of its effects on the CQAs that may impact product performance. When properly validated, data generated using 3D printed inhalation devices has the potential to provide supporting information for the scientific review of NDAs and ANDAs for oral inhalation drug products (OIDPs) submitted to the Agency.

The study of 3D printed device components using a series of innovative analytical tools, including 3D imaging, micro-computed tomography, high resolution, and high speed *in situ* spray visualization techniques, may help the pharmaceutical industry efficiently develop new and generic orally inhaled drug products. The information obtained from these studies may inform recommendations for MDI device constituent parts related to quality and performance, and current MDI device constituent part user interface recommendations for generic MDI products.

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