Spray Dried Porous Lipid Particles for Pulmonary Drug Delivery

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INTRODUCTION

Porous lipid particles have long been used as drug carriers in pressurized metered dose inhalers and dry powder inhalers for respiratory drug delivery for improved physical stability, content uniformity, and aerosolization efficiency [1]. However, the production of such porous particles is a multi-step, time-consuming process that also requires the use of a scarce oil as pore-forming agent [2]. We present in this study an alternative method of producing similar porous lipid particles to be used for pulmonary drug delivery.

MATERIALS AND METHODS

The feedstock for spray drying was prepared as illustrated in Figure 1. Water was first heated to 55 °C on a hotplate. Calcium chloride dihydrate ($CaCl_2$; CAS 10035-0408, Sigma-Aldrich, ON, Canada) and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC; CAS 816-94-4, Avanti Polar Lipids Inc., AL, USA) were then added to the heated water at a molar ratio of 1:2 to make the total solid concentration 20 mg/mL. While being heated, the feedstock was further dispersed by a high shear mixer (T18 Ultra-Turrax, IKA, NC, USA) at 25 krpm for 3 minutes. A peristaltic pump (Masterflex® L/S®, Cole-Parmer, QC, Canada) was then used to supply the feedstock to a twin-fluid atomizer (2.5 mL/min) installed in a custom-built laboratory-scale spray dryer for spray drying with a drying gas flow rate at 600 SLPM. Temperature of the feedstock was tracked during the entire

process. For the spray drying parameters, process models [3] were used to guide the selection of process conditions. In this study, the inlet temperature was set to 55ºC, the feed flow rate was set to 2.5 mL/min, and the corresponding atomizer air-to-liquid ratio was 10.

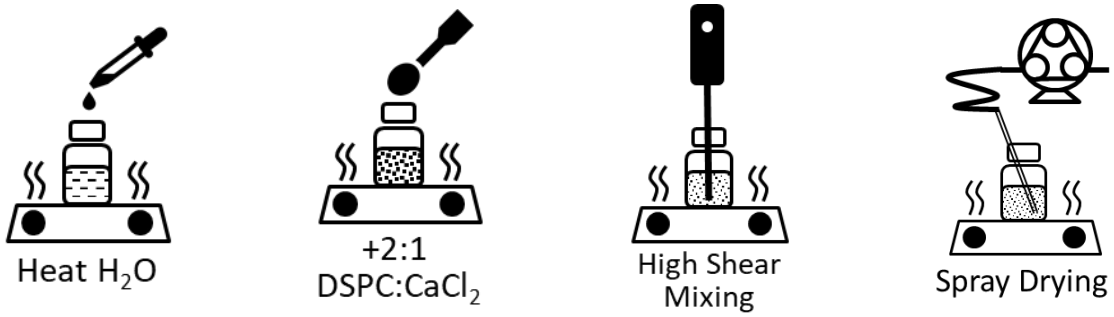

Figure 1. Feedstock preparation for lipid porous particle spray drying

Particles collected by a cyclone were transferred for characterization and performance testing. Scanning electron microscopy (Sigma FESEM, Zeiss, Germany) was used to characterize the morphology of the particles. A 7-point BET method (Brunauer–Emmett–Teller) method (Autosorb 1MP, Quantachrome Instruments, FL, USA) was used to determine the specific surface area of the bulk powder. 50 mg of the collected powder and 17 mL propellant HFA134a were filled into a borosilicate glass vial to test their compatibility. Suspension stability of the pMDI was measured with a shadowgraphic imaging method [4] at different time points after room condition storage for up to 6 months. Each stability measurement was for 30 minutes immediately after 30 seconds of manual shaking the pMDI canister. A non-dimensional instability index ranging from 0-1 was used to quantify the suspension stability: 0 for extremely stable samples, 1 for extremely unstable samples. Aged particles in the propellant after 6 months were also extracted from the pMDI for morphology characterization.

RESULTS AND DISCUSSION

After high shear mixing, the feedstock became a uniform opaque emulsion. The temperature of the feedstock was measured to be 53 ± 0.5 ºC during the spray drying process, which is close to the pretransition (50 ºC) and main transition (54.5 ºC) temperatures of DSPC [5]. The process model predicted an outlet temperature of 37.5 ºC and an outlet relative humidity of 11.6% for the selected spray drying conditions. The measured outlet temperature showed a good agreement with the model prediction and was between 38 – 39 ºC. A high yield of 80% was achieved for the spray dried batch size (0.5g). Based on the air-to-liquid ratio and characterization data of the atomizer [6], the initial mass median diameter of the atomized droplets was predicted to be ~9 μm, which corresponded to dried particles at about 2 μm in the respirable range.

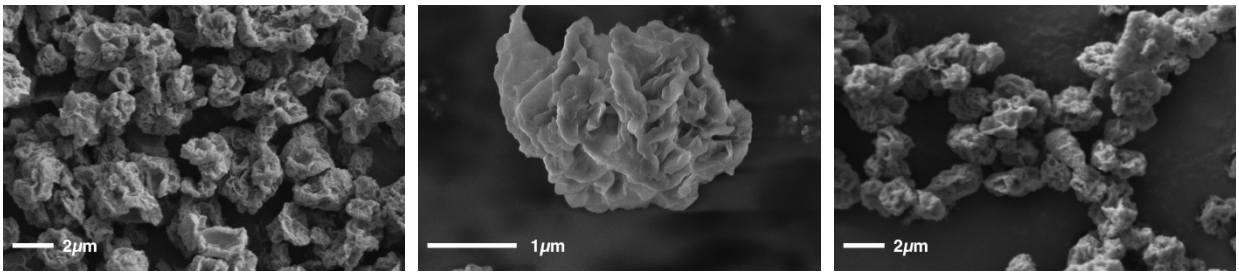

Figure 2. Highly rugose surface and porous structure of the spray dried particles (a)(b); no significant change of particle structure after 6 months aging in propellant HFA134a (c).

From the SEM images shown in Figure 2(a), highly rugose surface and porous structure can be observed for the freshly collected DSPC particles. The specific surface area determined by the 7-point BET method was 8.6 m^2/g for the bulk powder, which is significantly higher than the theoretical value (~2.5 m^2/g) when assuming only solid spherical lipid particles were formed. Higher magnification Figure 2(b) shows numerous lipid wrinkles on the surface that can be ideal sites for drug loading. Particles extracted

from the model pMDI after 6 months of room temperature storage show no apparent change of morphology and the porous structure and rugose surface feature retained as shown in Figure 2(c), demonstrating good compatibility between the porous particles and propellant HFA134a.

The suspension stability result in Figure 4 further proves their compatibility with propellant. On a scale of 0 - 1, the instability index for the model pMDI only slightly increased to ~0.01 after 30 minutes post manual shaking, demonstrating good dispersibility and colloidal stability. Instability index curves at different time points 0d, 1d, 2d, 3d, 4d, 6m overlap well, proving both short-term and long-term stability of this model pMDI. No significant creaming or sedimentation was detected within the 30 minutes observation at any time points as the inset shown in Figure 4.

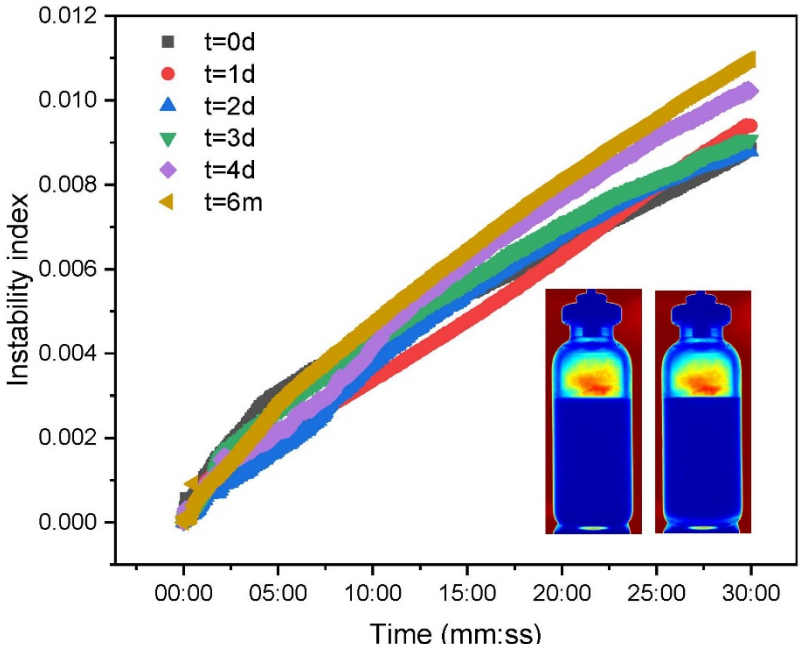

Figure 4. Suspension stability measurements demonstrate consistent colloidal stability of the porous particles in HFA134a over 6 months of aging. Inset shows a representative initial (left) and final (right) status of suspension.

CONCLUSIONS

A novel method of spray drying porous lipid particles without a pore-forming agent directly from its aqueous feedstock was introduced, which can significantly simplify the process and reduce the cost associated with the traditional method of porous particle production. Good compatibility with the propellant demonstrated its potential in pMDI formulations. The structural and surface features manifested by the produced particles are indications of good dispersibility and high drug loading capacity [7] which will be investigated in future work.

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