Aggregated High Surface Area Particle Technology for Pulmonary Drug Delivery

Michael J. Baltezor,[1] Philip J. Kuehl[2] and Keith T. Ung[3]

[1] *CritiTech, Inc, Lawrence, KS, USA*

[2] *Lovelace Biomedical, Albuquerque, NM, USA*

[3] *iPharma Labs, Inc., Union City, CA, USA*

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INTRODUCTION

Supercritical carbon dioxide precipitation (SCP) was investigated to produce low bulk density (<0.15 g/cm^3), aggregated, high surface area (>15 m^2/g) 1 to 5 μm micro-particles. SCP is an antisolvent precipitation process using an organic solution of the drug sprayed into a continuous flow of supercritical carbon dioxide that is mixed with sonic energy. Modification of the solvent, flow rates, sonic energy level and nozzle plus other variables allow achievement of desirable particle characteristics. Engineered particles of over 100 compounds have been made with SCP and two are currently being evaluated in Phase II oncology trials by direct intertumoral (IT) or intraperitoneal (IP) injection. The manufacturing process has been scaled up, validated and patented [1]. Because of the low bulk density, high surface area and primary particle size produced with SCP, we evaluated three drugs for pulmonary delivery; paclitaxel (PAC), fluticasone propionate (FLU) ciprofloxacin free base (CIP).

METHODS

Analysis of powder physical properties included particle size distribution by laser diffraction using a Malvern Mastersizer (wet method), BET specific surface area (SSA) using USP 29 <846>, bulk density using USP 38 <616>, crystalline structure and morphology by Siemens XRPD and Versa SEM, respectively. Aerodynamic particle size distribution (aPSD) was measured using two different cascade impactors; a low flow Mercer-Style cascade (MSC, CH Technologies) at Lovelace (Table 1) and a Next Generation Impactor (NGI, MSP Corp., USP<601> Apparatus 5) at iPharma (Table 2). A dry powder inhaler (DPI, Plastiape, RS01) was used to aerosolize the powder (17.5 mg fill mass) contained in size 3 capsules (Capsugel VCap Plus). NGI measurements were performed using a standard square-wave vacuum flow profile at 40 L/min (corresponding to 4 kilopascal pressure drop for RS01 having a flow resistance of 0.16 cm·$H_2O^{1/2}$·min/L) and 4-liter

volume. Rat PK studies for SCP PAC were described by Verco *et al*. [2]. The rat PK studies for SCP FLU and SCP CIP were conducted by Lovelace using three rats per time point, dosing by nose only inhalation or IV tail vein injection using IACUC approved protocols. Powder aerosolization used a rotating brush generator (RBG, PALAS, Gmb). Analysis of plasma and lung tissue was performed using LC-MS/MS methods. Analysis of the PK results was conducted using Phoenix WinNonLin 6.2 (Cetera, NJ) software.

RESULTS AND DISCUSSION

Particle Physical Characterization

The SCP particles and drug substance lots of PAC, FLU and CIP were tested for primary particle size and SSA. The physical size of the SCP FLU and SCP CIP particles was controlled to between 2–4 μm. The SSA of the aggregated particles has the largest impact on the drug release rate and the aerodynamic properties. The SSA's (m^2/g) increased from 4.1 for FLU to 28.2 for SCP FLU and 7.7 for CIP to 15.9 for SCP CIP. SCP PAC had similar results to SCP FLU. All SCP drug powders were found to be light and fluffy with bulk densities in the 0.06 to 0.12 g/cm^3 range. The powders were tested by XRPD (x-ray powder diffraction) and were crystalline. Scanning electron microscopy (SEM) photomicrographs (Figure 1) were obtained.

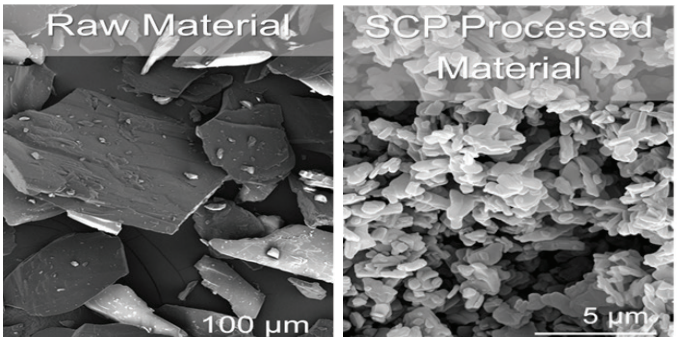

Figure 1. Example SEM Photomicrographs before and after SCP processing.

Pharmacokinetic Studies

PK studies with our SCP drugs were conducted to determine if we were able to obtain high levels in the lungs, relatively low systemic exposure and prolonged lung residence time. Previous researchers [3–6] have found improved lung residence time using large porous inhaled particles. The PK study with SCP PAC was conducted with a nebulized suspension rather than an inhaled dry powder because paclitaxel is cytotoxic [2]. The half-life of SCP PAC in the lungs was 56 hr compared to 19.9 hr for paclitaxel in the lungs from IV administration of nab-paclitaxel [2].

Lovelace conducted rat PK studies on SCP FLU and SCP CIP using dry powder inhalation. Results for MMAD and GSD shown in Table 1.

Table 1.

MMAD and RSD values from RGB at the nose-port.

	SCP PAC	SCP FLU	SCP CIP
MMAD	1.8μm–2.3μm	2.1μm–2.3μm	2.1μm
GSD	1.9–2.0	1.55–1.66	1.5

Two rat PK studies for SCP FLU at 3 mg/Kg were conducted. Results from both sets of samples are shown in Figure 2. The two sets of lung and plasma data were consistent. The results show high levels of fluticasone in the lung and a long residence time.

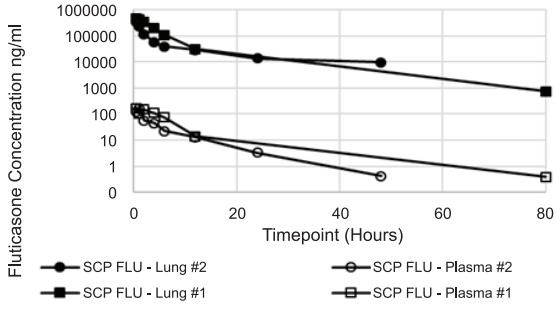

Figure 2. SCP Fluticasone PK Study.

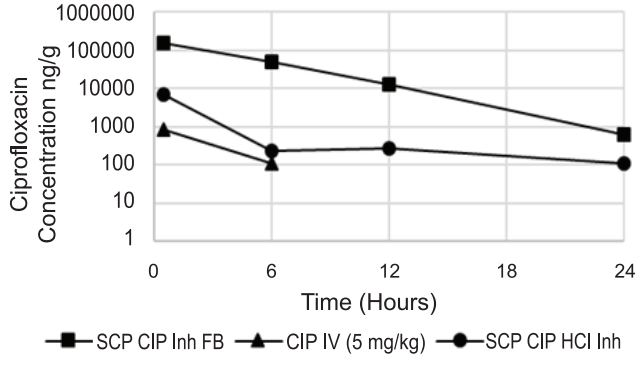

Figure 3. SCP Ciprofloxacin PK Study.

Two 2 rat PK studies for SCP CIP were conducted. The first with SCP CIP HCl and the second with SCP CIP free base, both dosed at 3 mg/Kg as inhaled dry powders. CIP IV at 5 mg/Kg was a comparator. Lung tissue samples were collected and results from both sets of samples are shown in Figure 3. We found that the inhaled SCP CIP HCl dissolved too quickly and results were close to the IV results. By contrast, SCP CIP free base had high levels of CIP in the lung and a long residence time compared to the IV dose. The SCP CIP free base was a less soluble, stable polymorph of CIP free base.

Dry Powder Inhaler Results

An evaluation of the *in vitro* aerosol performance of (a) SCP FLU and (b) SCP CIP from a DPI was performed and presented in Table 2 and Figure 4. Smaller MMAD and lower NGI recovery was measured for the SCP CIP than SCP FLU powder.

Table 2.

SCP FLU and SCP CIP NGI Results.

(a) SCP FLU	MMAD (μm)	GSD	FPF% <5μm	NGI Recovery (%DD)
Run 1	3.5	1.6	79	74
Run 2	3.7	1.6	73	80
Run 3	3.7	1.6	74	73

(b) SCP CIP	MMAD (μm)	GSD	FPF% <5μm	NGI Recovery (%DD)
Run 1	2.8	2.0	78.2	47
Run 2	2.7	1.9	81.4	49
Run 3	3.1	2.0	75.4	42

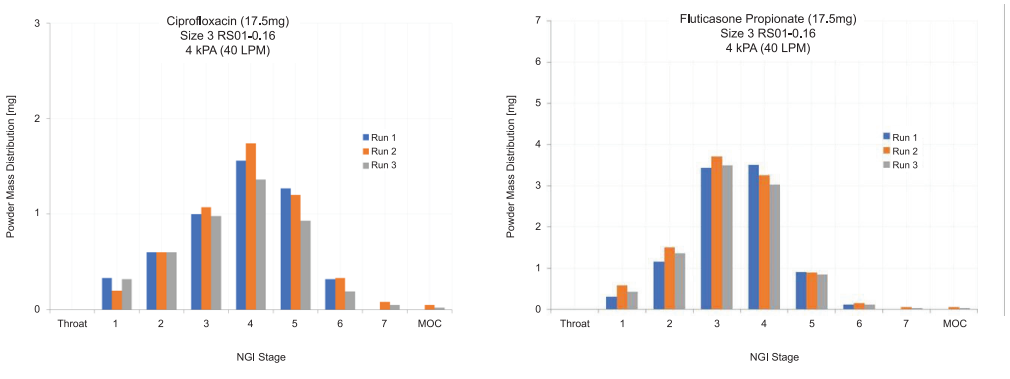

Figure 4. The NGI powder mass distributions from the two drugs.

The uniformity of powder delivery was also performed for 10 individual capsules with RS01 DPI at 40 L/min for each drug. SCP CIP also measured lower delivery efficiency than SCP FLU with SCP CIP and SCP FLU being 59% and 71% of the capsule fill, respectively. The SCP CIP powder

was observed to be denser and cohesive particles, which resulted in higher powder retention in the capsule and DPI. Additional development work is needed to improve the SCP CIP and select an appropriate DPI with the right flow resistance.

CONCLUSIONS

The results suggest that the SCP technology may serve as a platform technology for the pulmonary delivery of poorly water-soluble drugs where the increased specific surface area of the particles can provide the most benefit. The technology should be considered when high concentrations in the lungs for an extended time and lower systemic exposure would be beneficial. This work was with particles that are 100% drug and haven't been optimized for pulmonary drug delivery. Refinement of the particles, the possible inclusion of inhalable excipients to reduce capsule and inhaler powder retention and optimizing the inhaler used are all planned for further investigations.

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