Supercritical Carbon Dioxide Precipitation (SCP) Technology Can Help Your Drugs Fly

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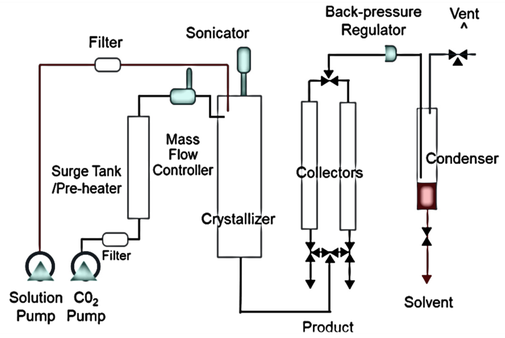
CritiTech Particle Engineering Solutions

Supercritical Carbon Dioxide ($scCO_2$) Precipitation Particle Engineering

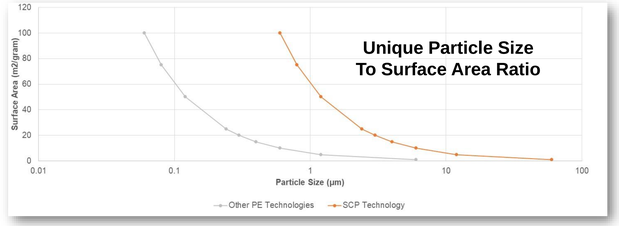
- Drug must be soluble in an organic solvent and insoluble in $scCO_2$
- Drug dissolved in organic solvent, injected through the selected nozzle
- Turbulent flow from sonic probe strips away the solvent. **Mixing causes random and frequent particle collisions**
- Continuous flow of fresh $scCO_2$ at the solvent removal point carries the precipitated particles into the 20nm filter collectors
- Collectors are alternated between harvesting and collection as $scCO_2$ **flow continues uninterrupted**
- Adjustable parameters including the **solvent**, the **concentration and flow** of the drug in solvent, the **nozzle**, the **sonic energy intensity**, the **flow rate of fresh $scCO_2$**, **temperature and pressure**. Once established and locked, these parameters give excellent control over particle attributes



Benefits of Supercritical Precipitation

- **Low bulk-density and high surface area** result in **increased residency time** in the lungs or nasal cavity
- **Pure drug** – excipients may not be required – especially useful when the amount of drug that can be dosed is limited
- **Improves dissolution and pharmacokinetics** of poorly-soluble drugs
- Reformulation of existing drugs can provide **patent protection on improved formulations with lower adverse drug events due to lower systemic exposure**
- Much **better control over particle size distribution and other attributes** compared to conventional micronization technologies plus ability to produce large particles that have the surface area of small particles
- Commercial-scale ~ 2 Kg/day

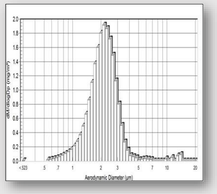
- SCP particles are larger with surface areas of much smaller particles
- Improved flow, less static agglomeration, and easier to handle compared to smaller particles produced by other technologies



SCP Technology Inhaled Delivery of Paclitaxel, Ciprofloxacin and Fluticasone Propionate

Particle Size	SCP Paclitaxel	SCP Ciprofloxacin	SCP Fluticasone Propionate
MMAD*	1.8µm – 2.3µm	2.1µm	2.1um – 2.3µm
GSD	1.9µm – 2.0µm	1.5µm	1.55µm – 1.66µm

*Powder plume from rotating brush generator



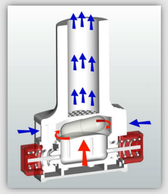
Ciprofloxacin
Particle Size Distribution (as an example)

- The SCP Technology has been used to reformulate numerous drugs including paclitaxel, ciprofloxacin and fluticasone – all with **agglomerated, high-surface area, low bulk density particles**
- The aerodynamic particle size (MMAD) of drugs reformulated with the SCP Technology are very consistent

LOVELACE BIOMEDICAL

Example of Delivery of SCP Powders with a DPI

SCP Fluticasone particle characterization studies showed excellent flowability and a large percentage of the drug delivered from a DPI even though the particles and formulation have not been optimized.

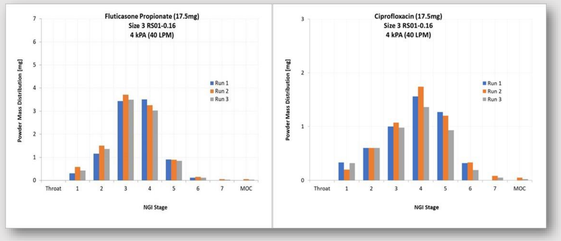


Plastiape RS01

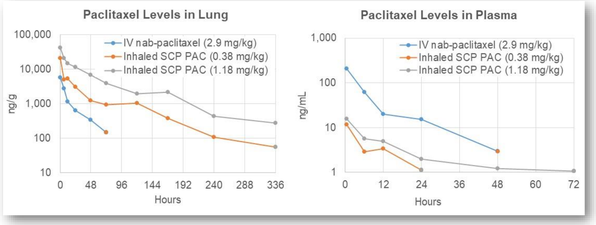
	MMAD (um)	GSD	FPF % < 5 um	% Drug Delivered
Run 1	3.5	1.6	79%	74%
Run 2	3.7	1.6	73%	80%
Run 3	3.7	1.6	74%	73%
Average	**3.63**	**1.6**	**75.3%**	**75.6%**

iPHARMA

iPharma tested the mass distribution of SCP Fluticasone and SCP Ciprofloxacin powders from the DPI. The results were **very consistent over multiple runs**.



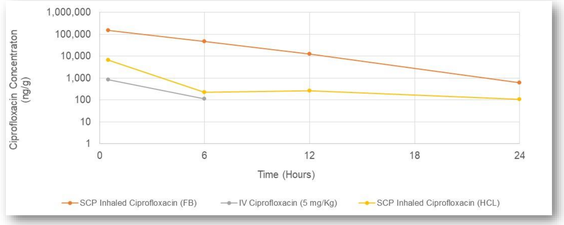
SCP Paclitaxel – Rat Pharmacokinetic Studies*



*Studies conducted using nebulized suspension

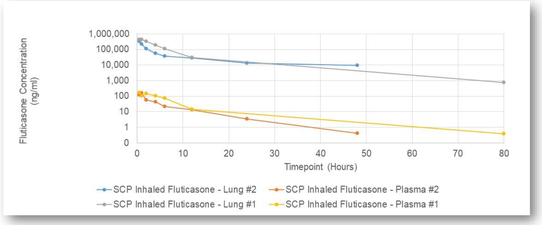
- **High concentration** and **long duration** of SCP Inhaled Paclitaxel in the lungs
- Lung half-life for SCP Paclitaxel was 56 hours vs 19.9 hours for IV nab-paclitaxel
- Lower systemic exposure of SCP paclitaxel compared to the IV route of delivery

SCP Ciprofloxacin – Rat Pharmacokinetic Studies



- SCP Inhaled Ciprofloxacin (free base) is delivered into the lungs at a much **higher concentration** and for a **longer residence time** compared to the marketed IV formulation of ciprofloxacin.
- The SCP Inhaled Ciprofloxacin was dosed at 3mg/Kg versus 5mg/Kg for the marketed IV formulation of ciprofloxacin.

SCP Fluticasone – Rat Pharmacokinetic Studies



- SCP Inhaled Fluticasone is delivered into the lungs at **high concentrations** and for **long residence times** with minimal systemic exposure.
- The SCP Inhaled Fluticasone concentration and duration in the lungs are expected to be greater than the current marketed formulation of fluticasone.

CritiTech Respiratory Drug Development Pipeline

Drug	Current Use	Current Route of Administration	Use of SCP Reformulation for Pulmonary Delivery	Formulation Development	Animal POC	Human Studies Phase I/II
Paclitaxel	Treatment of Solid Tumors	IV	NSCLC			
Fluticasone	COPD, Asthma	Nasal Spray Inhaled	COPD, Asthma			
Ciprofloxacin	Antibiotic	IV, Oral	Antibiotic			
Nintedanib	Pulmonary Fibrosis	Oral	Pulmonary Fibrosis			
Niclosamide	Treatment for Tapeworms	Oral	• Severe COPD, Asthma, CF • Broad Spectrum Antiviral, including COVID-19 • Pulmonary Protectant/Treatment for Chemical Warfare Agents			
Camostat Mesylate	Pancreatitis, some cancers, fibrosis	IV	COVID-19			
Cisplatin	Treatment of Solid Tumors	IV	NSCLC			