CrystecPharma

Particles ‘R’ Us

SCF engineering solutions for product performance

FSTG Conference, University of Birmingham,
21st March 2012

Introduction

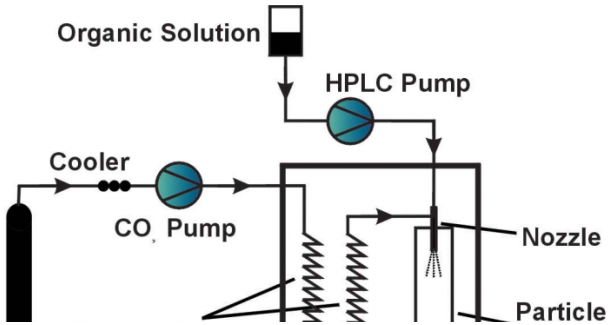
- Background
  - Crystec – our mission
  - Overview of SCF capability
- Application – case studies (*in vitro* and *in vivo* data)
  - Enhancing solubility
    - Solid state manipulation
    - Crystalline composites
    - Semi-crystalline and amorphous composites
  - Inhalation
- Product manufacture
- Summary / Key benefits

Fulfilling the Promise of SCF Technology - Our Mission

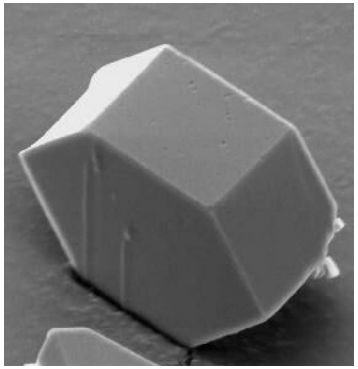
- Developing modern medicines often requires special solutions to specific problems (e.g. Poorly soluble drugs, Inhaled delivery, Stabilisation of large molecules)
- In the last decade significant progress has been made using supercritical fluid (SCF) technology to address these challenges
- The first SCF based medicine ('Levadex') has recently filed its NDA (New Drug Application)
- A need to capitalise on progress to date, and invest in the next generation of SCF drugs

Crystec Modified Supercritical Anti-Solvent Process (SAS)

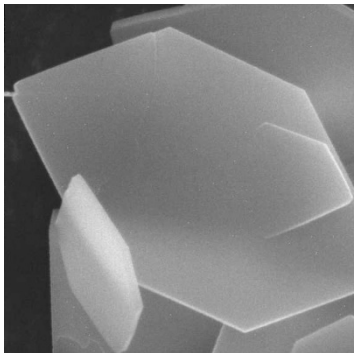
- Solution of therapeutic agent prepared in a suitable solvent
- Solution introduced into particle formation chamber with supercritical CO_2
- Rapid extraction of the solvent into the SCF occurs causing precipitation of solid particles (within milliseconds)
- Proprietary nozzle arrangement (Mod-SAS) allowing intimate mixing of SCF and multiple solution streams, and control of processing conditions
- Crystec process allows controlled formation of particle solid-state, size and shape for a wide range of small and large molecules



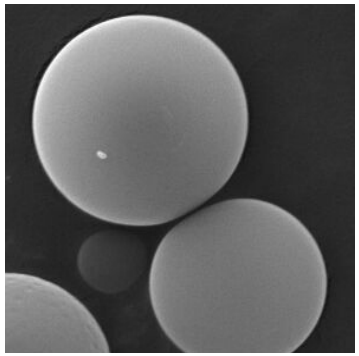
Particle Morphology with SCF Technology



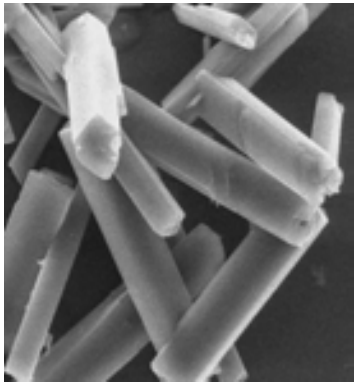
Bulky



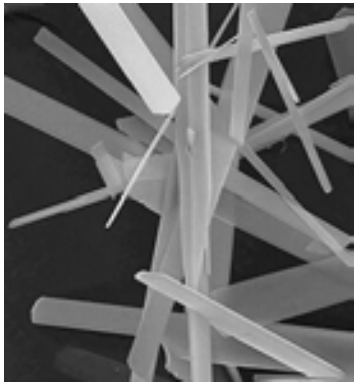
Faceted



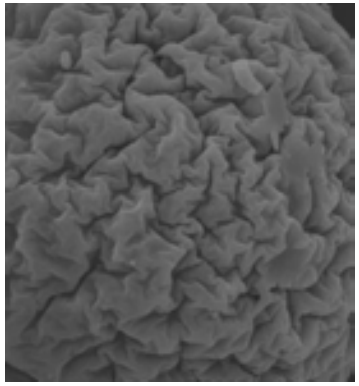
Spherical



Columnar



Needles



Fractal

Reduction of Processing Complexity

Crystallization and Milling

Drug Solvent

Crystallization

Harvesting

Drying

Milling

Sieving

Micron Sized Product

Supercritical Fluid Process

Drug Solvent Sc-Fluid

Sub-Micron / Micron Sized Product

Pure API or API composite; this includes molecular complexes containing more than one active ingredient

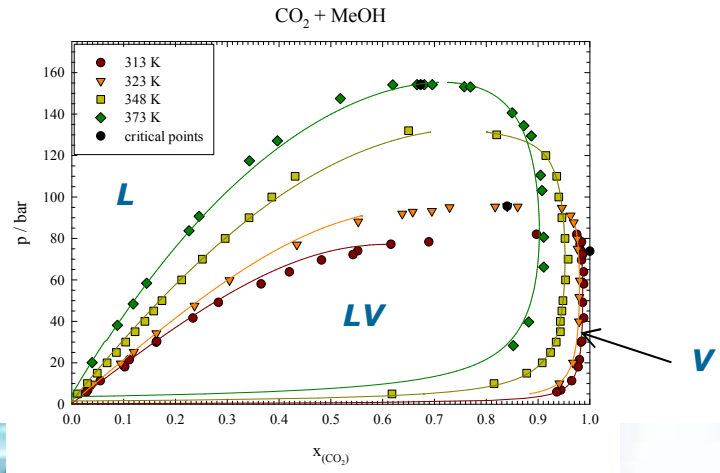
SCF Product Development Pathway

Active molecule

- Melting point,
- Solvent solubility
- Chemical structure
- Polymorphism ?
- Chemical / physical stability

Identify processing solvent (s)

SCF Phase behavior



DOE

Preliminary polymorph screen

Characterisation

- Physical characterisation eg PXRD, DSC, Raman, FTIR, PSA, moisture absorption etc
- Chemical characterisation eg HPLC analysis
- Stability assessment – physical and chemical

Composite

Molecular, physical, eutectic, semi-crystalline, amorphous or coating

Size, surface area, solid state

Poorly soluble

Desired product profile

Particle size for target delivery

eg nasal, lung, injectable, oral?

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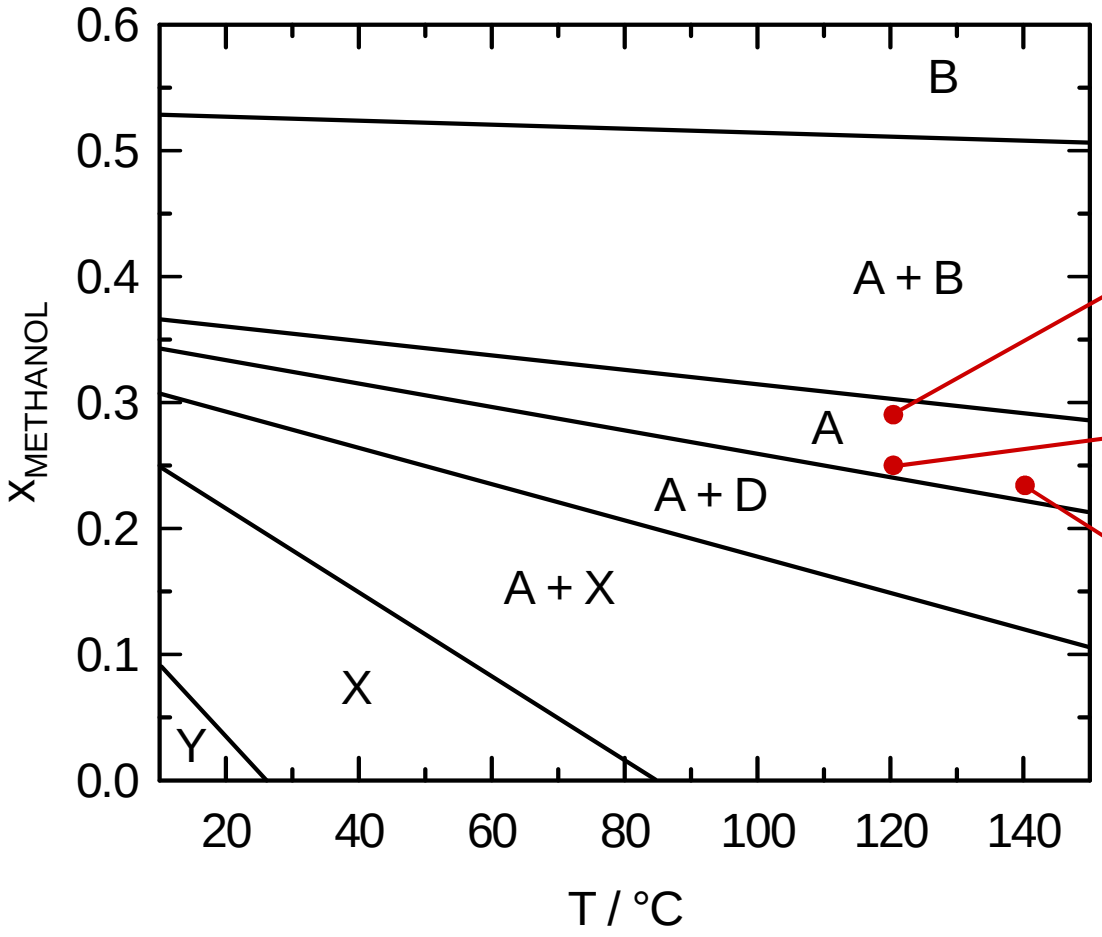
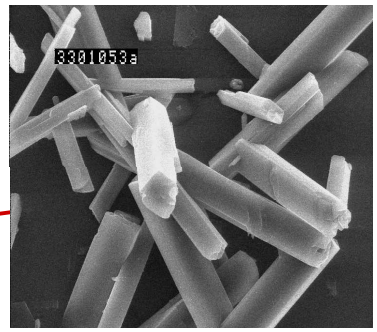
Solid State Manipulation

Simultaneous Size and Polymorph Control



15 µm



18 µm

12 µm

Polymorphic Separation of Conformational Polymorphs

M. pt 205.2˚C onset

M. pt 210.7˚C onset

- Separation of closely related polymorphs
  - Polymorph separation affected by both process condition and solvent choice

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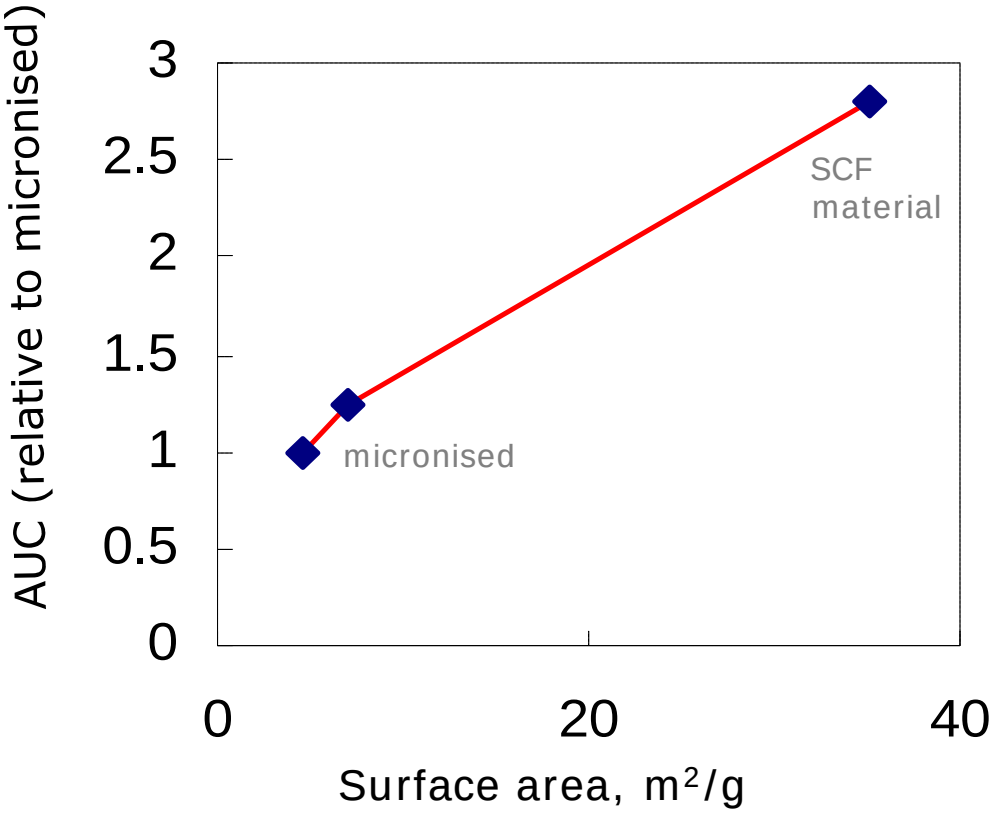
Improving solubility / Modifying Release

Bioavailability of Poorly Aqueous Soluble Compound – Effect of Surface Area



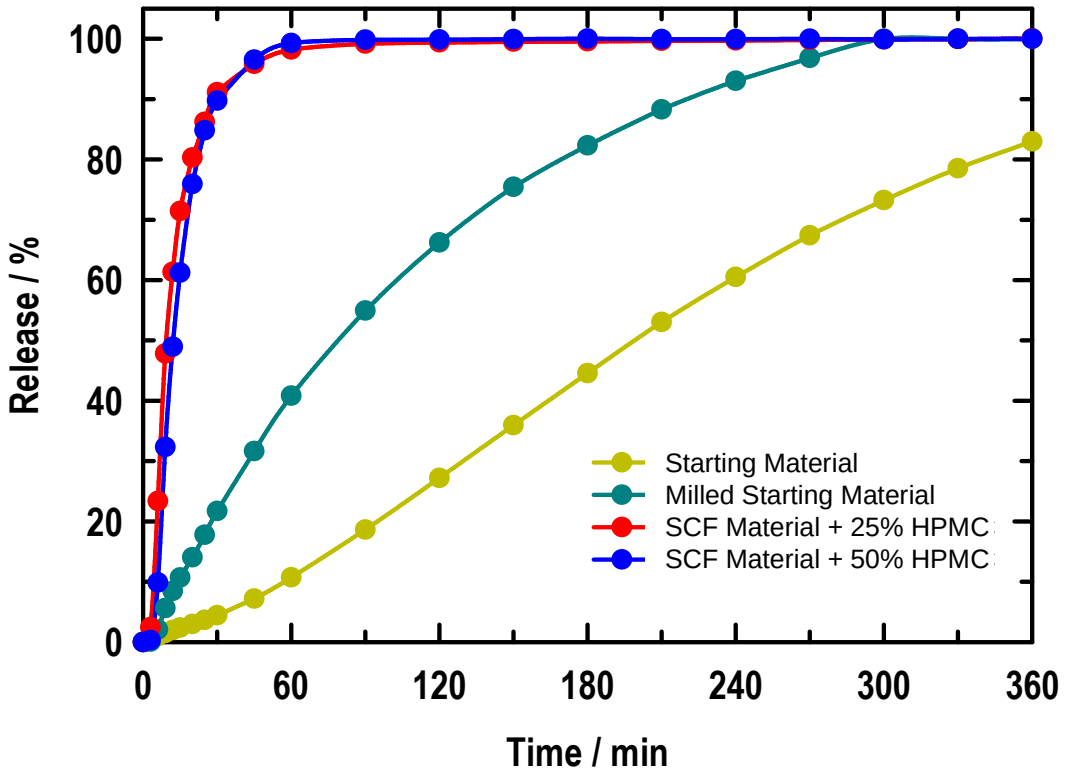
SCF processed particles

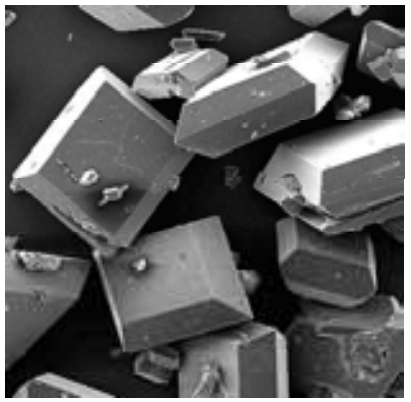
- Size between 2-5 µm (VMD, Sympatec)
- Particle aspect ratio between 2-3
- Particle thickness < 1 µm

Surface area can be altered by choice of solvent(s) and process conditions

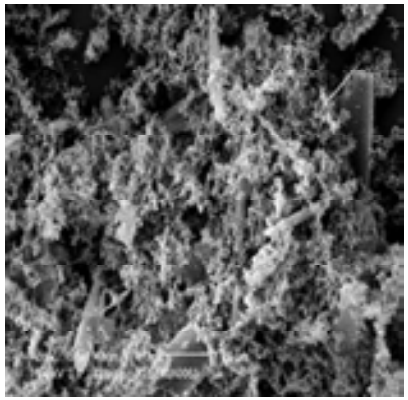
Enhanced Dissolution

- Drug dissolution increased through polymer addition





raw material



polymer co-formulate

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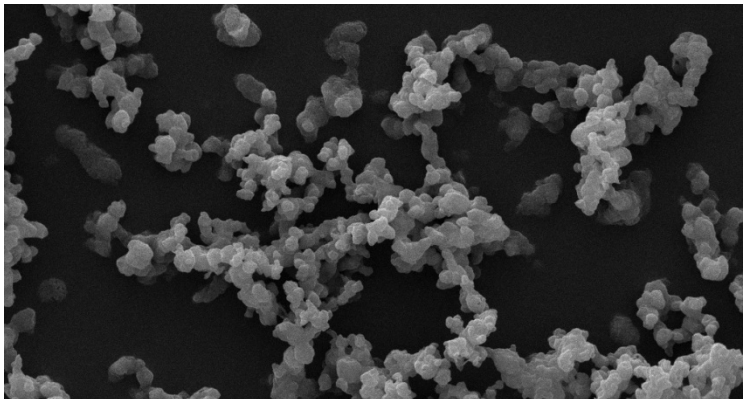
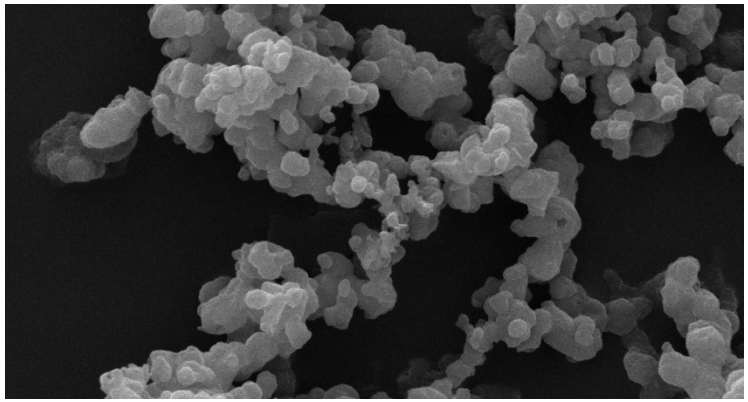
Inhalation Applications

Particle Size Control and Uniformity





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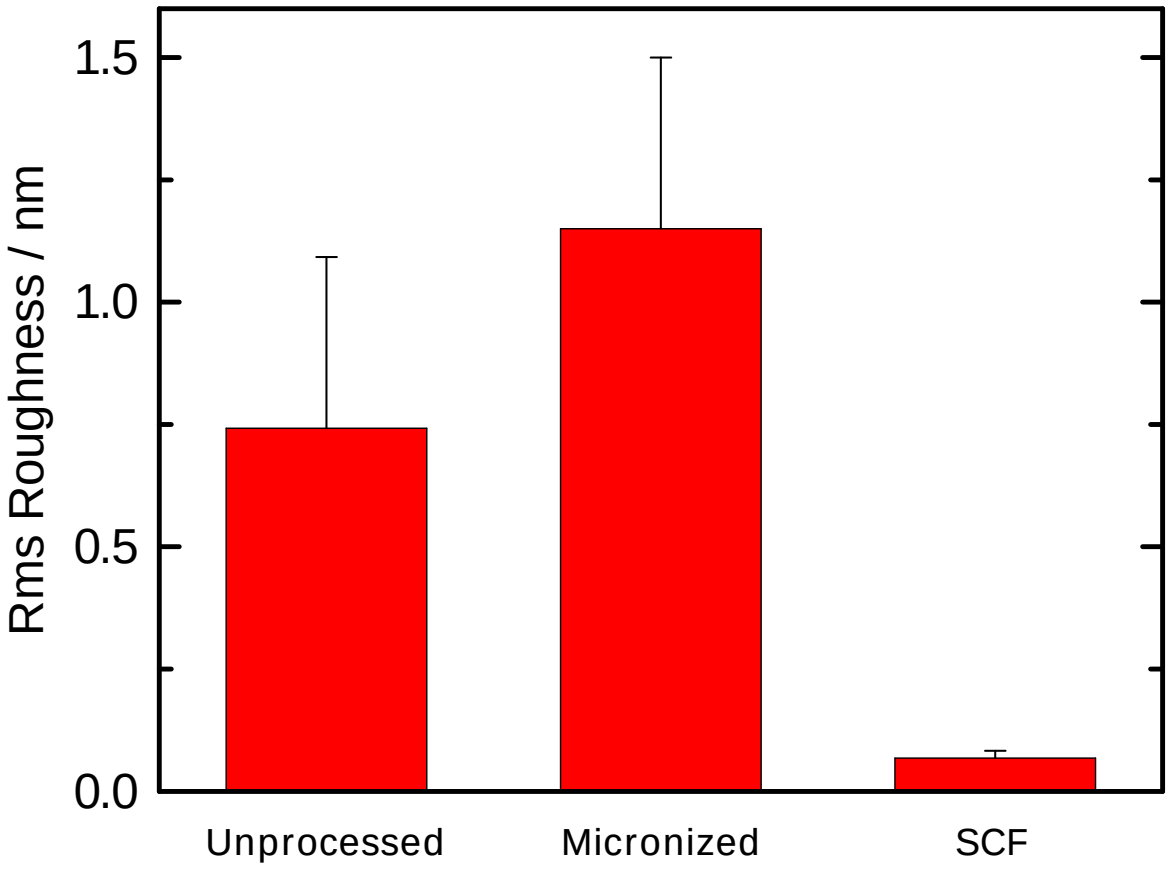
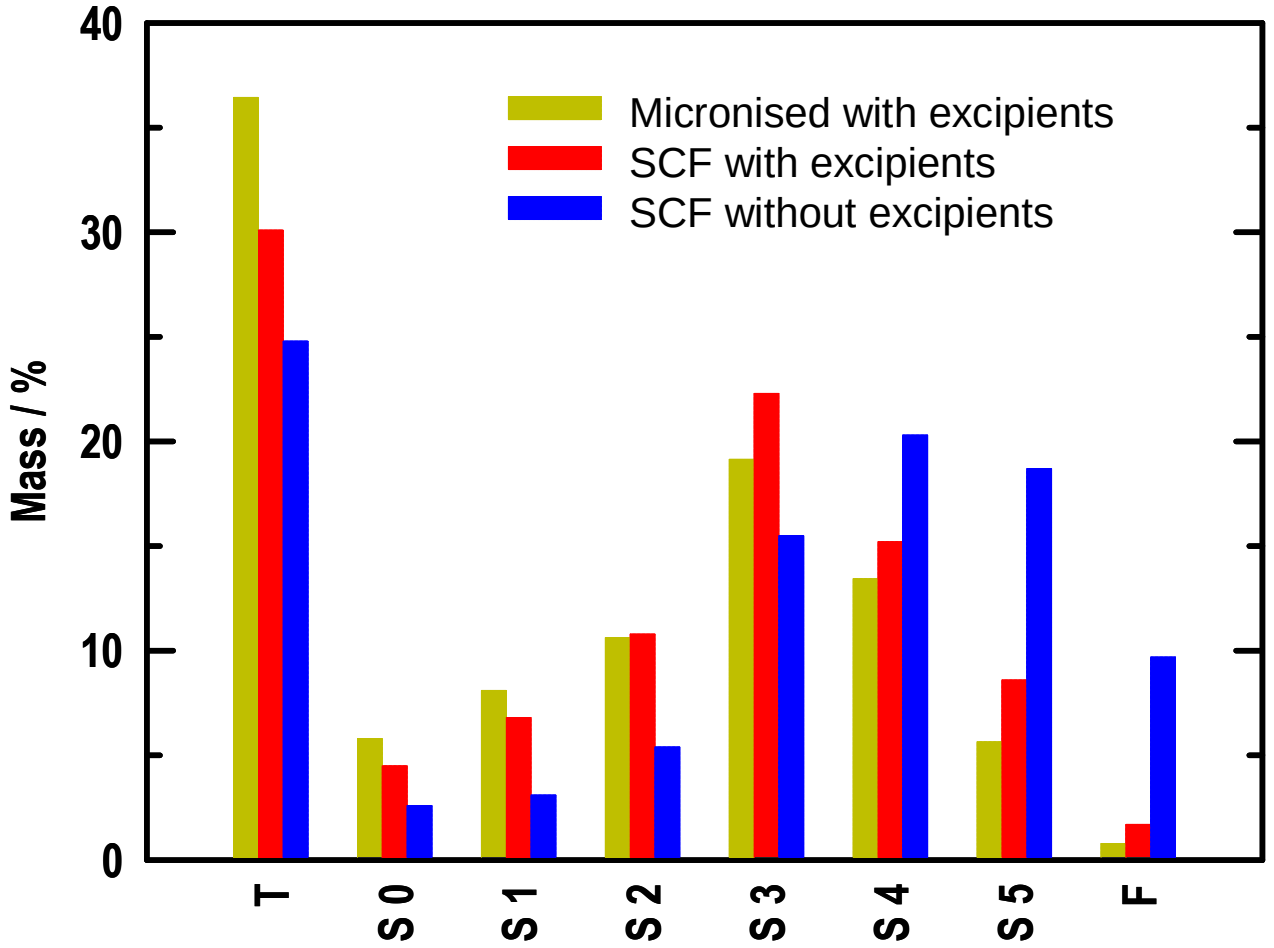
Surface Roughness Comparison



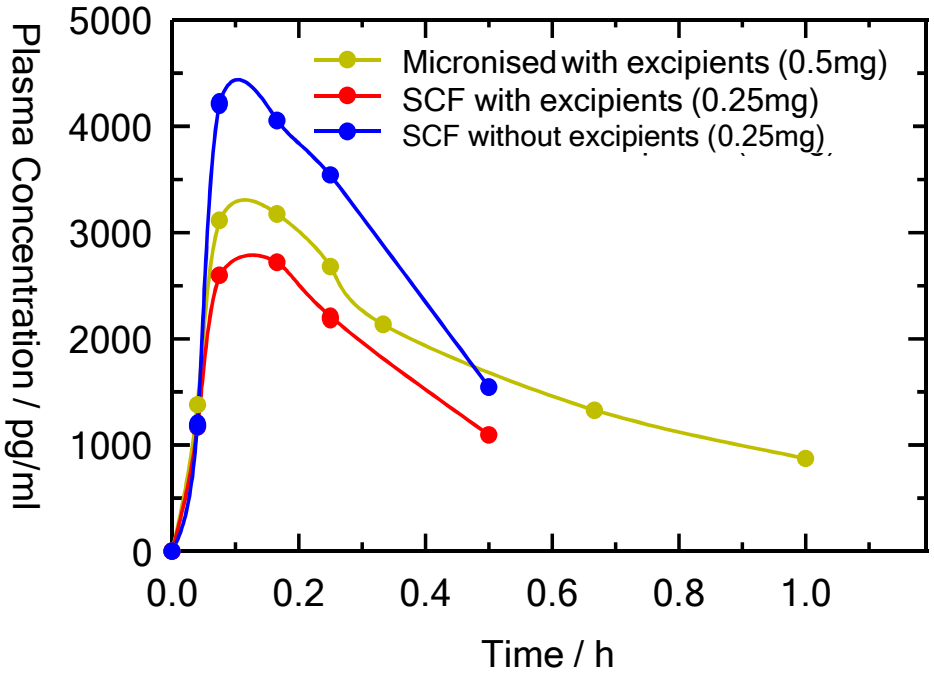
ACI Profiles for Clinical Batches

ACI – Anderson Cascade Impactor



Plasma Concentration-Time Profiles

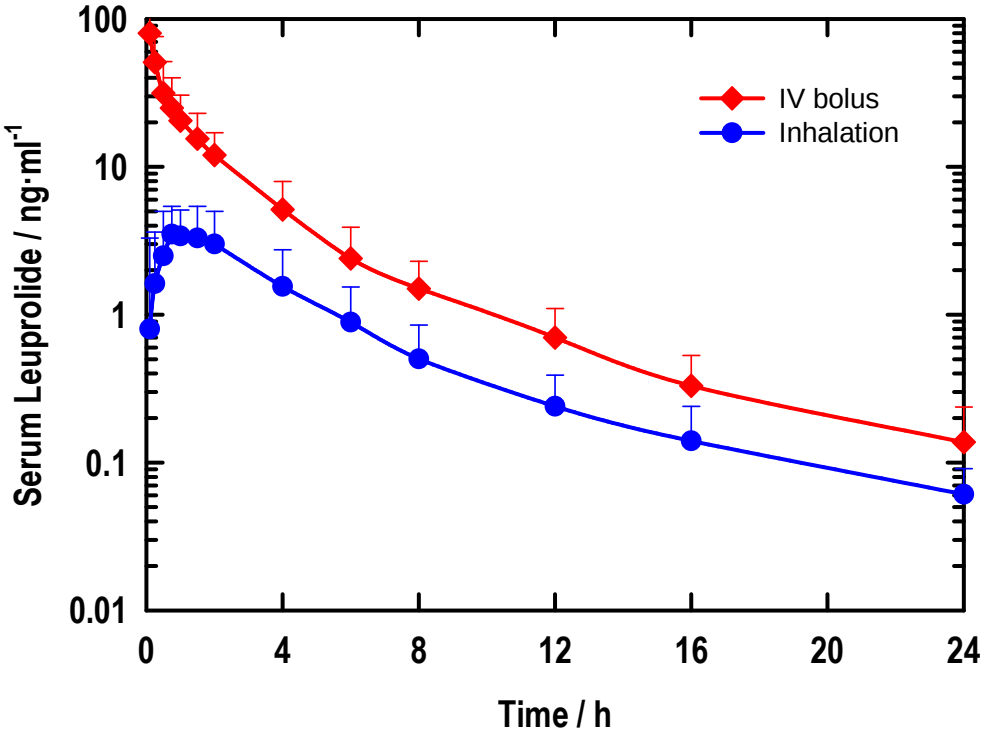
- MDI - improved lung delivery
- Potential for rapid systemic delivery
- Potential for reduced dose



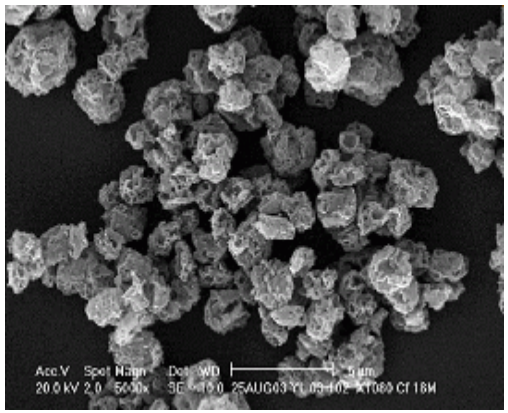
Comparison of C_{max} data (mean ±SD)

	Conventional MDI	SCF Without Excipients	SCF With Excipients
Dose (µg)	500	250	250
C_{max} (pg/ml)	3359 ± 972	4785 ± 1897	3034 ± 1172
Relative C_{max} (pg/ml)	3359	9570	6068

Plasma-Time Profiles – IV and MDI – Peptide Drug



	IV bolus	SCF drug formulation
c_{max}/ng·ml	---	4.0±1.2
T_{max}/h	---	1.1±0.4
AUC(0-∞)/ng·h/ml	91±24	16±6
$T_{1/2}$/h	3.5±0.4	3.0±0.4



- **Bioavailability of SCF processed drug in MDI: 17±3 %**

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Product Manufacture

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Product Manufacture

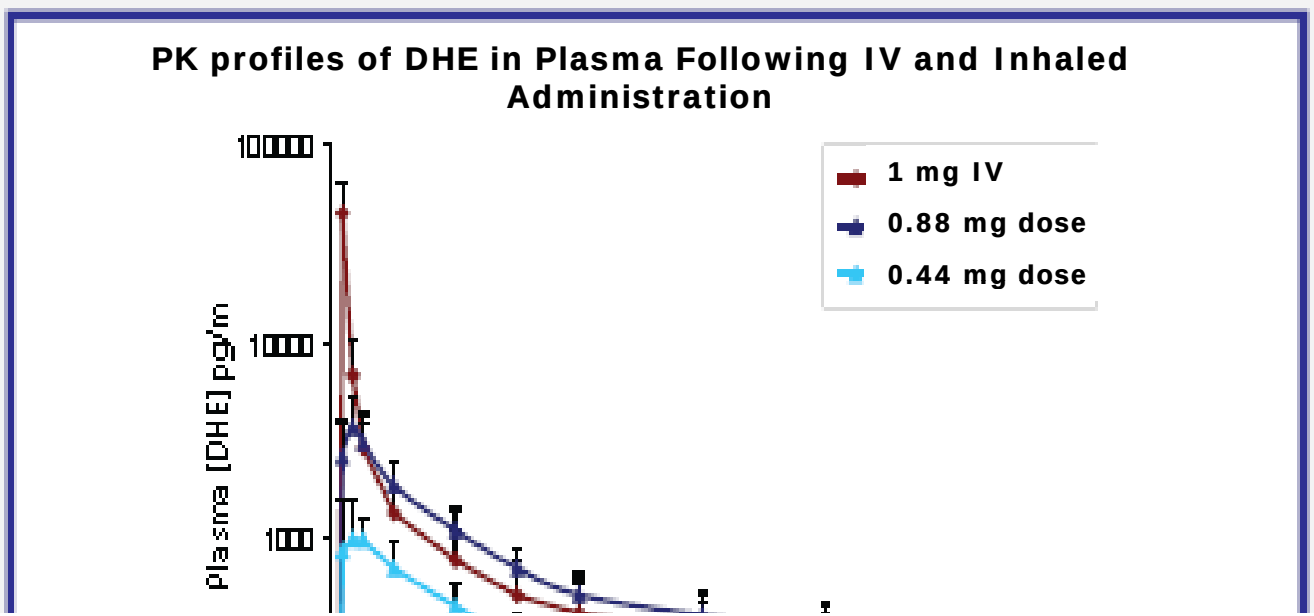
- Tech transfer and scale-up
- Batch consistency
- Single step process
- Low residual solvents
- GMP proven and regulatory authority approved plant

Product concepts scaled to efficient GMP manufacture

MAP Pharmaceuticals Inc. Files NDA for Levadex

- Inhaled product for migraine
  - Di-hydro-ergotamine (DHE)
- 'Novel formulation' = SCF engineered particles
  - Only technology capable of engineering particles to specification for DHE
- First SCF product to market
  - Stable process at manufacturing scale
- Exceptional control of particle size distribution
- Exceptional batch to batch reproducibility
- Process designed and scaled by members of the Crystec team
- New regulatory standards for particle engineering?

Pharmacokinetics of IV Bolus and MDI Formulation of SCF Processed Di Dihydroergotamine (DHE) – LEVADEX see www.mappharma.com for details



Summary / Key SCF Benefits

- One step process
- FDA approved technology
- Technology lends itself to quality by design
- Good yield (>90%) and high reproducibility
- Ability to manipulate particle / surface properties
- Narrow size distribution
- Applicable to small and large molecules
- Ability to form new IP
  - Single API or multi-component crystalline composites
  - Polymorph separation
  - New formulations

Thank you

Please Keep in Touch!

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