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Continuous Filtration Washing & Drying:

Addressing a Critical Gap in Developing Continuous Pharmaceutical Manufacturing Processes

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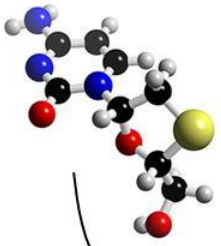
31 May Chemspec Europe, Munich, Germany

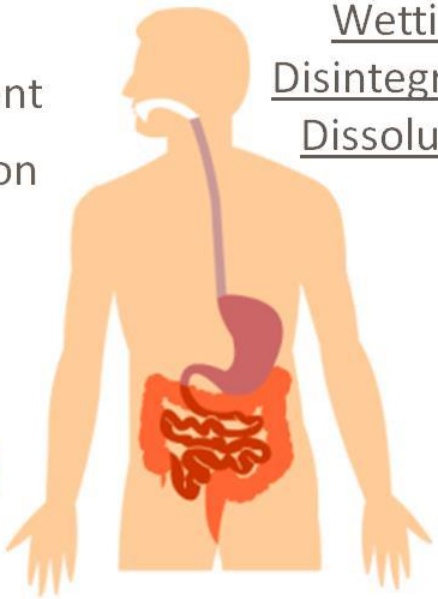
Isolation Context and Challenge

"Consider crystallization as the first step in formulation"

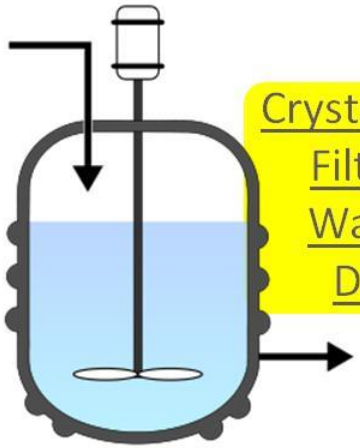


Track particles on their journey from crystallizer to patient

Creating & maintaining API attributes during formulation to control their impact on product performance.



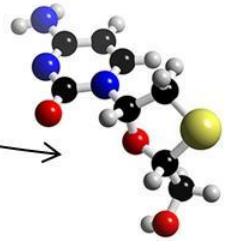
Wetting
Disintegration
Dissolution



Crystallization
Filtration
Washing
Drying

Blending
Wet granulation
Drying
Compression

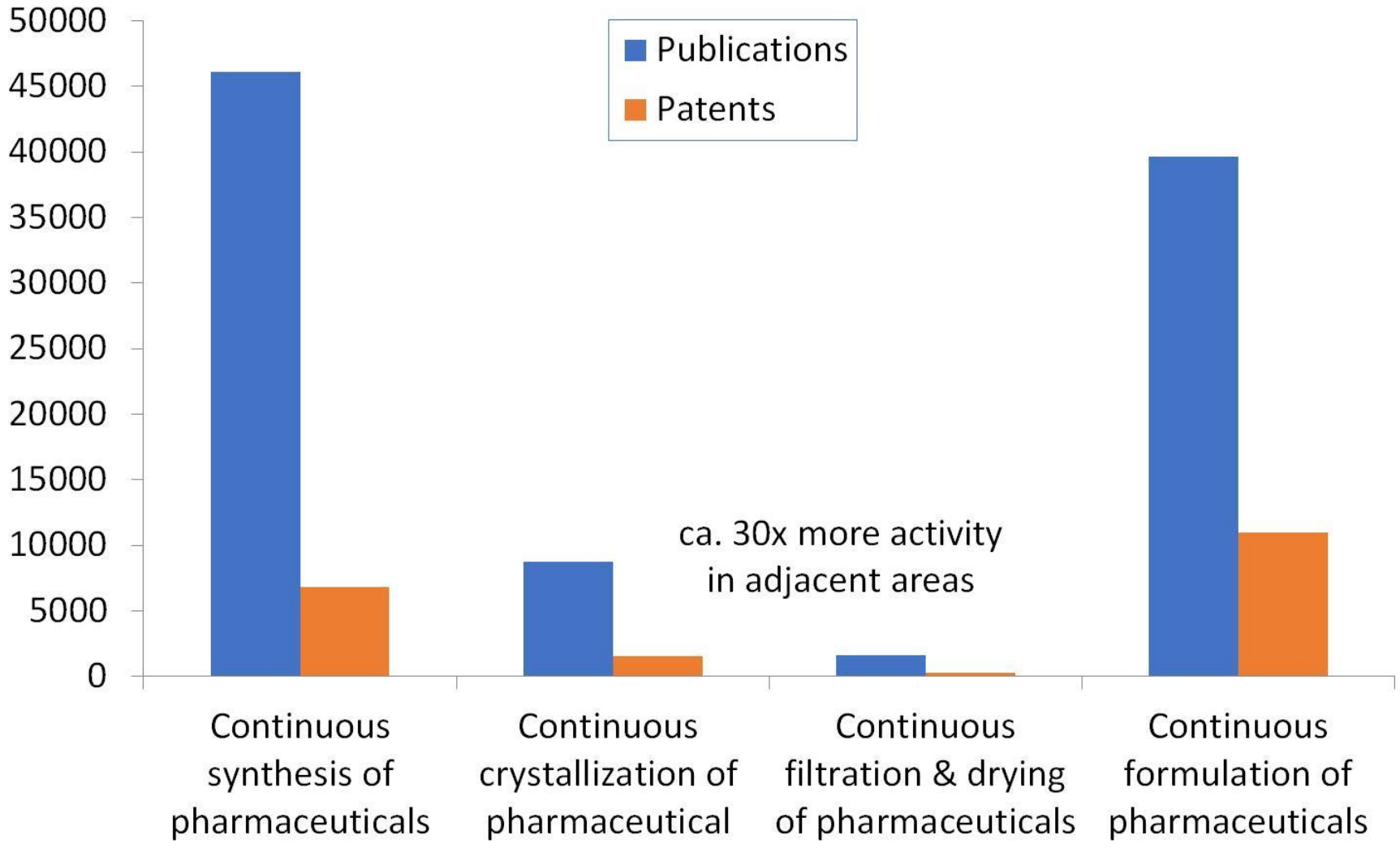
Isolated API formulated into unit dose



"Consider an API molecule dissolving in the patient as the last step in formulation"

Each process step can affect one or more subsequent processes and the final outcome

The isolation gap: A barrier to connecting synthesis with formulation continuously



Starting Assumptions & Success Criteria

Continuous (or batch) crystallization delivers:

- Pure crystals of required phase, size distribution & habit.
- Suspended in mother liquors:
  - Solvent saturated (or supersaturated) in product
  - Impurities in solution (some below solubility some may be supersaturated.)

Successful continuous isolation recovers all crystals without impurities

- No dissolution
- No impurity precipitation
- No residual solvent
- No breakage
- No agglomeration
- Short processing time
- Minimal wash solvent use, energy consumption and waste generation
- Scalable and robust to fluctuations in feed stream

Setting realistic success criteria

Recover almost all crystals without significant impurities

- No dissolution – up to 1%?
- No impurity precipitation – product meets purity spec
- No residual solvent – as low as practicable, within ICH limits (driven by solvent selection)
- No breakage – understand crystal habit, fragility, impact on subsequent processing and product performance
- No agglomeration – modest, weak agglomeration? understand agglomerate strength, impact on subsequent processing
- Short processing time < crystallization time
- Minimal; wash solvent use < 3 cake void volumes, energy consumption and waste generation (mother liquor + 3 cake void volumes)
- Understand role of crystal habit and size distribution….

Wider message each subsequent step can modify particles.

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Considering equipment options

- Classical pharmaceutical batch filtration washing and drying
  - Agitated filter dryer
  - Centrifuge and agitated dryer
- Continuous filtration, washing and drying
  - Rotary drum filter
  - Belt filter
  - Centrifuge (continuous or semi-batch eg inverting bag)
  - Fluidised bed drier – possibly segmented
  - Spray dryer (no impurity removal)
- Barrier to implementation = lack of small scale continuous equipment for development and early clinical trials material

Target: Isolate pure API ready to formulate

- Pharmaceutical crystallization occurs in the presence of impurities
  - Crystal purity: Bulk sample vs individual crystals vs individual faces / growth sectors
  - Segregation factors
  - Impurity location and quantification
  - Face specific interactions
- Filtration & washing
  - Maintain impurities in solution and displace mother liquor whilst minimising product dissolution
  - Consider solubility of both API, and each impurity – individually & together
  - Wash curves
- Drying
  - Impurity transport during drying
  - Capacity for significant inhomogeneity
  - Achieving impurity content uniformity (or looking for impurity hot spots)

Filter, wash & dry API continuously

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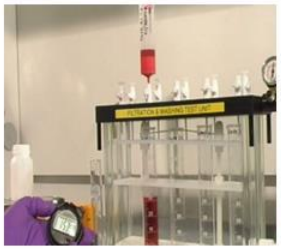
Prior knowledge, process understanding

Slurry transfer



Filtration

Washing

University of Strathclyde Engineering

The most effective washing requires an un-cracked cake of appropriate thickness this is rare in industrial practice.

ReMediES

RE-configuring MEDIcines End-to-end Supply

- Deliver components for an end to end continuous pharmaceutical supply chain.
- Innovate new processing technologies to increase efficiency, eliminate waste and accelerate development.

UoS - AWL collaboration facilitated by a 2 year Knowledge Transfer Partnership

FORTY YEARS OF KTP @40 KNOWLEDGE TRANSFER PARTNERSHIPS

Alconbury Weston Ltd
Continuous Processing Solutions
Designed around you

Carousel based continuous filtration concept: Addresses feeding, filtering, deliquoring and discharge

Innovative prototype scaled for rapid process development and manufacturing up to a few tons per year

Paul Firth, Steve Hulse, Alastair Barton (AWL)
Liz Meehan, Sadie Finn, Claire Macleod (AZ)
Andy Mitchel (Perceptive Engineering) Sara Ottoboni, Chris Steven, Chris Price (CMAC)

Approach

Material attributes

- API solubility in primary solvent at isolation temperature
- Identity, solubility and concentration of each impurity in primary solvent, solubility and metastable zone width in mixture of primary and wash solvent at isolation temperature
- API particle size distribution
- API solubility in wash solvent at isolation temperature and drying temperature
- Solution miscibility, viscosity and volatility

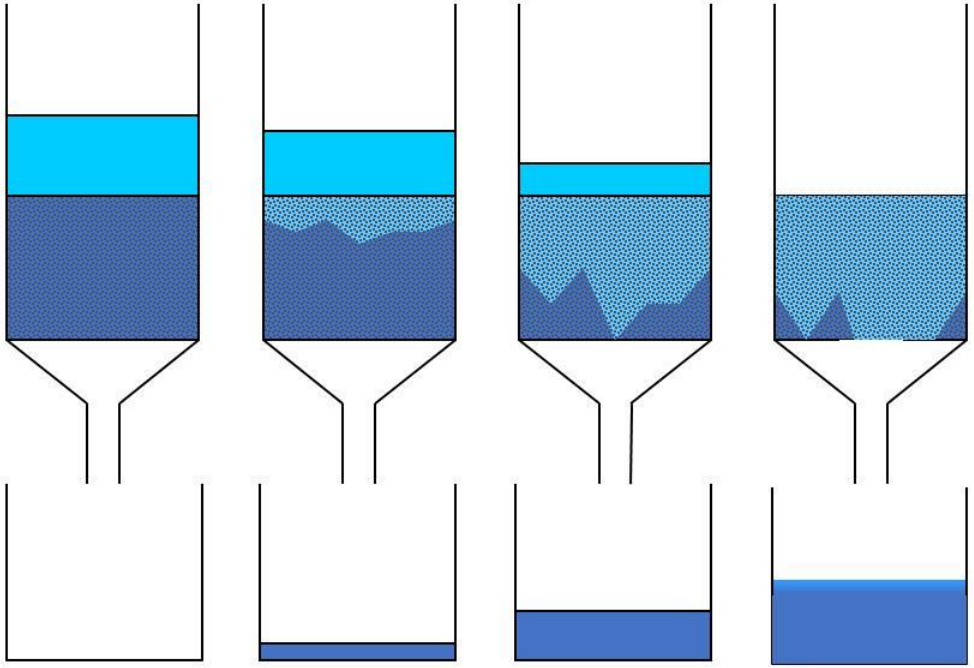
Methodology

- Measure filtration rate and cake void fraction
- Use solubility data to select potential wash solvents to deliver pure free-flowing product
- Investigate wash performance in terms of product loss, impurity removal avoiding agglomeration and fines generation
- Optimise drying based on residual solvent identity & quantity focus on avoiding granulation during drying

Machine

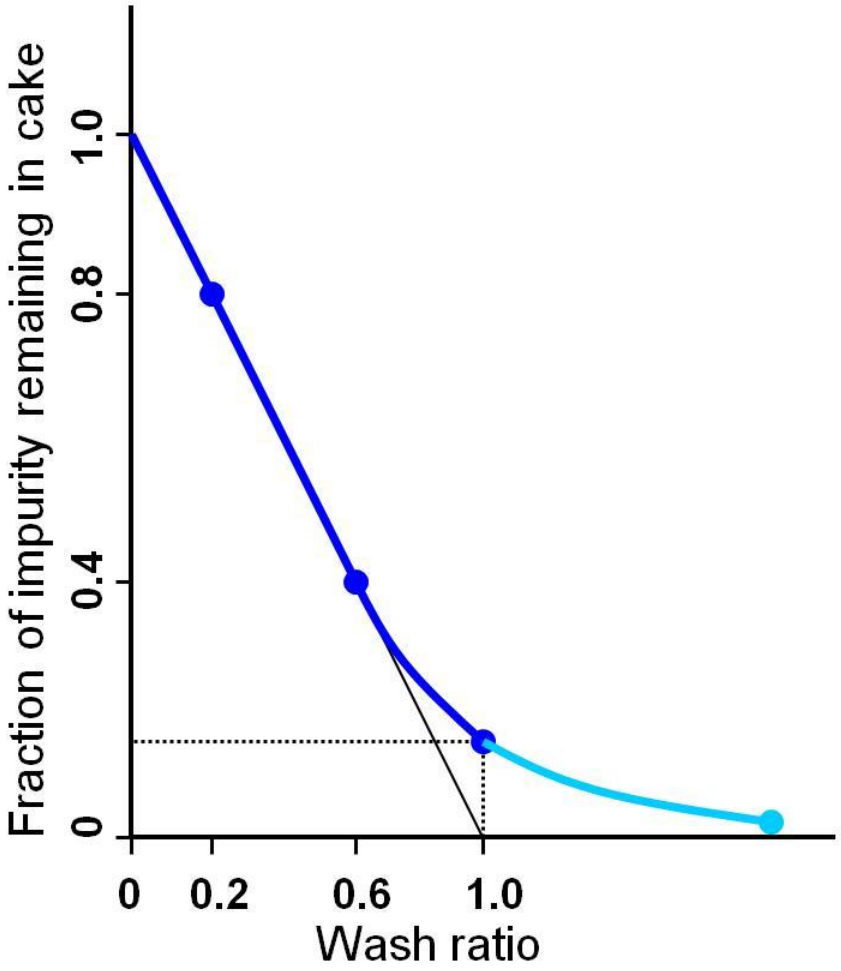
- Representative slurry sample delivered to filter every aliquot
- Controlled filtration capable of stopping at dry land.
- Controlled wash delivery without disturbing filter cake
- Quantify flows, close mass balance segregate liquors for assay.
- Controlled pressure temperature and flow during drying
- Scalable to ca. 5t/y and cleanable

Real washing: Wash solvent break through

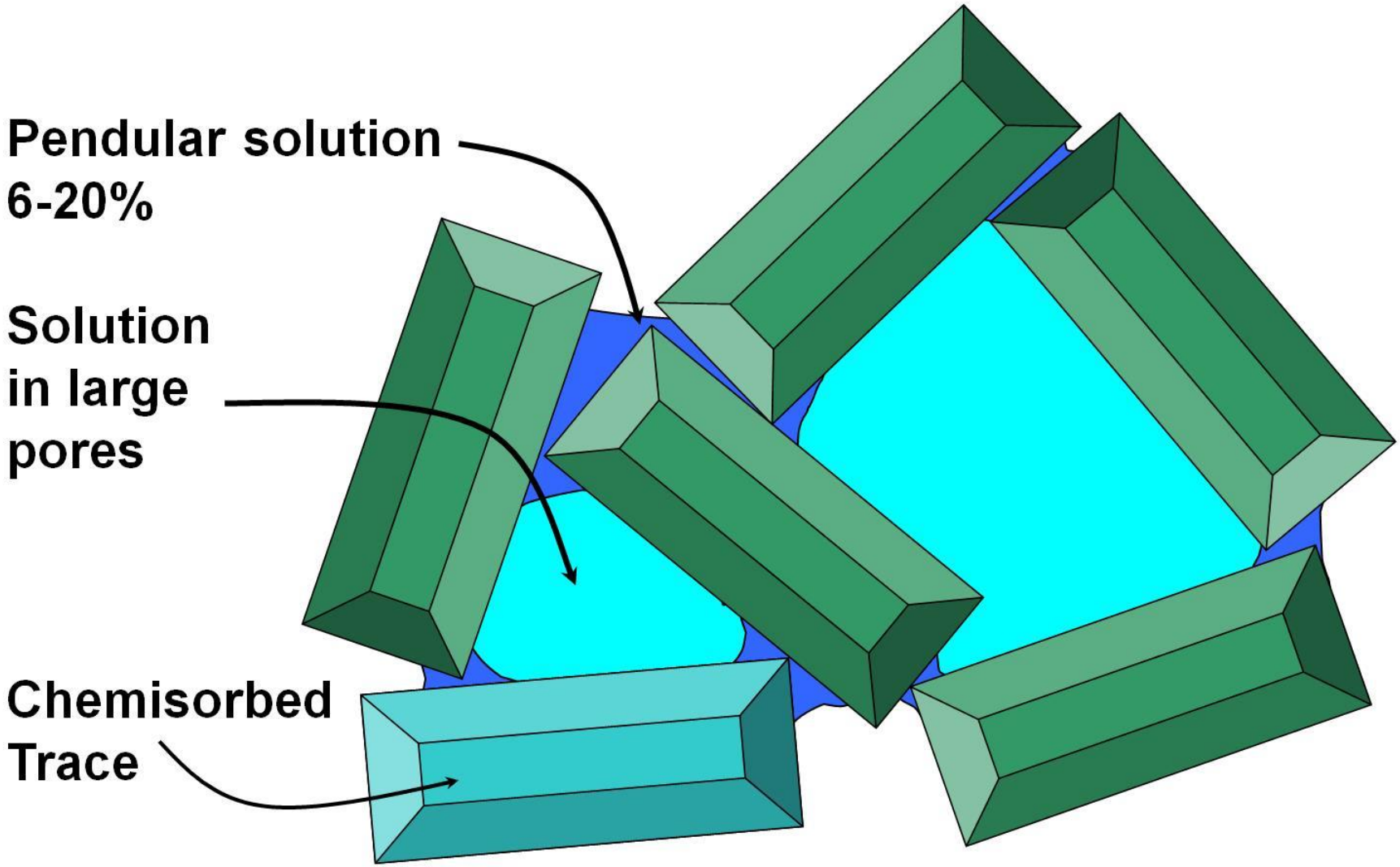


W = 0 W = 0.2 W = 0.6 W = 1

$$W = \frac{Volume\ of\ \ filtrate\ \ \ collected}{Volume\ of\ \ voids\ in\ cake}$$

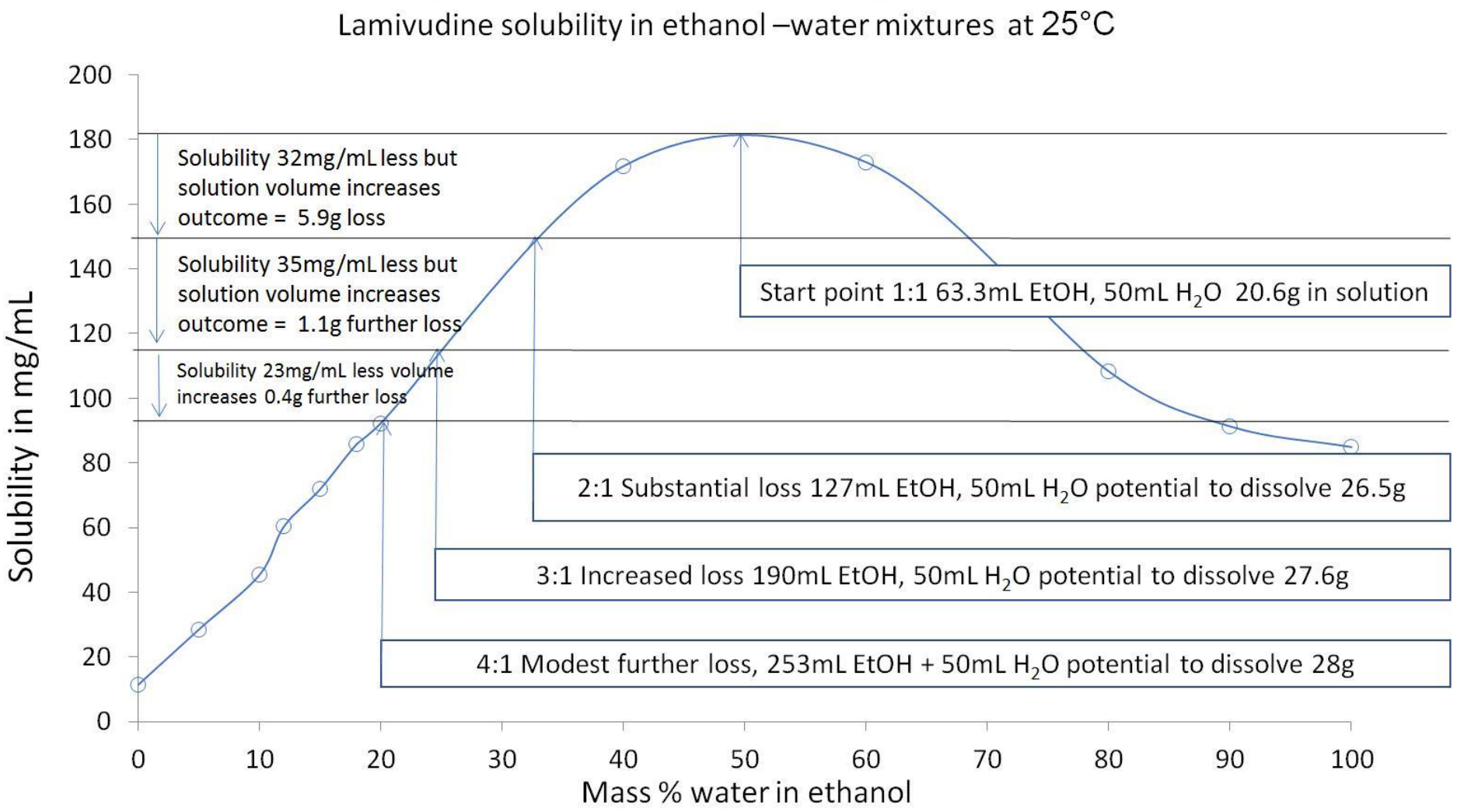


Mother liquor retention in filter cake



Large pore network drains to different extents depending on crystal size & habit, liquor viscosity, wettability, equipment and operating regime

Washing challenge: Impact of API solubility in solvent mixtures



Displacement washing scenario plausible with modest product loss

May still need to switch to a non-solvent to eliminate granulation on drying

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Fraction collection system

Evaluation of wash solvent aliquots

Initially mother liquor is displaced …….

……then a mixture of mother liquor and wash is collected……

……the colour fades as as wash solvent predominates……

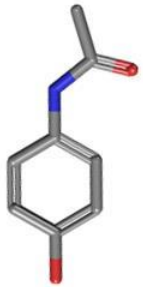
……Then……

5 of 35 ten drop aliquots show nucleation and crystallization of product

S Ottoboni & C Price

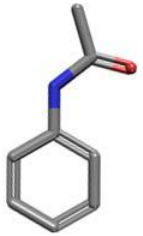
Understand what is happening to impurities

PARACETAMOL

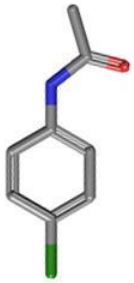


4-acetamido benzoic acid

Acetanilide



4'-Chloroacetanilide

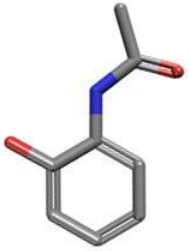


Methyl 4-hydroxybenzoate

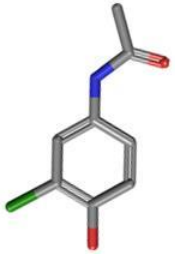
Acetaminophen acetate

4-hydroxy acetophenone

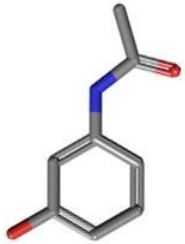
Orthocetamol



N-(3-chloro-4-hydroxyphenyl) acetamide



Metacetamol

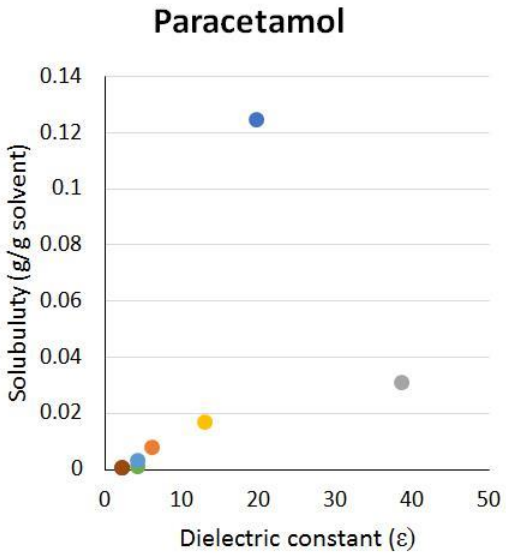


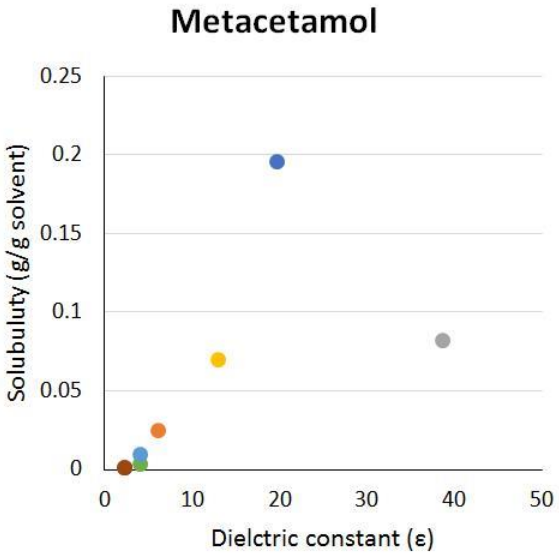
4-Nitrophenol

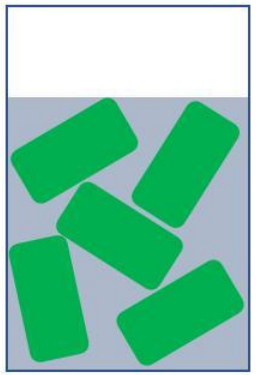
4-Aminophenol

Consider stoichiometric reaction by-products as well as closely related imps
Solubility and MZW of each component in primary solvent & wash solvent(s)
Effect of impurities on API solubility
Assay wash liquors – close mass balance
Objective keep impurities in solution during displacement washing

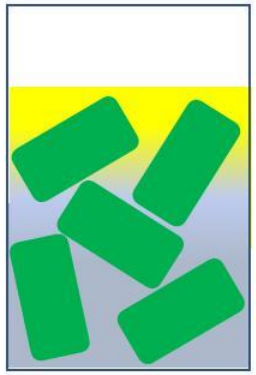
Solubility of impurities relative to paracetamol in a range of solvents of varying dielectric constant



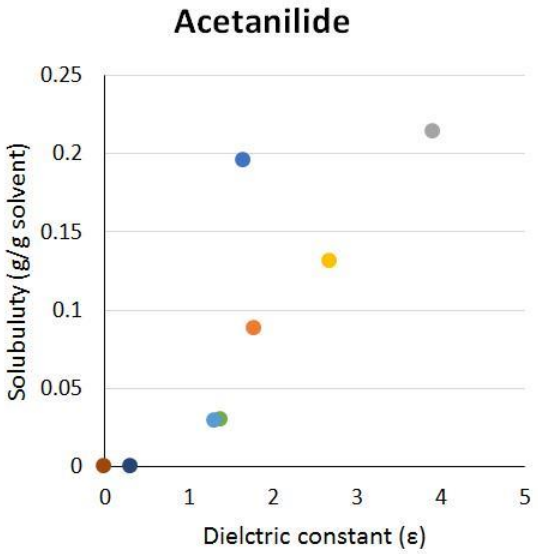


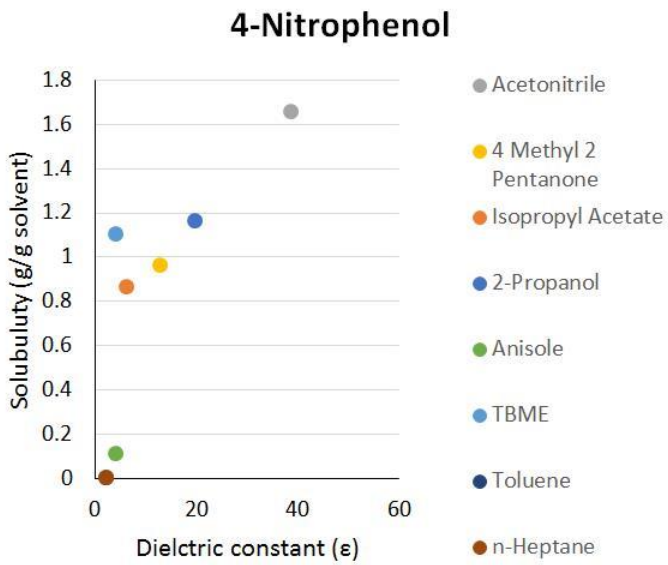


Fully saturated cake



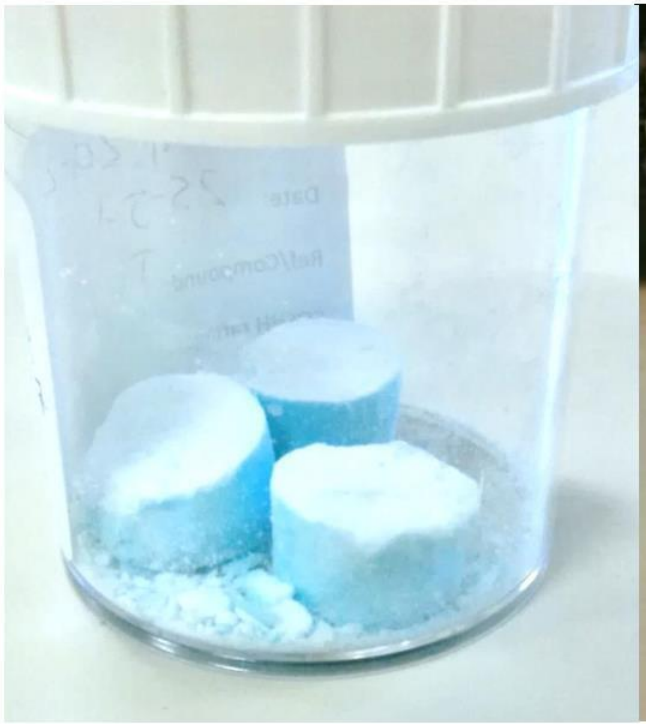
Wash front becomes diffuse as it progresses through the cake



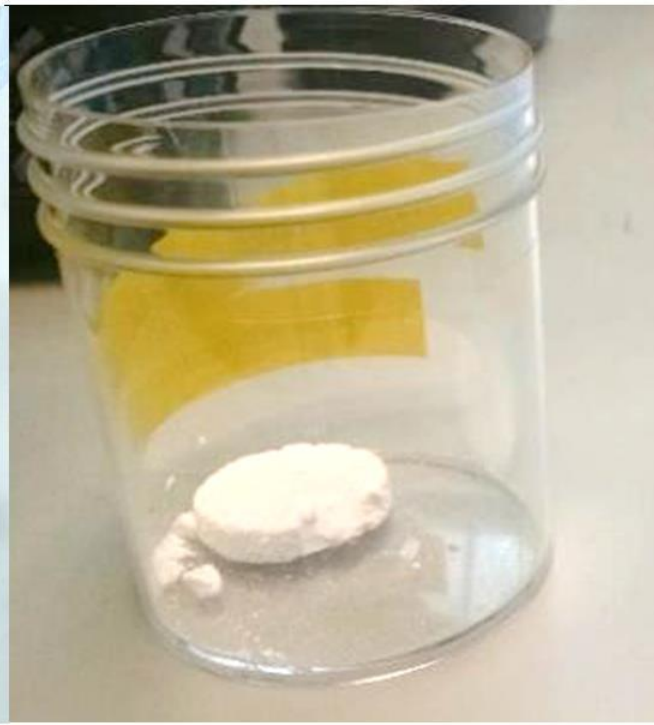


Unpublished results
Samantha Wilson

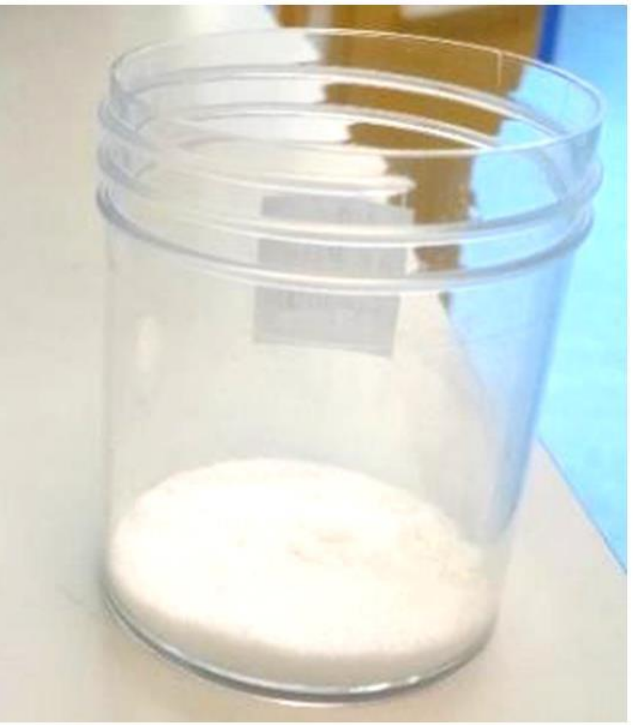
Role of solvent in washing & drying



A coloured tracer shows inhomogeneous impurity distribution



Filter cake dried directly from the crystallization solvent



Filter cake washed with a non-solvent and then dried

Unpublished results Azeem Kahn

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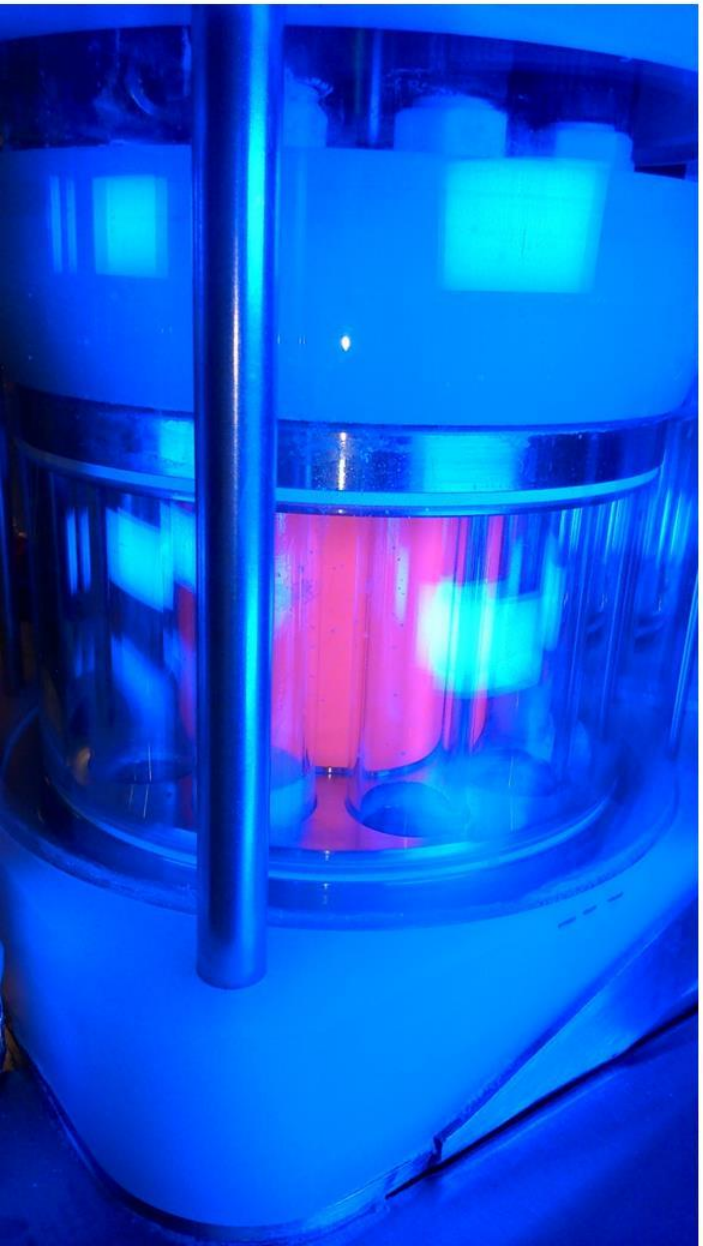
Effect of particle size on drying behaviour
Same procedure different input PSD

Unpublished results Martin Simurda

AWL Continuous Filter Dryer



- Carousel approach replicates “batch best practice”
- 50mL sample, multi-dose for lean suspensions
- Appropriate cake thickness (100 to 1000 particles)
- Narrow filter diameter minimises cake cracking
- Filtration and washing monitored and end point controlled using machine vision
- Drying warm N_2 and reduced pressure
- Onboard data collection and retention
- Capability to track single aliquot
- Two modes of operation – early development and manufacturing
- CIP system
- Capacity ca. 50-150g/hr
- Compatible MOCs for typical API processes

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Design concept

- Carousel based approach replicates “batch best practice”
- Transfer 50mL of representative suspension, multi-dose for lean suspensions
- Form an appropriate cake thickness (100 to 1000 particle dimensions)
- Relatively narrow filter diameter minimises cake cracking
- Filtration and washing monitored and end point controlled using machine vision
- Extract filtration rate from image file, confirm by balance log
- Drying cycle - warm N_2 and reduced pressure
- Onboard data collection and retention
- Capability to track single aliquot and reject a failed portion (image file?)
- Two modes of operation – early development and manufacturing
- CIP system
- Capacity ca. 50-150g/hr
- Compatible MOCs for typical API processes

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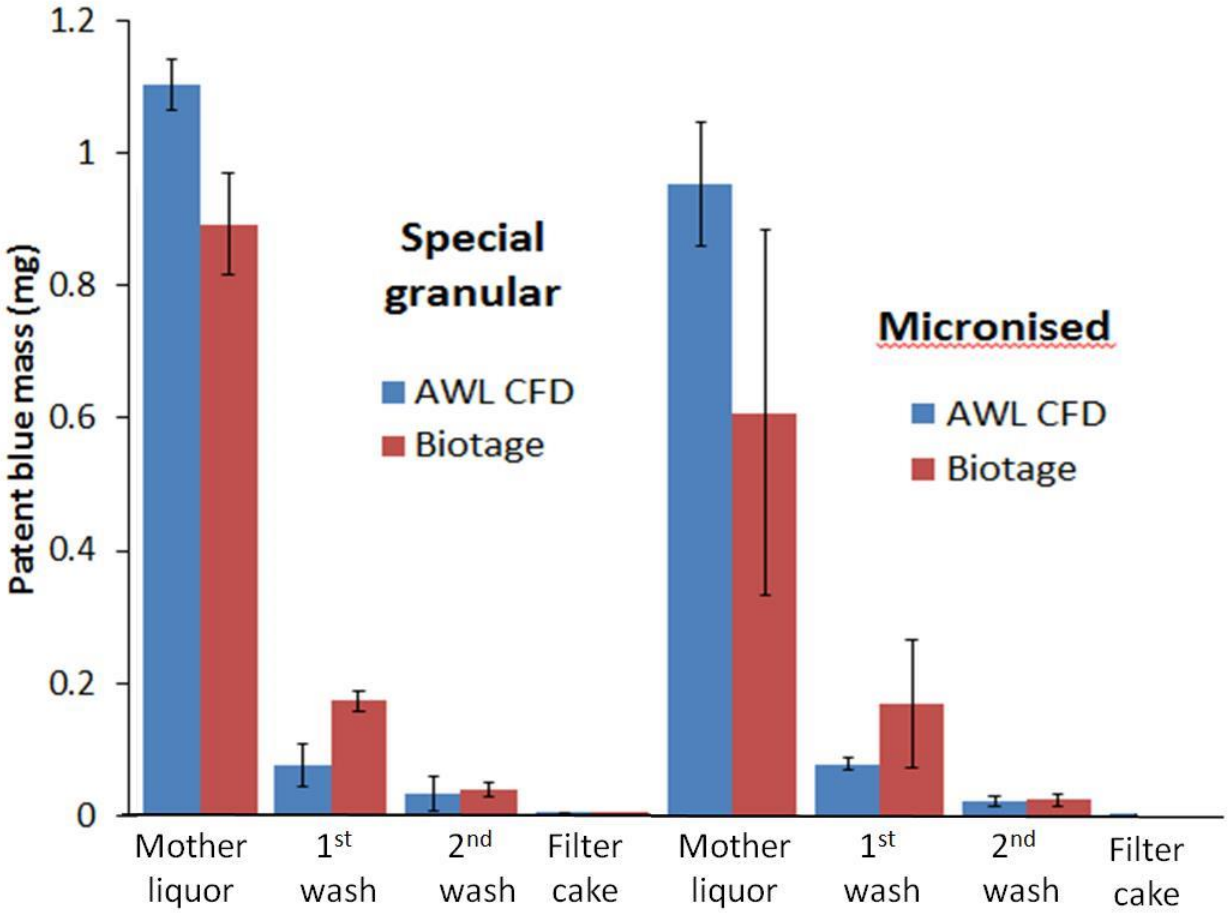
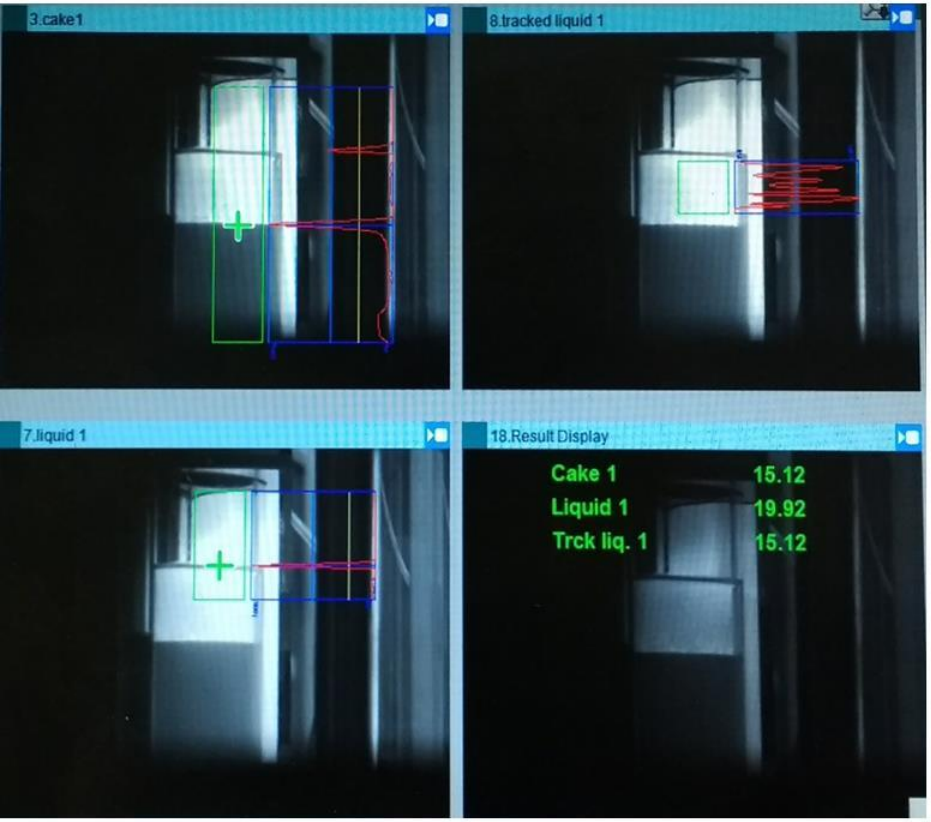
Two operating modes:

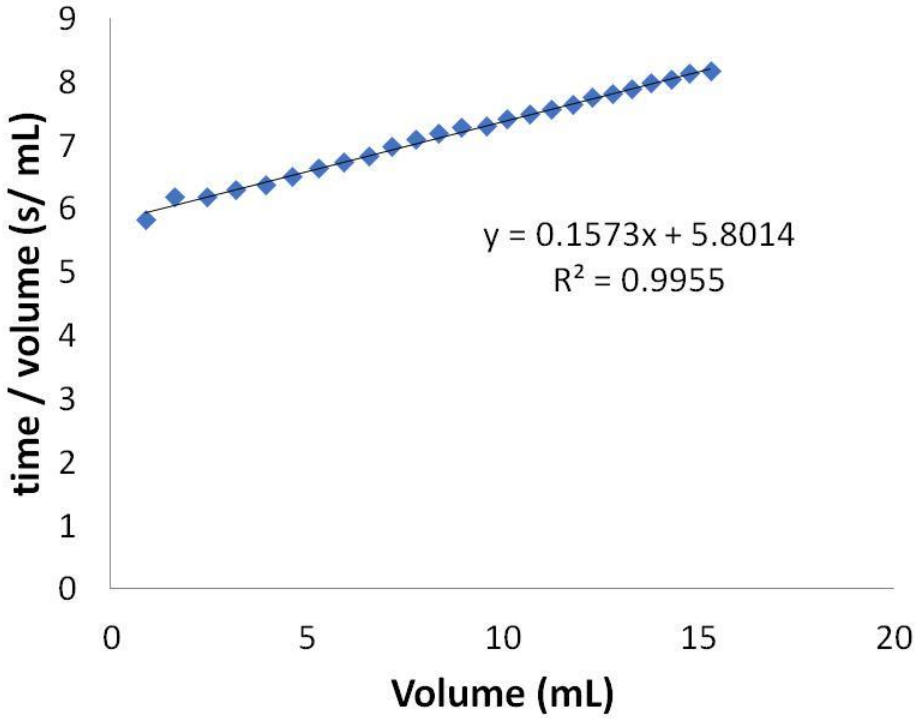
- Early development
  - Operate in single shot (batch) mode, conduct a complete cycle per sample investigate key parameters by DoE.
    - Charge crystal suspension (quantity)
    - Filter (to dry land or break through)
    - Wash (up to 3 times, each wash ca 1.0, 1.1, 1.2 cake void volumes)
    - Investigate contact time / wash flow rate
    - Investigate wash solvents aiming to reach a non-solvent to aid drying
    - Dry with warm N_2 (temp, flow, operating pressure)
    - Assay segregated wash liquors to track product loss, impurity removal
  - Evaluate product quality and select optimum conditions
- Manufacturing
  - Operate selected process with every chamber filled (semi continuous) mode
    - Apply (optimum) operating conditions and verify robustness
    - Track changes, evaluate sensitivity to changes in the feed particle stream

Purity - mass of tracer removed during washing as a function of particle size



Tracking cake and liquid surfaces to determine filtration rate





In summary

Filtration, washing and drying are non-trivial operations

Limited availability of appropriate continuous filtration, washing and drying equipment for pharmaceutical applications especially at the interface between development and manufacturing.

The operational challenges have been outlined:

- Material
- Methodology
- Machine

Two approaches have been illustrated and some initial experimental data shared

Next steps include:

- Evaluating removal of structurally related impurities from “hard to filter crystals” such as plate-like habits
- Refine wash solvent selection strategy
- Demonstrate data driven process development methodology

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