A World Leading SFI Research Centre

Science Foundation Ireland
For what's next

SSPC

The SFI Research Centre for Pharmaceuticals

University College Dublin
Ireland's Global University

DCU

Maynooth University
National University of Ireland Maynooth

OÉ Gaillimh
NUI Galway

RCSI

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

UCC
Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

University of Limerick
Ollscoil Luimnigh

Waterford Institute of Technology

Overview

Steven Ferguson, SSPC Manufacturing Theme Lead,
School of Chemical and Bioprocess Engineering, UCD.
steven.ferguson@ucd.ie

- **Introduction: Co-processed APIs**
- Direct Precipitation of ASDs in DS operations
- Integrated DS-DP Operation: Direct Isolation of Engineered Particles via Fluidized Bed Coating
- Integrated DS-DP Operation: Solidification of Ionic-liquid APIs

Proposed Terminology

- **Co-processed API:** A drug substance, manufactured in a drug substance facility, that contains the API in addition to one or more non-covalently bonded, nonactive component, and differs from salts, solvates and/or co-crystals
  - Differing from salts, solvates, and cocrystals since API and nonactive component(s) do not exist in the same crystal lattice and do not always require a defined stoichiometry

- **Nonactive component:** A component such as a carrier, additive, or other excipient that is non-covalently bonded to the API and is included in the co-processed API to improve the physical properties.
  - Generally, nonactive components (e.g. excipients/additives) will be compendial and/or GRAS
    - For novel materials, relevant CMC info (along with relevant tox info) will be provided in CTD

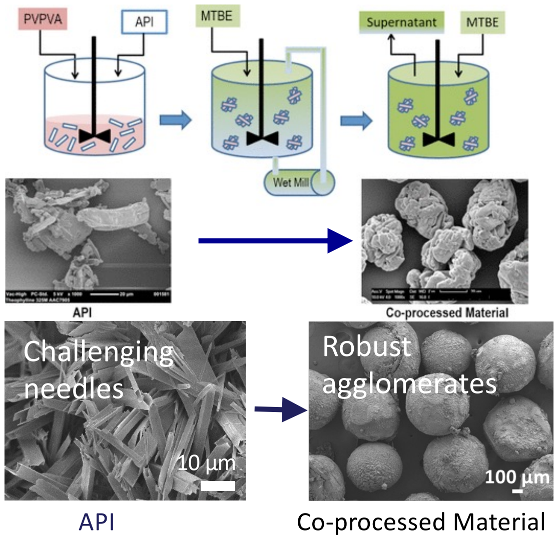
L. Schenck, D. Erdemir, L. Saunders Gorka, J. Merritt, I. Marziano, R. Ho, M. Lee, J. Bullard, M. Boukerche, S. Ferguson, J. Florence, S. Khan, C. Sun;
Recent Advances in Co-processed APIs and Proposals for Enabling Commercialization of These Transformative Technologies, *Mol Pharm.* **2021***,*
17, 2232-2244

Co-processed API Technologies

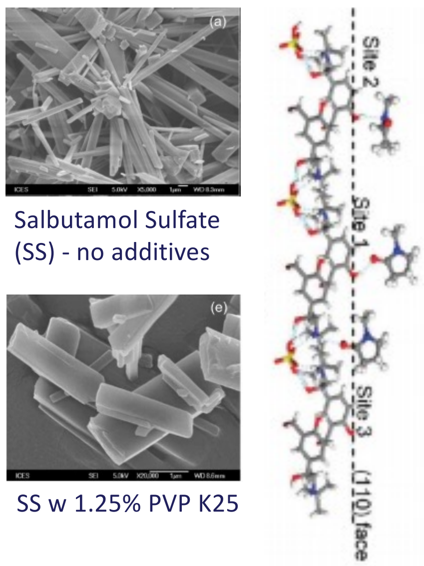
	1	2	3	4
Route	Crystallization and/or Precipitation of API and/or Nonactive Component(s)	Additive Mediated Crystallization of API	Carrier Particles	Nonactive Component Addition During API Isolation
Mechanisms	» Agglomeration » Heteronucleation » Surface coating » Dispersion of API in polymer matrix	» Relative growth-rate modification of crystal faces by adsorption of additive » Modification of nucleation kinetics	» Adsorption » Confinement	» Surface coating » API/nonactive component ordered mixtures
Physical State of API	» Crystalline » Amorphous	» Crystalline	» Crystalline » Amorphous » Gel/Oil » Liquid	» Crystalline » Amorphous

L. Schenck, D. Erdemir, L. Saunders Gorka, J. Merritt, I. Marziano, R. Ho, M. Lee, J. Bullard, M. Boukerche, S. Ferguson, J. Florence, S. Khan, C. Sun; **Recent Advances in Co-processed APIs and Proposals for Enabling Commercialization of These Transformative Technologies,** *Mol Pharm.* **2021**, *17*, 2232-2244

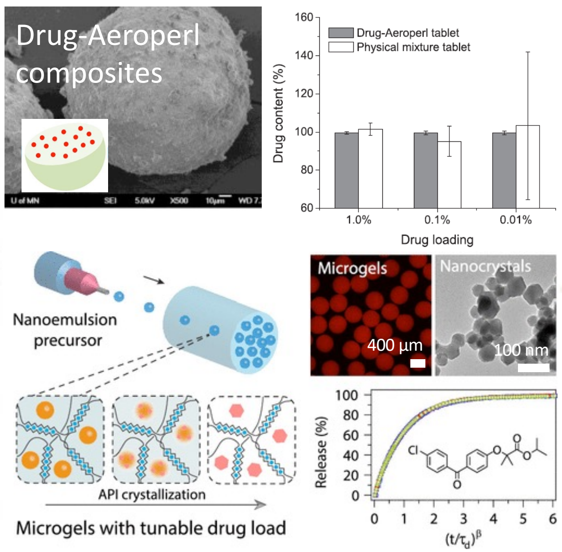
Cryst./Precip. of API and Nonactive Component(s) ①



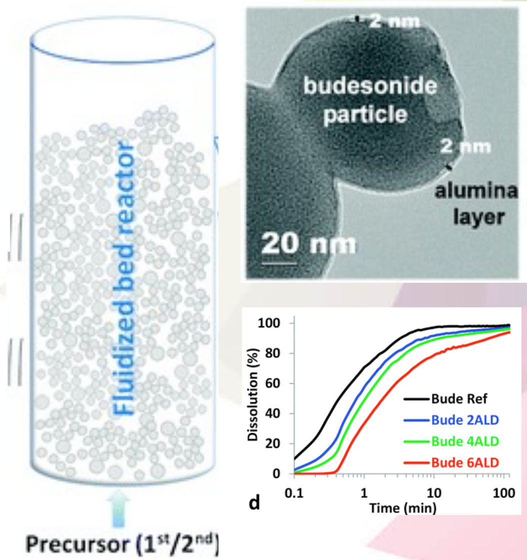
Additive-mediated crystallization of API ②



Carrier particles ③



Nonactive Component Addition During API Isolation ④



Bristol Myers Squibb™ · NUS National University of Singapore · MIT · SMART Singapore-MIT Alliance for Research and Technology · Agency for Science, Technology and Research SINGAPORE · Lilly · M · AstraZeneca · TU Delft Delft University of Technology

Erdemir *et al.*, *Organic Process Research & Development* **2019**, 23, 2685-2698; Yeap *et al.*, *Organic Process Research & Development* 2019, 23, 375-381; Xie *et al.*, *Crystal Growth & Design* 2010, 10, 3363-3371; Sun *et al.*, *International Journal of Pharmaceutics* 2018, 539, 184–189; Domenech *et al.*, *Chemistry of Materials*, 2020, 32, 1, 498–509; Zhang *et al.*, *Nanoscale* 2017, 9, 11410-11417.

Co-processing: the opportunities

CHALLENGES

processability
e.g. to enable continuous DP manufacturing or for surface property modification

stability
including physical, e.g. amorphous materials

high potency ingredients
enable dosage uniformity, reduce industrial hygiene concerns

Bioavailability
Increasing challenges with lack of bioavailability within clinical pipeline

CO-PROCESSED API

BENEFITS

assurance of supply

simplification
eliminate unit ops

additional control

greener processes
less materials
less energy

supply chain modernization

facilitate novel DPs

L. Schenck, D. Erdemir, L. Saunders Gorka, J. Merritt, I. Marziano, R. Ho, M. Lee, J. Bullard, M. Boukerche, S. Ferguson, J. Florence, S. Khan, C. Sun;
Recent Advances in Co-processed APIs and Proposals for Enabling Commercialization of These Transformative Technologies, *Mol Pharm.* **2021***, 17*, 2232-2244

Overview

Steven Ferguson, SSPC Manufacturing Theme Lead,
School of Chemical and Bioprocess Engineering, UCD.
steven.ferguson@ucd.ie

- Introduction: Co-processed APIs
- **Direct Precipitation of ASDs in DS operations**
- Integrated DS-DP Operation: Direct Isolation of Engineered Particles via Fluidized Bed Coating
- Integrated DS-DP Operation: Solidification of Ionic-liquid APIs

Formulation of amorphous solid dispersions of hydrochlorothiazide and Kollidon® VA 64 by spray drying and co-precipitation

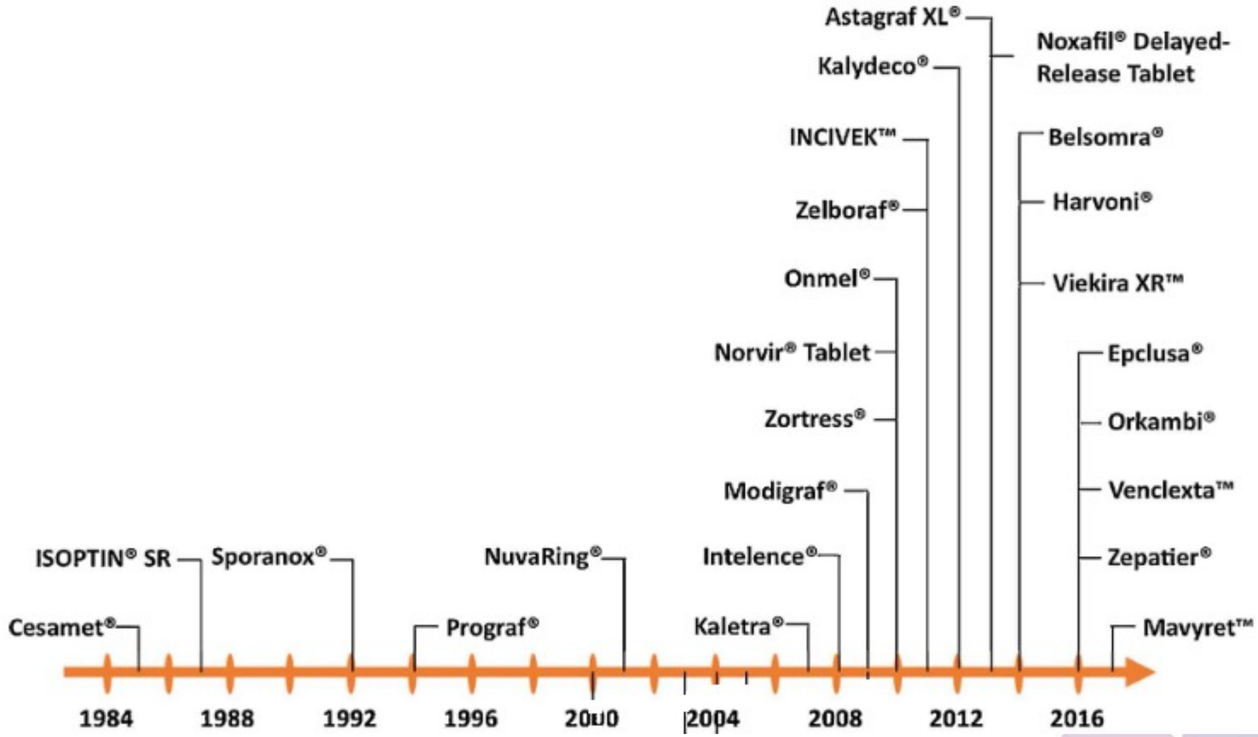
PhD student: Monika Myślińska
Supervisors: Prof. Anne Marie Healy
& Dr Steven Ferguson

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Introduction

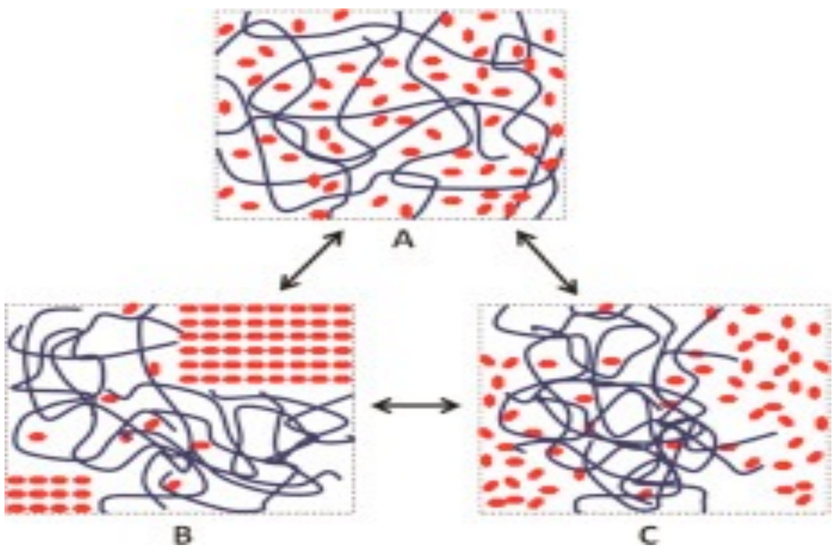
Amorphous solid dispersions on market

Manufacturing methods
HME
Coprecipitation
Spray Drying
KinetiSol®



Timeline of FDA approval of medicines with APIs in the amorphous state. Adapted from 2.

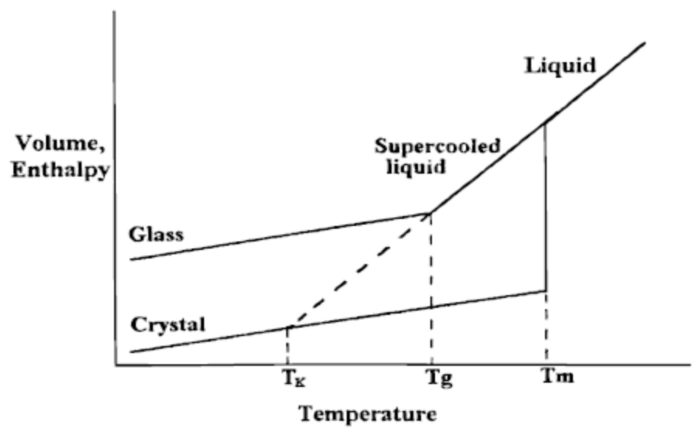
Amorphous Solid Dispersion (ASD)



Schematic image of amorphous solid dispersion (ASD) from [3].

Parameters that affect stability of ASD

- Glass transition temperature
- Miscibility with polymer
- Molecular mobility
- Crystallization tendency
- Crystallinity

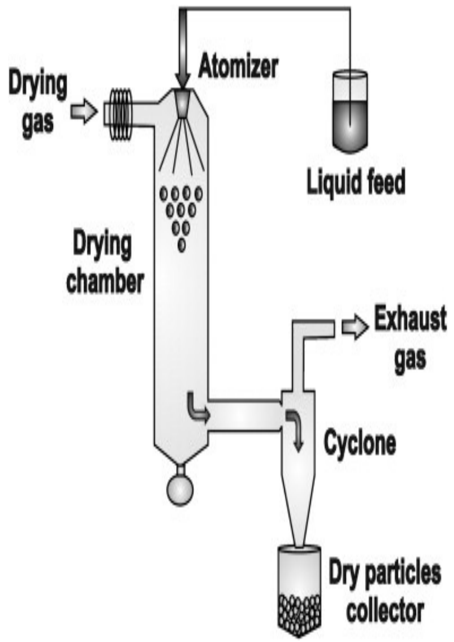


Schematic graph on relationship of volume, enthalpy with temperature for crystal and glass form from [4].

Methods

Parameters of the SD and CP solution.

Spray-drying



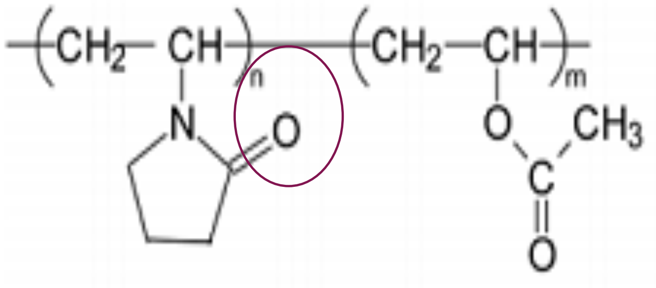
Schematic representation of spray-drying machine from [5].

Sample	API (%(w/w)	Polymer (%(w/w)	Total solid content (%(w/v)	Solvent/Antisolvent*
SD 1	30	70	2.5	EtOH/ Water
SD 2	40	60		
CP 1	30	70	5	EtOH/ Hexane*
CP 2	40	60		

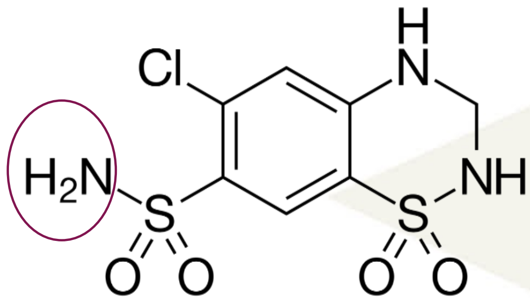
Coprecipitation

Photograph of Easymax™ 102 standard set system from Mettler Toledo Easymax ™ Product Catalog.

Materials



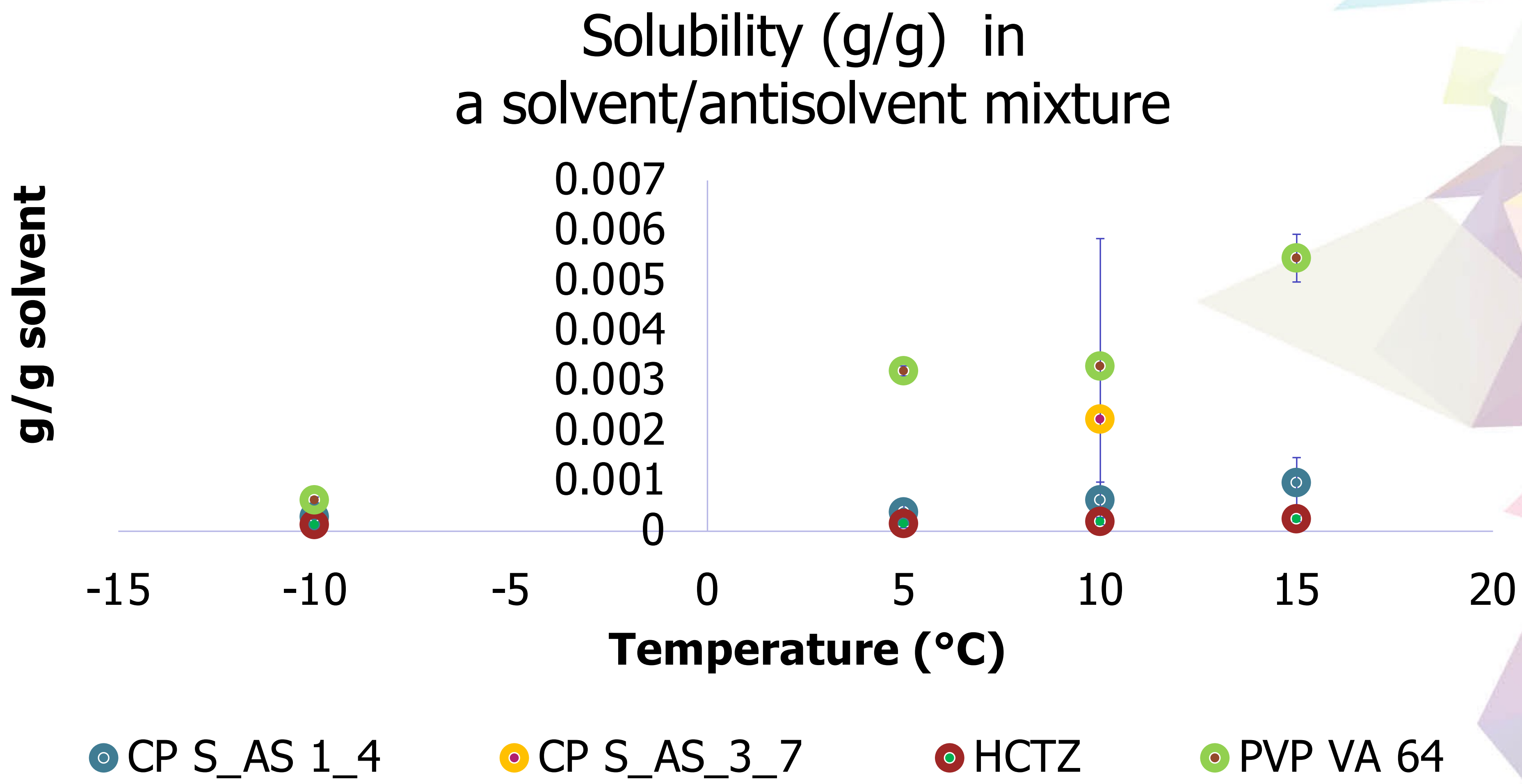
Chemical structure of Kollidon VA 64® - (Vinylpyrrolidone-vinyl acetate copolymer).



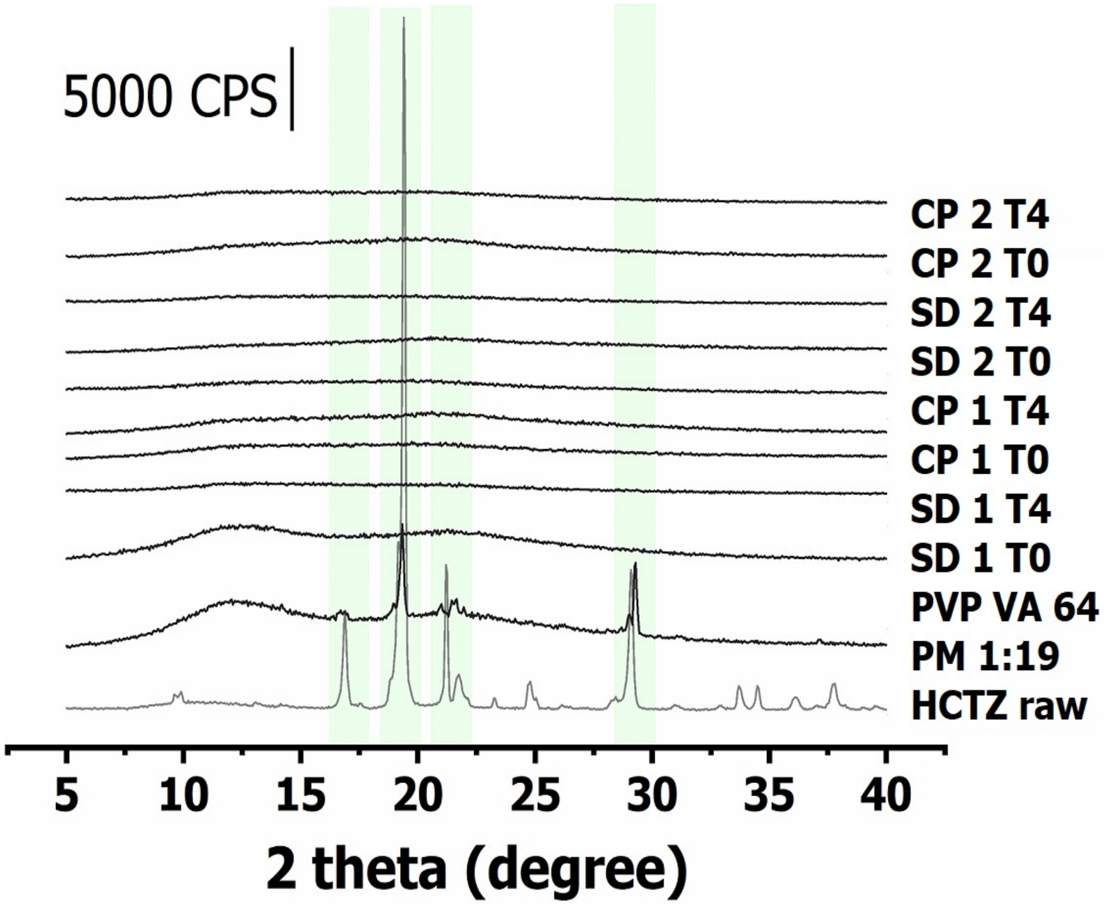
Chemical structure of hydrochlorothiazide.

Parameter	HCTZ	PVP VA 64
Hansen Solubility Parameters	26.44 δ (MPa 0.5)	23.4 δ (MPa 0.5)
Fragility	GFA II (SD), GFA III (MQ)	

Coprecipitation Parameters

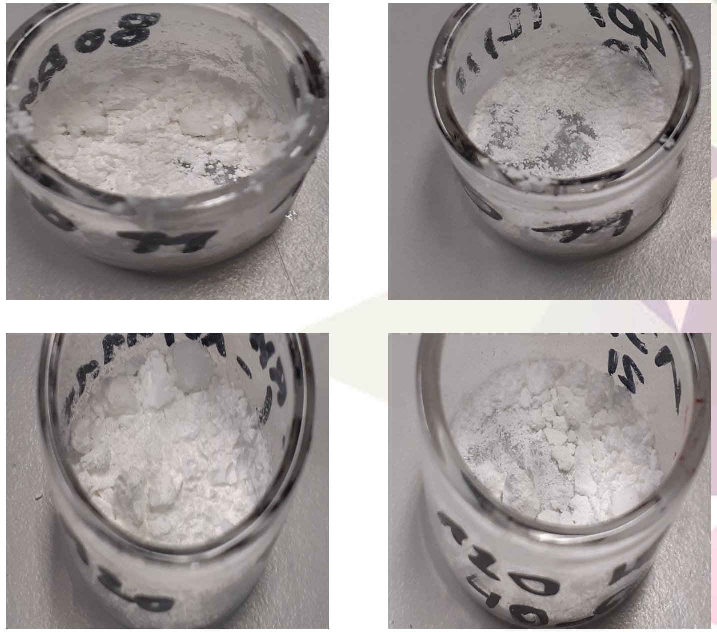


PXRD



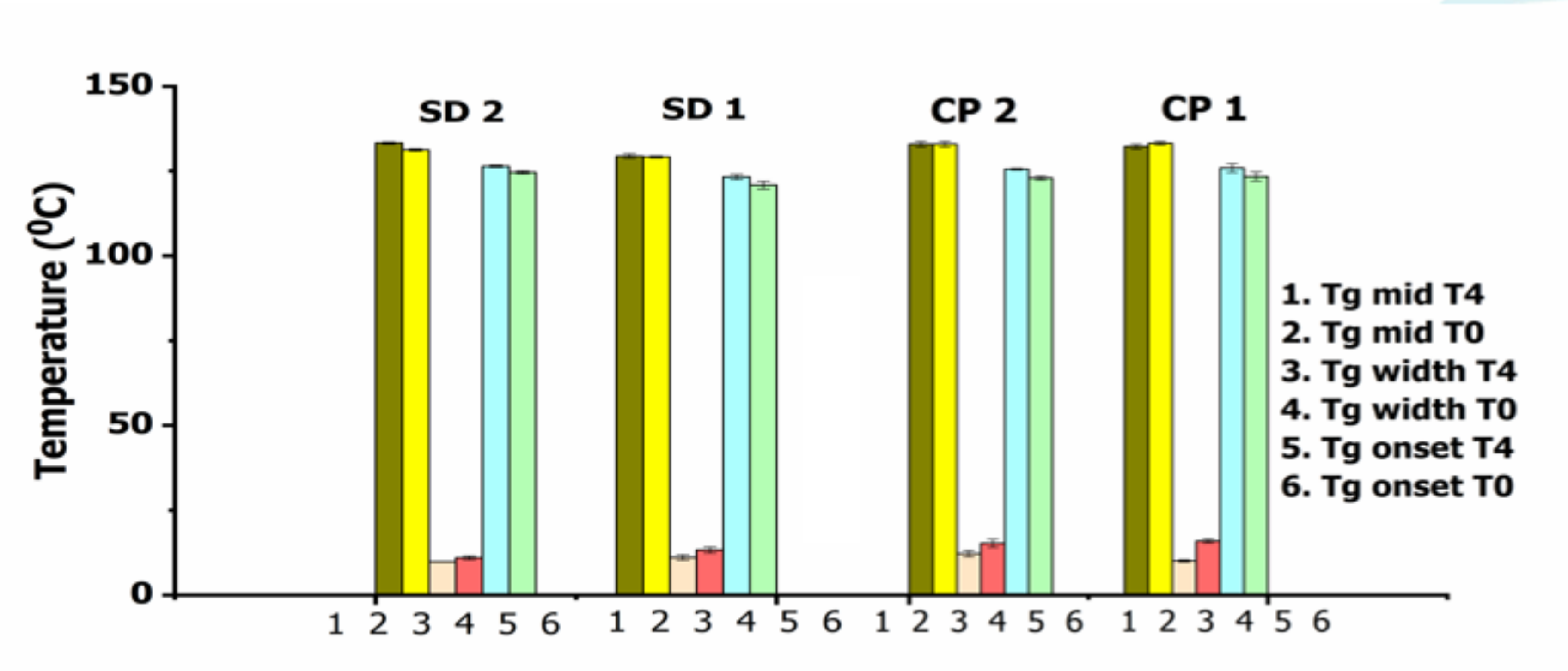
XRD for CP 1, CP 2, SD 1, SD 2 samples at T0 and T4 of physical stability study.

A) B)



A) Sample SD 2 (upper), CP 2 (lower) T0 B) Sample SD 2 (upper), CP 2 (lower) T4

Glass Transition Temperature



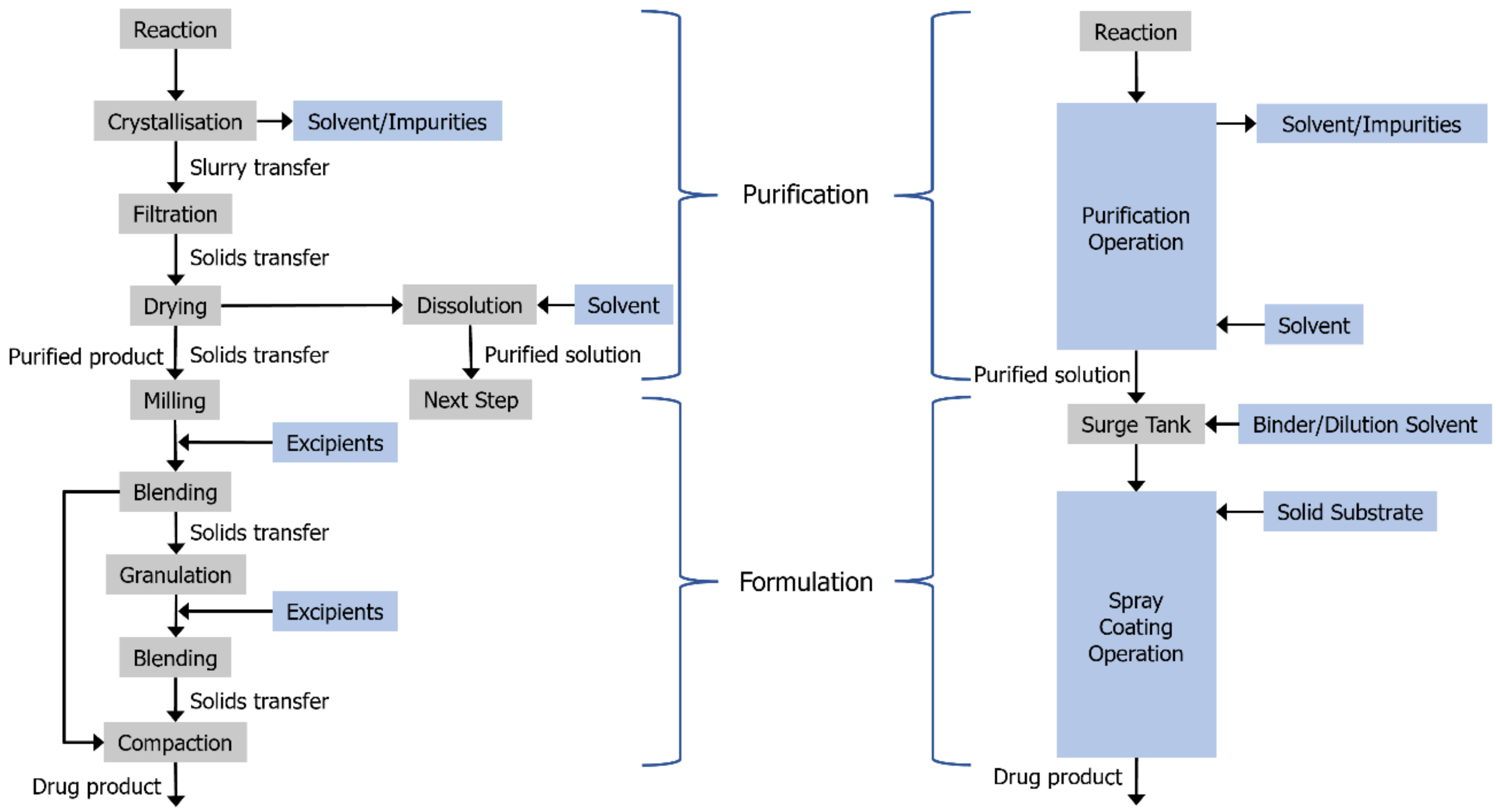
Glass transition temperature (Tg) onset, width, midpoint for samples CP 1, CP 2, SD 1, SD 2 at T0 and T4 of the study.

Overview

Steven Ferguson, SSPC Manufacturing Theme Lead,
School of Chemical and Bioprocess Engineering, UCD.
steven.ferguson@ucd.ie

- Introduction: Co-processed APIs
- Direct Precipitation of ASDs in DS operations
- **Integrated DS-DP Operation: Direct Isolation of Engineered Particles via Fluidized Bed Coating**
- Integrated DS-DP Operation: Solidification of Ionic-liquid APIs

Integrated Upstream& Downstream Operations



Stocker, M.W.; Harding, M.J.; Todaro, V.; Healy, A.M.; Ferguson, S. Integrated Purification and Formulation of an Active Pharmaceutical Ingredient via Agitated Bed Crystallization and Fluidized Bed Processing. *Pharmaceutics* **2022**, *14*, 1058. https://doi.org/10.3390/pharmaceutics14051058

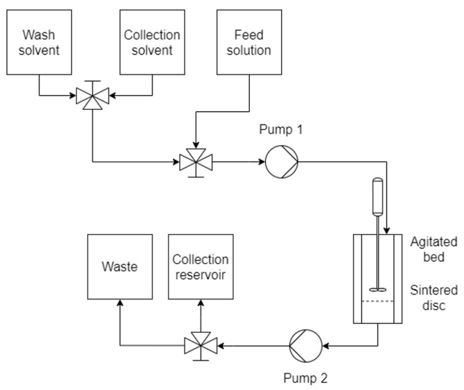
Integrated Upstream& Downstream Operations

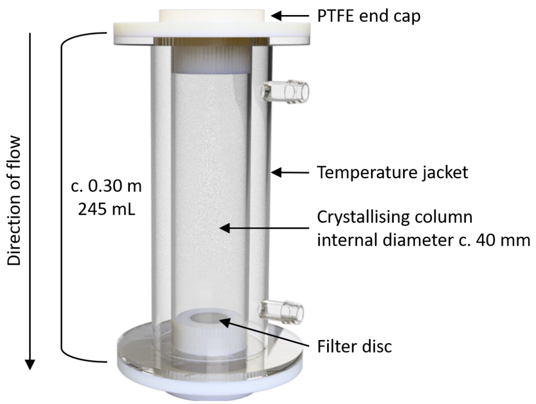
Purification

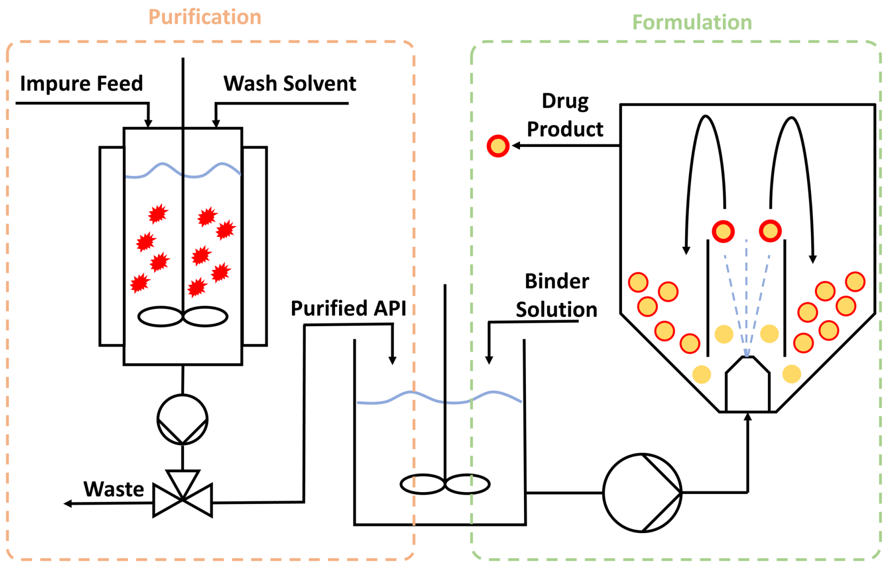
- API Isolation avoided
- Cyclical partial dissolution of API salt was used to produce purified liquid phase stream conditioned for integrated formulation operation

Formulation

- Spray coating used to process to conditioned effluent
- Sodium Ibuprofen deposited on MCC beads
- Can apply controlled release coatings
- Micro-tablets or Engineered Powders for direct compression easily accessible







Stocker, M.W.; Harding, M.J.; Todaro, V.; Healy, A.M.; Ferguson, S. Integrated Purification and Formulation of an Active Pharmaceutical Ingredient via Agitated Bed Crystallization and Fluidized Bed Processing. *Pharmaceutics* **2022**, *14*, 1058. https://doi.org/10.3390/pharmaceutics14051058

Primary Isolation via FB Spray Coating

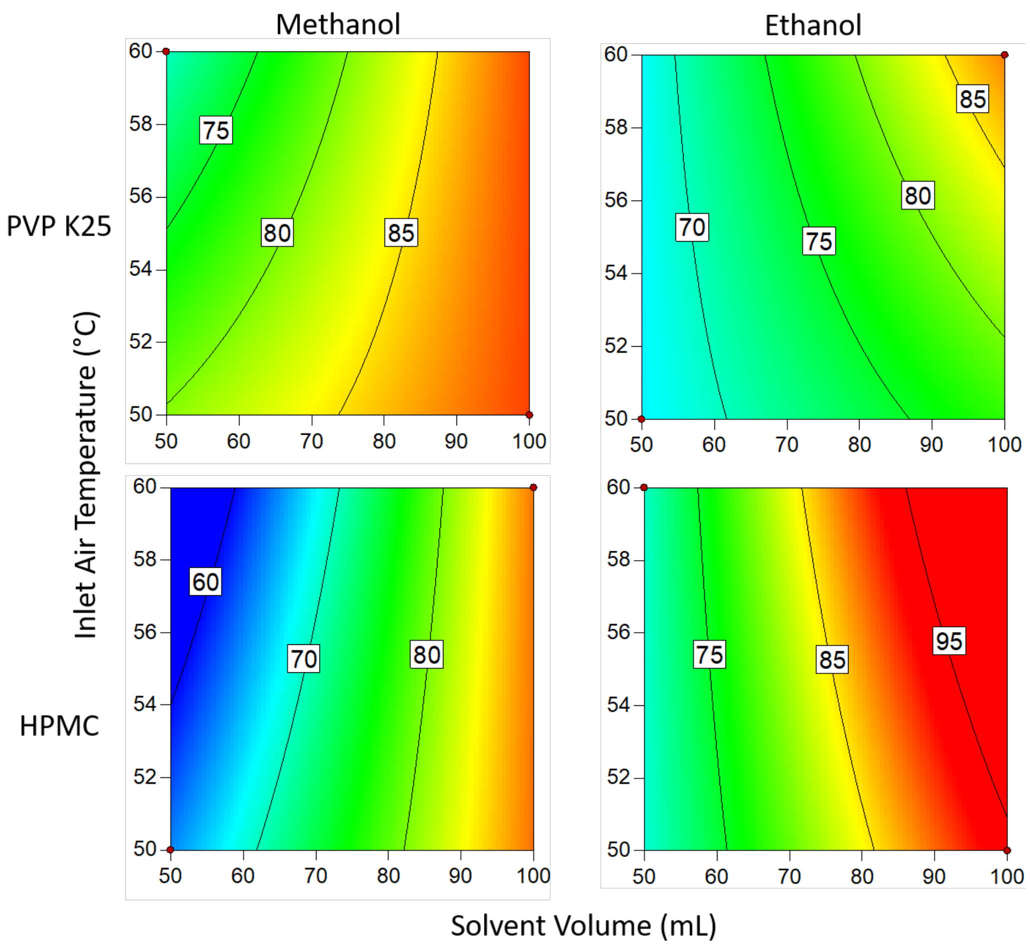


Figure 8. Drug loading efficiency when 3 g of binder is used. Numbers and tie lines correspond to points of equal DLE (%).

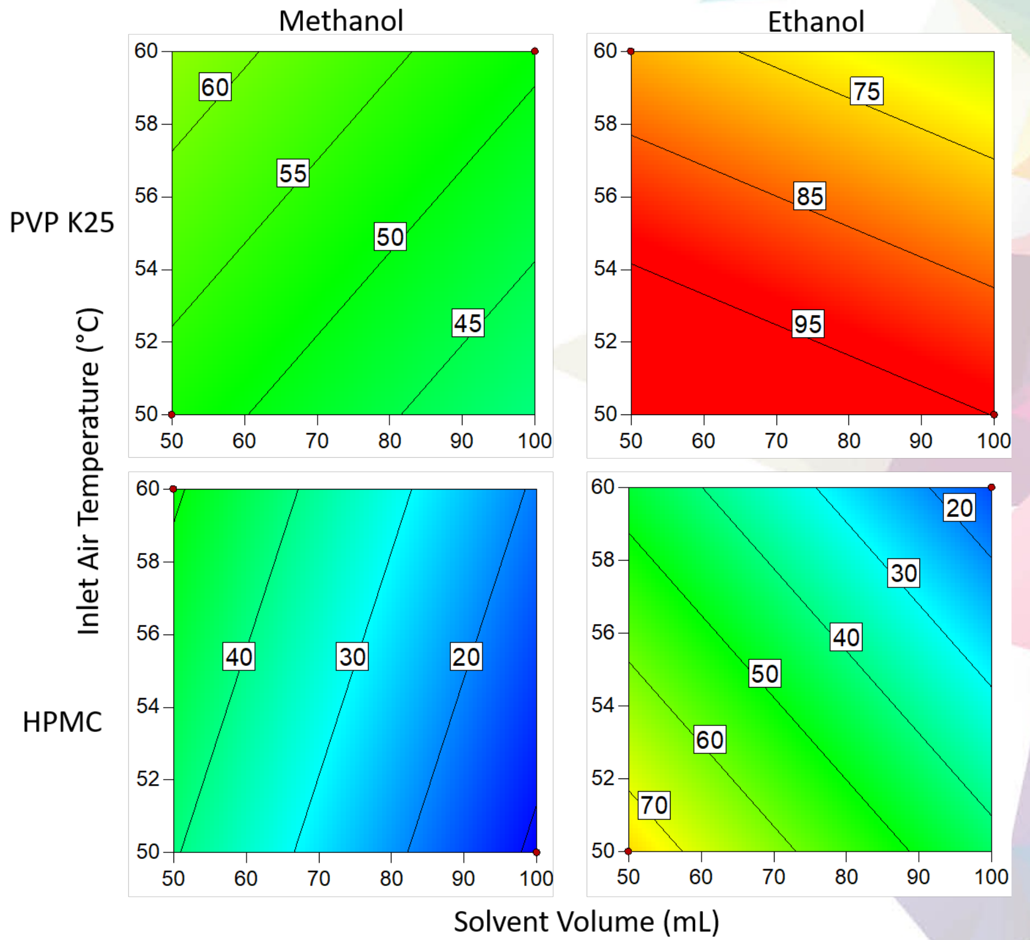


Figure 9. Degree of crystallinity when 1 g of binder is used. Numbers and tie lines correspond to points of equal DoC (%).

Overview

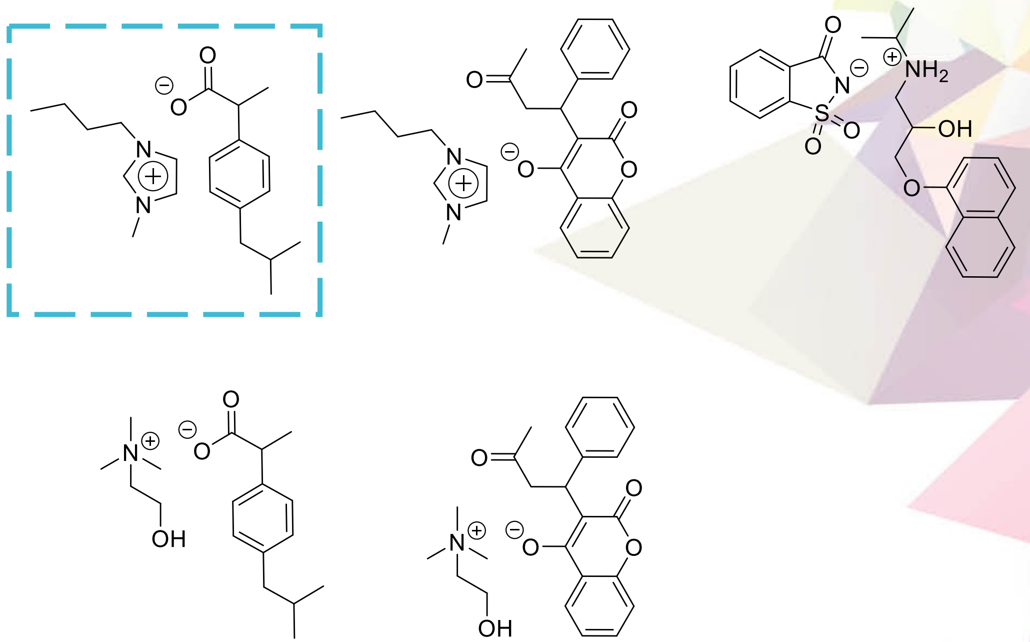
Steven Ferguson, SSPC Manufacturing Theme Lead,
School of Chemical and Bioprocess Engineering, UCD.
steven.ferguson@ucd.ie

- Introduction: Co-processed APIs
- Direct Precipitation of ASDs in DS operations
- Integrated DS-DP Operation: Direct Isolation of Engineered Particles via Fluidized Bed Coating
- **Integrated DS-DP Operation: Solidification of Ionic-liquid APIs**

Ionic Liquid Forms of Drugs

- 'Liquid salts'
  - T_m < 100 °C
  - Highly tuneable properties
  - Eliminate solid forms of APIs
- Drug structures suitable for forming ILs
- Model system:
  - **BMIm Ibu**
  - $T_m = T_g$ = -26 °C
  - Viscous oils
    - Solidify in order to formulate
- Design and synthesis of novel ILs
  - BMIm War, Cho Ibu, Cho War, Pro Sac

Ibuprofen-Based ILs Warfarin-Based ILs Propranolol-Based IL



Isolation-Free Solidification of API-ILs

- API-ILs can be formed on small scale via metathesis.
- Ion exchange resin method developed
  - Avoid solid product from metathesis reaction
- Combined with isolation free purification processes provides a purified liquid stream.
- Possible to adapt processes to run semi-continuously if desired
- However physical properties of IL streams make further processing problematic

Metathesis Reaction

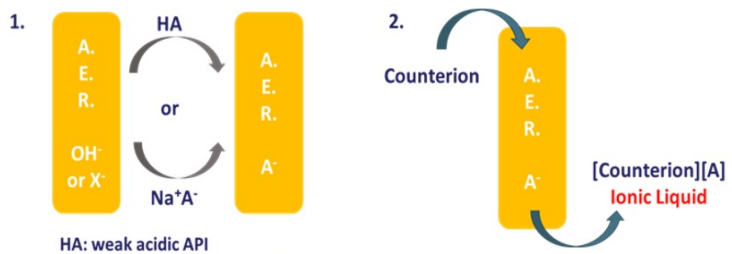
$$R_1^+X^- + R_2^-A^+ \rightarrow R_1^+R_2^- + A^+X^-$$

X = halide, (Cl^-, Br^-, I^-)
A = alkali (Na^+, K^+)

Anion Exchange Resins (A.E.R.)

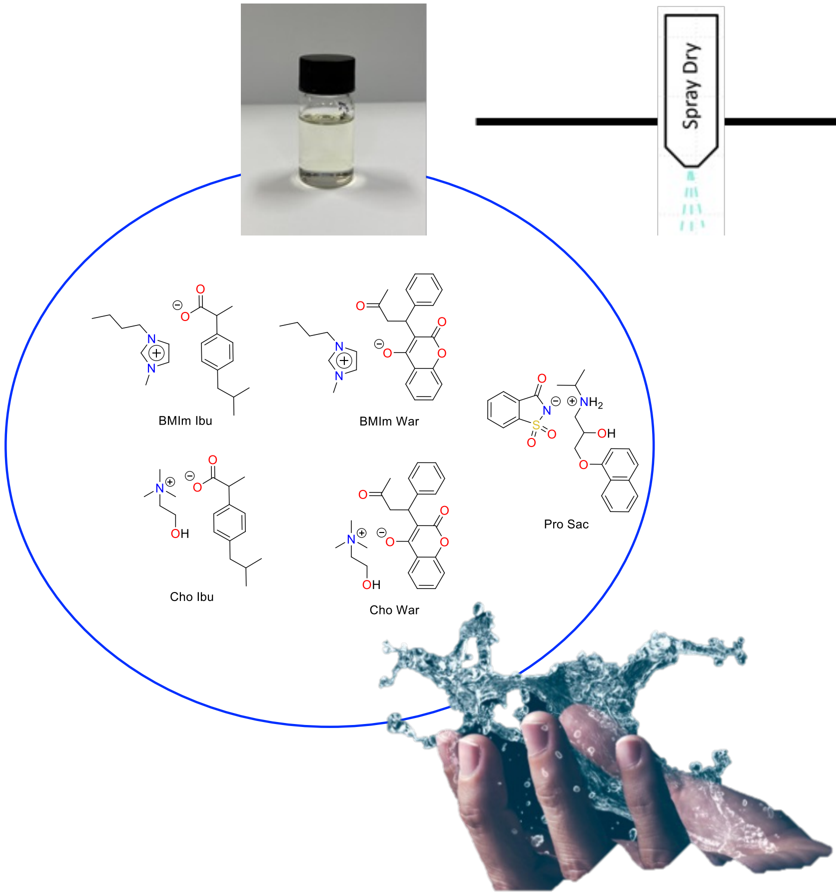
General procedure:

1. API or counterion loading
2. IL formation



HA: weak acidic API
Na^+A^-: sodium salt of weak acidc API

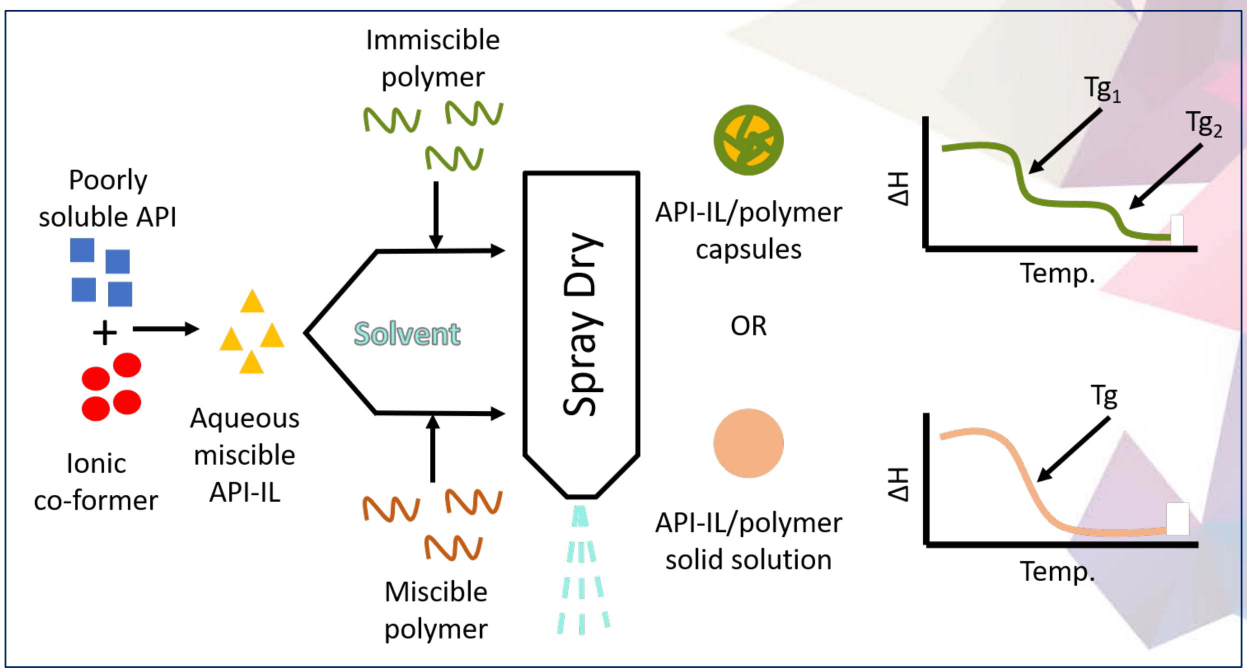
ILs that you can hold




International Journal of Pharmaceutics
Available online 12 May 2021, 120669
In Press, Journal Pre-proof

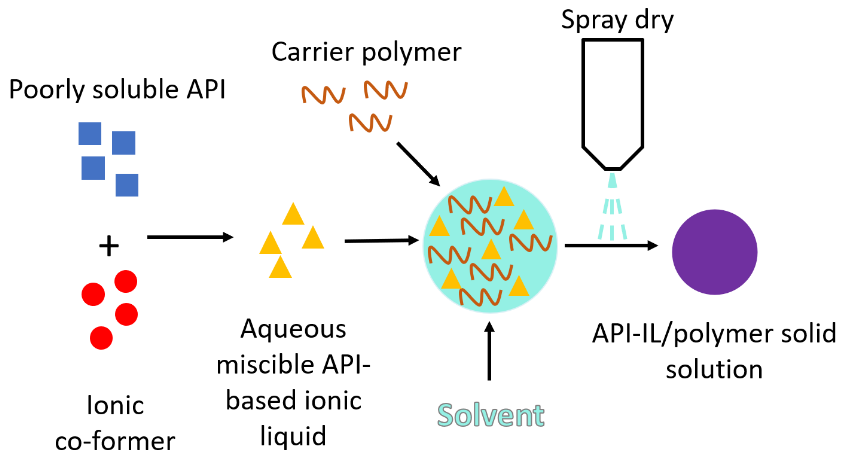
Formulation of ionic liquid APIs via spray drying processes to enable conversion into single and two-phase solid forms

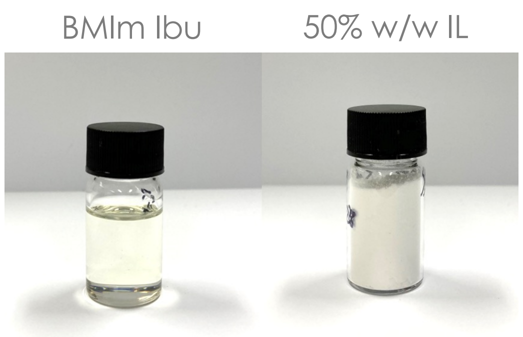
Evangelia Tsolaki [a, b, c, 1], Michael W. Stocker [a, 1], Anne Marie Healy [d], Steven Ferguson [a, b, e, f]



Miscible System

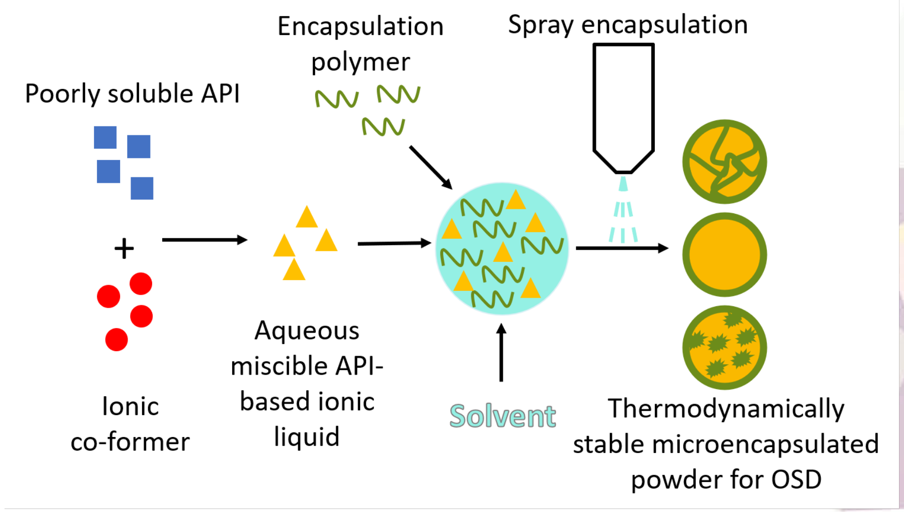
- Form solid solution
- Failed with standard polymers
  - T_g suppression
- Difficult with extreme low T_g materials
- Maltodextrin
  - T_g = c. 200 °C
  - Only soluble in water
- Achieve c. 50% w/w API-IL loading
- Solid state characterised
  - mDSC, ATR-FTIR, pXRD

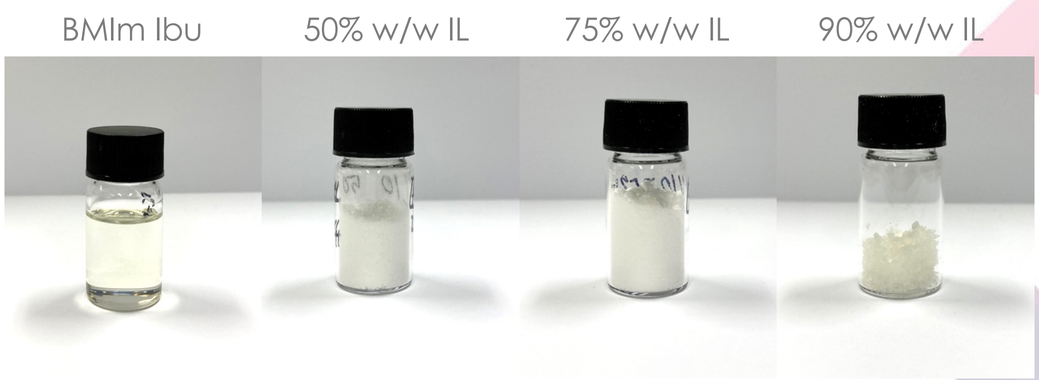




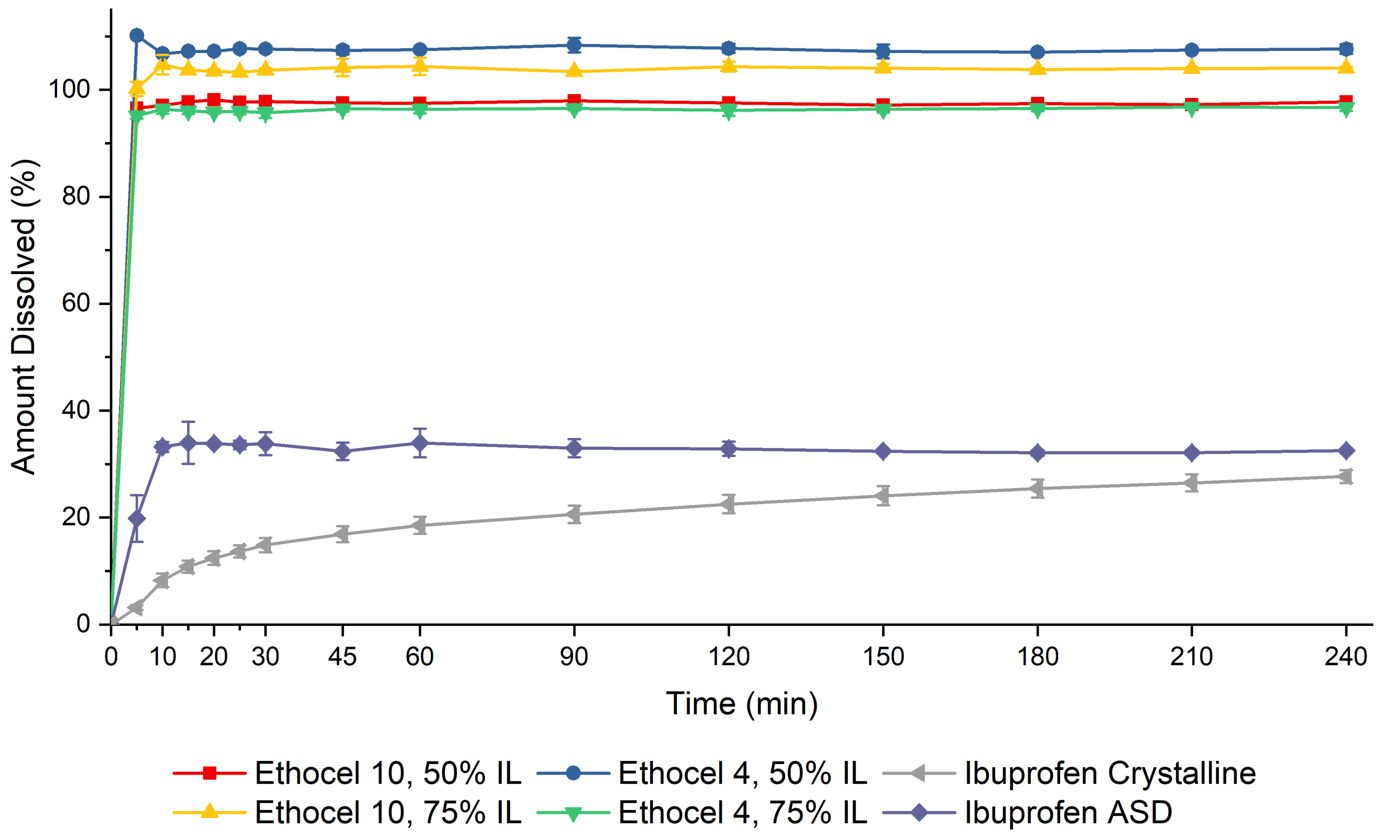
Immiscible System

- Encapsulate liquid in immiscible polymer
  - Ethyl cellulose
- High loading
  - Failure point 90% w/w API-IL
- Engineer ILs with more favourable bio properties
  - Overcome poor physical properties
- Solid state characterised
  - mDSC, ATR-FTIR, pXRD

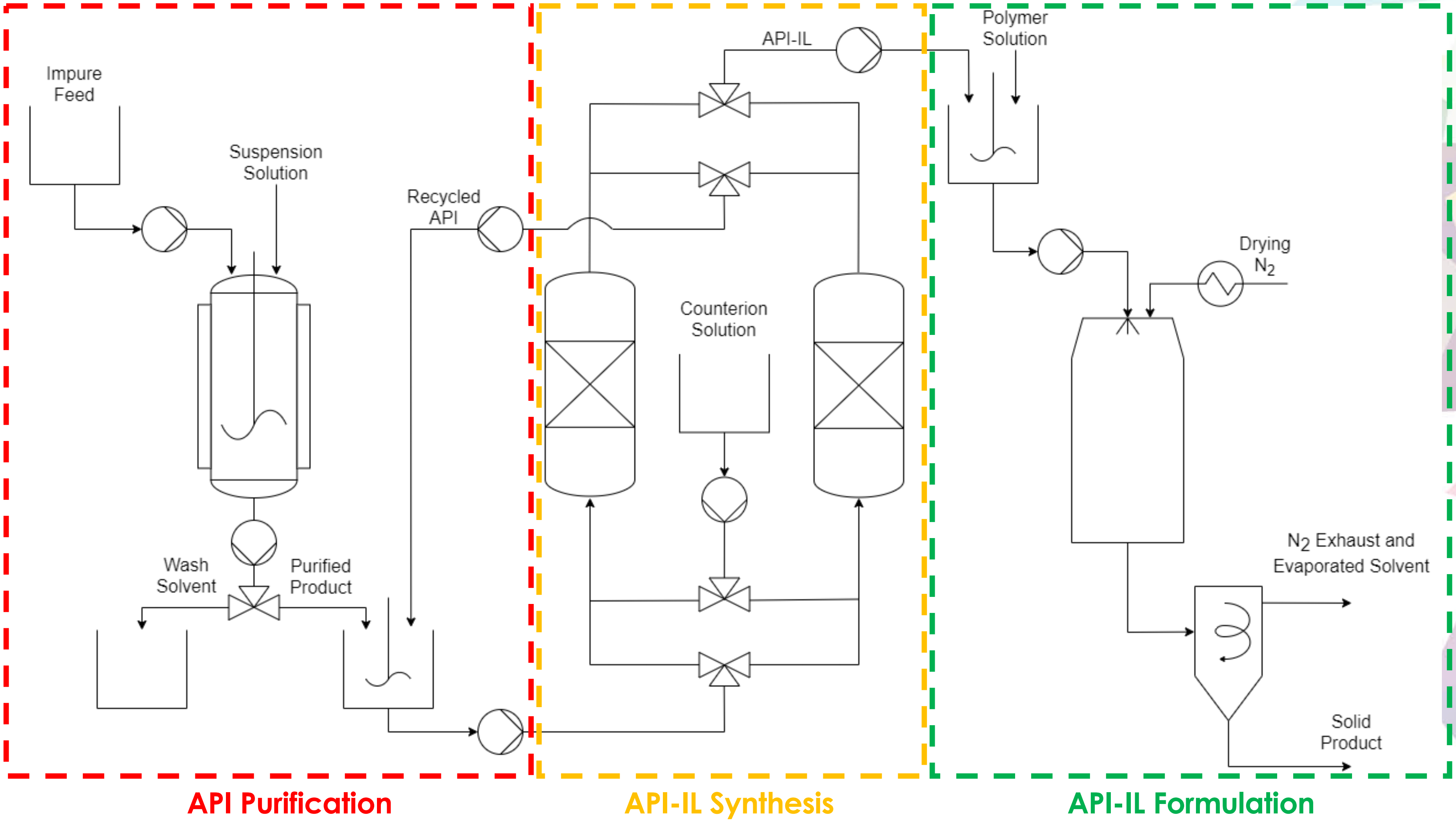




Immiscible System Dissolution Performance



Isolation-Free Solidification of API-ILs



Thank you for your attention!