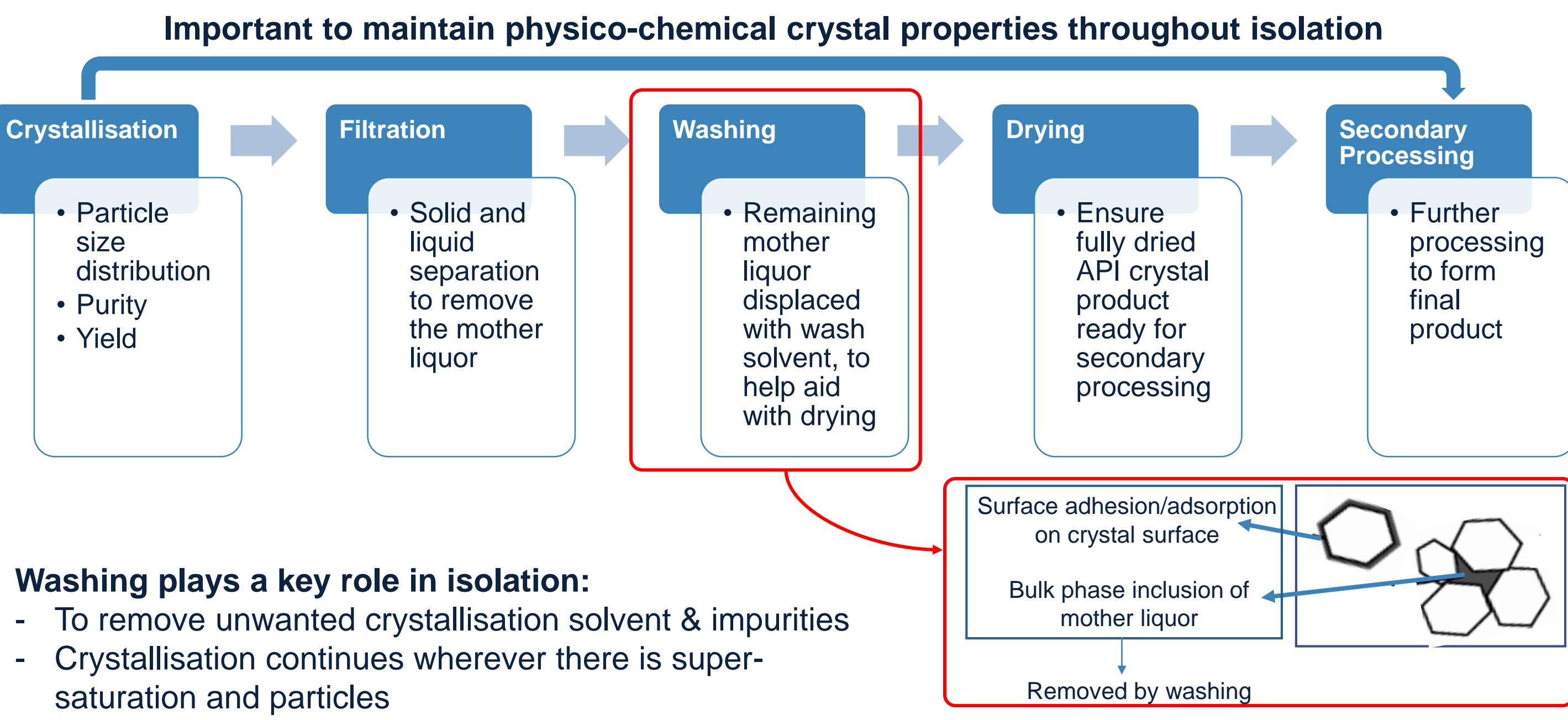


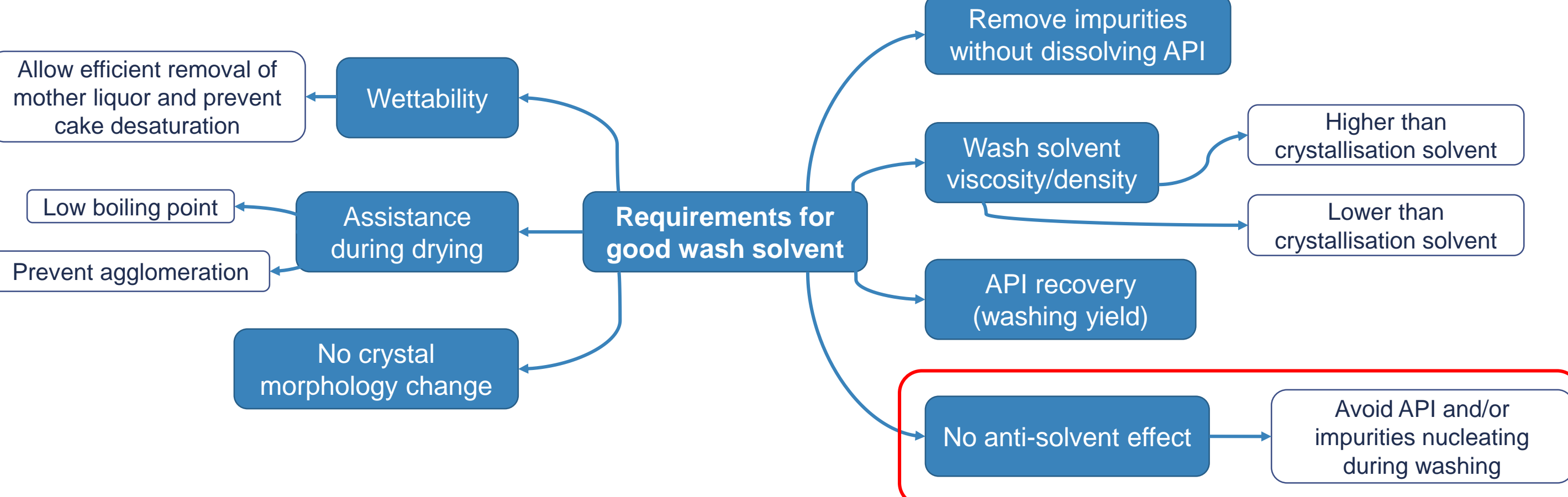


Introduction



Project Aim & Objective

A wash solvent guide is designed to look at various important factors while selecting a wash solvent:

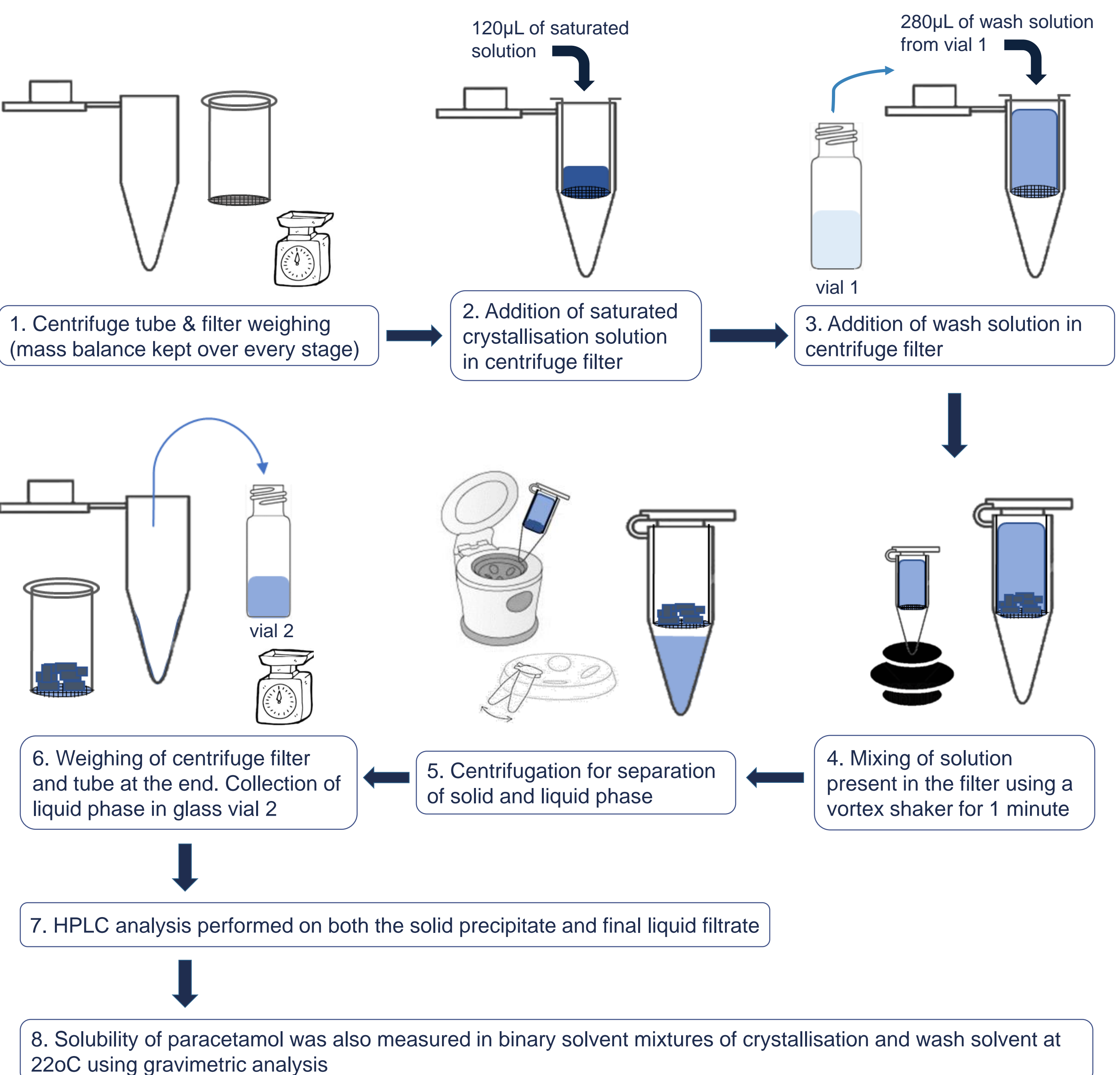


This project looks at developing a screening methodology to quantitatively analyse the propensity for precipitation of API and its impurities during the washing process.

Materials & Method

- This analysis is conducted on paracetamol crystallised from three different crystallisation solvents; ethanol, isopropanol and isoamyl alcohol
- Three wash solvents are evaluated; heptane, acetonitrile and isopropyl acetate
- Saturated solution is prepared using paracetamol and two related impurities (at 2mol %); metacetamol & acetanilide
- For wash volume, different ratios of crystallisation and wash solvents are used; 90:10, 75:25, 50:50, 40:60, 30:70, 20:80, 10:90, 100% wash solvent (% by volumes)

Anti-solvent screening procedure:



Results

- Anti-solvent effect observed from previous 1ml glass vial procedure (where 300µL of saturated solution and 700 µL of wash solution is used):

Crystallisation Solvents	Wash Solvents	Heptane	Acetonitrile	Isopropyl acetate
		Ethanol	40-60% (v/v)	No nucleation
Isopropanol	40-60% (v/v)	No nucleation	0-100% (v/v)	
Isoamyl alcohol	20-80% (v/v)	No nucleation	No nucleation	

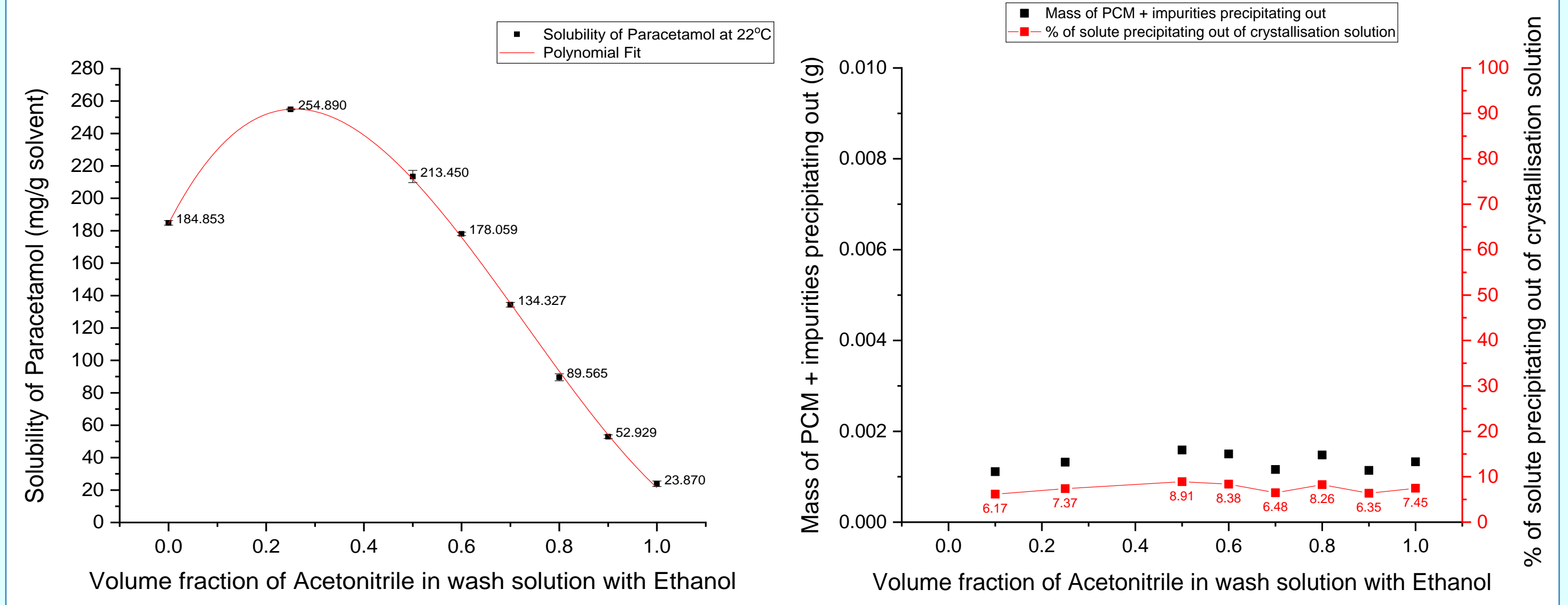
- Anti-solvent effect observed from centrifuge filter vial method (where 120 µL of saturated solution and 280 µL of wash solution is used):

Crystallisation Solvents	Wash Solvents	Heptane	Acetonitrile	Isopropyl acetate
		Ethanol	30-70% (v/v)	No nucleation
Isopropanol	30-70% (v/v)	No nucleation	No nucleation	
Isoamyl alcohol	10-90% (v/v)	No nucleation	No nucleation	

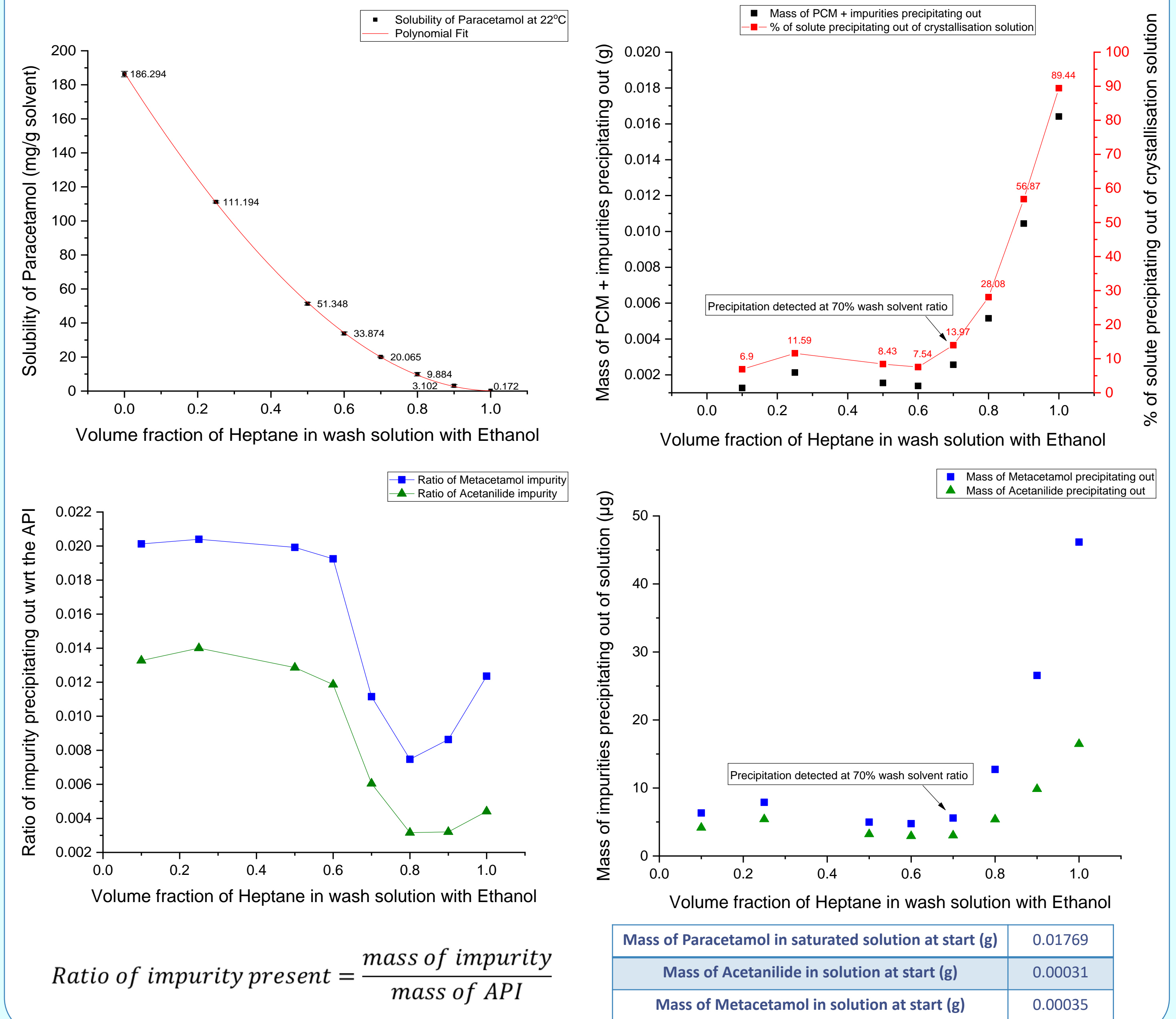
Delayed precipitation of solutes observed using the centrifuge vial method is due to the kinetics of nucleation (mixing and scale of the experiment?).

- Two distinct examples:**

- **Ethanol – Acetonitrile:** no anti-solvent effect was observed



- **Ethanol – Heptane:** anti-solvent effect was observed



Conclusion & Future Work

- Poorly designed washing process can result in uncontrolled crystallisation of both API and impurities, affecting final product quality
- Binary solvent mixture's solubility data (crystallisation & wash solvent) assist in developing washing strategy that prevents product dissolution & agglomeration
- Ethanol – Heptane system, washing should be carried out in steps (first wash: 40:60 ratio (cryst : wash solvent) of wash solution; final wash: pure heptane)
- In future, this work on mapped wash solvent composition boundaries will be used to explore the role of uncontrolled washing on product purity and agglomeration