



*"On-Demand Manufacturing of Pharmaceuticals"*

***End-to-End Integrated Continuous Manufacturing  
with Modular Unit Operations***

Salvatore Mascia

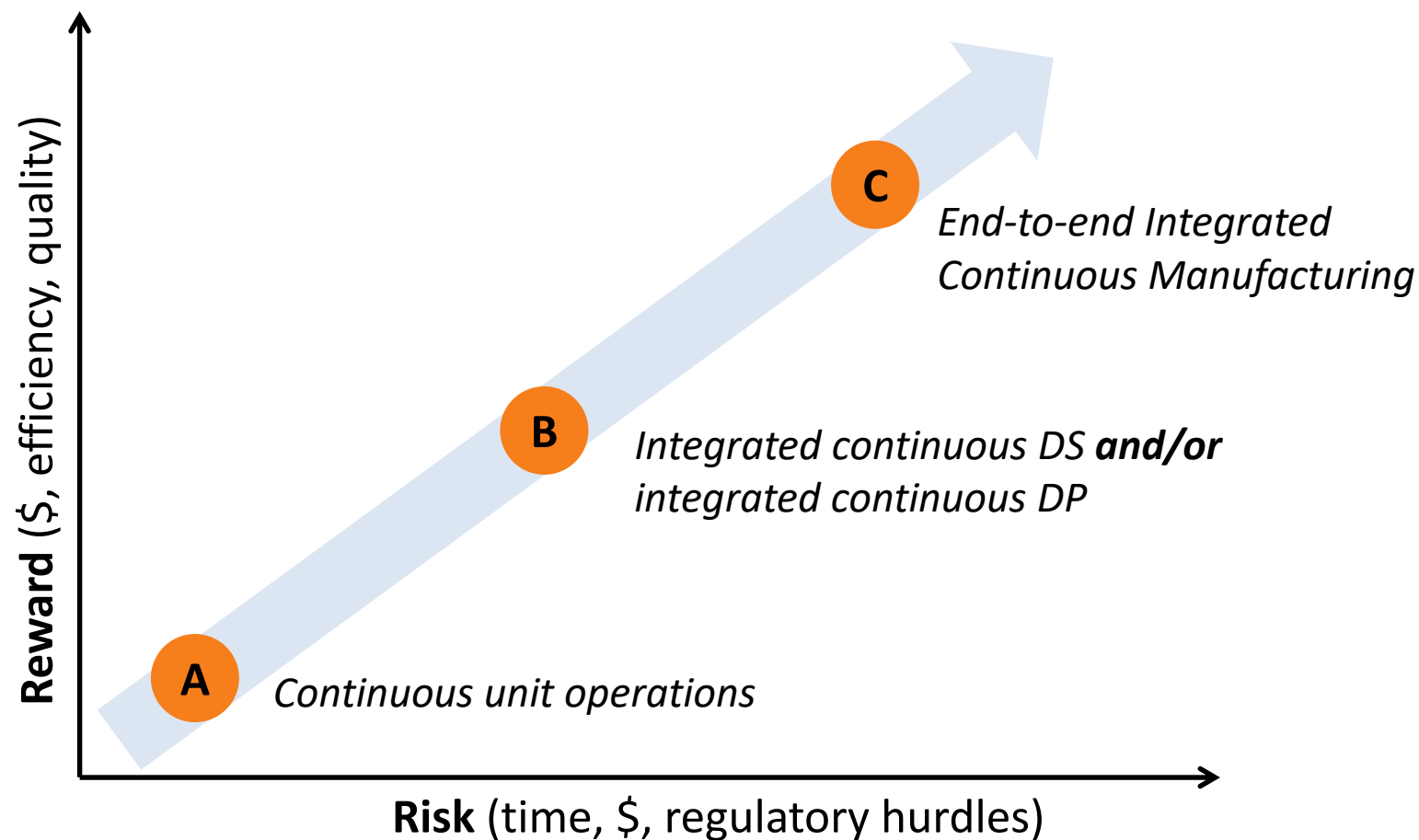
October 17, 2019



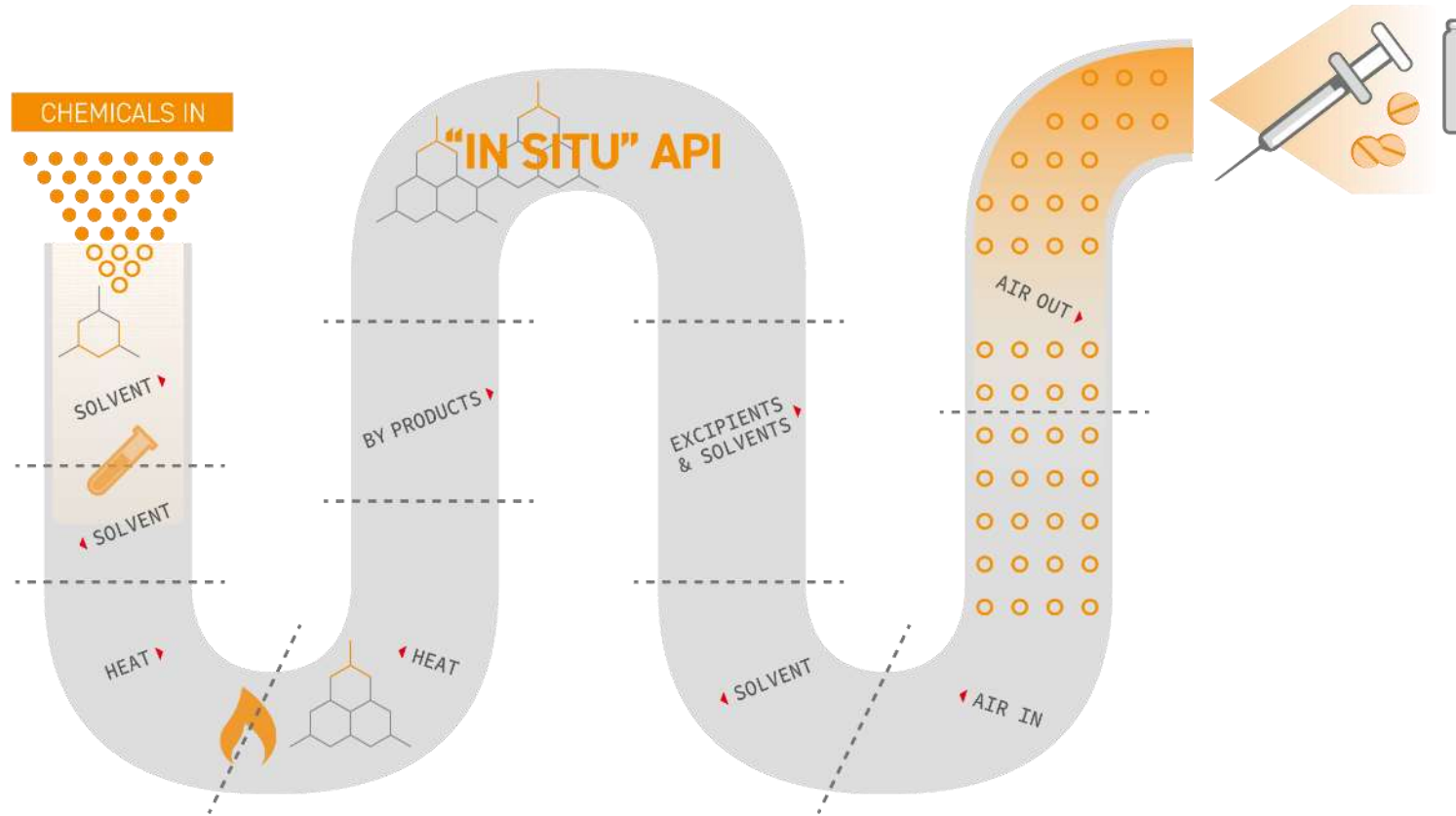
# Learning Objectives

- Integration is key in continuous manufacturing!
- Integration provides higher degree of control over product quality
- New technologies facilitate integration in continuous manufacturing

# Continuous Manufacturing Solutions: Matching Risk Tolerance with Reward

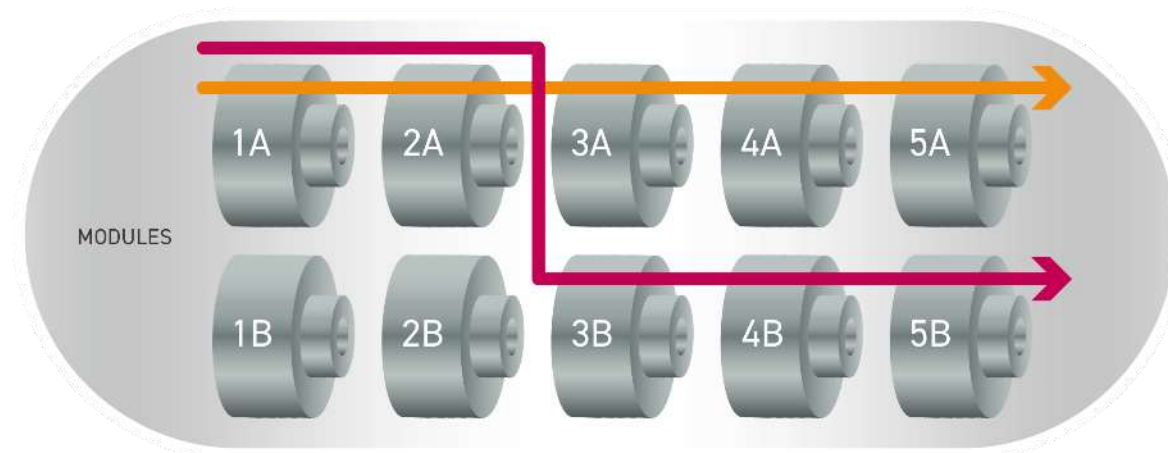
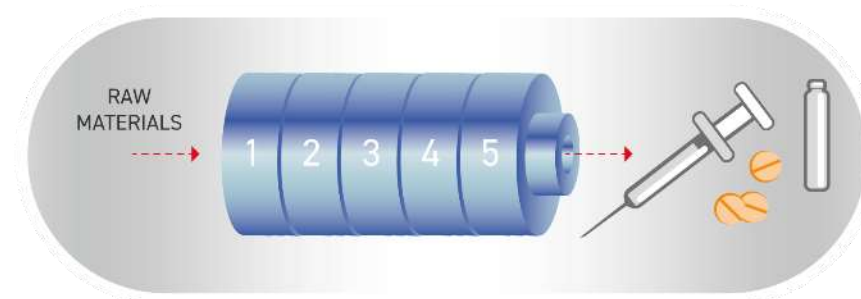
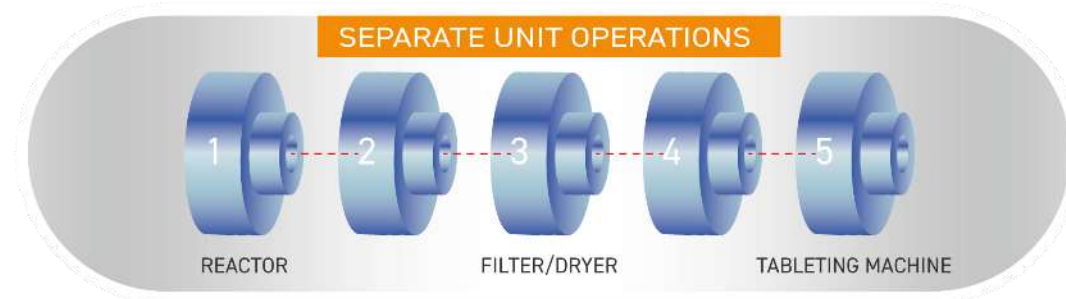


# Integrated Continuous Manufacturing (ICM)

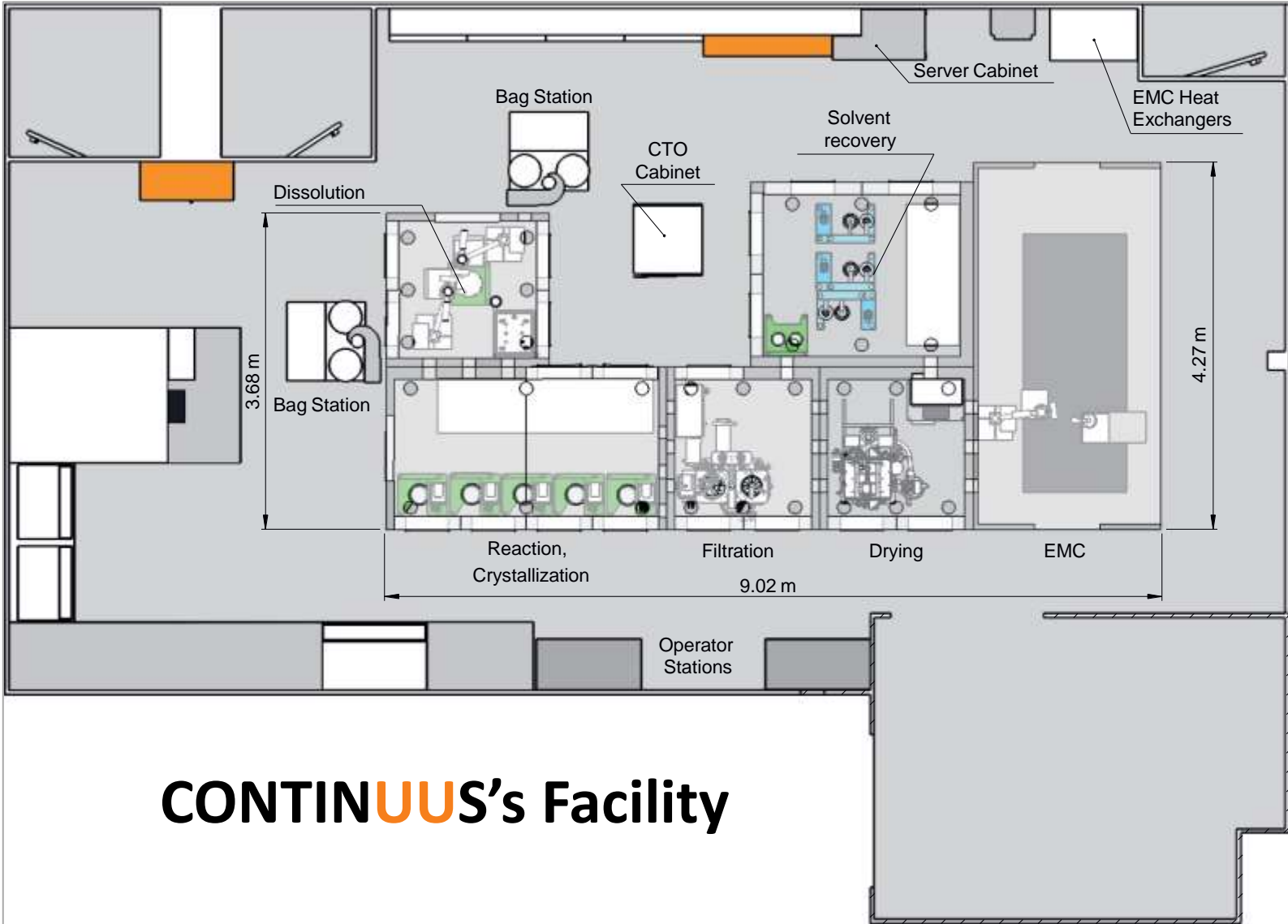


***Continuous Flow - End to End Integration - System Approach - Integrated Control Strategy***

# ICM: *How it works*

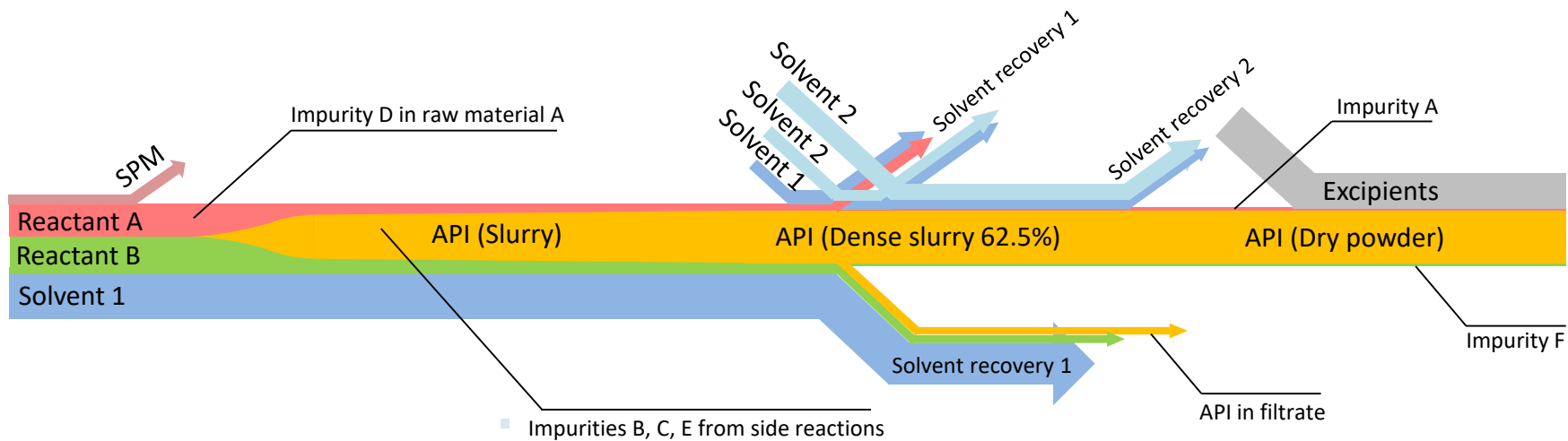
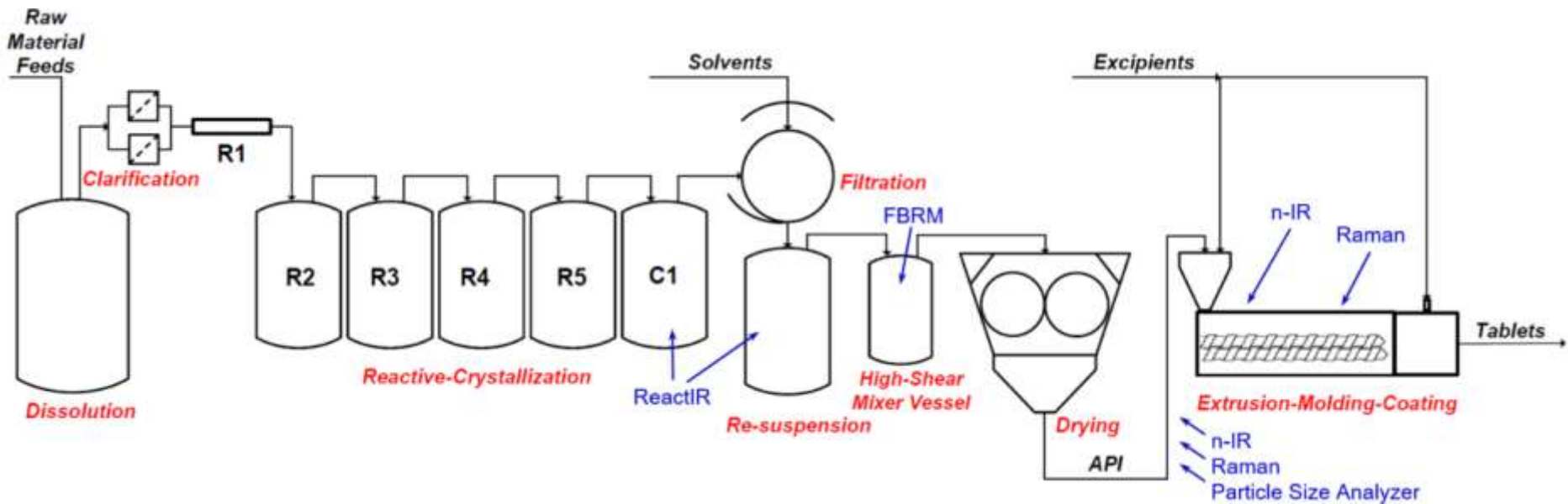


# ICM Facility Floor Plan

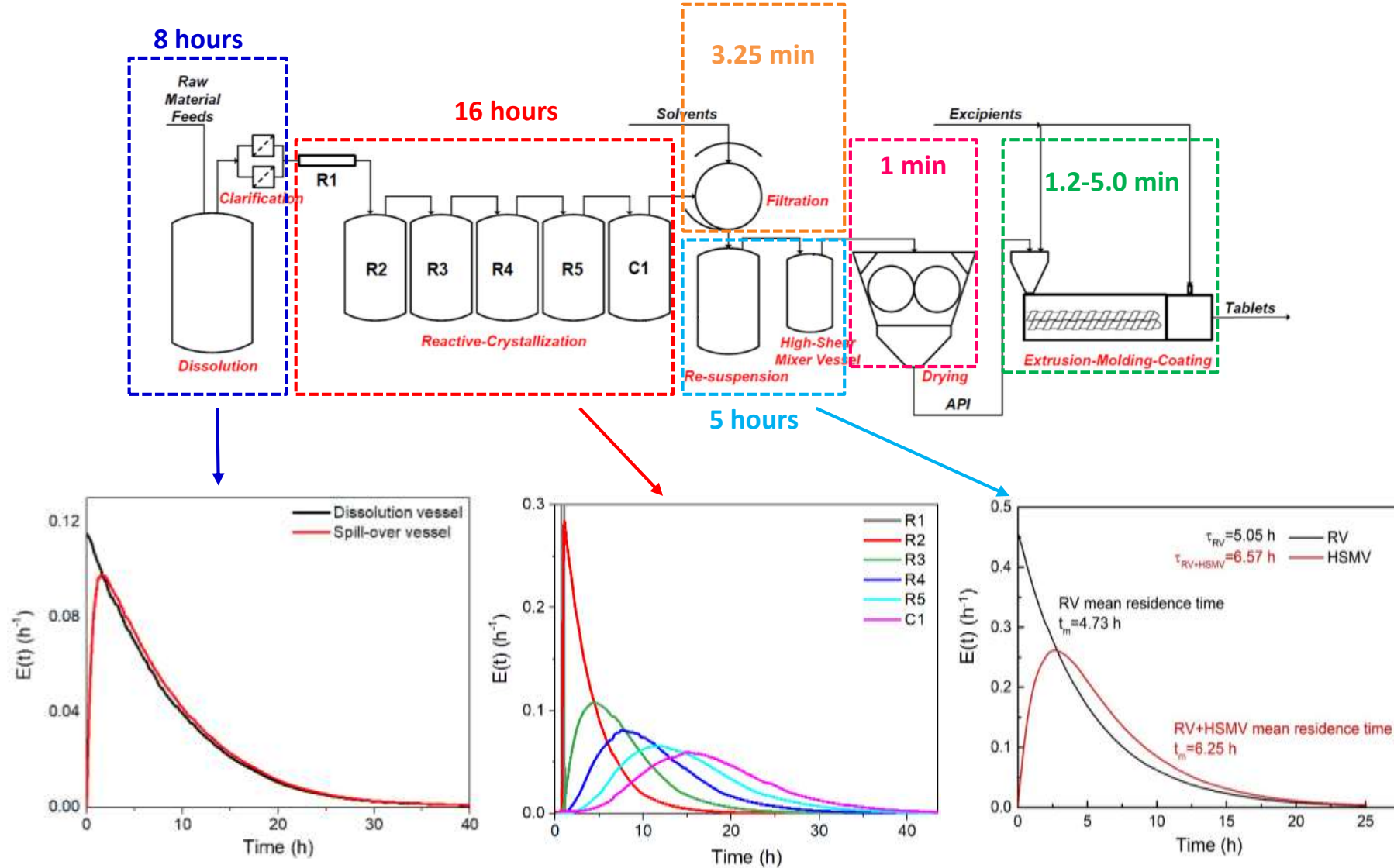


**CONTINUUS's Facility**

# Unit Operations and PATs – Overview

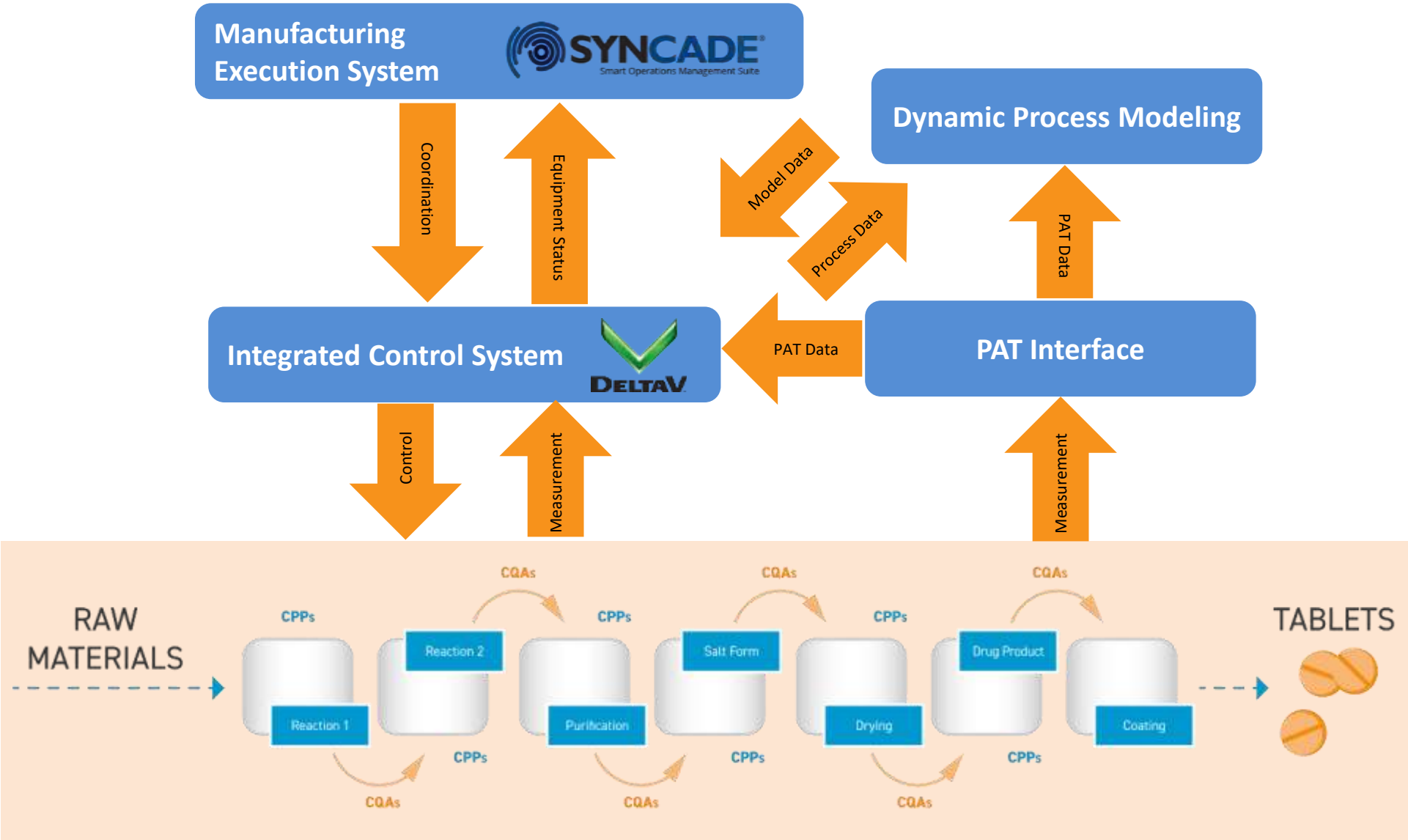


# RTD Overview: ~30 hrs end-to-end





# Control Architecture for ICM



# ICM Pilot Plant is Operational



**CONTINUUS ICM Pilot Plant**

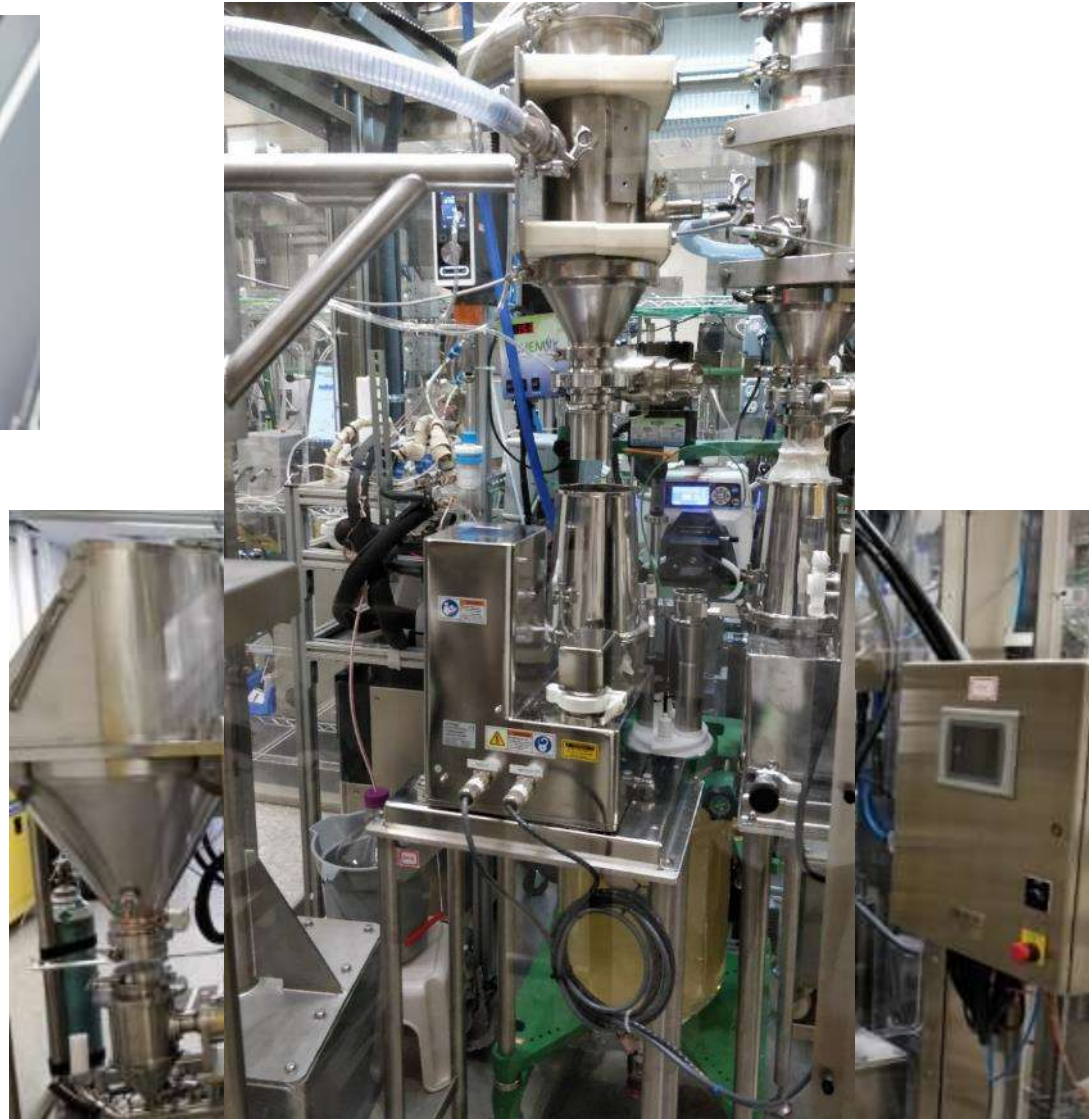
# ICM Pilot Plant is Operational

**CONTINUUS ICM Pilot Plant**

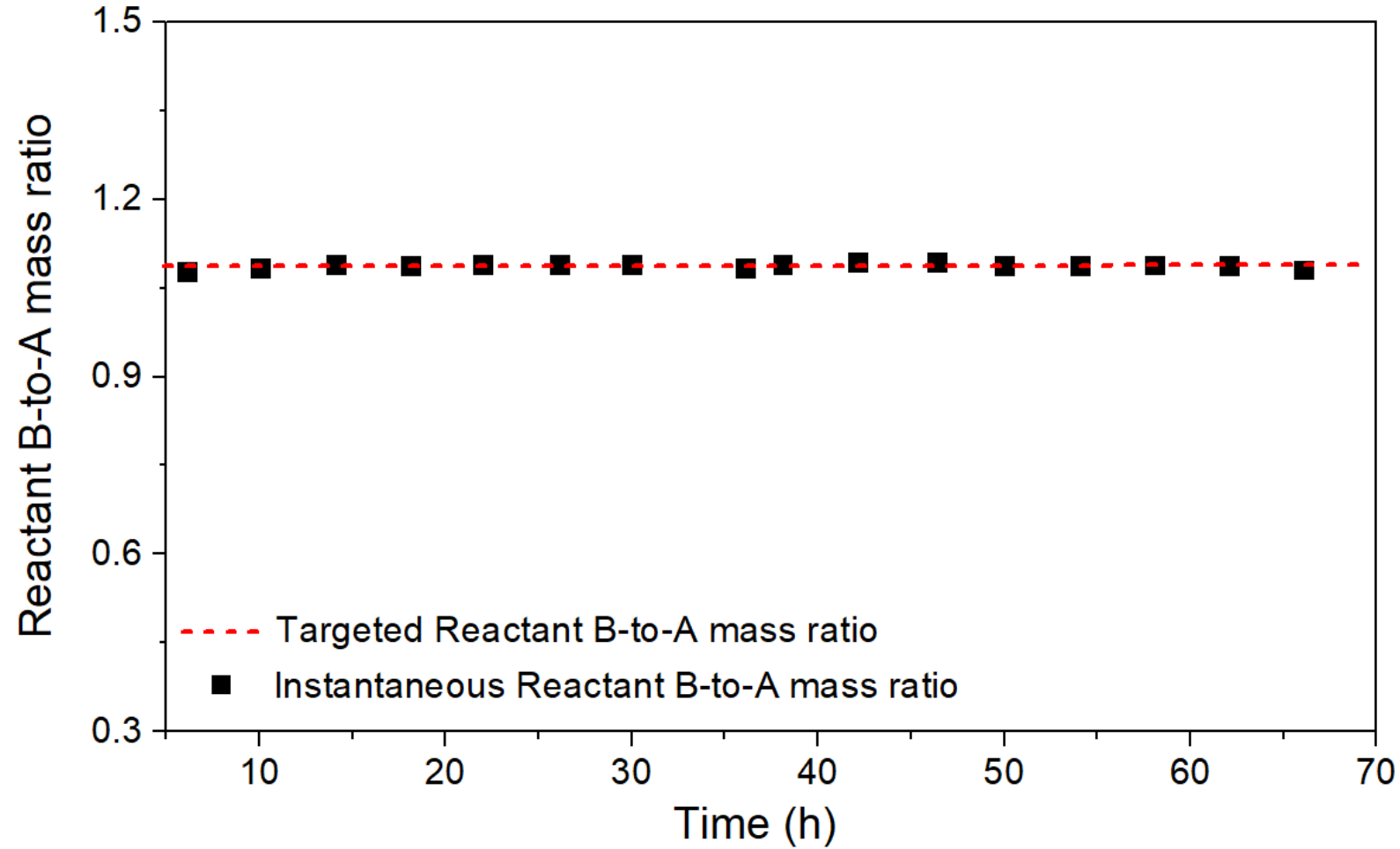
# Feeding & Dissolution of Raw Materials



Two Solid feeds: **Reactants A & B**  
One Liquid feed: **Solvent 1**

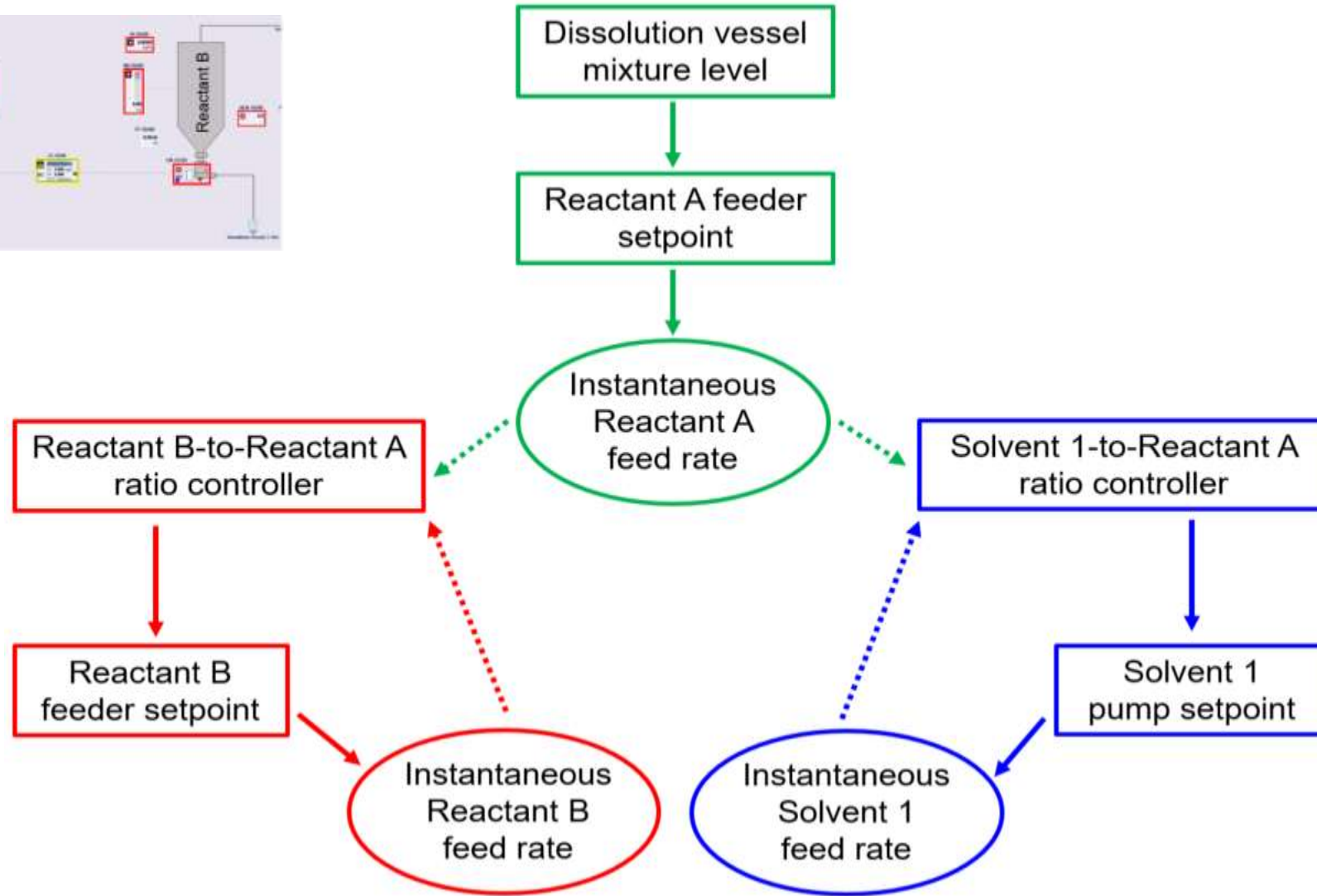
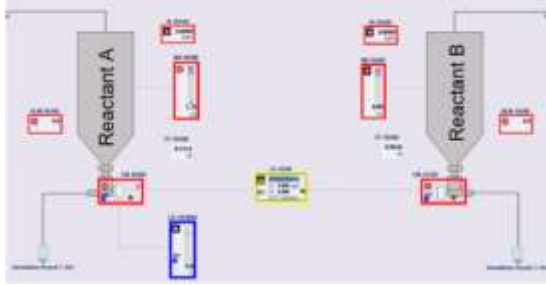


# Raw Material Feeds: *Example of CMA*

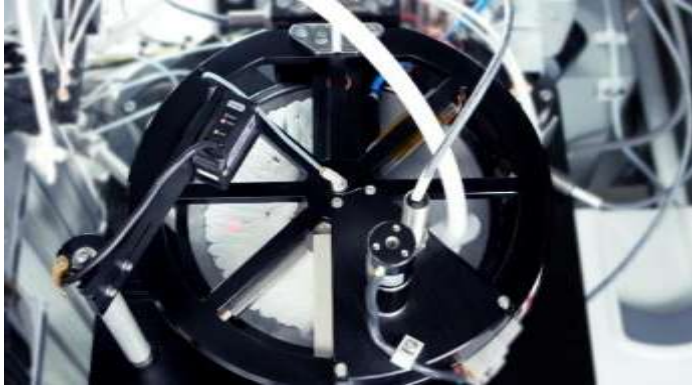




# Reactant A-Reactant B-Solvent Ratio Controller



# Continuous Filtration



*Filter plate top view*



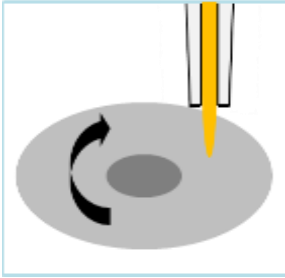
*Filter plate side view*



*Front view with resuspension and  
high-shear mixer vessel*

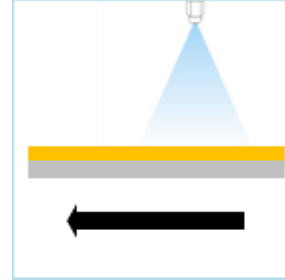
# Continuous Filtration: *Operations*

1



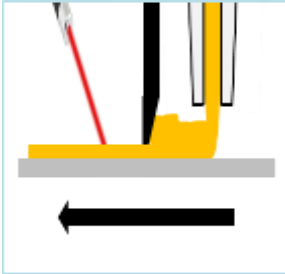
**DELIVERY OF SLURRY**

4



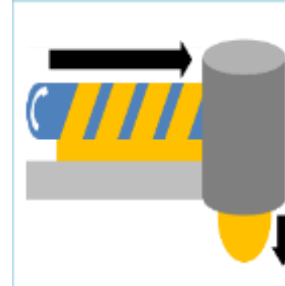
**WASHING OF WET CAKE  
(Solvent 1 + 2)**

2



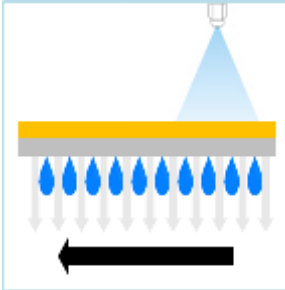
**DISTRIBUTION OF SLURRY**

5



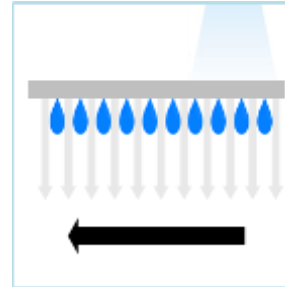
**COLLECTION OF WET CAKE**

3



**VACUUM FILTRATION**

6

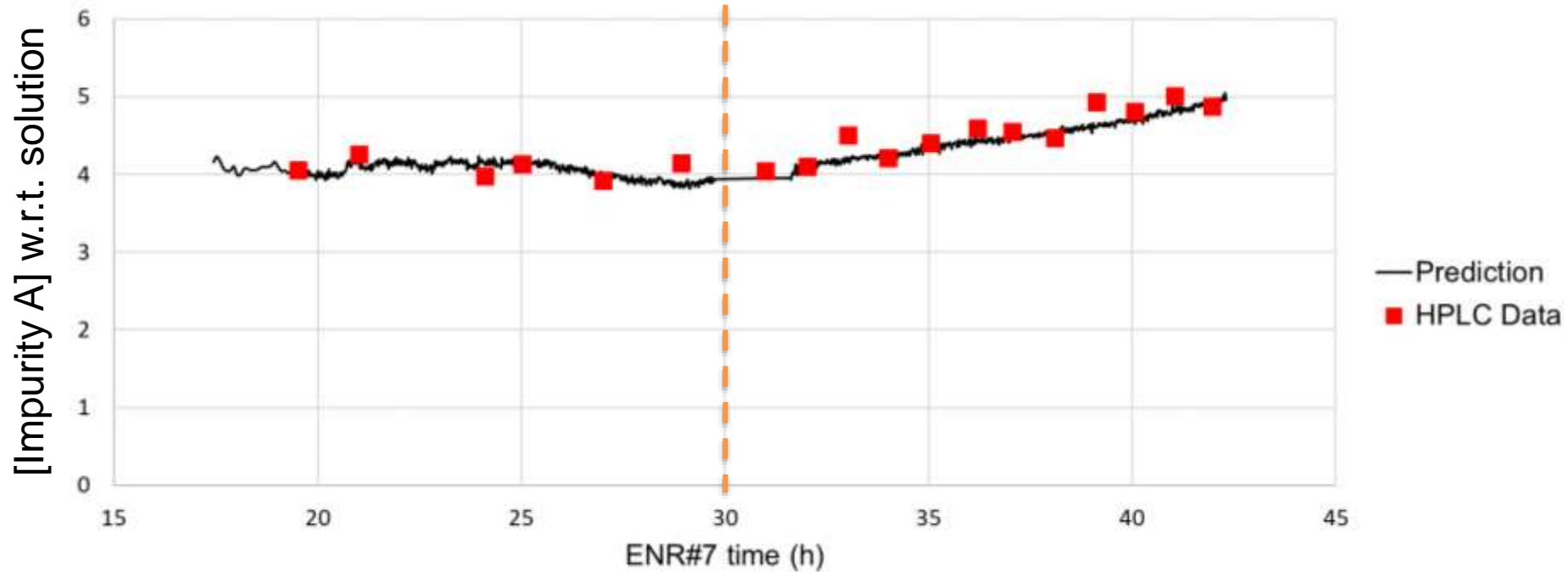


**CLEANING OF FILTER PLATE  
(Solvent 1)**



# Pre-Filtration PATs: In-line Quality with *ReactIR*

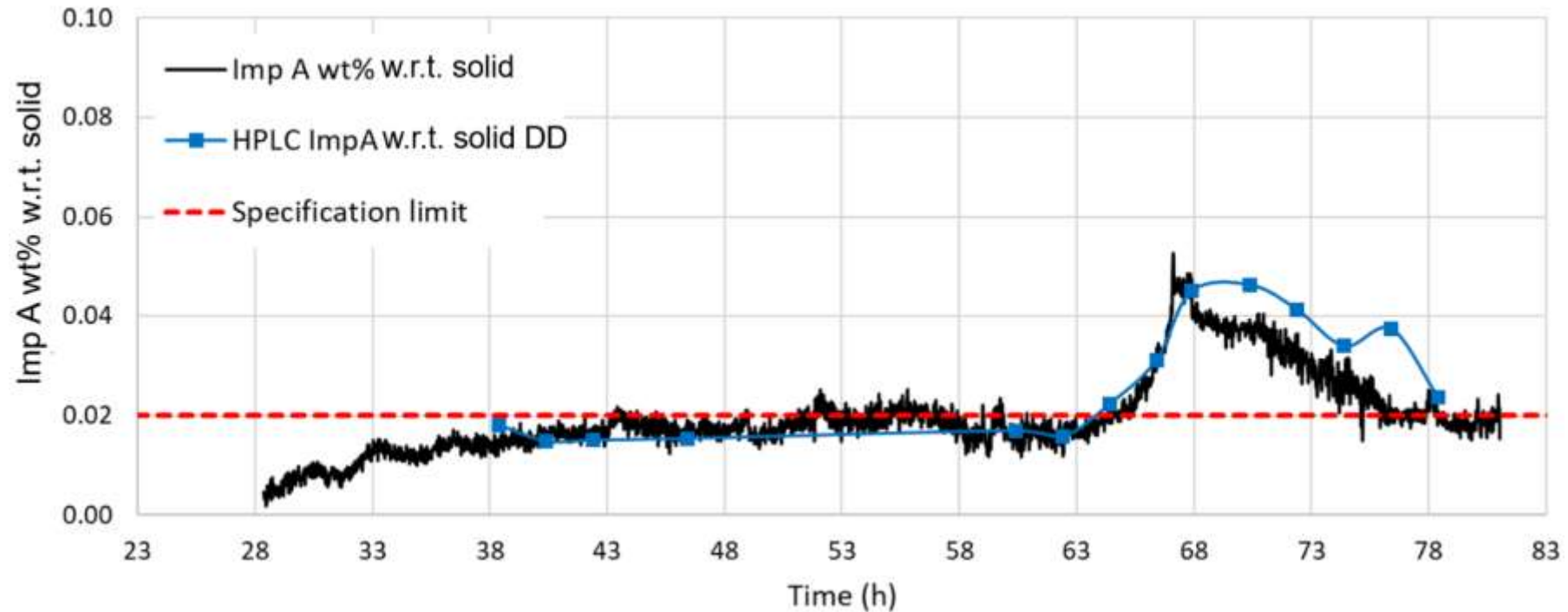
[Impurity A] prediction in crystallizer vs HPLC results



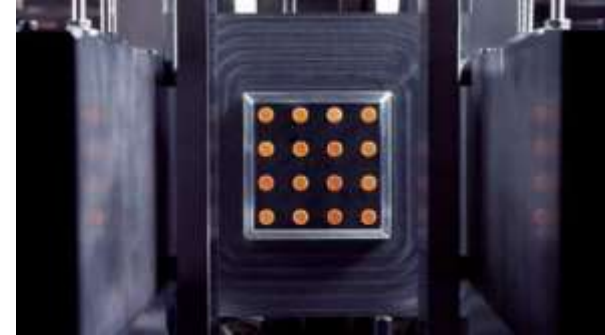
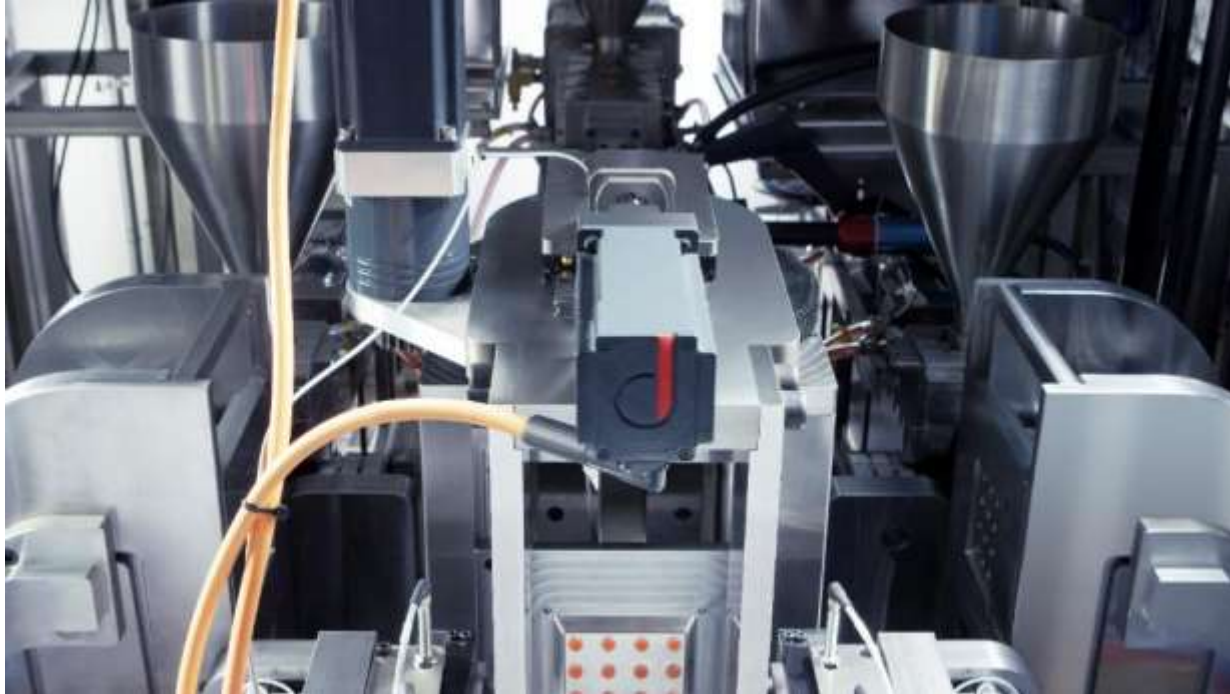
- Constant [Imp A] from 17 h to 30 h
- Increase of [Imp A] from 30 h to 42 h due to lower Reactant B feed to the process

# Post-Filtration PATs: In-line Quality with *ReactIR*

[Impurity A] prediction in resuspension vessel vs HPLC results in dry API



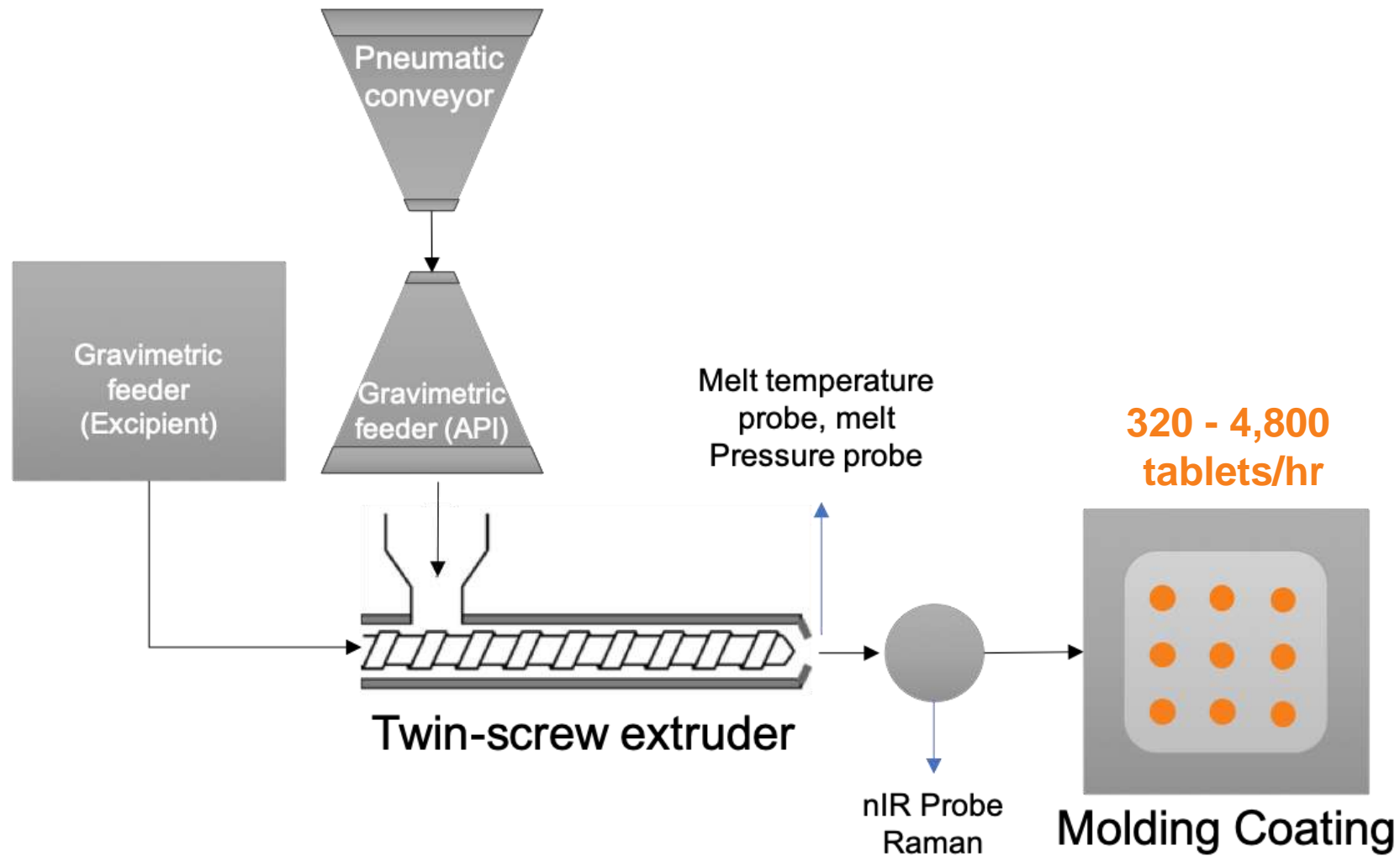
# Extrusion-Molding-Coating (EMC)



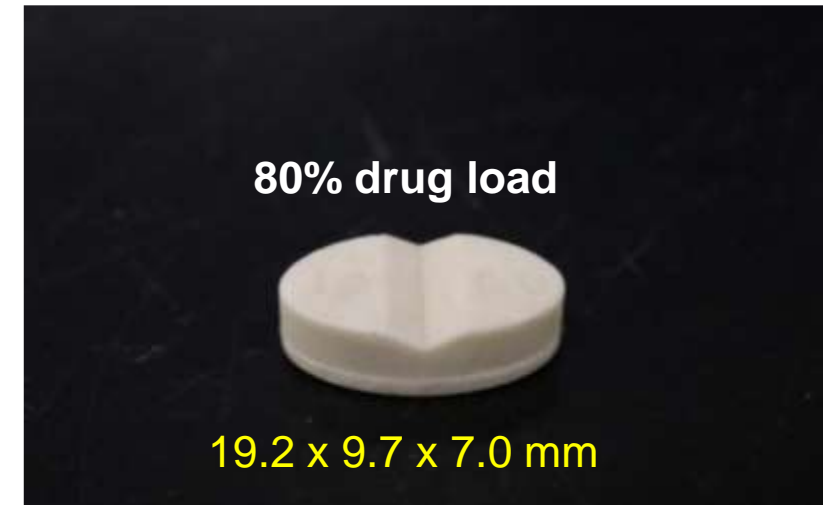
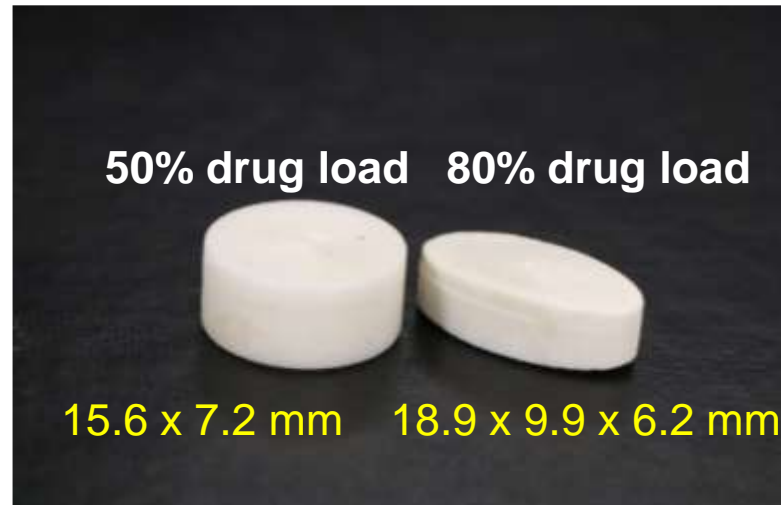
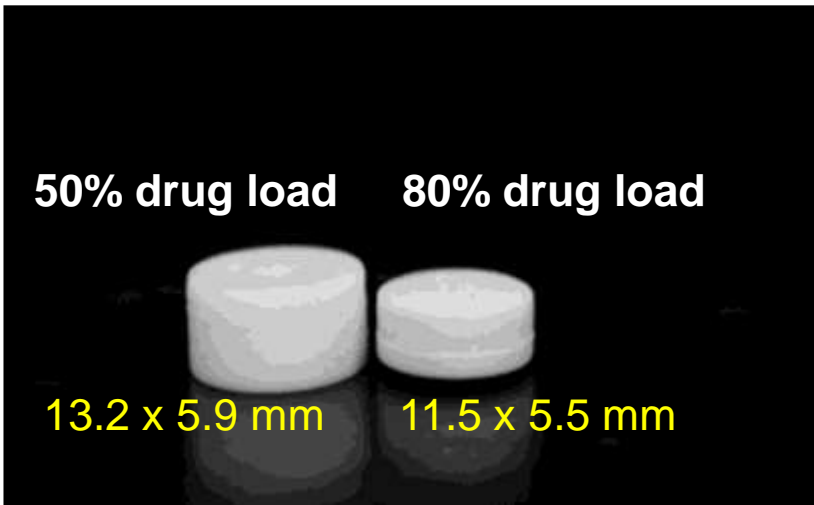
***Three-in-one drug product  
manufacturing***



# EMC: *Schematic*



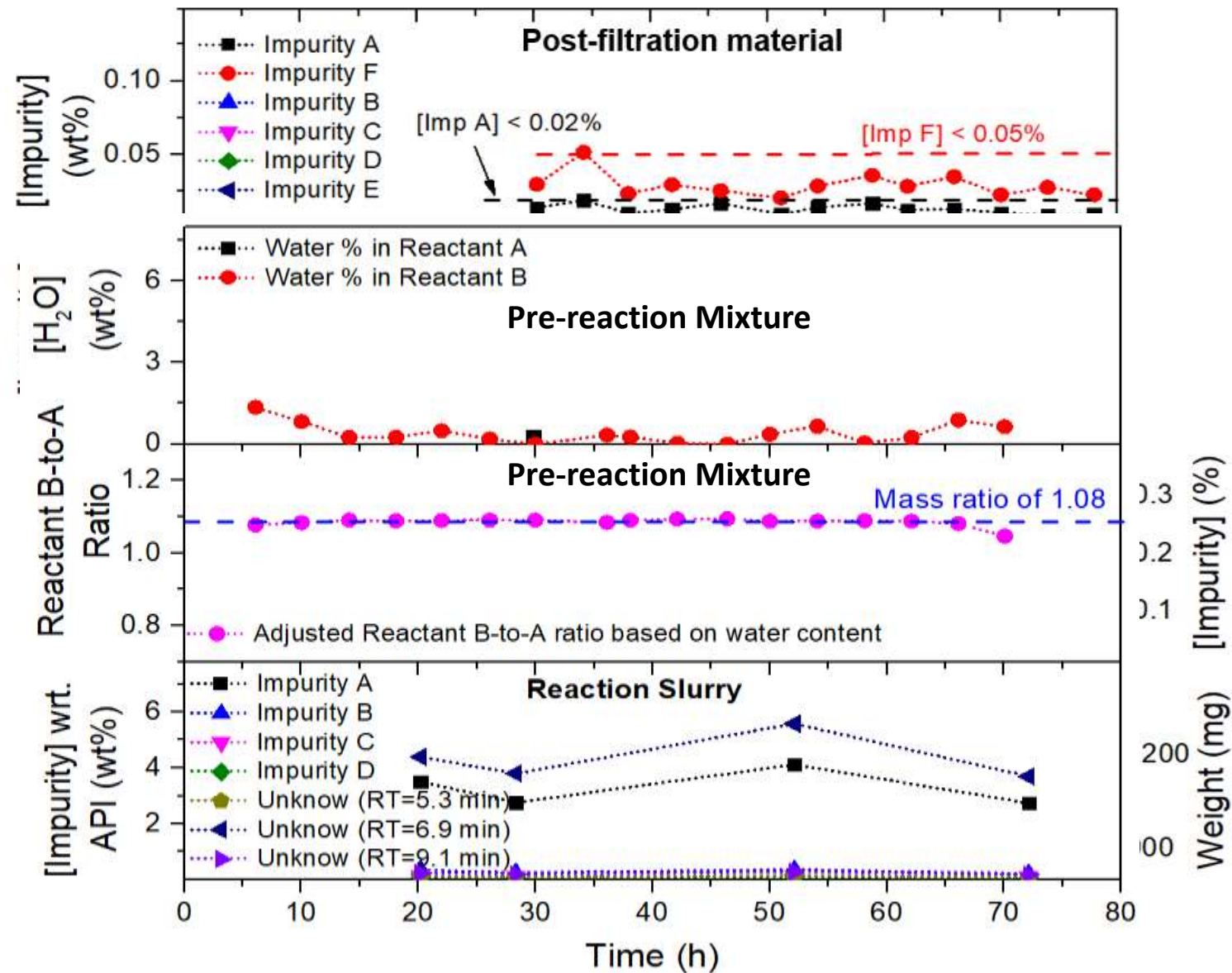
- We processed and obtained tablets of 3 different dosage strengths ✓



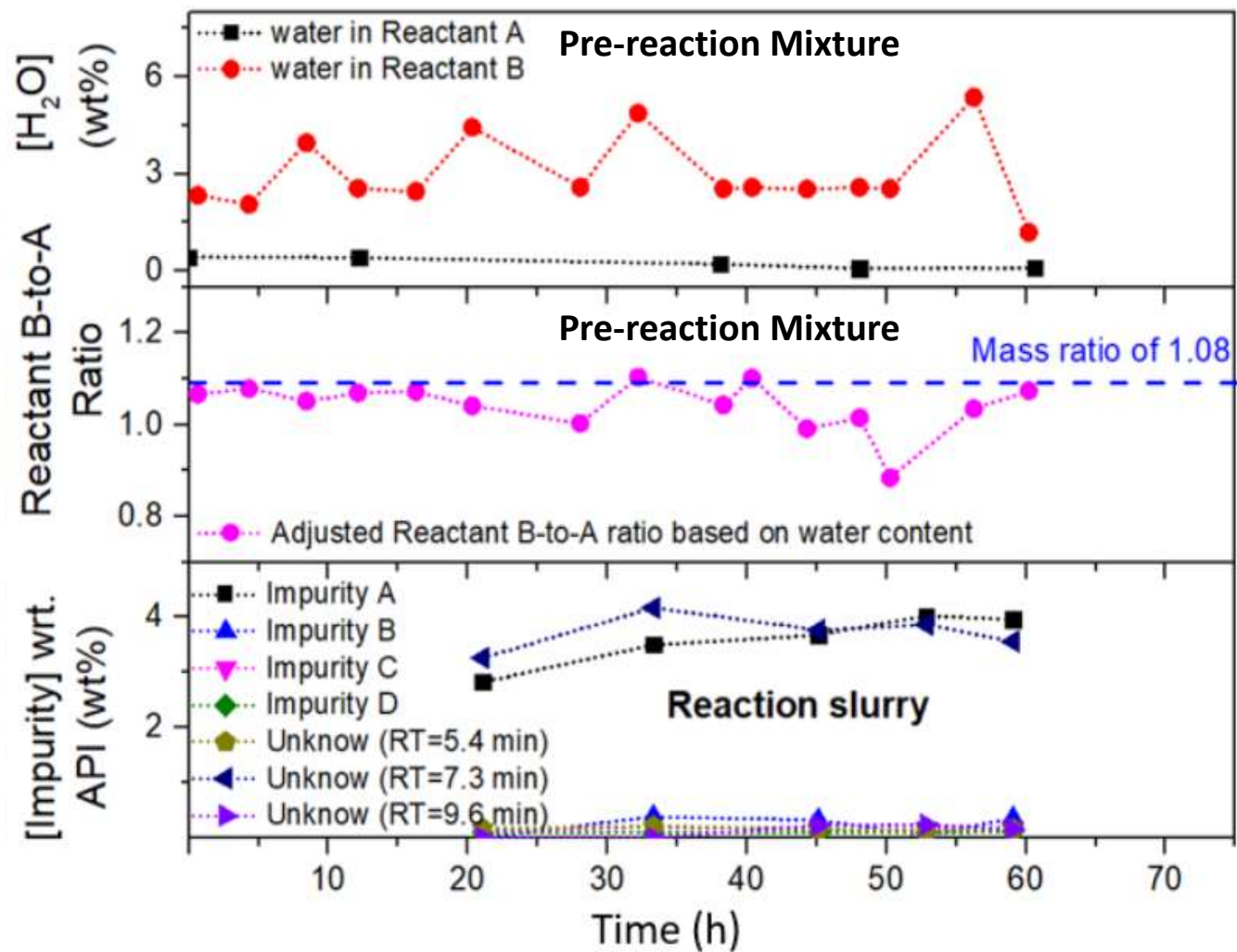
*EMC based tablets with different dosage strengths*



# Integration Results from End-to-End Runs



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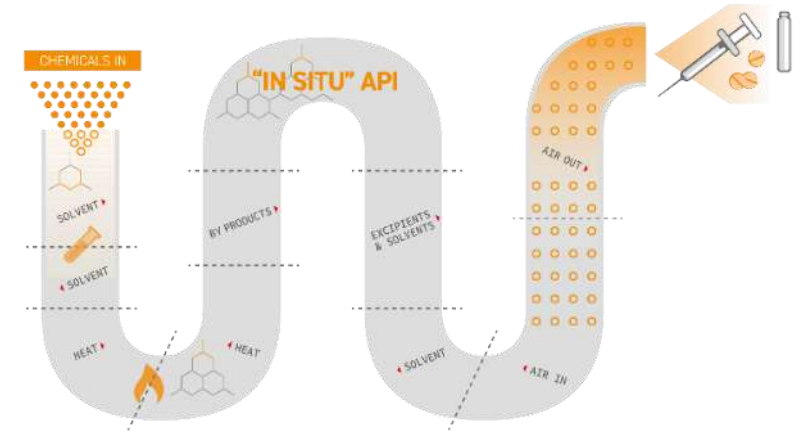
# Conclusion

## Advantages of ICM

- Fully automated process with built-in quality (higher quality assurance)
- Very fast production lead time: RT ~ 30 h, with throughput up to 4,800 tablets/h
- Miniaturized plant with modular unit operations

## Learnings

- End-to-end integrated continuous manufacturing is advantageous and with product “on-demand”
- Integration = higher degree of control over quality
- New process technologies capture full benefits of continuous manufacturing





*Thank you!*  
*The CONTINUUS Pharmaceuticals Team*

[www.continuouspharma.com](http://www.continuouspharma.com)  
[info@continuouspharma.com](mailto:info@continuouspharma.com)