

From Prediction to Performance: ML-Guided Co-Amorphous Rifampicin Formulations for Inhalation Therapy in Tuberculosis

12/12/2025

Sarah Zellnitz-Neugebauer

Background

Lung disease

- Asthma
- Chronically obstructive pulmonary disease (COPD)
- Tuberculosis (TB)

Challenge

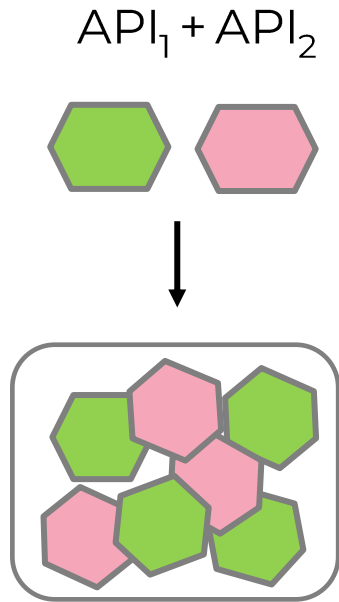
- Multidrug therapy
- Application of multiple different commercial products
- Poor patient compliance

Goal: Novel co-processed API combinations

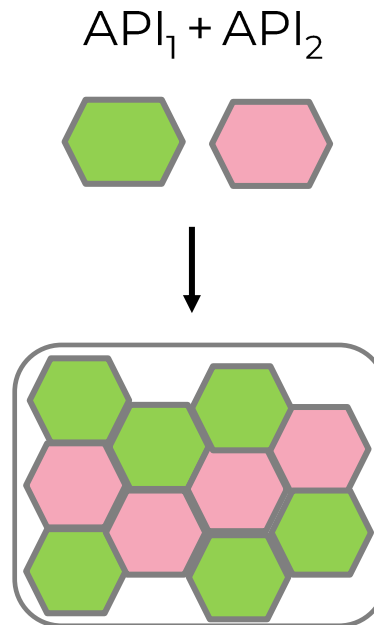
- Reduce dose variability and number of different inhalers/products to use
- Improve patient compliance
- Leaner and more economic manufacturing

Co-processed systems

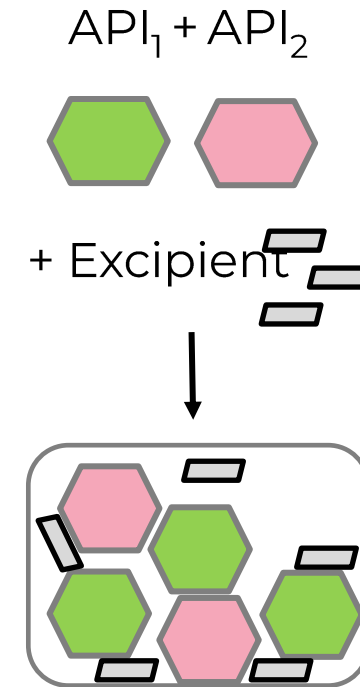
Co-amorphous



Co-crystals

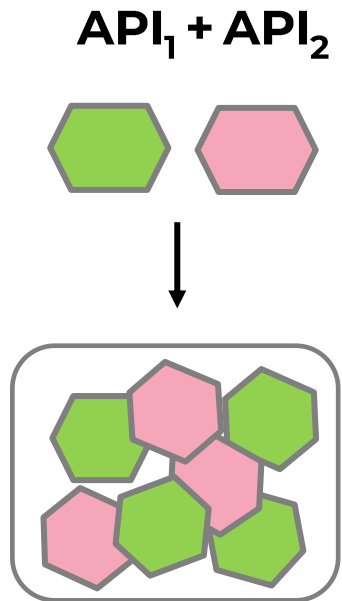


Ternary systems

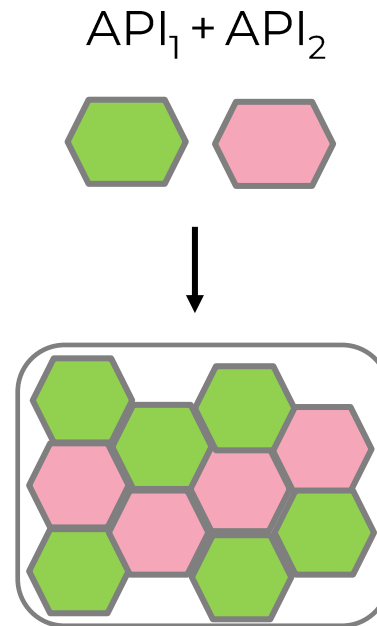


Co-processed systems

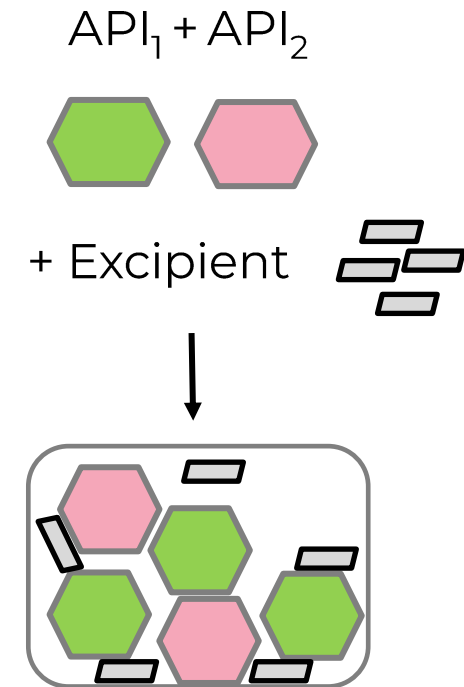
Co-amorphous



Co-crystals

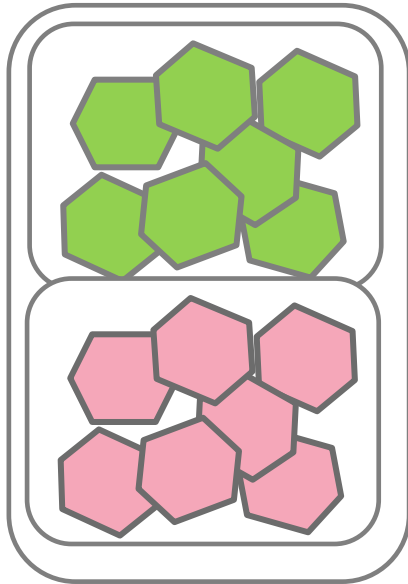


Ternary systems



Amorphous systems

Amorphous blend



Advantages



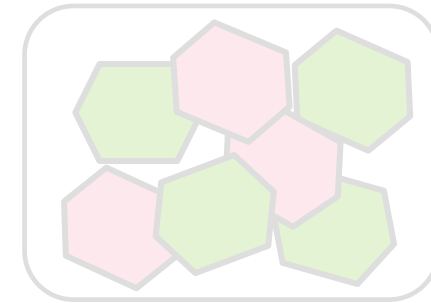
- ↑ Solubility
- ↑ Dissolution rate
- ↑ Bioavailability

Challenges



- Instability
- Recrystallization

Co-amorphous system (COAMS)



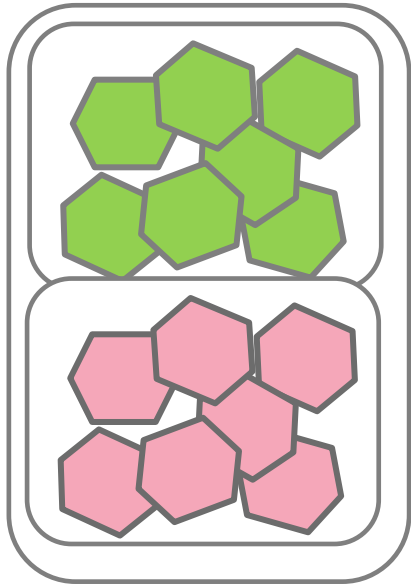
Advantages



- Homogenous single-phase system
- Stabilized through co-former

Amorphous systems

Amorphous blend



Advantages



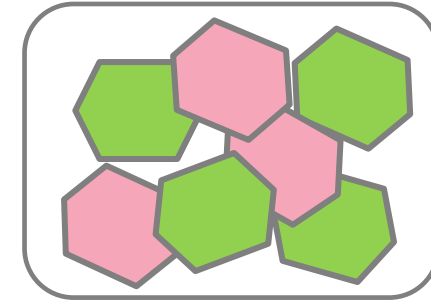
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Co-amorphous system (COAMS)



Advantages



- Homogenous single-phase system
- Stabilized through co-former



Prediction of COAMS

Challenge

- Co-former selection is difficult
- Various mechanisms of COAMS stabilization
- Experimental screening takes time and cost
- Very few modeling approaches in the literature

GOAL Simple ML screening tool to speed up the development and save time and cost during experimental screening

Data
Collection

Molecular
Descriptor
Selection

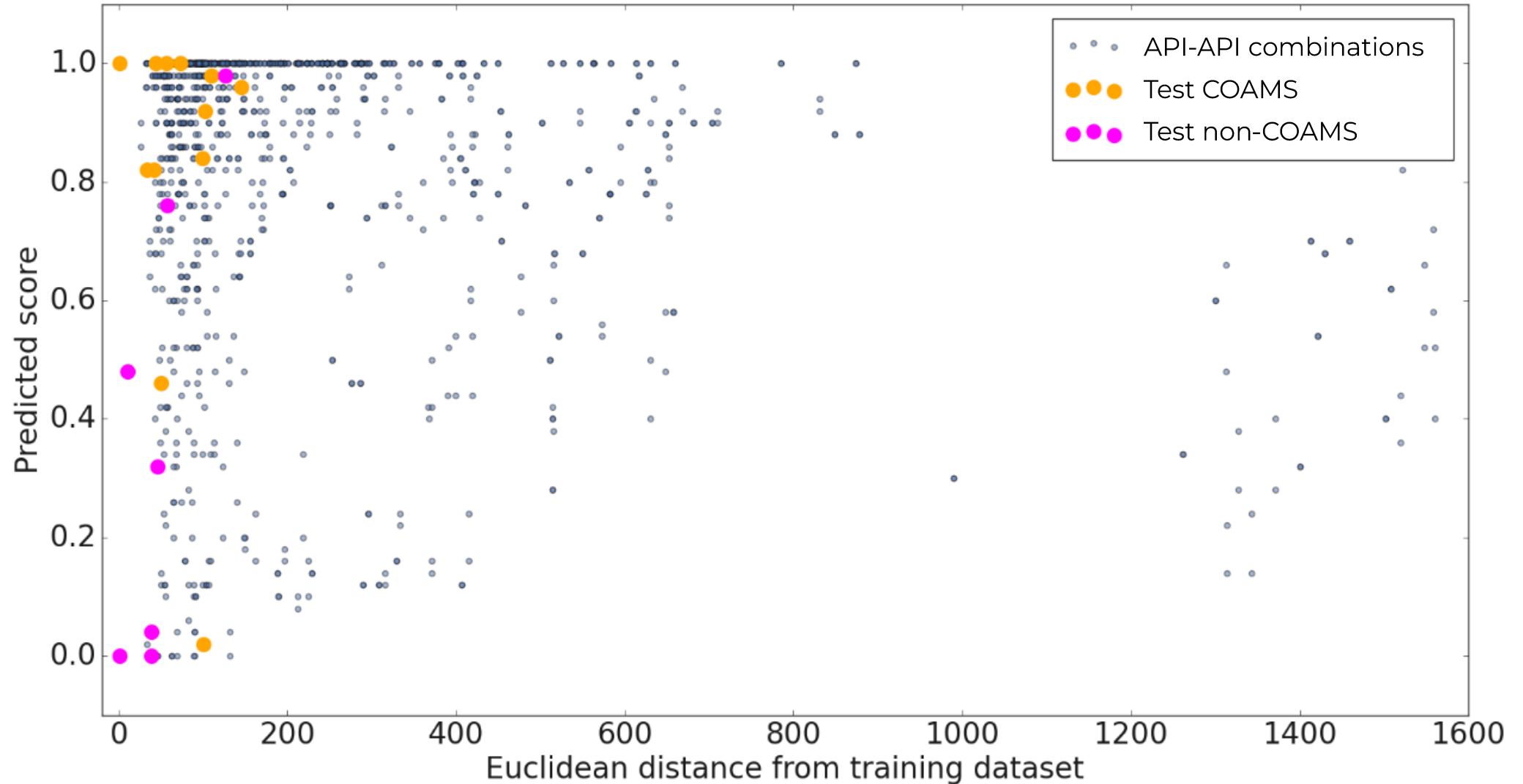
Input
Feature
Calculation

Model
Training &
Validation

Application
to „New
Systems“

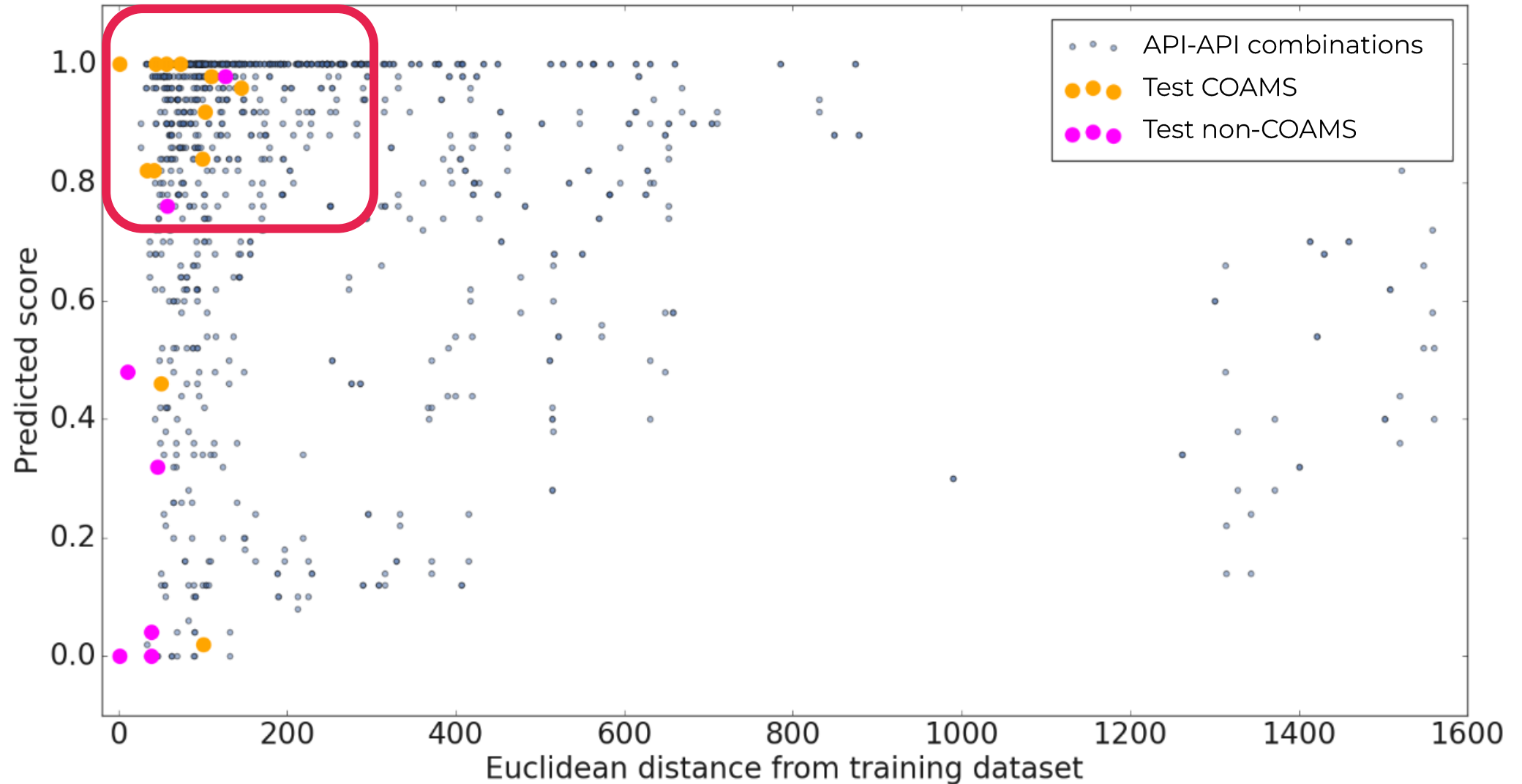
Model
Prediction

Application to Novel Systems



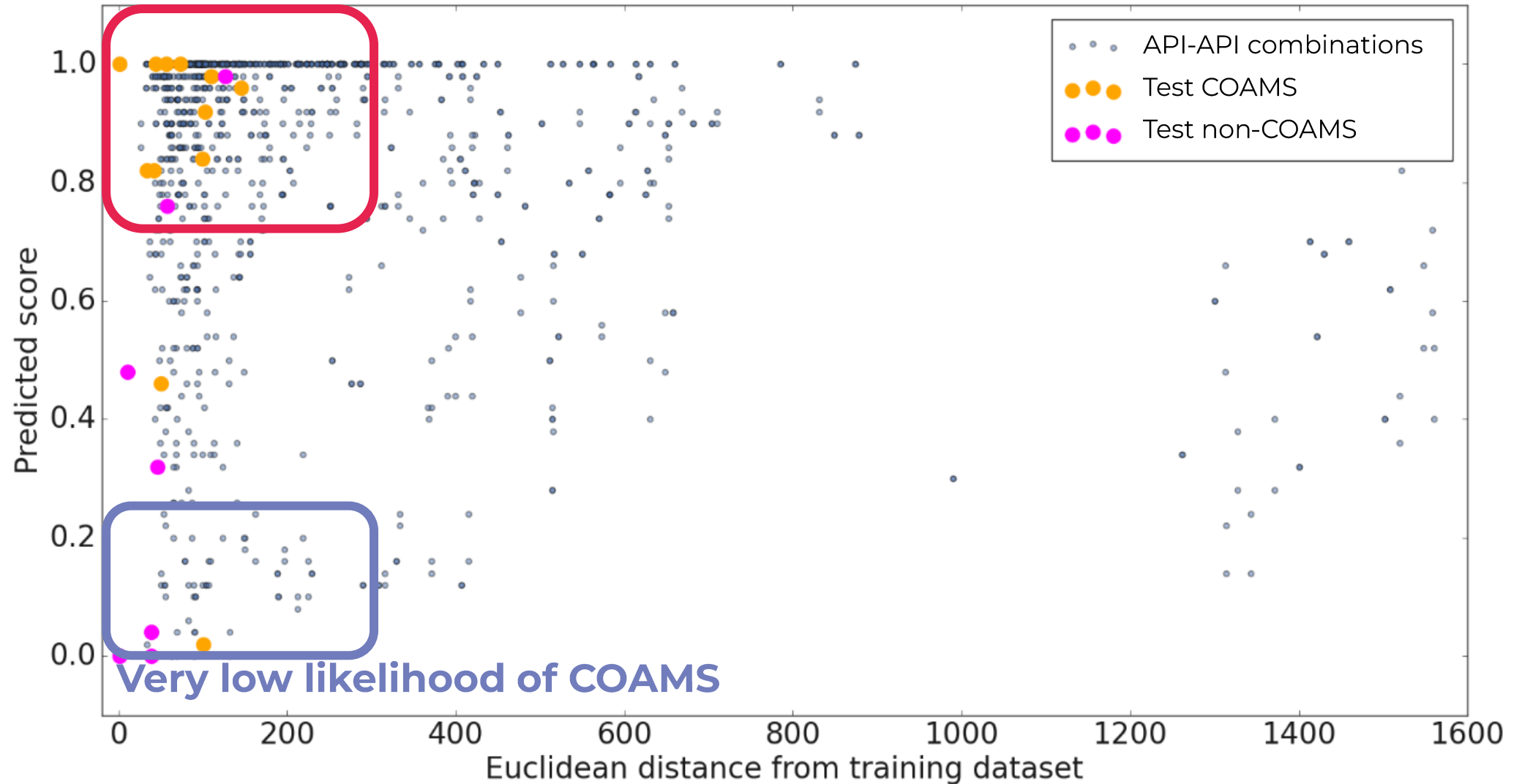
Application to Novel Systems

High likelihood of COAMS



Application to Novel Systems

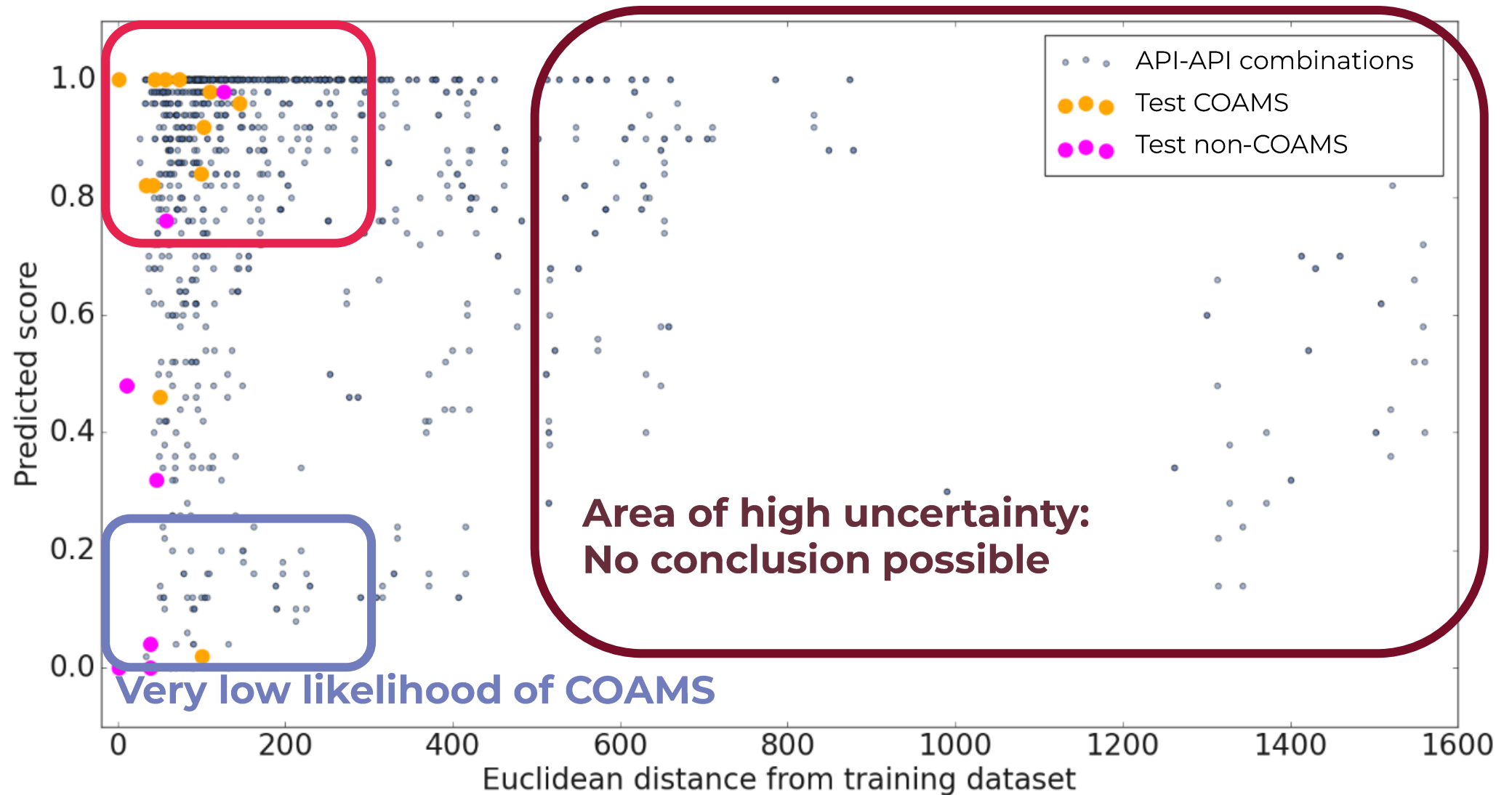
High likelihood of COAMS



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Application to Novel Systems

High likelihood of COAMS



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COAMS for tuberculosis (TB) treatment

RIF-ETH

(Rifampicin) – (Ethambutol)

RIF-MOX

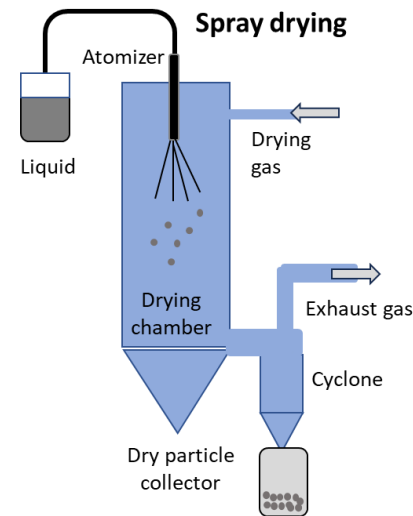
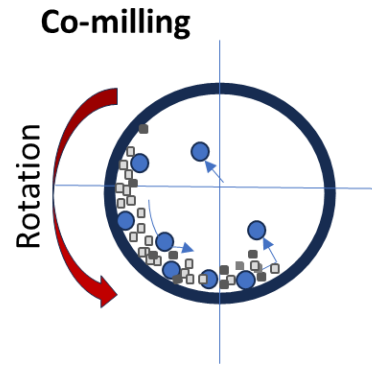
(Rifampicin) – (Moxifloxacin)

Molar ratio
predicted **1:1**

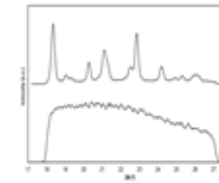
Therapeutic
molar ratios:

RIF:MOX **1:1.25**

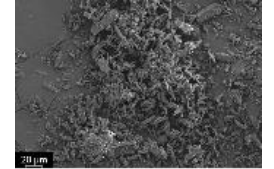
RIF:ETH **1:6**



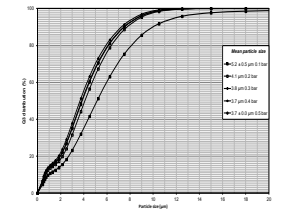
Particle Characterization



XRPD



SEM



Laser diffraction

Particle Performance



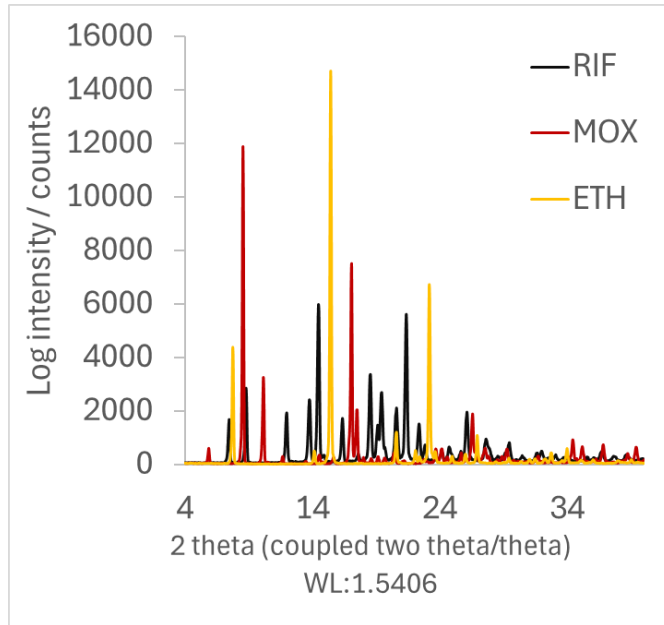
Cyclohaler® + FSI

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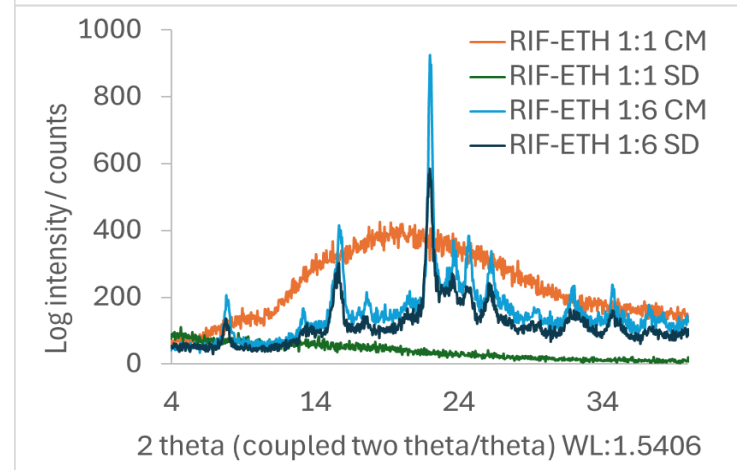
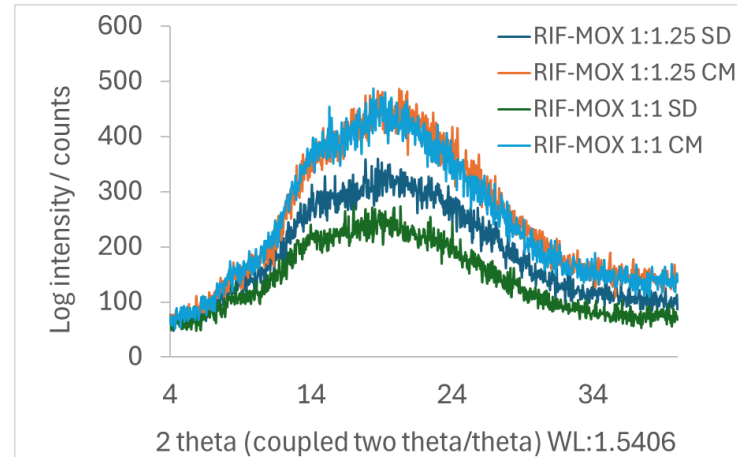
Particle properties

XRPD Analysis

Formulation 1



Starting materials



Formulation 2

- RIF, MOX and ETH crystalline bragg peaks.
- All RIF-MOX formulations show an amorphous halo, independent of molar ratio and preparation.
- RIF-ETH is only in a molar ratio of 1:1 amorphous.
- RIF-ETH 1:6 still shows crystalline peaks from ETH.

Conclusions

- ✓ A simple universal **screening tool** for the formation of COAMS was developed based on literature data and **machine learning** (ML).
- ✓ Experimental model validation (18 systems) - **experimental accuracy 72%**.
- ✓ Promising API-API combinations for TB treatment identified.
- ✓ Successful experimental validation for **molar ratios 1:1**.
- ✓ Deviation from molar ratio 1:1 to physiologic relevant ratio was only possible for RIF-MOX.





Article

Data-Driven Prediction of the Formation of Co-Amorphous Systems

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Article

Development of Co-Amorphous Systems for Inhalation Therapy—Part 1: From Model Prediction to Clinical Success [†]

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³ Institute of Electron Microscopy and Nanoanalysis (FELMI), Graz University of Technology, Steyrergasse 17, 8010 Graz, Austria; stefan.mitsche@felmi-zfe.at (S.M.); hartmuth.schroettnner@felmi-zfe.at (H.S.)
⁴ Graz Centre for Electron Microscopy (ZFE), Steyrergasse 17, 8010 Graz, Austria
* Correspondence: sarah.neugebauer@rcpe.at
[†] Part of this work was presented at the 5th European Conference on Pharmaceutics in Porto in March 2025.



Article

Development of Co-Amorphous Systems for Inhalation Therapy—Part 2: In Silico Guided Co-Amorphous Rifampicin–Moxifloxacin and –Ethambutol Formulations

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 Federal Ministry
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Climate Action, Environment,
Energy, Mobility,
Innovation and Technology

 Federal Ministry
Republic of Austria
Labour and Economy



This project would have been impossible without:



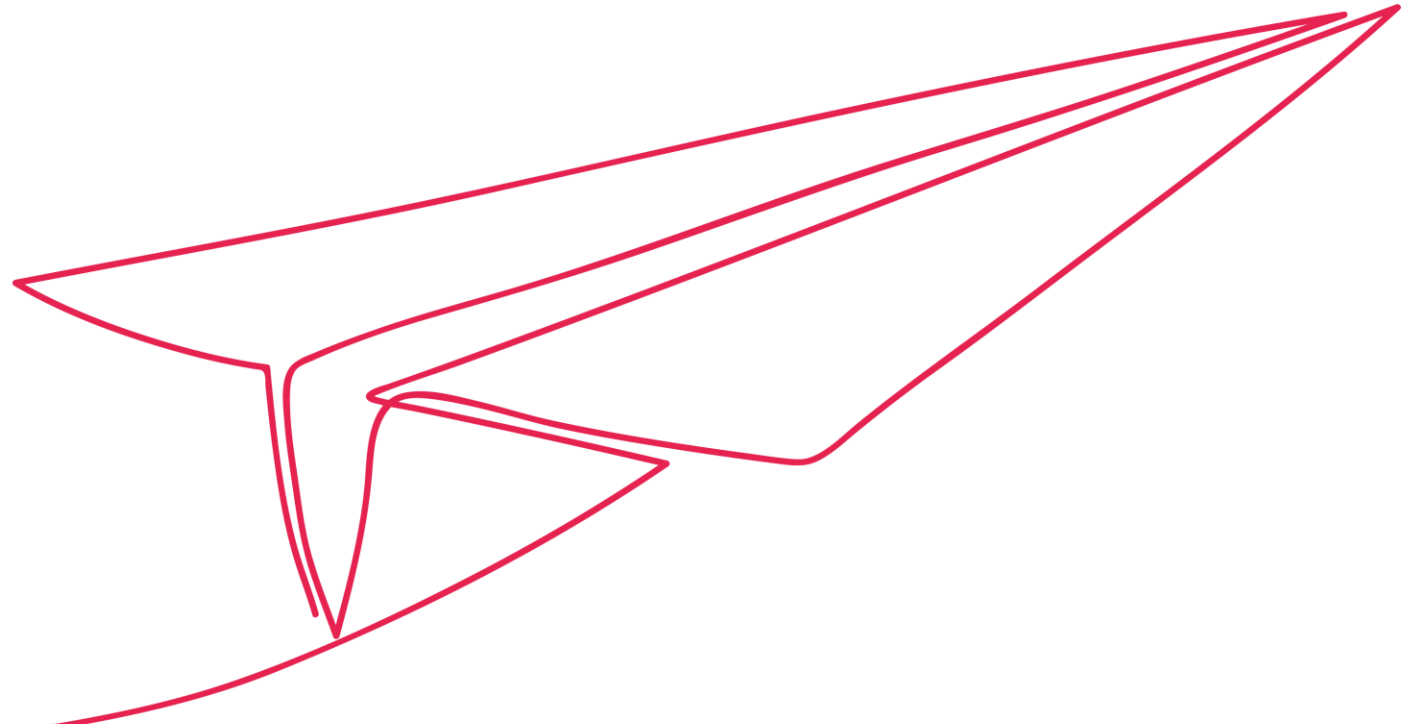
Hertha-Firnberg grant no.
T1105



Elisabeth Fink, Eleonore Fröhlich, Aurora Bordoni, Valerie Reinisch, Nila Mohsenzada, Stefan Mitsche, Laboratory and Analytical Team @ RCPE

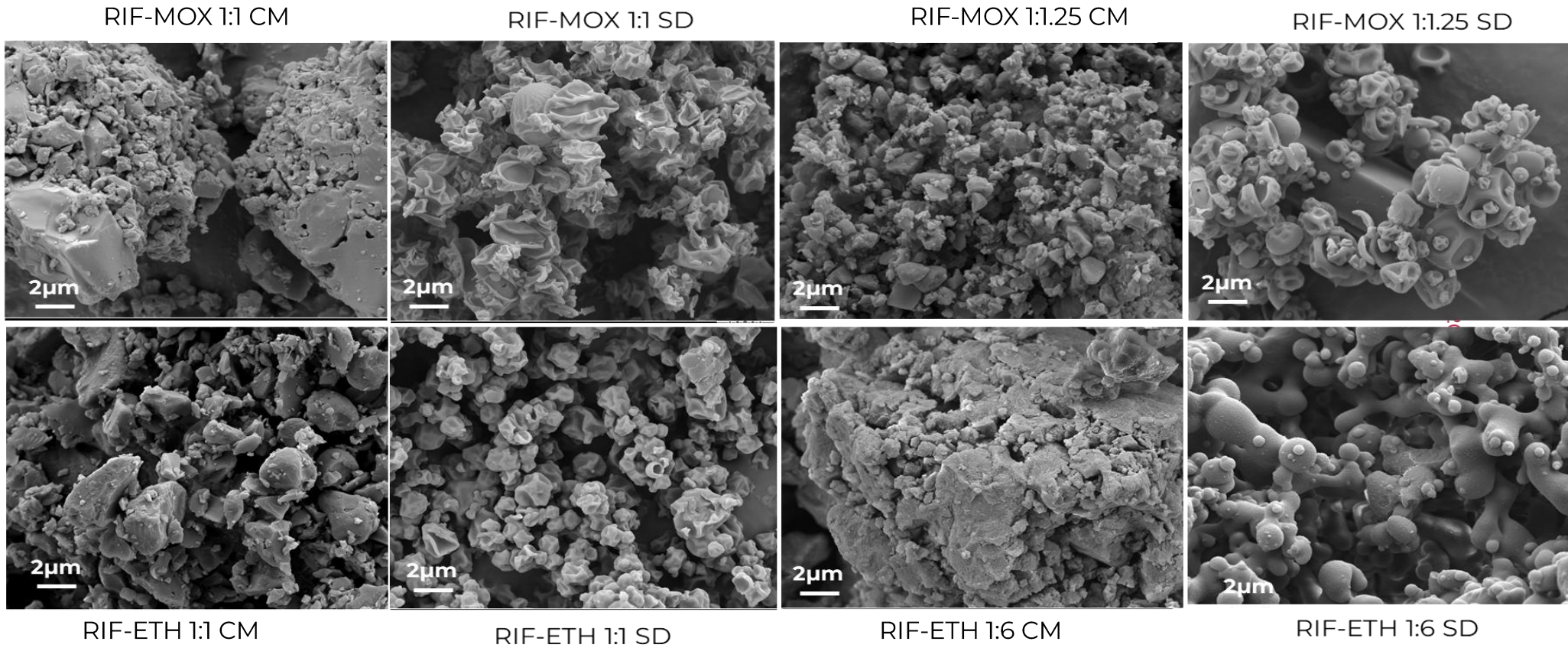
LET'S CONTINUE THE CONVERSATION

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Particle properties

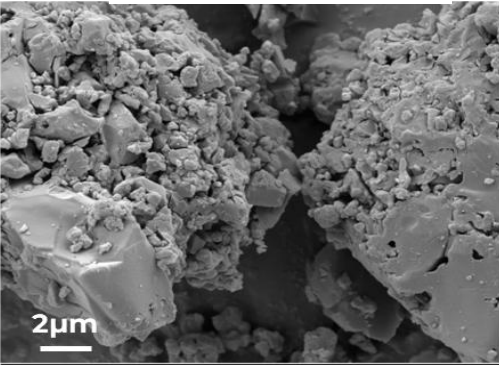
Surface morphology & particle size



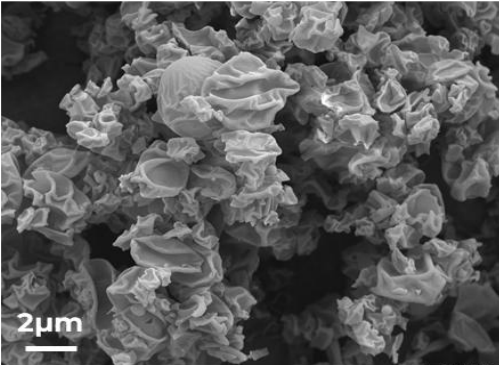
Particle properties

X₅₀	4.31 ± 0.18	2.82 ± 0.07	3.84 ± 0.25	3.00 ± 0.18
SPAN	4.40 ± 0.39	1.39 ± 0.01	1.62 ± 0.06	1.45 ± 0.02

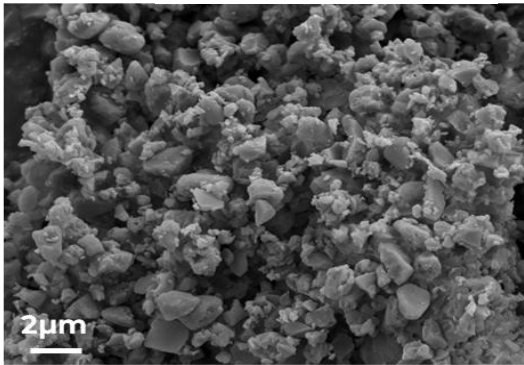
RIF-MOX 1:1 CM



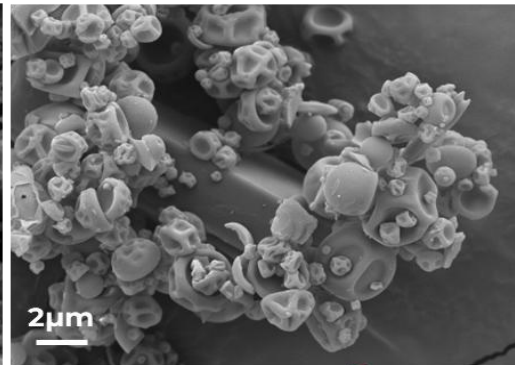
RIF-MOX 1:1 SD



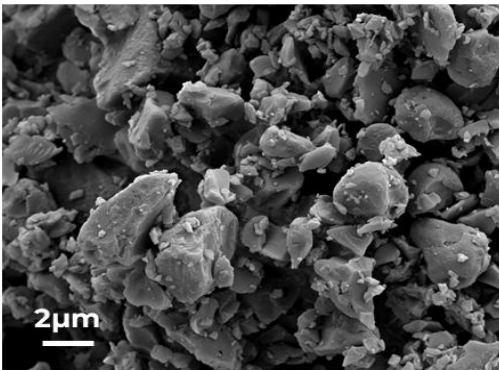
RIF-MOX 1:1.25 CM



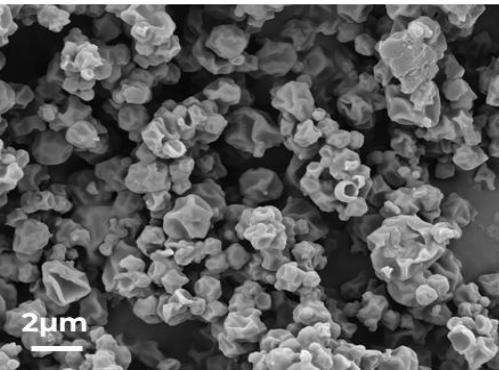
RIF-MOX 1:1.25 SD



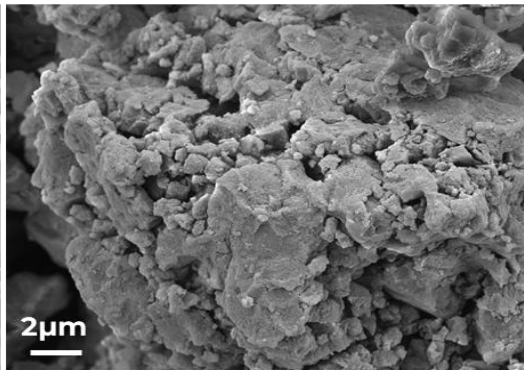
RIF-ETH 1:1 CM



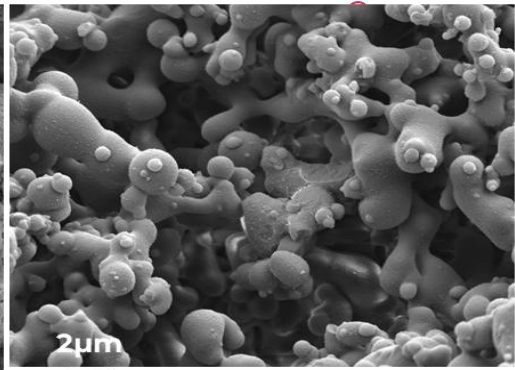
RIF-ETH 1:1 SD



RIF-ETH 1:6 CM



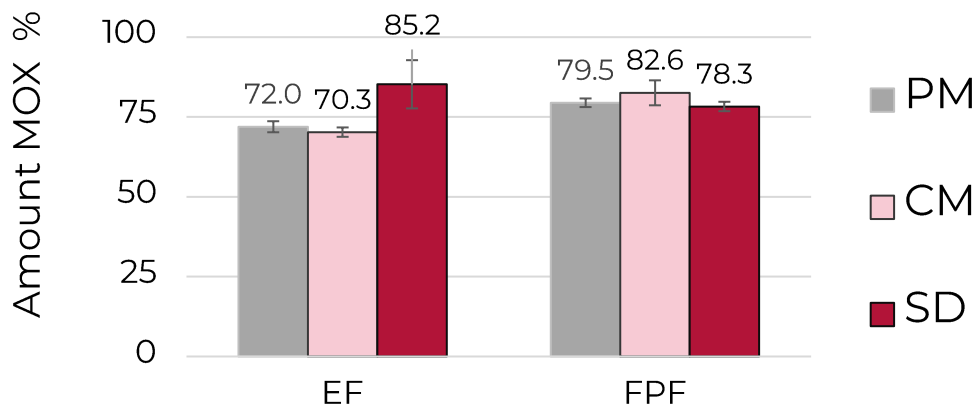
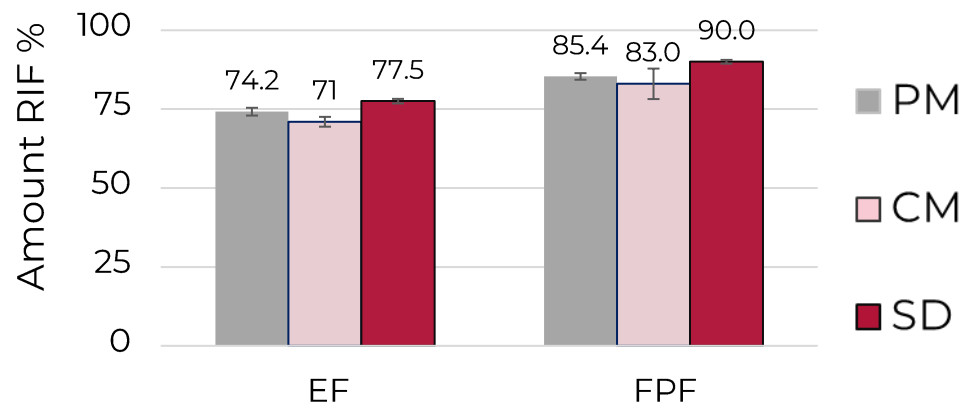
RIF-ETH 1:6 SD



X₅₀	2.87 ± 0.95	2.01 ± 0.65	23.06 ± 5.94	6.68 ± 0.22
SPAN	4.23 ± 6.87	0.98 ± 0.02	4.93 ± 0.75	3.2 ± 0.19

Particle Performance

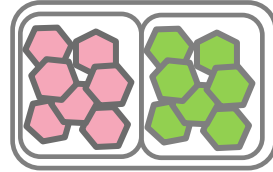
Aerodynamic assessment – RIF-MOX 1:1.25



- 25 mg co-amorphous API only formulations administered (SD & CM).
- Compared with crystalline physical mixture (PM) of RIF-MOX 1:1.25.
- Highest ED achieved for SD formulation (RIF 78% and MOX 85%).
- SD formulation superior FPF with low deviations (RIF 90% and MOX 78%).

Amorphous systems

Amorphous blend

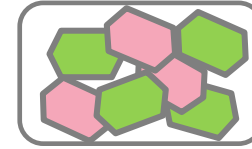


Advantages

- Increased
 - Solubility
- Dissolution rate
- Bioavailability

Disadvantage

- Instability/
Recrystallization



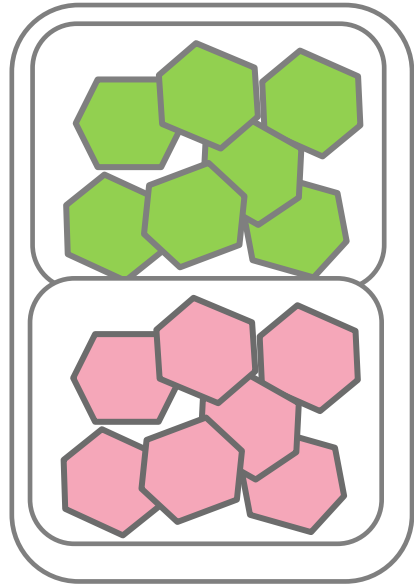
Co-amorphous system (COAMS)

Advantage

- Homogenous single-phase system
- Stabilization through co-former
- Reduced tendency for recrystallization

+

Amorphous systems



Amorphous blend

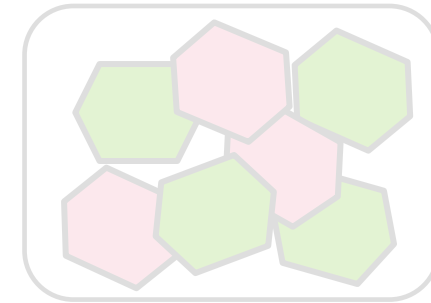
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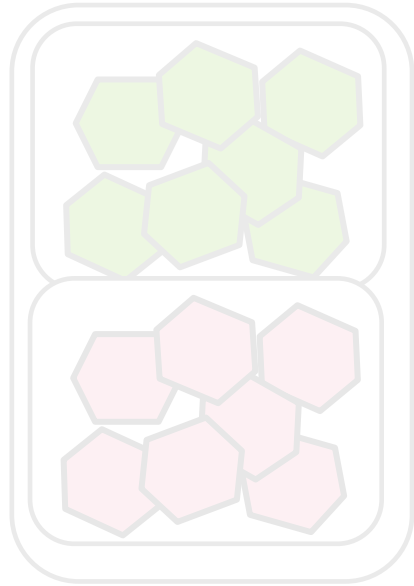
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Amorphous systems



Amorphous blend

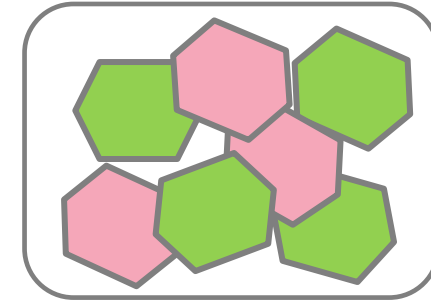
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