The effect of controlled mixing on ROY-polymorphism

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Importance of polymorphism

Importance for Pharmaceutical Field: Production of Active Pharmaceutical Compounds

- Importance of size distribution and polymorph selection
- Polymorphs: different stability, dissolvability, physiological activity and/or bioavailability

1. ROY as model system for studying polymorphism

2. Supersaturation protocol

3. Controlled mixing
   - Confinement
   - Microfluidic chip
   - Acoustic and diffusive mixing within microfluidic channel

1. **ROY as model system for studying polymorphism**

2. Supersaturation protocol

3. Controlled mixing
   - Confinement
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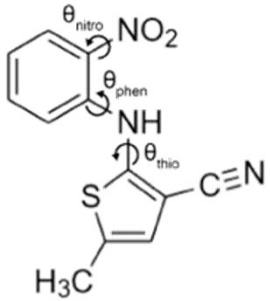
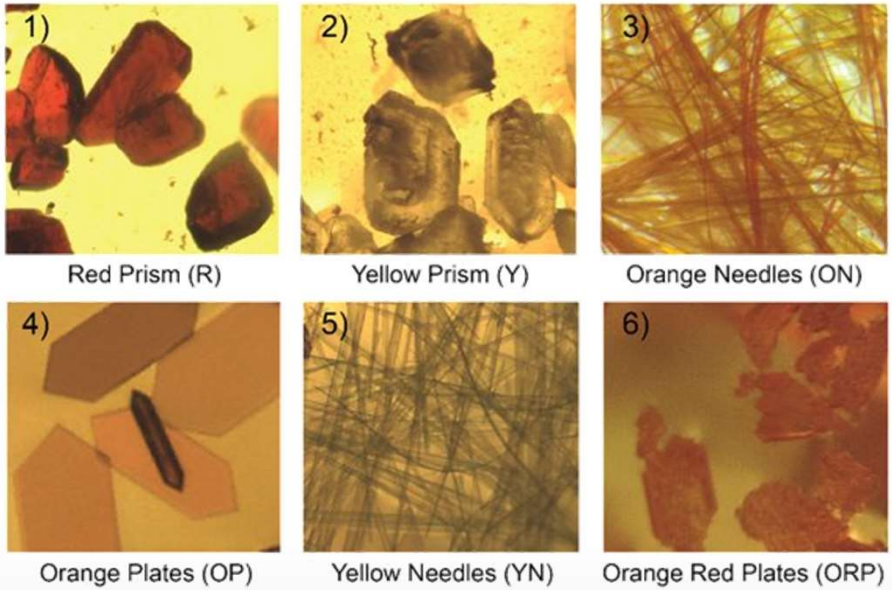
   - Acoustic and diffusive mixing within microfluidic channel

1. ROY as model system for studying polymorphism



ROY (5-methyl-2- [(2-nitrophenyl)amino] -3- thiophen carbonitrile)



- Six stable polymorphs at room temperature
- Visual distinction
- Acetone as solvent
- Water as antisolvent

From Ziemecka et al., 2019

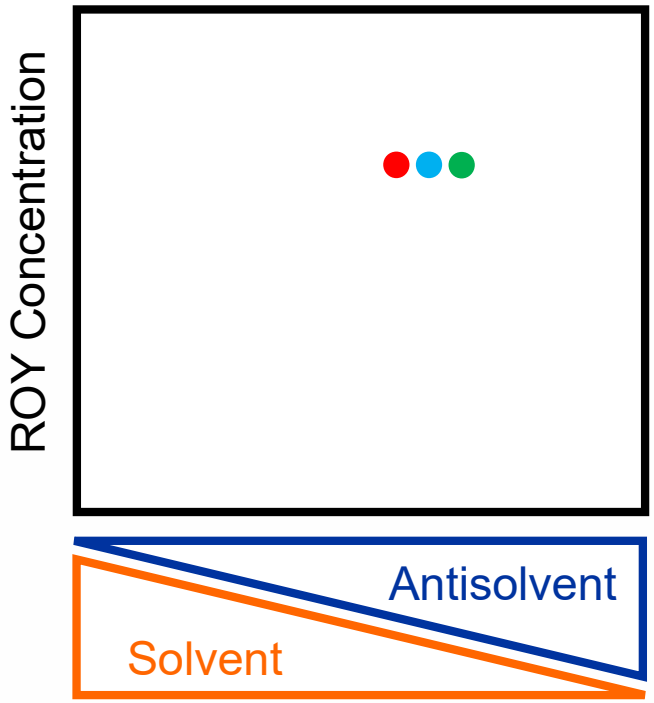
1. ROY as model system for studying polymorphism

2. **Supersaturation protocol**

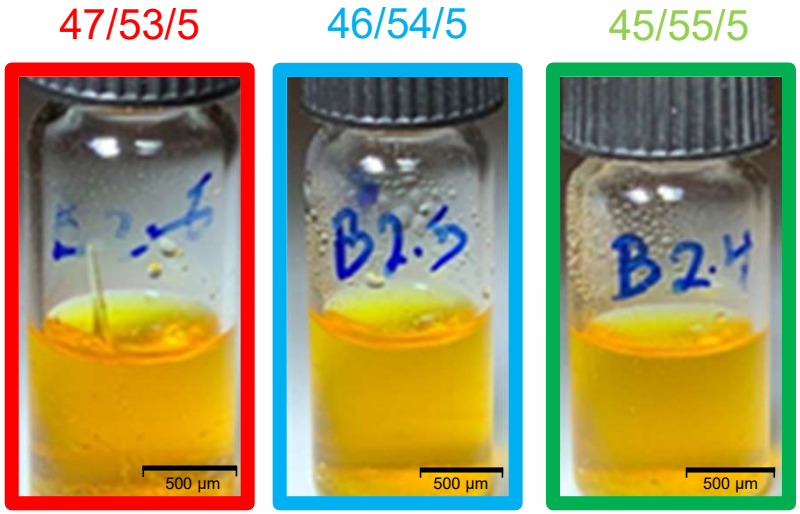
3. Controlled mixing
   - Confinement
   - Microfluidic chip
   - Acoustic and diffusive mixing within microfluidic channel

2. Supersaturation protocol

Phase diagram ROY polymorphism

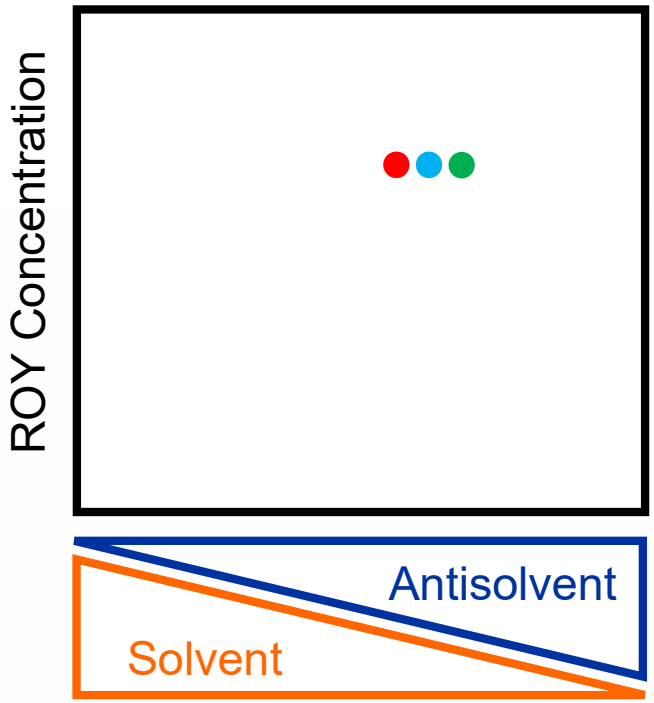


Acetone (Vol%) / Water (Vol%) / ROY (mg/mL)

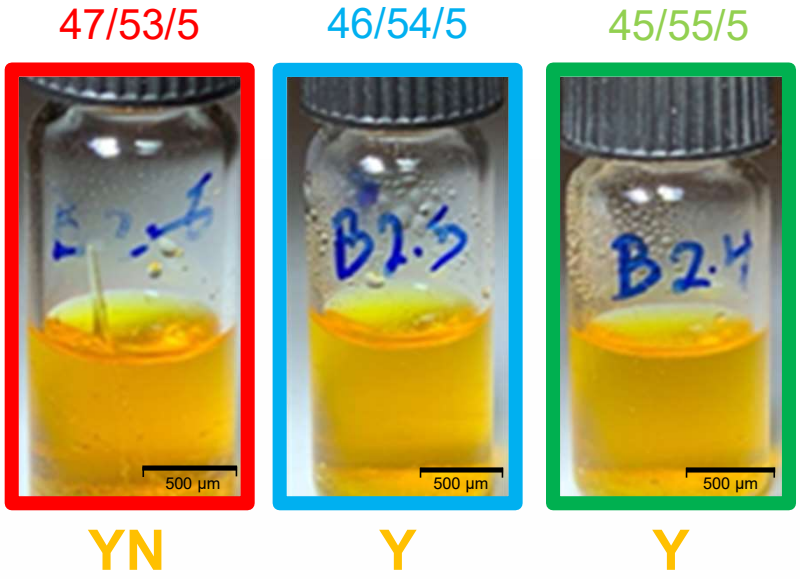


2. Supersaturation protocol

Phase diagram ROY polymorphism



Acetone (Vol%) / Water (Vol%) / ROY (mg/mL)



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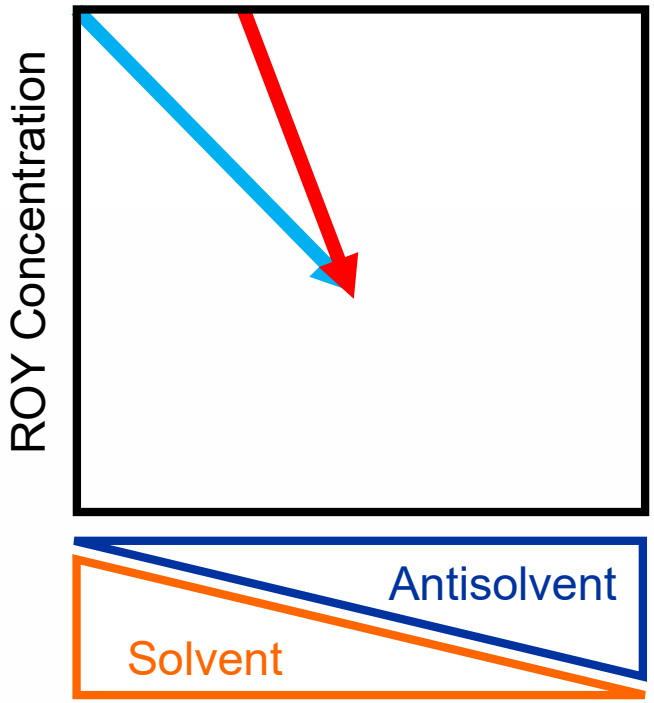
Very slight changes in solvent to antisolvent ratio induce drastic change in ROY polymorphism.

2. Supersaturation protocol

Phase diagram ROY polymorphism

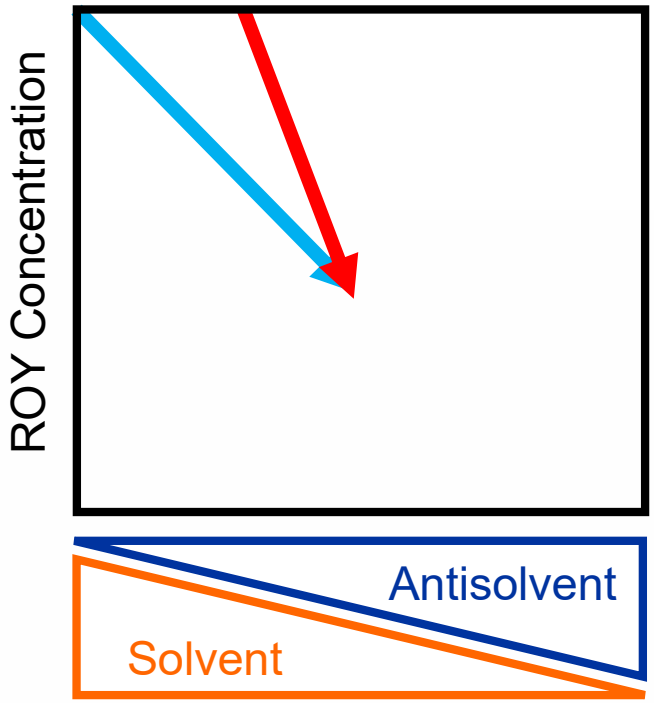


Supersaturation protocol

1. Initial concentration

2. Supersaturation protocol

Phase diagram ROY polymorphism



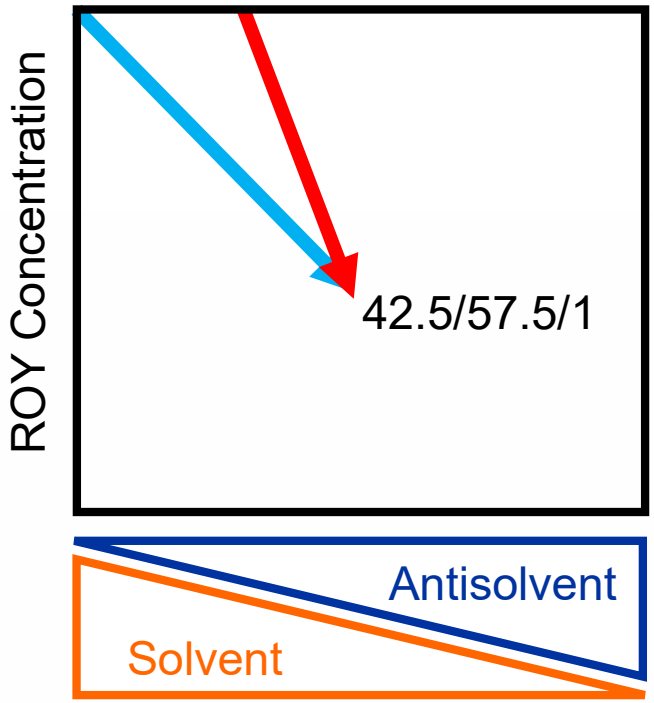
Supersaturation protocol

1. Initial concentration

- 10 minutes
- 1mL
- 100 rpm

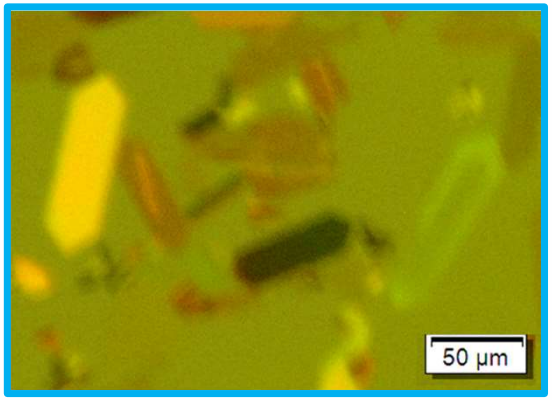
2. Supersaturation protocol

Phase diagram ROY polymorphism

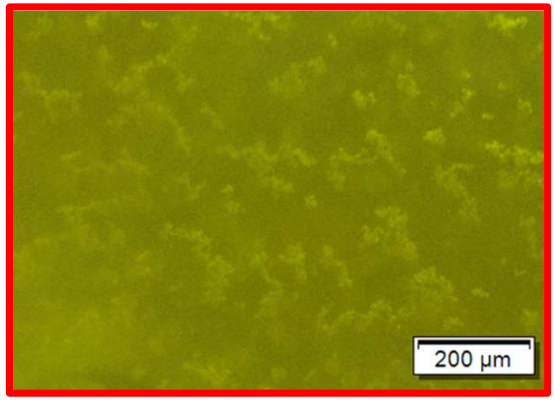


Supersaturation protocol

1. Initial concentration



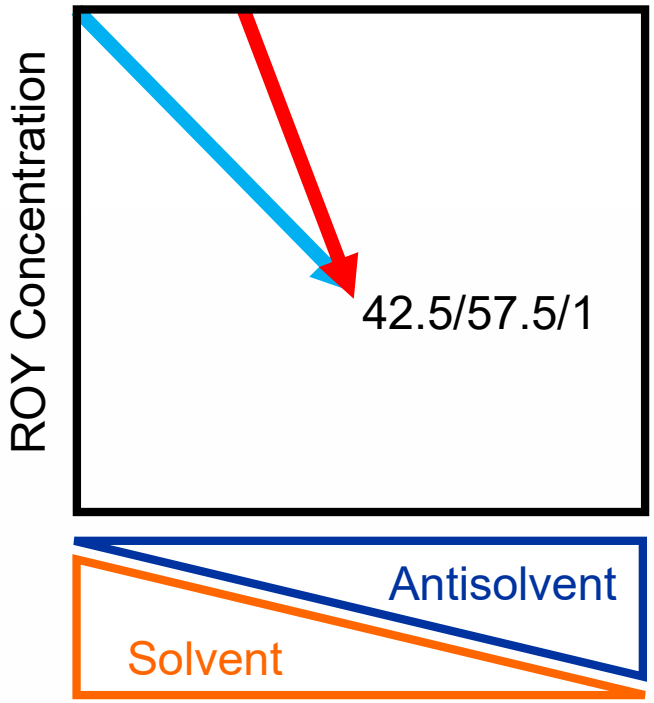
OP - ORP



Y

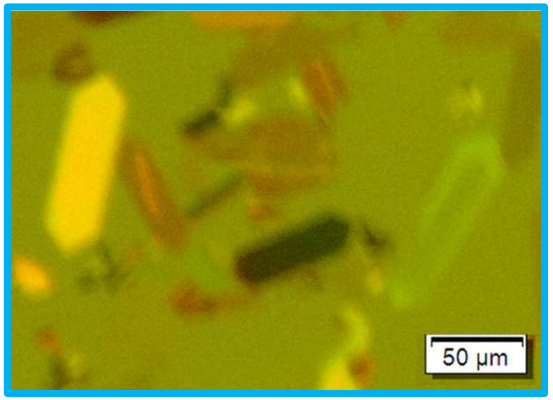
2. Supersaturation protocol

Phase diagram ROY polymorphism

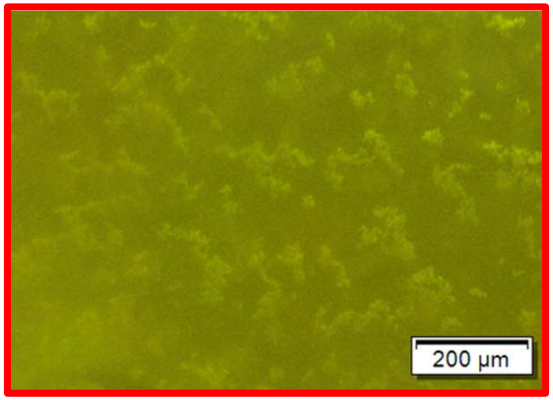


Supersaturation protocol

1. Initial concentration



OP - ORP



Y

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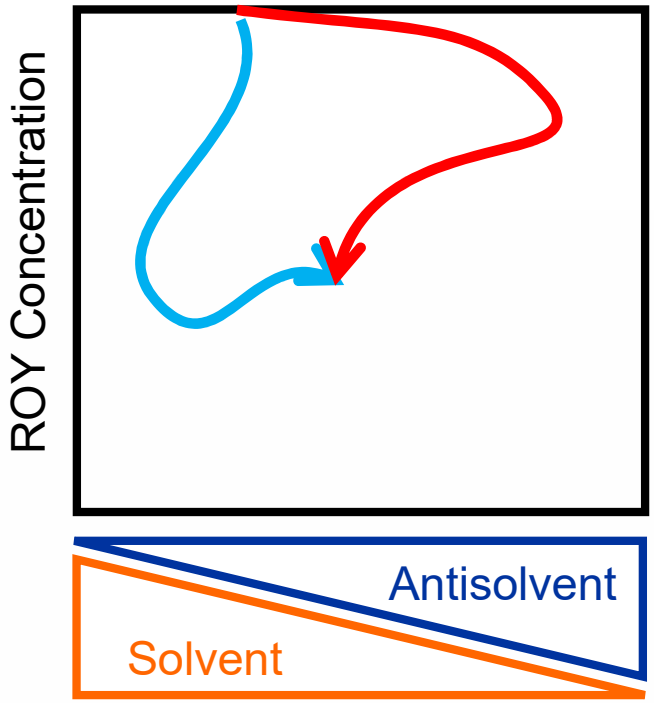
Initial condition of supersaturation protocol affects ROY polymorphism

2. Supersaturation protocol

Phase diagram ROY polymorphism

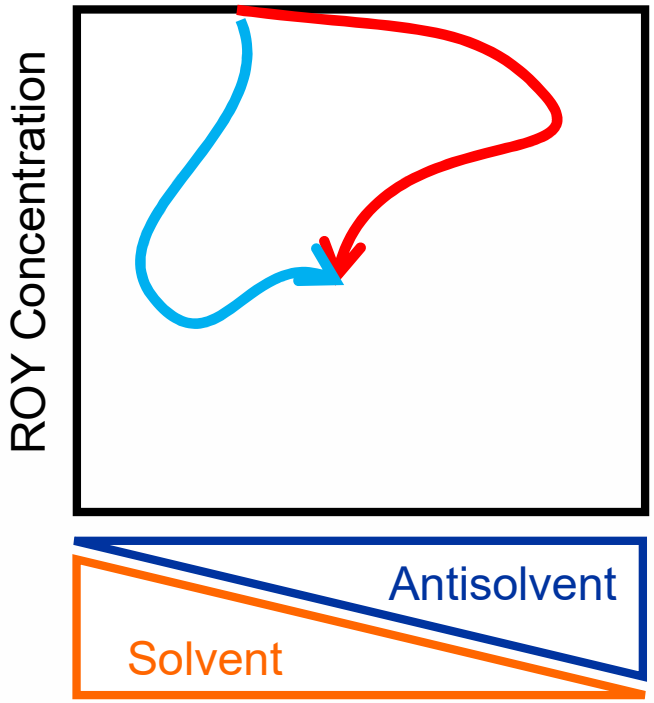


Supersaturation protocol

1. Initial concentration
2. Mixing method

2. Supersaturation protocol

Phase diagram ROY polymorphism



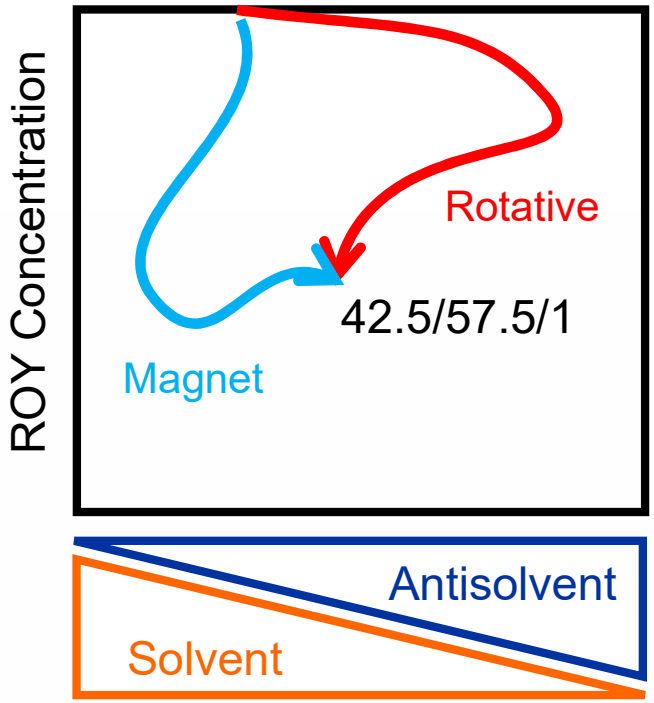
Supersaturation protocol

1. Initial concentration
2. Mixing method

- 10 minutes
- 1mL
- 100 rpm/400rpm

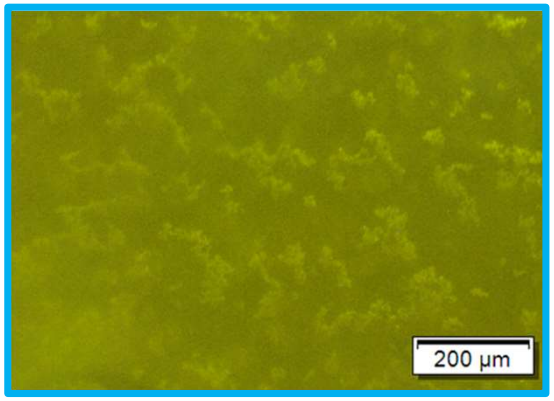
2. Supersaturation protocol

Phase diagram ROY polymorphism

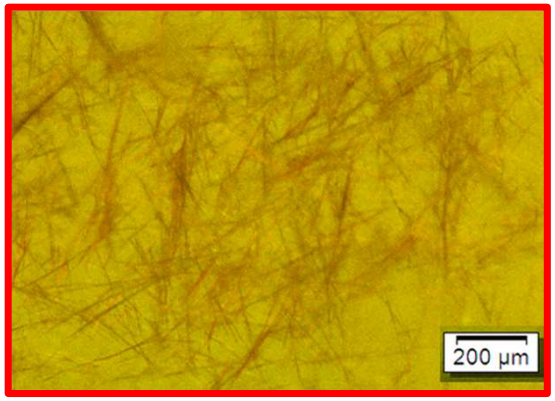


Supersaturation protocol

1. Initial concentration
2. Mixing method



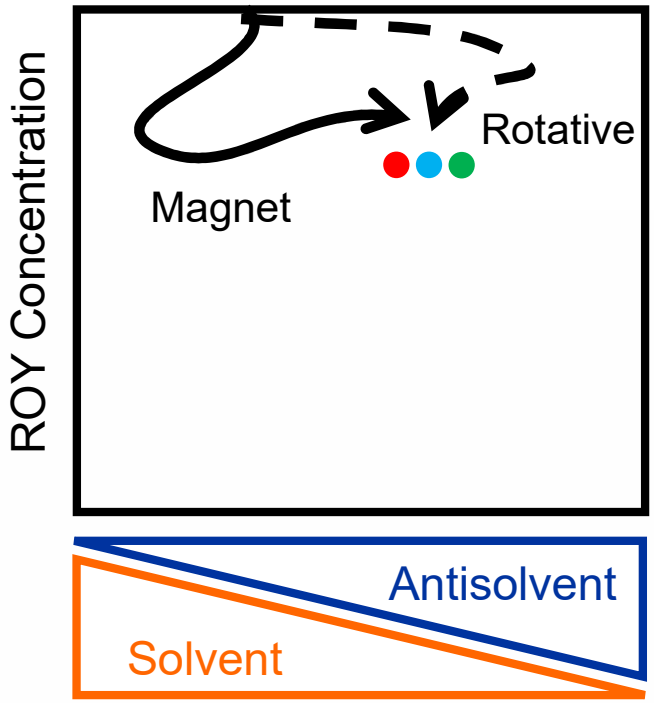
Y



ON - YN

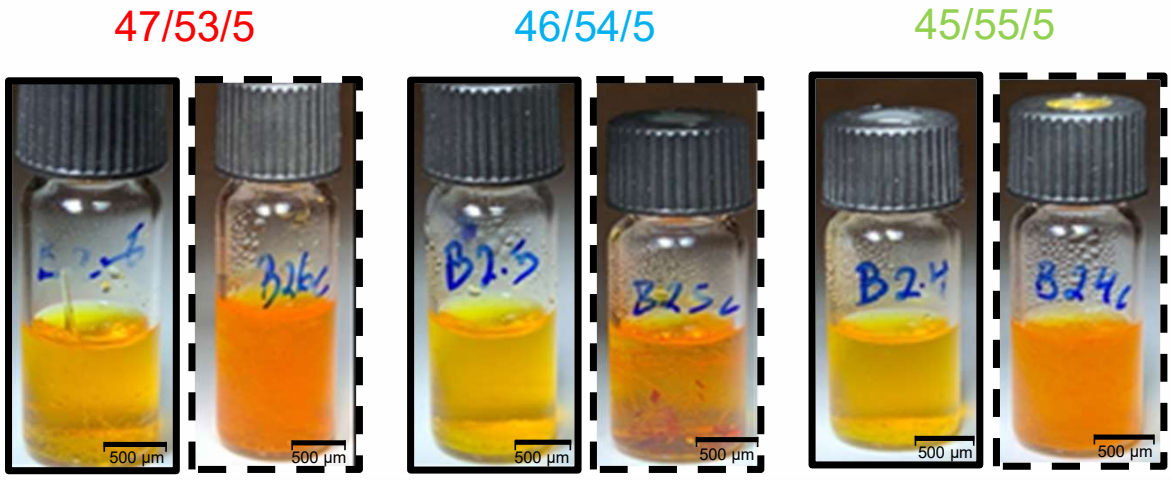
2. Supersaturation protocol

Phase diagram ROY polymorphism



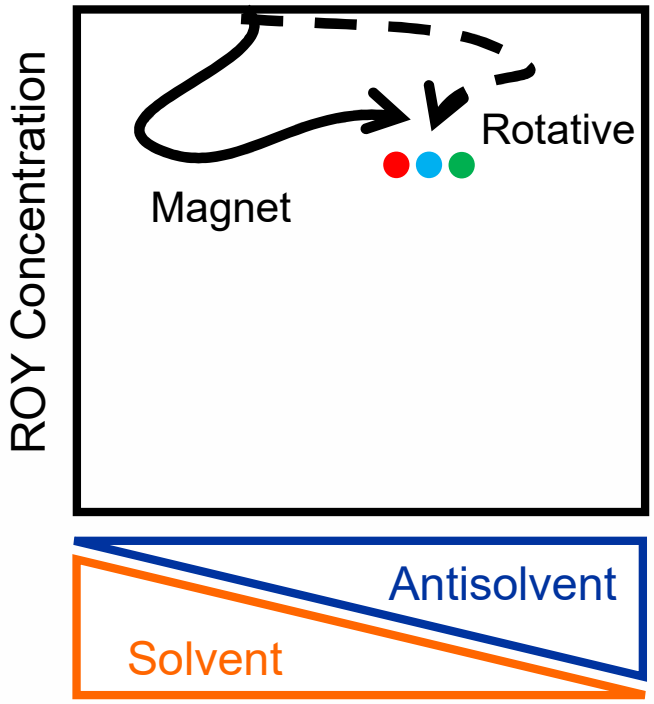
Supersaturation protocol

1. Initial concentration
2. Mixing method



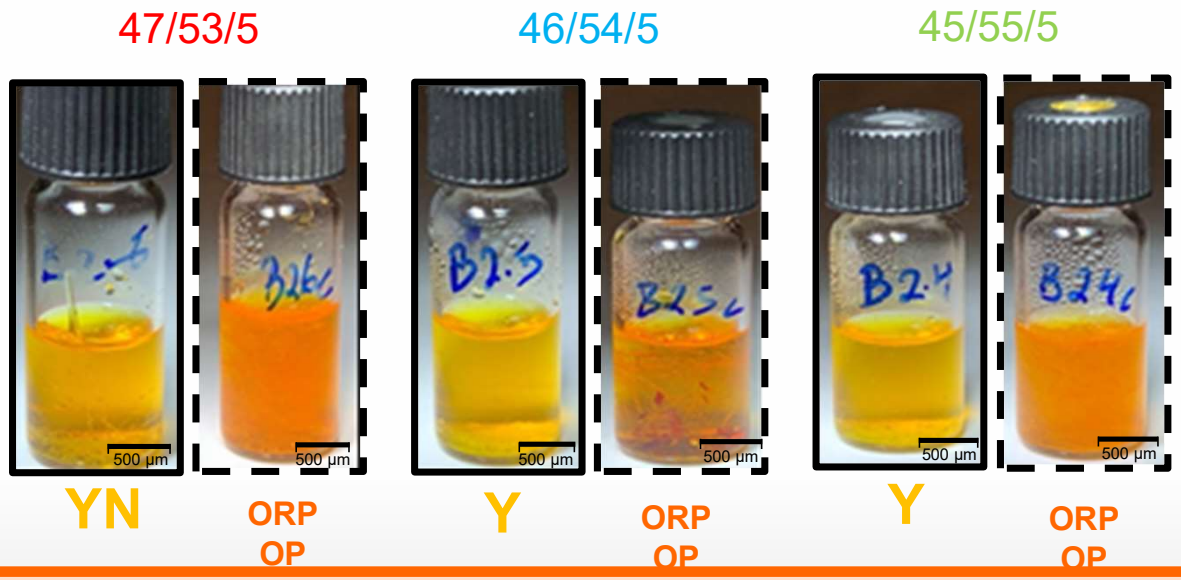
2. Supersaturation protocol

Phase diagram ROY polymorphism



Supersaturation protocol

1. Initial concentration
2. Mixing method



Mixing method affects ROY polymorphism

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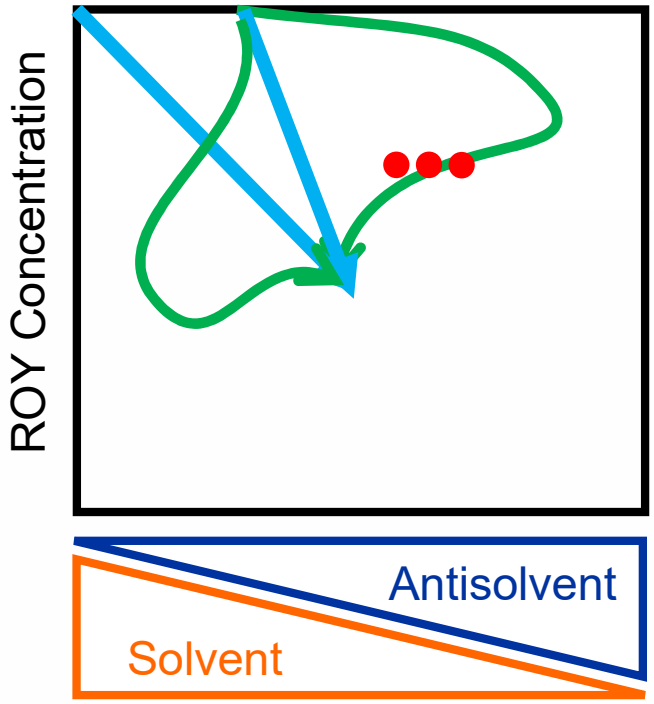
2. Supersaturation protocol

Phase diagram ROY polymorphism



1. Phase diagram
2. Start concentration
3. Mixing method

- Road to supersaturation affects ROY Polymorphism
- Limited reproducibility
- Controlled mixing required

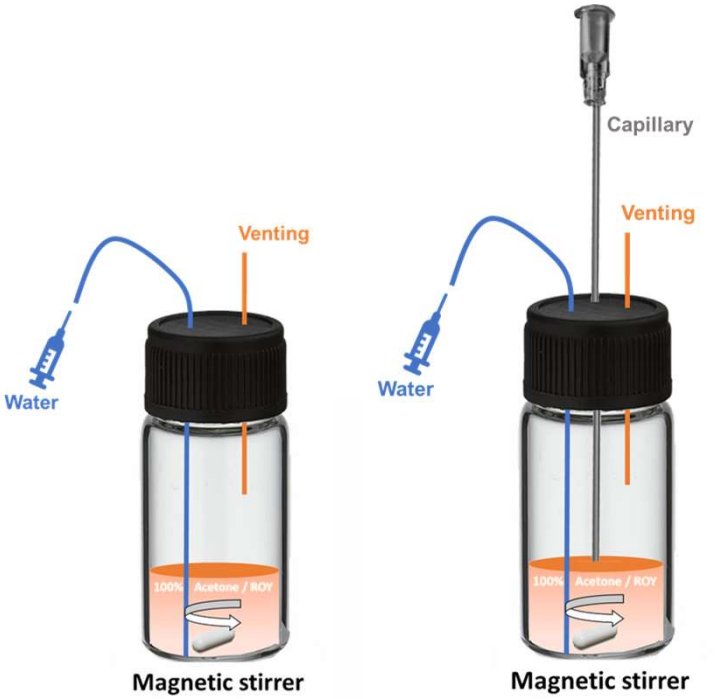
➡ **Microfluidic approach**

1. ROY as model system for studying polymorphism

2. Supersaturation protocol

3. **Controlled mixing**
   - **Confinement**
   - Microfluidic chip
   - Acoustic and diffusive mixing within microfluidic channel

3. Controlled mixing - Confinement

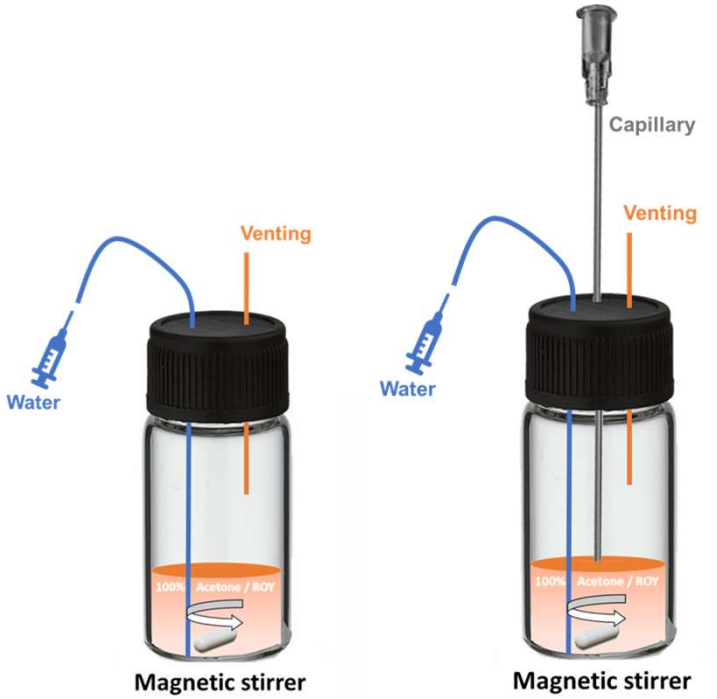


BULK

Confinement

After mixing, the mixture is confined in a 100µm capillary.

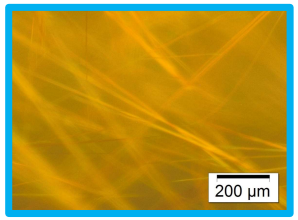
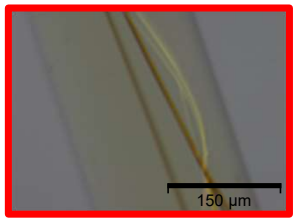
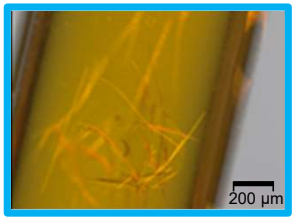
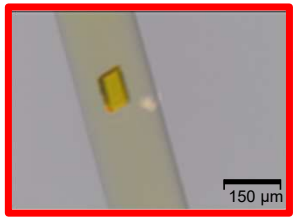
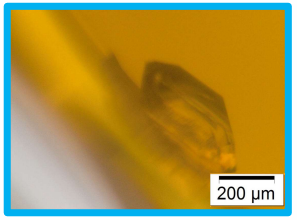
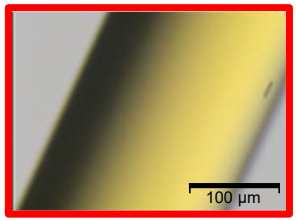
3. Controlled mixing - Confinement



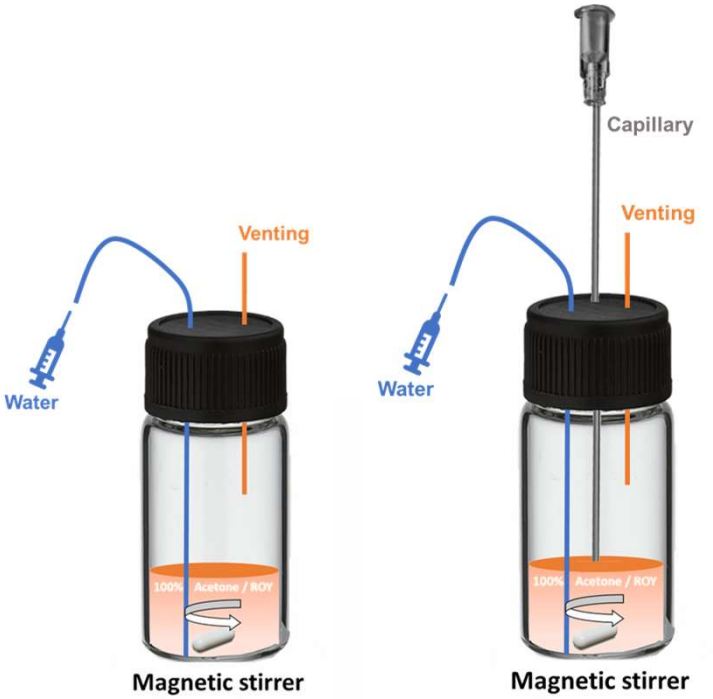
BULK

Confinement

After mixing, the mixture is confined in a 100µm capillary.

	Bulk	Confined
40% Acetone – 1mg/mL ROY		
	ON - YN	ON - YN
42.5% Acetone – 1mg/mL ROY		
	ON - YN	OP
45% Acetone – 1mg/mL ROY		
	OP	OP

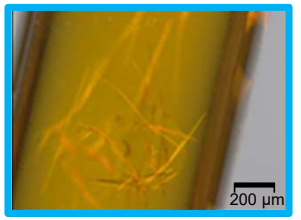
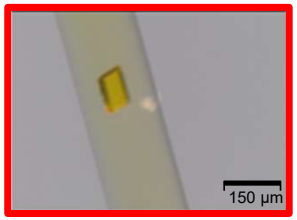
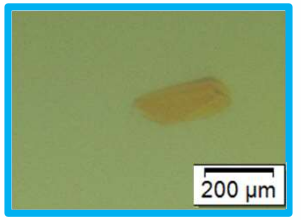
3. Controlled mixing - Confinement



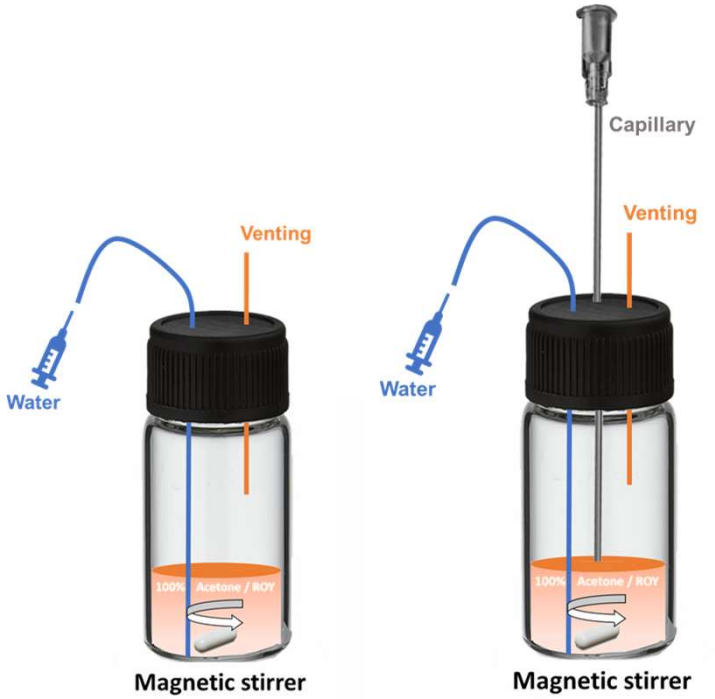
BULK

Confinement

After mixing, the mixture is confined in a 100µm capillary.

	Bulk	Confined
42.5% Acetone – **1mg/mL** ROY	 **ON - YN**	 **OP**
42.5% Acetone – **0.8 mg/mL** ROY	 **OP**	

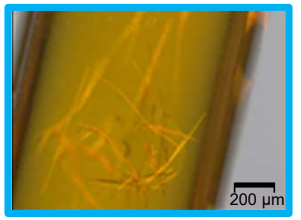
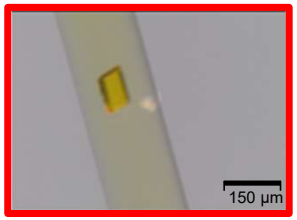
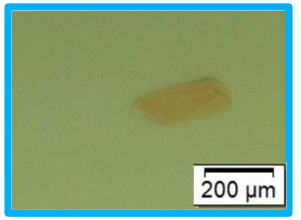
3. Controlled mixing - Confinement



BULK

Confinement

After mixing, the mixture is confined in a 100µm capillary.

	Bulk	Confined
42.5% Acetone – **1mg/mL** ROY		
	ON - YN	**OP**
42.5% Acetone – **0.8 mg/mL** ROY		
	OP	

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Effect of confinement can be explained by decrease in ROY availability (depletion)

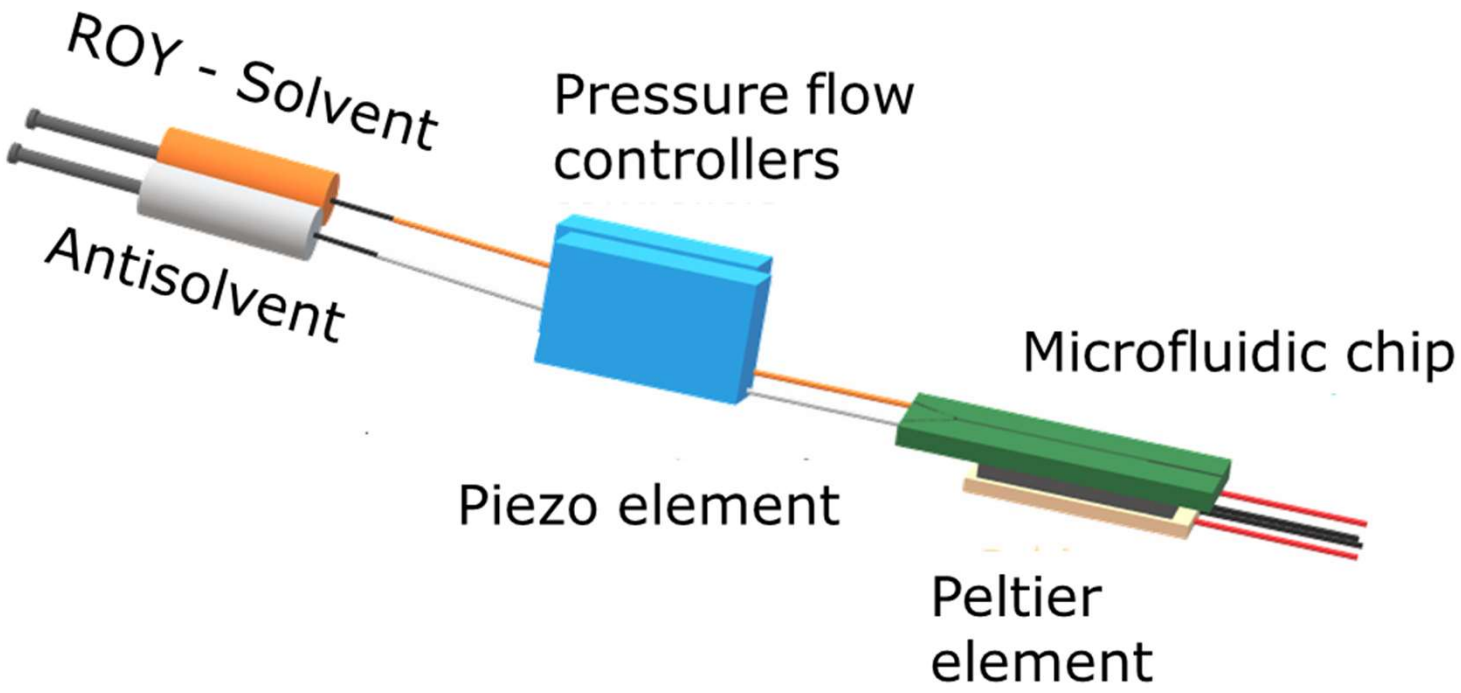
1. ROY as model system for studying polymorphism

2. Supersaturation protocol

3. **Controlled mixing**
   - Confinement
   - **Microfluidic chip**
   - Acoustic and diffusive mixing within microfluidic channel

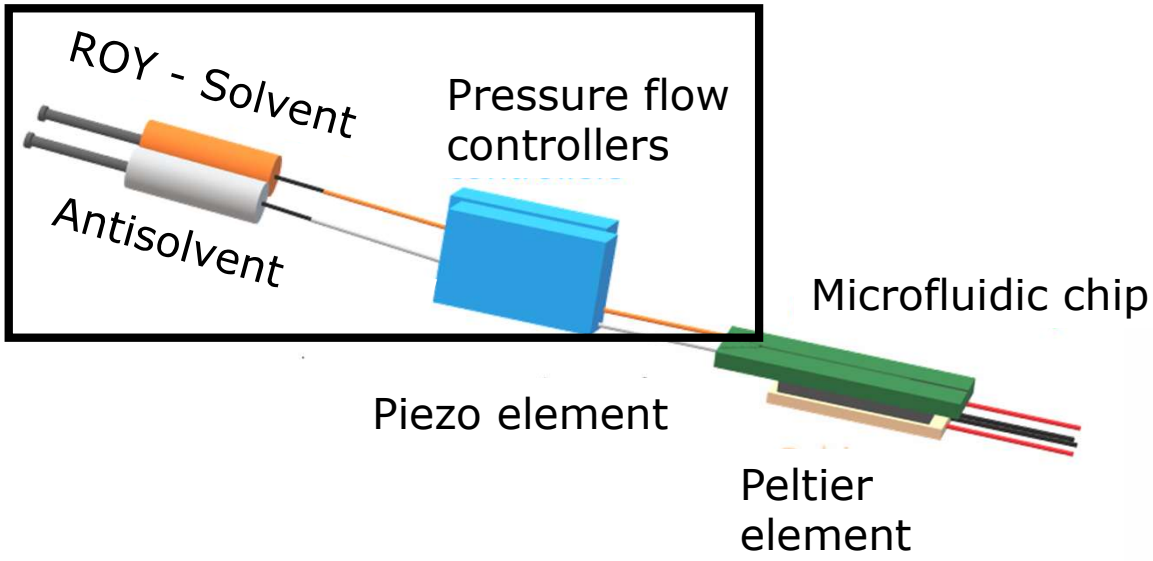
3. Controlled mixing – microfluidic chip

Experimental setup



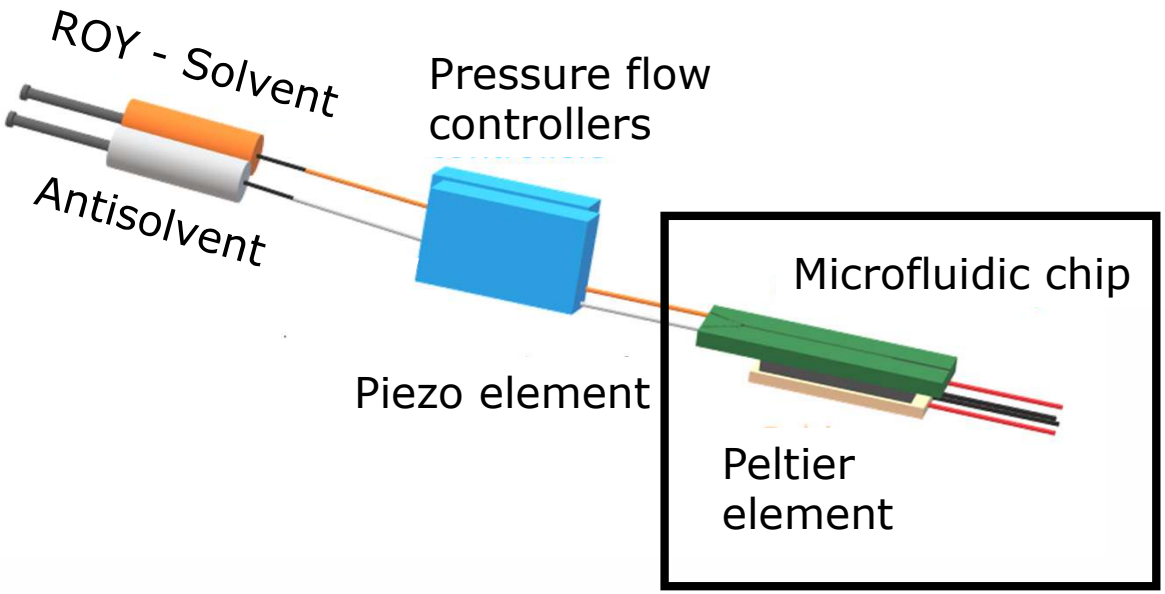
3. Controlled mixing – microfluidic chip

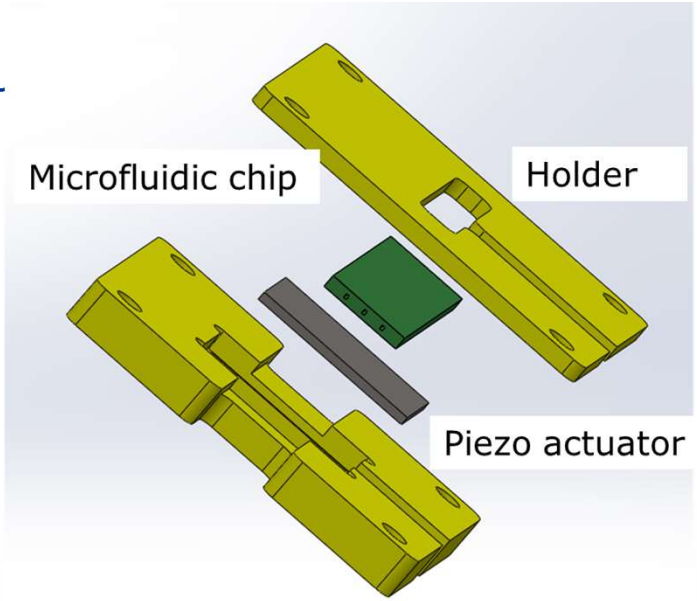
Experimental setup

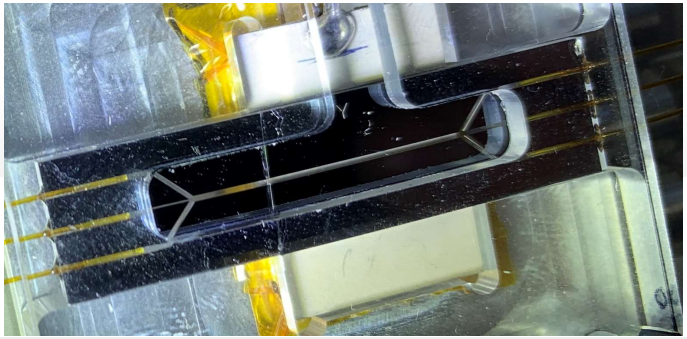


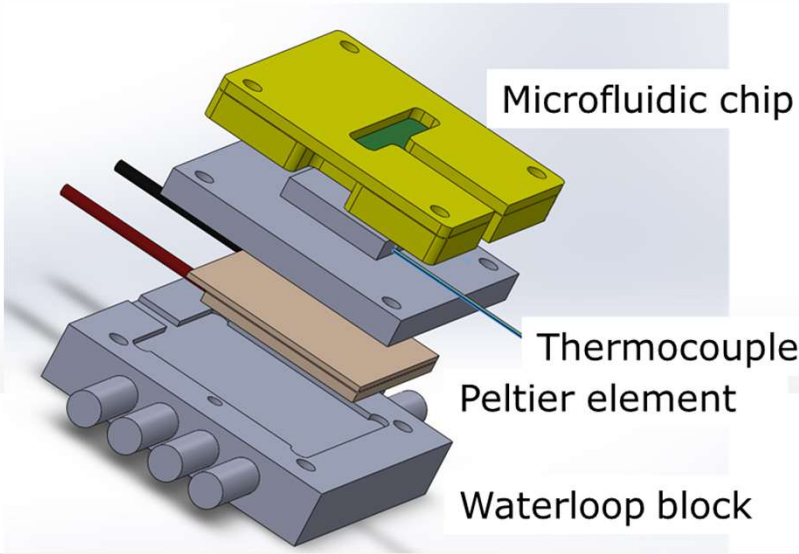
3. Controlled mixing – microfluidic chip

Experimental setup



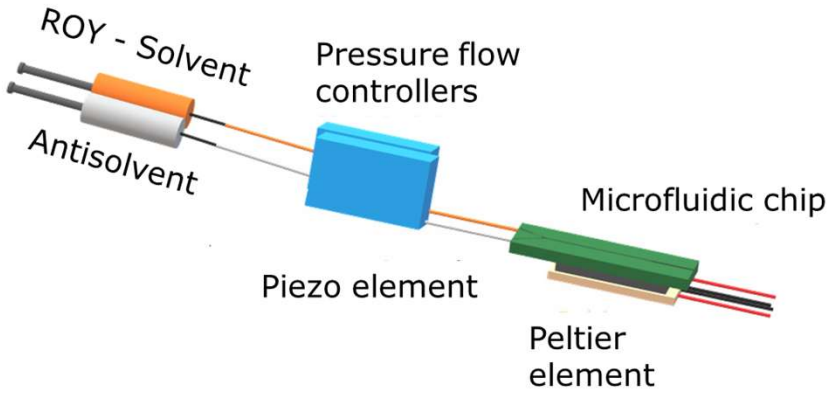


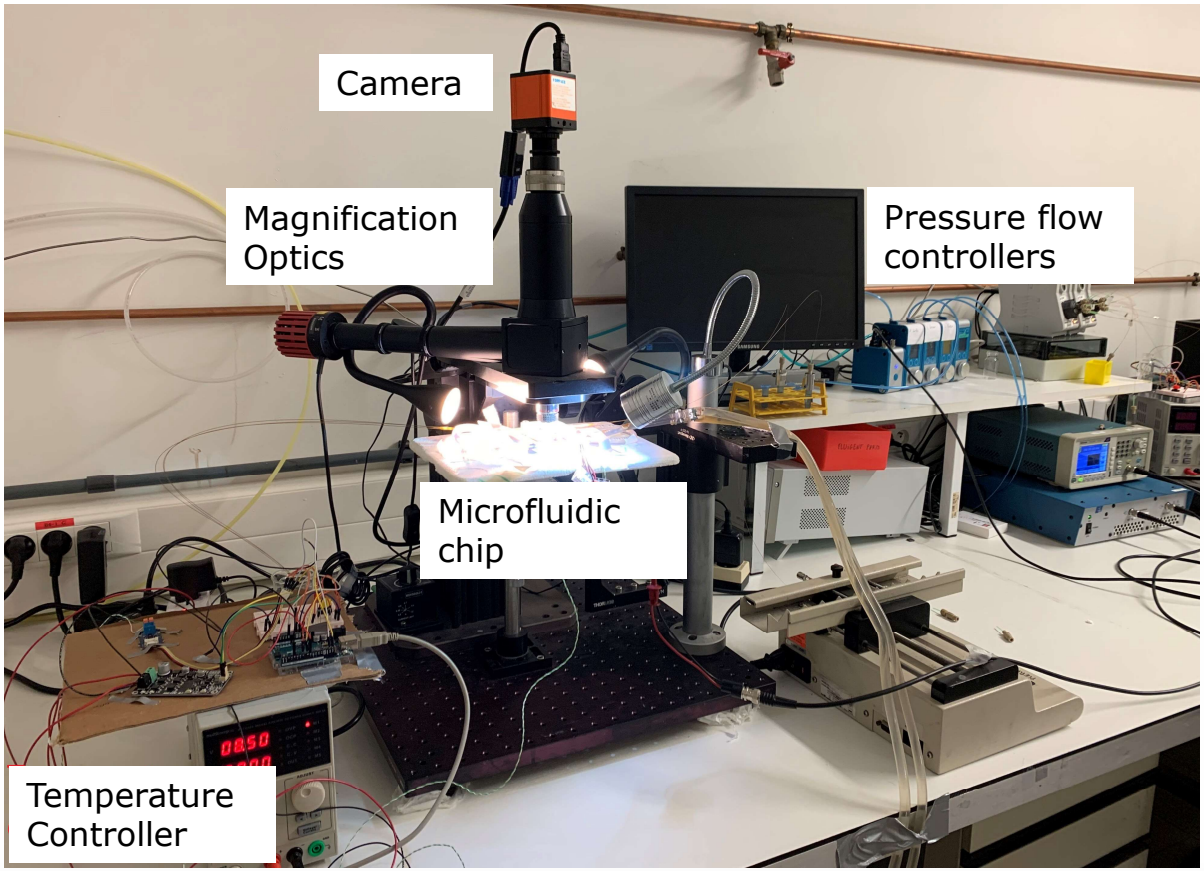




3. Controlled mixing – microfluidic chip

Experimental setup





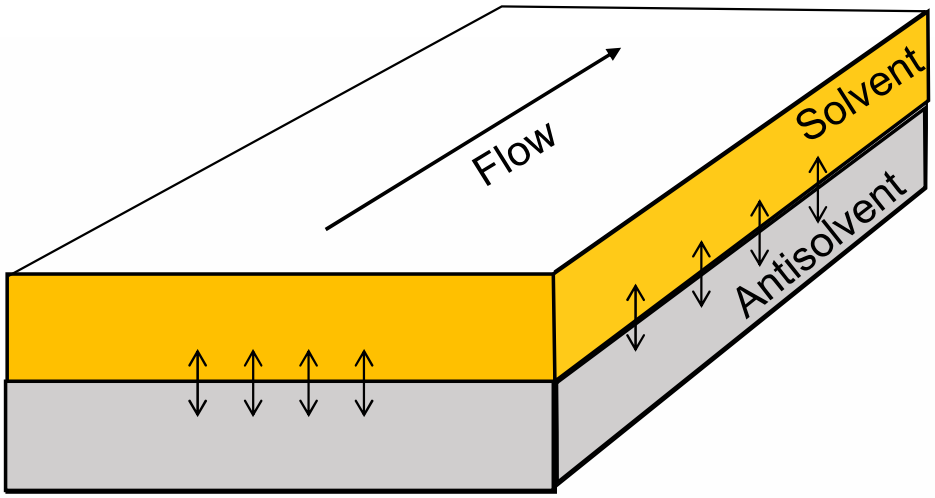
1. ROY as model system for studying polymorphism

2. Supersaturation protocol

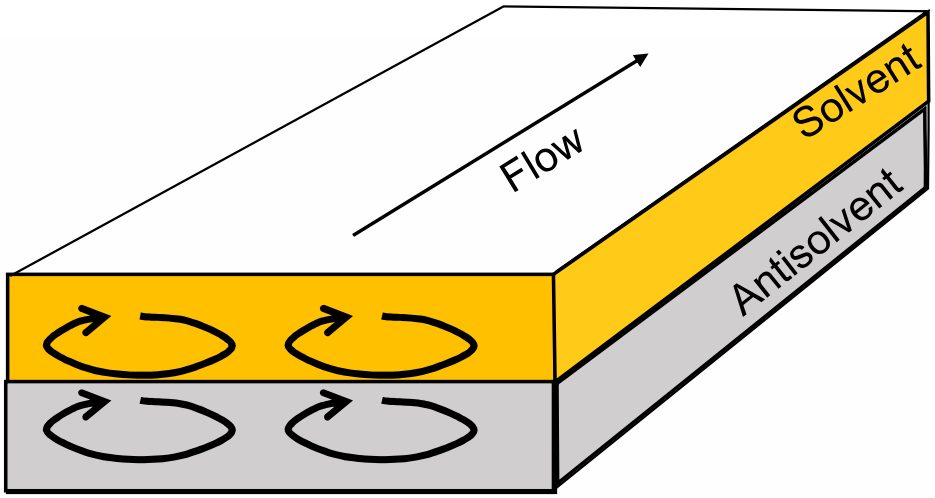
3. **Controlled mixing**
   - Confinement
   - Microfluidic chip
   - **Acoustic and diffusive mixing within microfluidic channel**

Mixing within microfluidic channel

1. Diffusive mixing

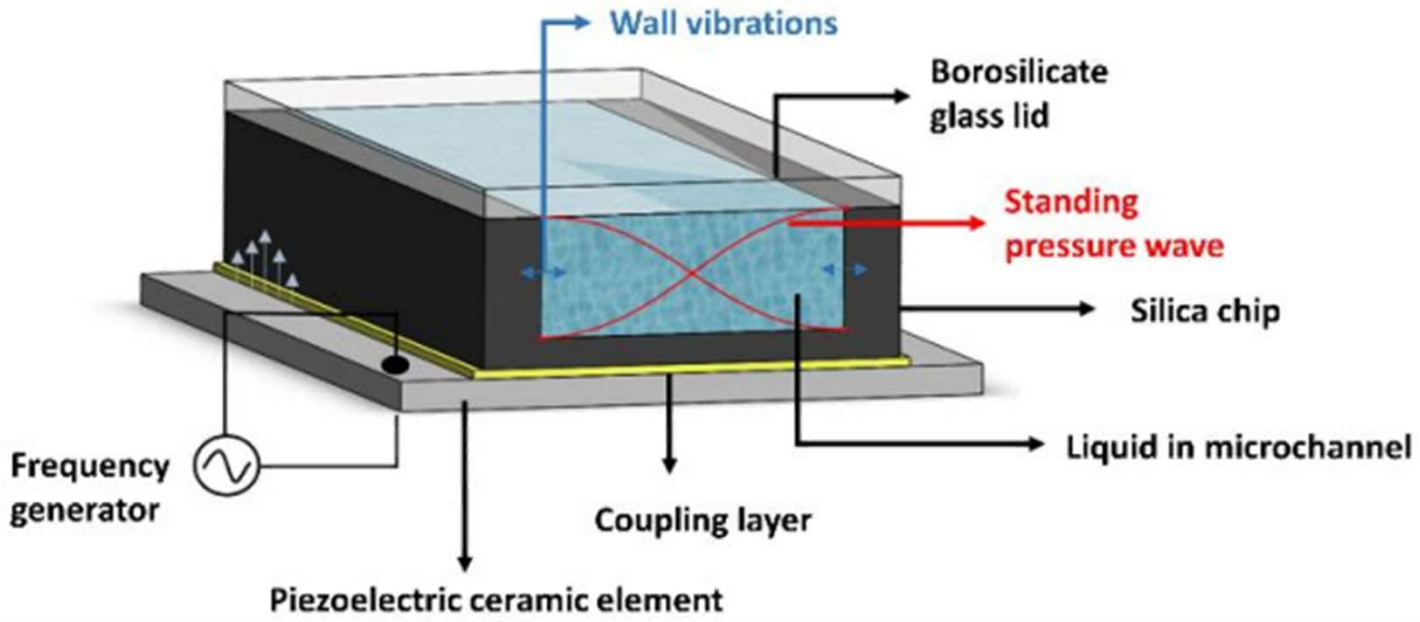


2. Acoustic mixing



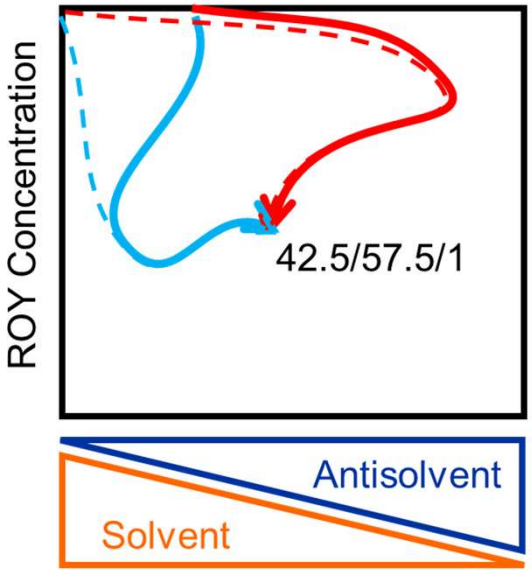
Mixing within microfluidic channel

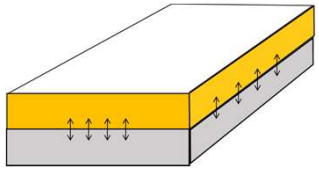
2. Acoustic mixing



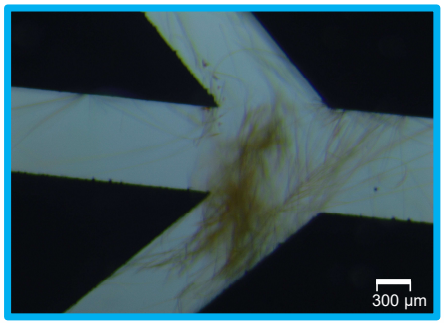
From Gelin et al., 2019

Mixing within microfluidic channel

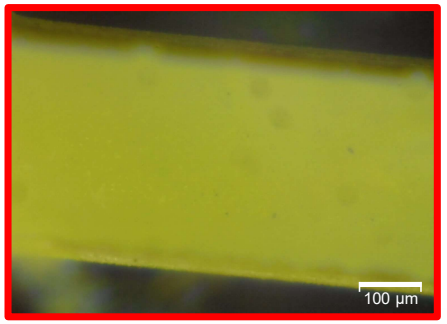




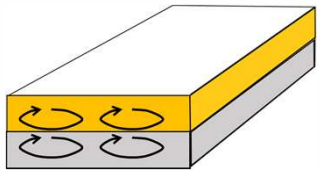
Diffusive mixing



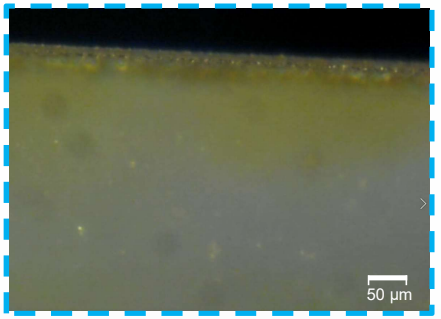
ON - YN



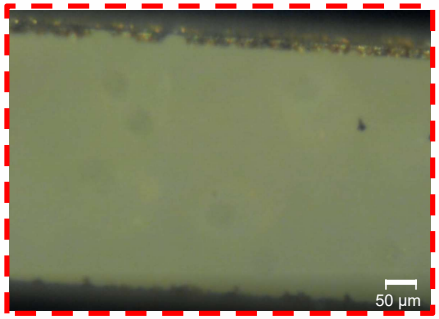
Y



Acoustic mixing



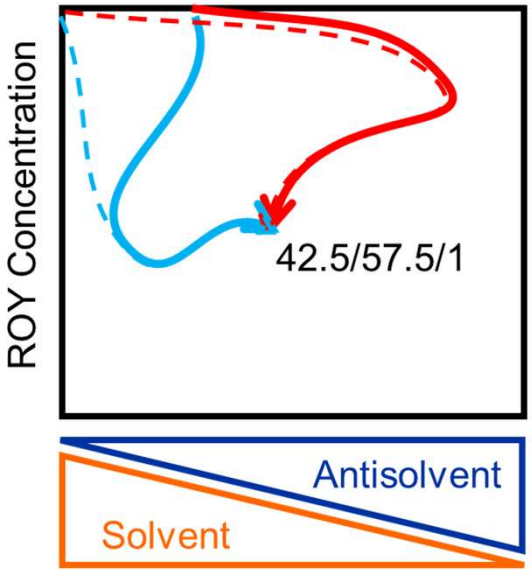
OP - Y

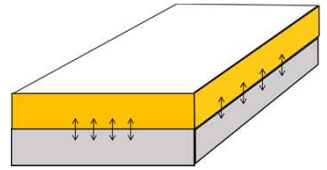


Y

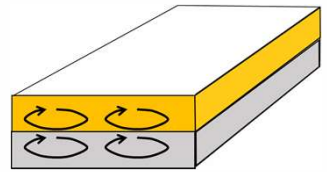
3. Controlled mixing – acoustic and diffusive mixing within microfluidic channel

Mixing within microfluidic channel

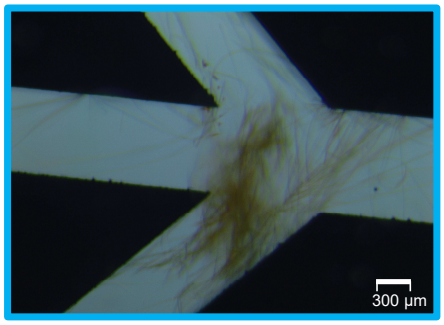




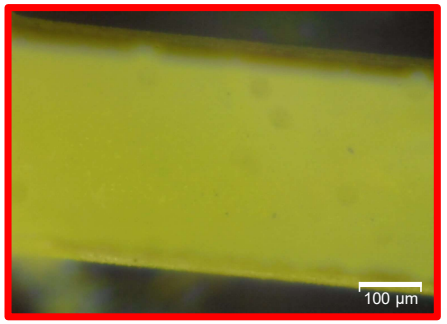
Diffusive mixing



Acoustic mixing



ON - YN



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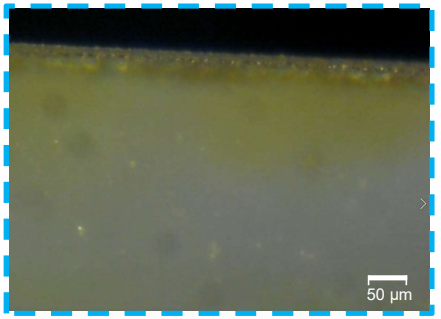
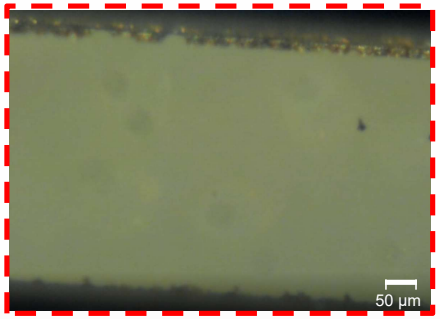


OP - Y



Y

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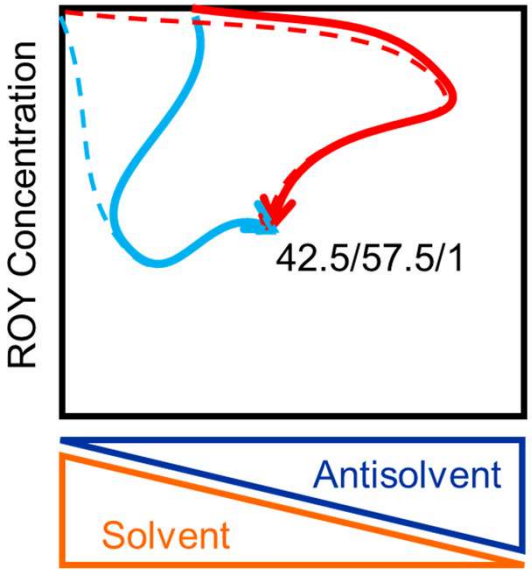
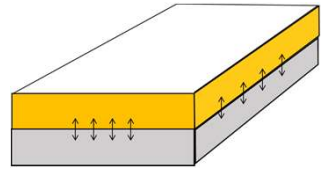
Supersaturation protocol initial conditions also affect ROY polymorphism in microfluidic channel.

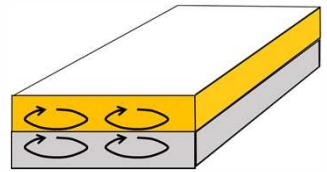
3. Controlled mixing – acoustic and diffusive mixing within microfluidic channel

Mixing within microfluidic channel

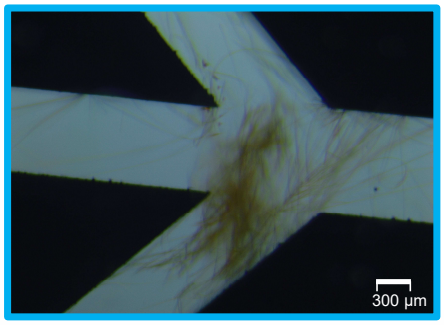




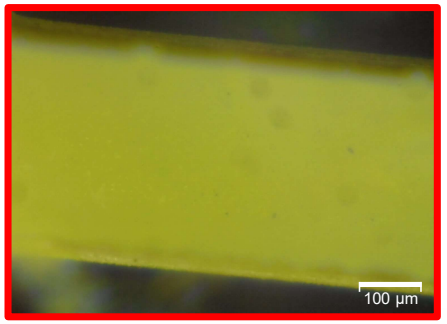
Diffusive mixing



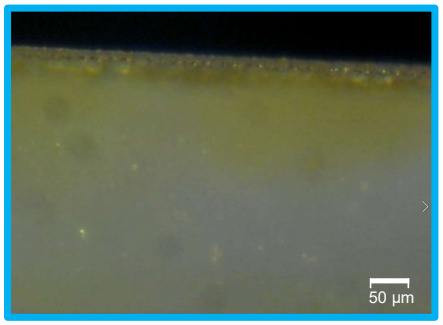
Acoustic mixing



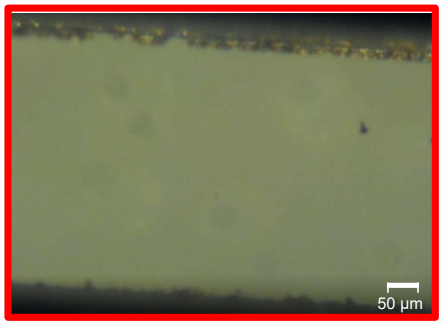
ON - YN



Y



OP - Y



Y

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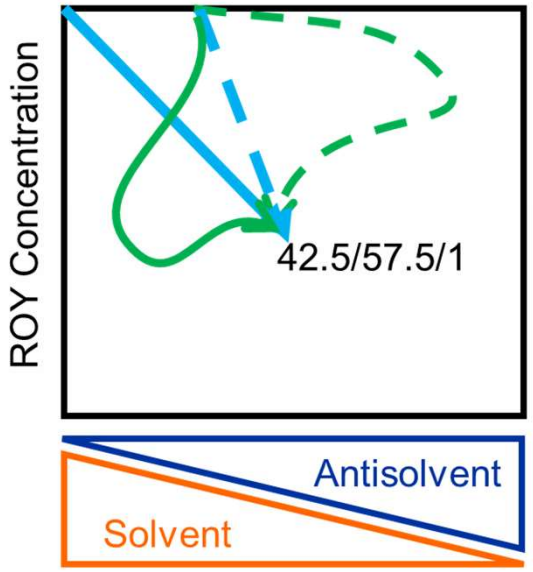
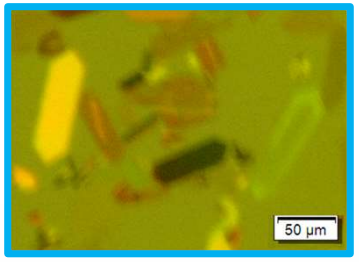
Mixing method also affects ROY Polymorphism in microfluidic channel.

4. Conclusion



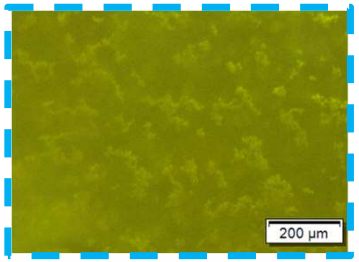
Bulk

100% acetone



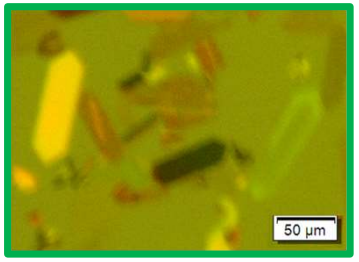
OP - ORP

70% acetone



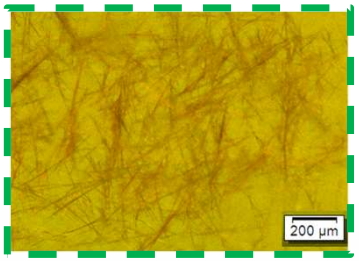
Y

Magnet



OP - ORP

Rotative



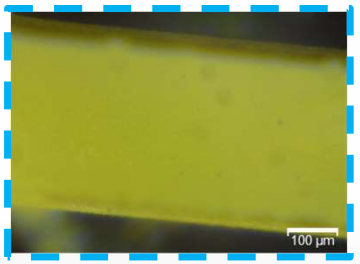
ON - YN

Microfluidic chip

100% acetone

OP - Y

70% acetone



Y

Acoustic mixing

OP - Y

Diffusive mixing

ON - YN

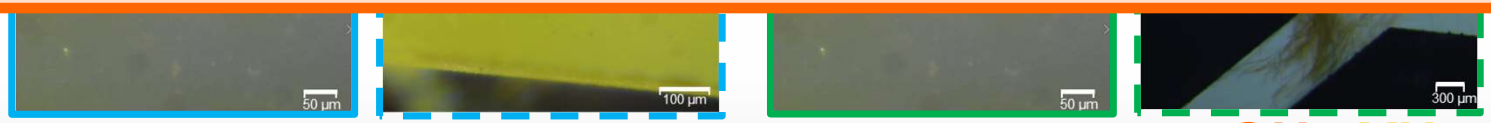
4. Conclusion

Bulk

100% acetone | 70% acetone | Magnet | Rotative

- Many parameters influence ROY polymorphism
  - Both in bulk and in microfluidic channel
- Comparison between bulk and microfluidic channel
  - Magnetic stirrer in bulk ↔ Acoustic mixing in microfluidic channel
  - Rotation in bulk ↔ Diffusive mixing in microfluidic channel

  } Shear stress?
- First step towards tuning a controlled mixing regime favoring one polymorph



OP - Y | Y | OP - Y | ON - YN

Acknowledgements

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