超臨界CO2を利用した機能性材料創製

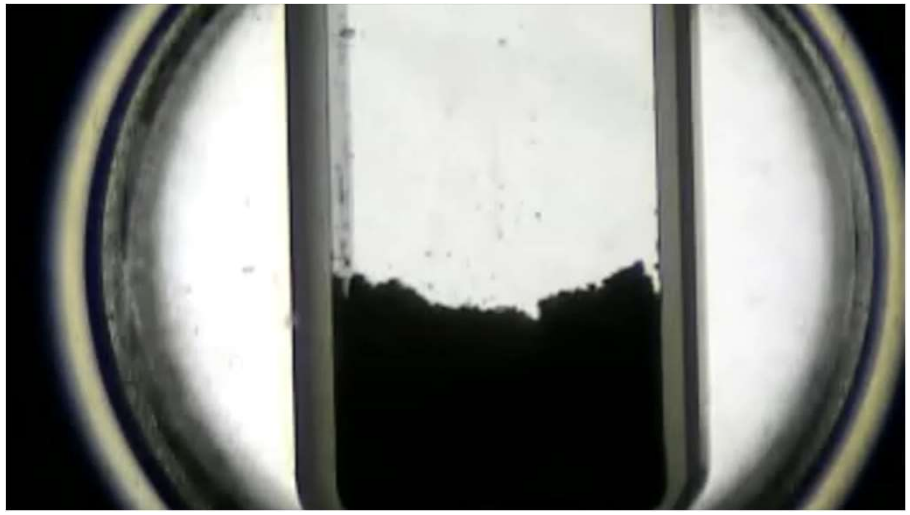
東京工業大学 物質理工学院

下山 裕介

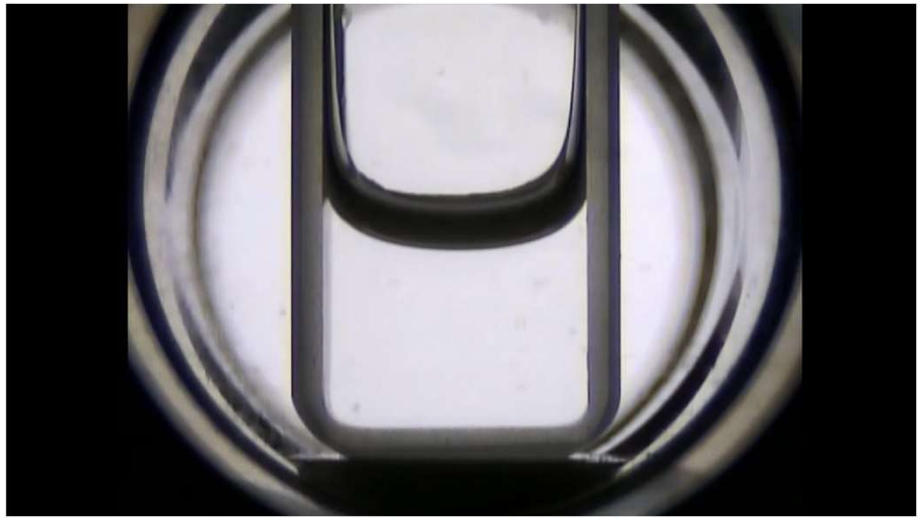
超臨界流体部会 2022年度基礎セミナー@東北大学東京分室, 2022.11.28

Supercritical CO_2

- Fluid over critical point at 31.1 °C and 7.38 MPa
- Practical application for extraction in food, cosmetic and pharmaceutic industries
- CO_2 as “safe solvent” for human body
- CO_2 with specific properties unlike “common CO_2”



Solid solute dissolution



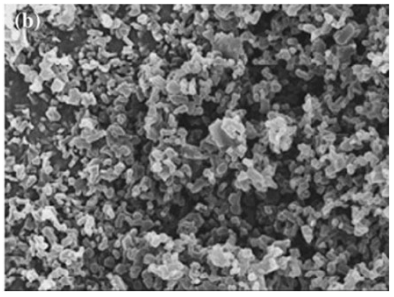
Miscible with liquid solvent

超臨界CO2を利用した材料プロセス

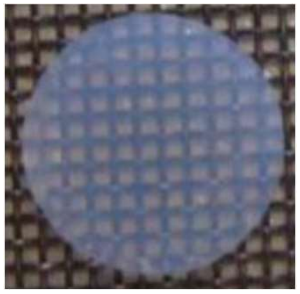
Material fabrication process using supercritical fluid

SCF as solvent
- Supercritical drying
- Supercritical fluid extraction of emulsion
- Supercritical solvent impregnation
- Rapid expansion of supercritical solution

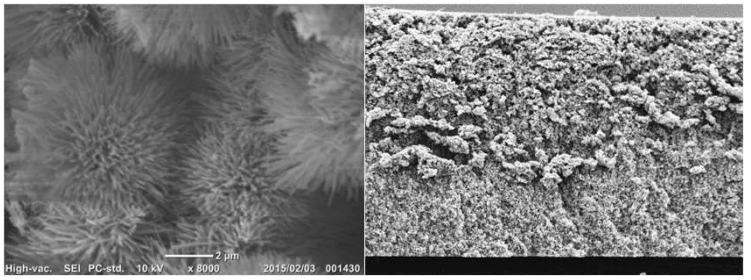
SCF as antisolvent
- Supercritical antisolvent
- Solution-enhanced dispersion of solids



Nanoparticle



Aerogel



Porous material

本日の講演

[A] 超臨界CO2の溶解性を利用した材料プロセス

A-1 : Supercritical Extraction of emulsion

A-2 : LipTube for liposome formation

[B] 超臨界CO2の浸透性を利用した材料プロセス

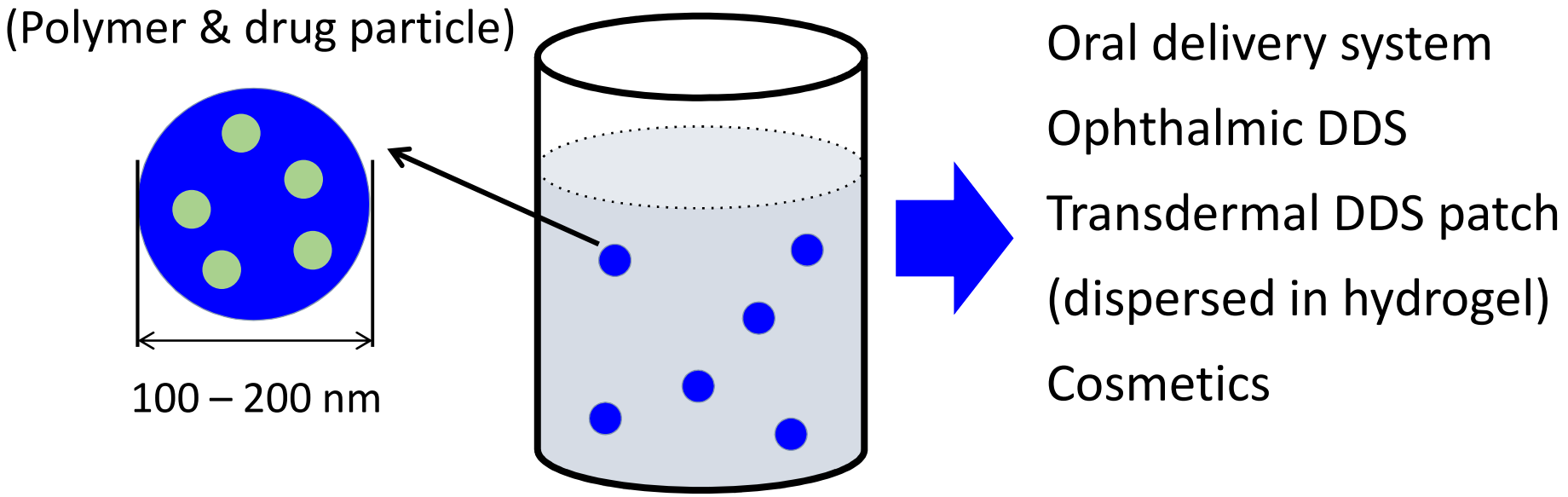
Pharmaceutical crystal formation

Nanosuspension for formulation

>> Drug release or cosmetic application

>> Controlling drug release and dose of drug

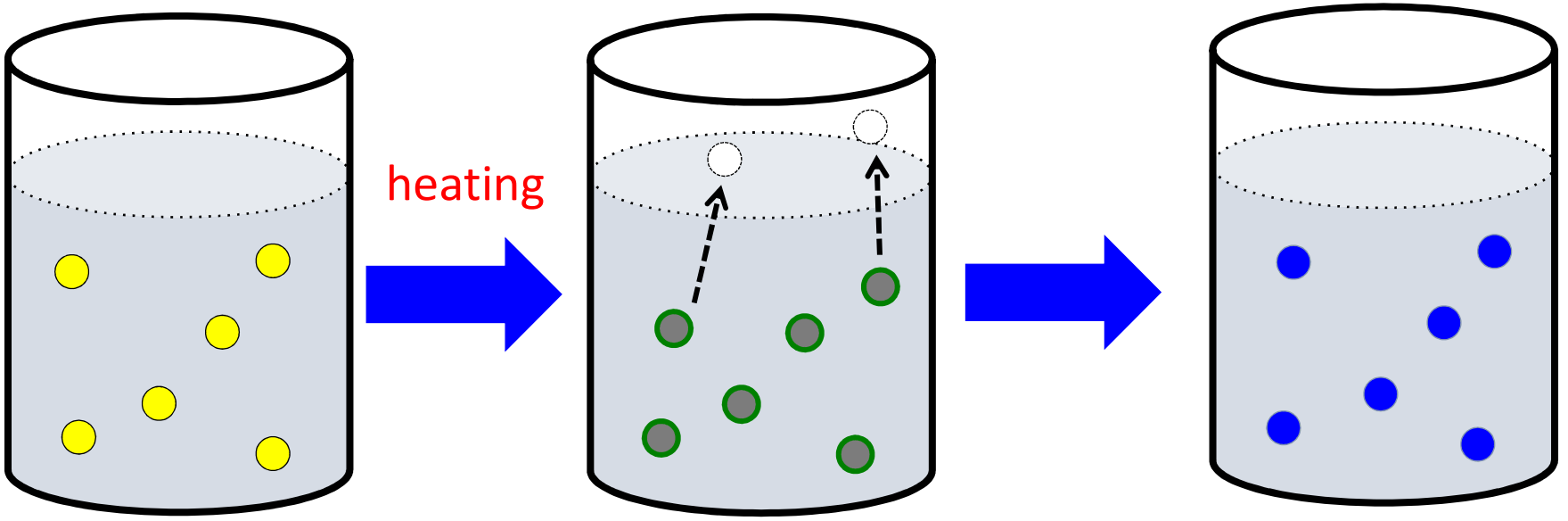
>> Polymer particle size and size distribution control



Extraction of emulsion technique

Int. J. Pharm., 447 (2013) 214; Chem. Commun., 47 (2011) 10001; Natur. Nanotechnol., 3 (2008) 50

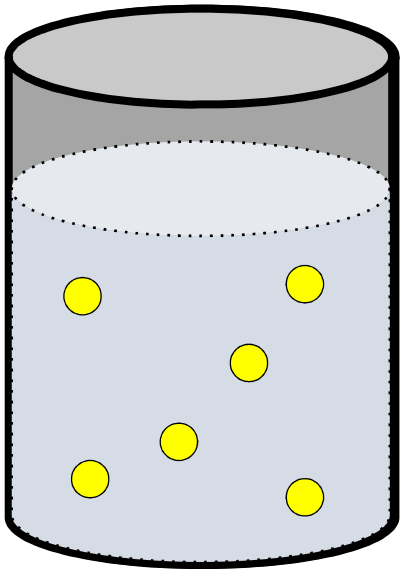
● Oil droplet dissolving polymer



(O / W emulsion) (Oil evaporation) (polymer nanoparticle dispersed solution)

- Slow mass transfer of oil on evaporation
- Particle aggregation after oil evaporation

Supercritical fluid extraction of emulsion (SFEE)



SFEE

Supercritical CO_2

Chattopadhyay et al., J. Pharm. Sci., 95 (2006) 667

- Enhanced extraction of oil phase
- Reduction of polymer particle aggregation
- Batch type process

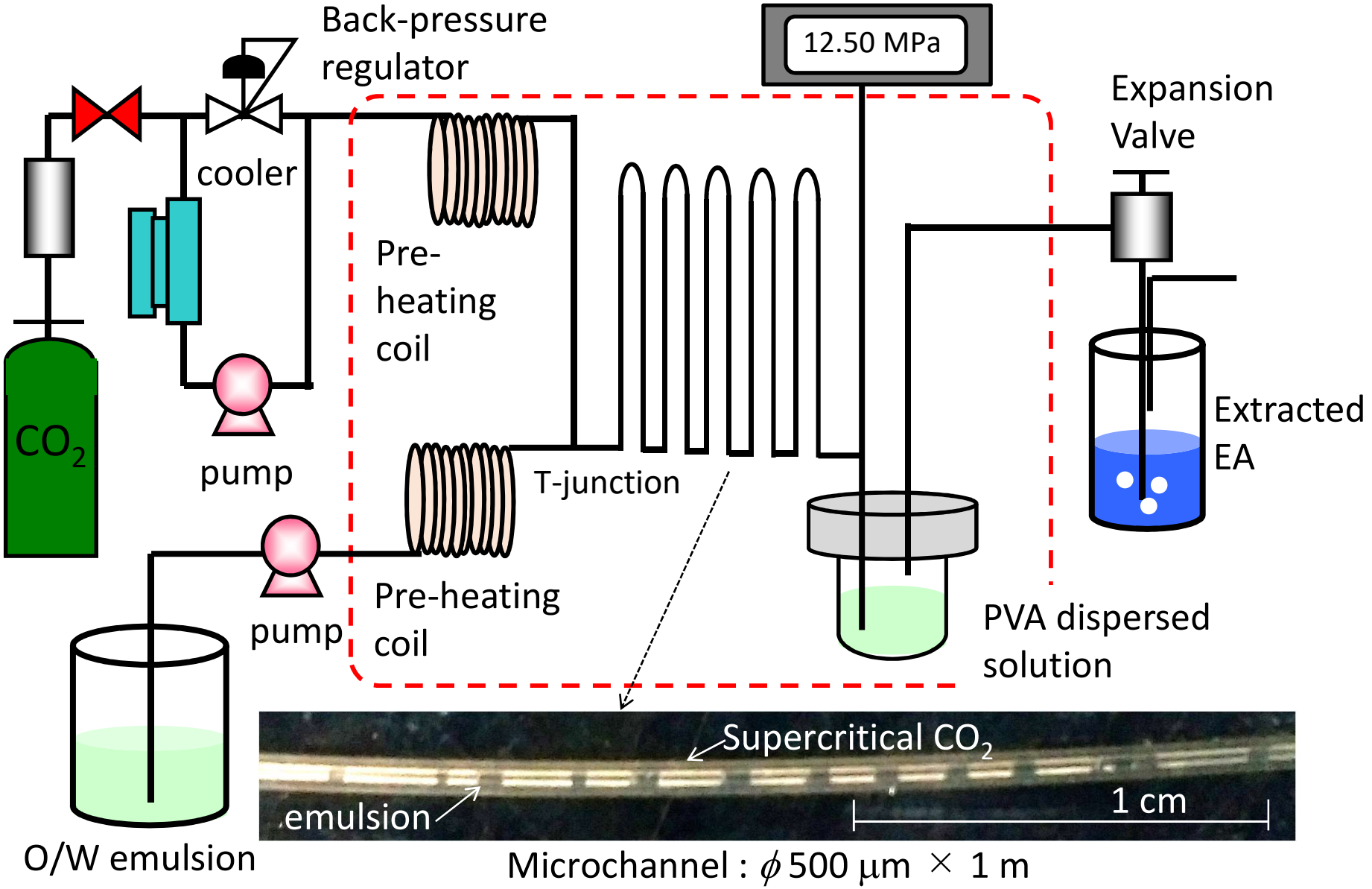
Proposed in this work

Slug flow in microchannel

- High contact probability between $SCCO_2$ and emulsion
- Continuous process

Y. Murakami, Y. Shimoyama, J. Supercrit. Fluids (2016), (2017)
T. Wijakmatee, Y. Shimoyama, Y. Orita, Ind. Eng. Chem. Res. (2022)

A-1 : Supercritical Extraction of emulsion 8



Microchannel : ϕ 500 μm × 1 m

Y. Murakami, Y. Shimoyama, J. Supercrit. Fluids (2016), (2017)

Carbon dioxide : purity over than 99.95 %

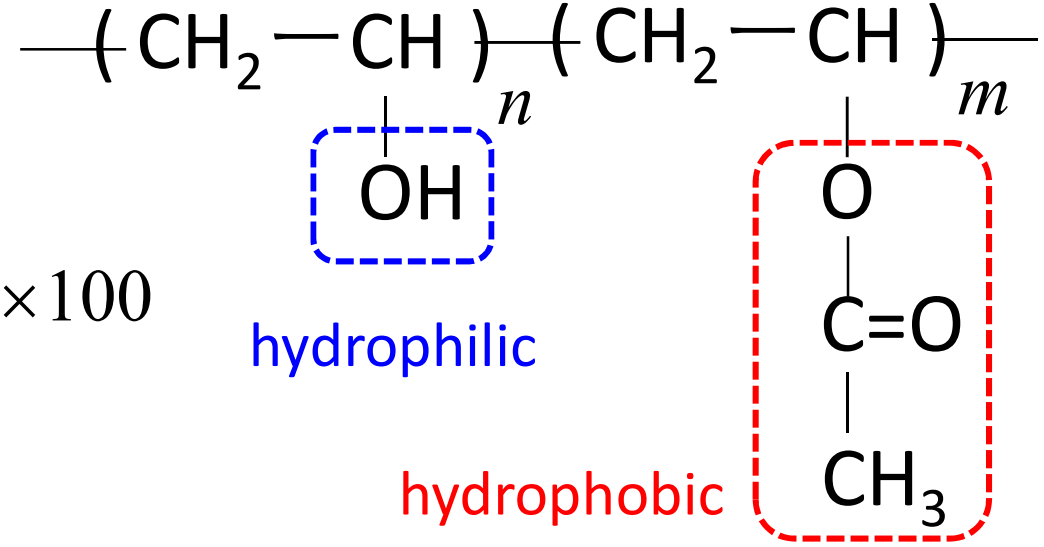
Oil phase : Ethyl acetate (EA), purity over than 99.5 %

Polymer and surfactant : Poly(vinyl alcohol) (PVA)

(1) Mw : 31000 – 50000, 98-99 % hydrolyzed (Sigma-Aldrich)

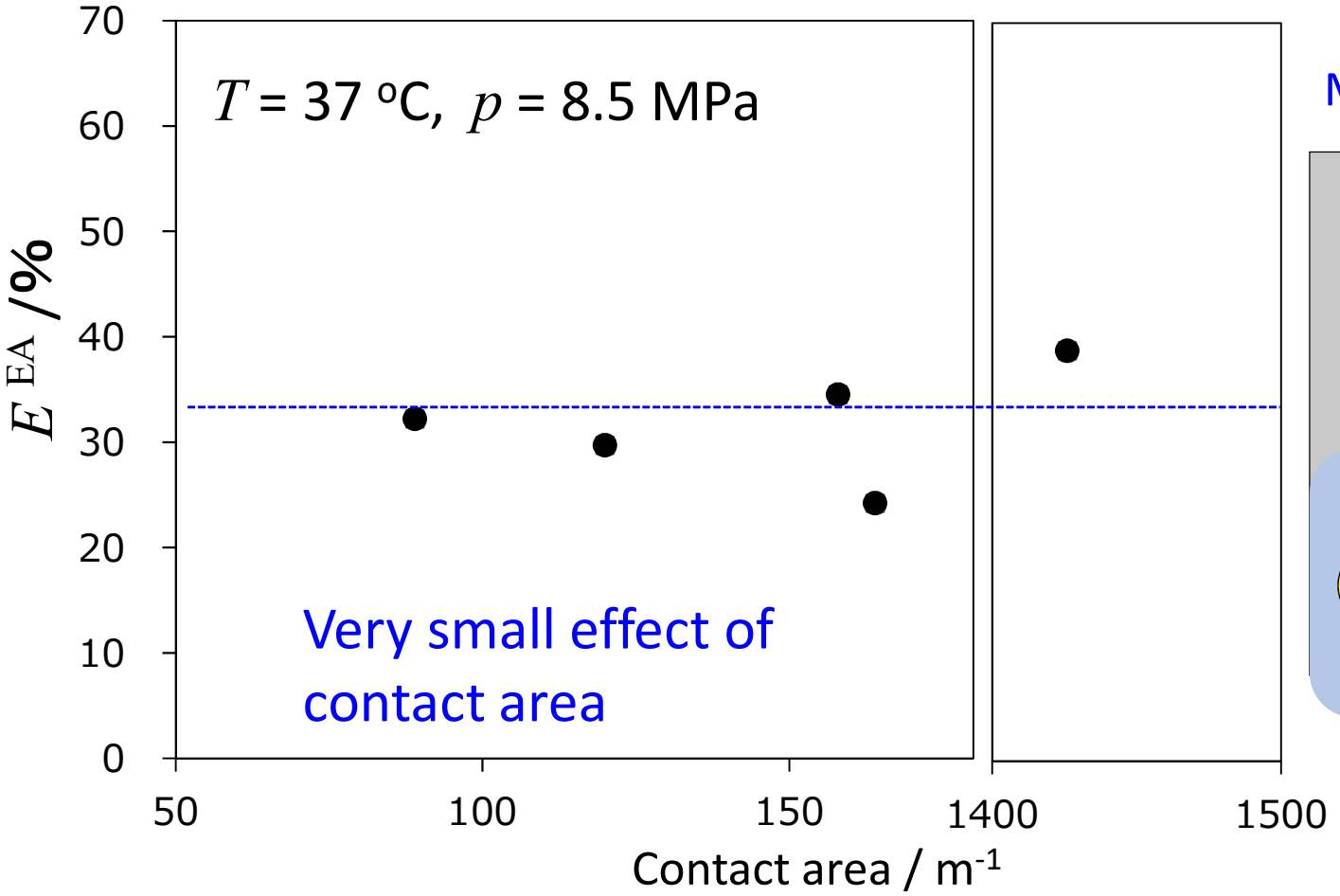
(2) Mw : 66000 – 79000, 78-82 % hydrolyzed (Wako Pure Chem.)

(PVA)

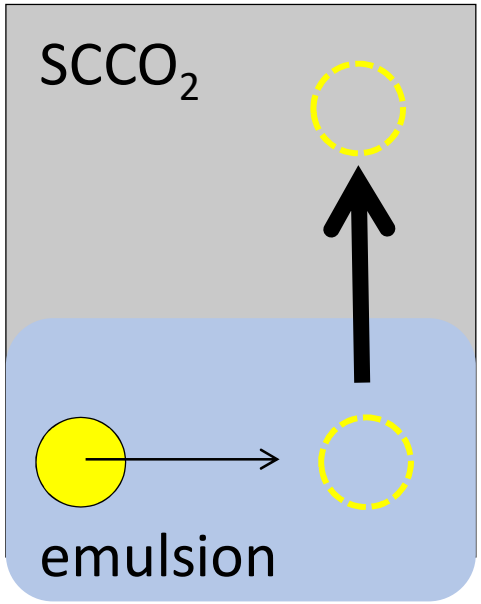


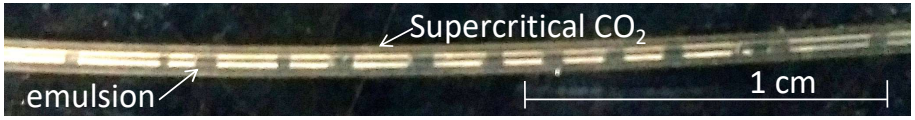
$$\text{hydrolyzed ratio} = \frac{n}{n+m} \times 100$$

Effect of slug contact area on extraction efficiency

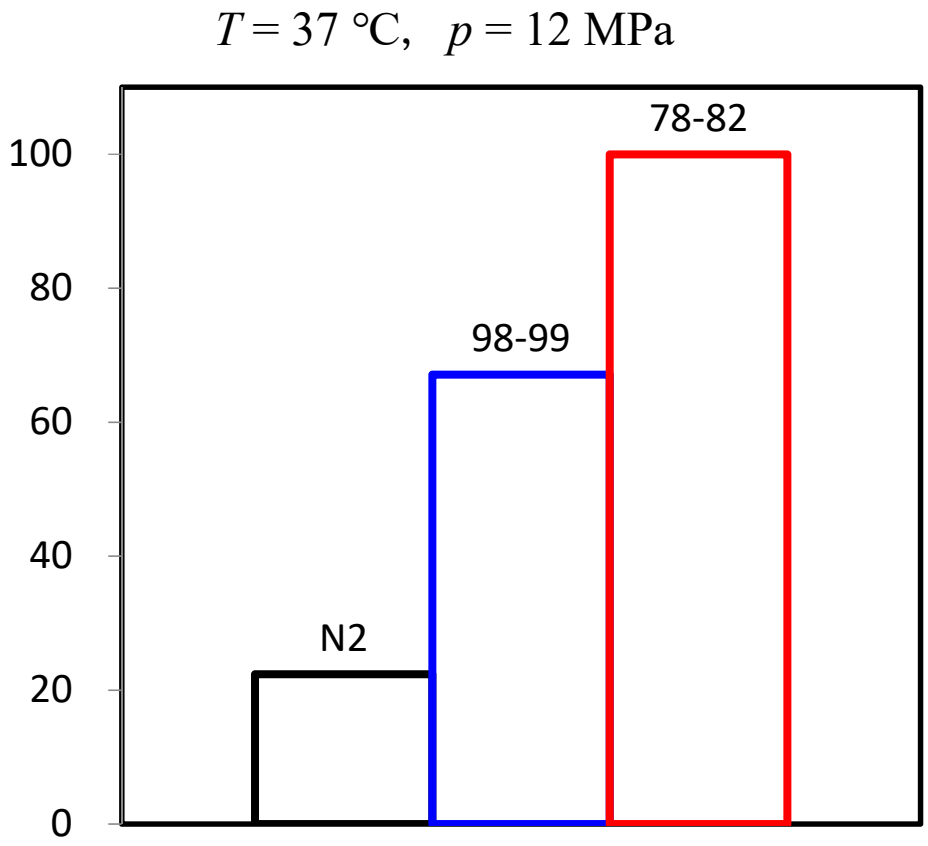


Mass transfer of EA



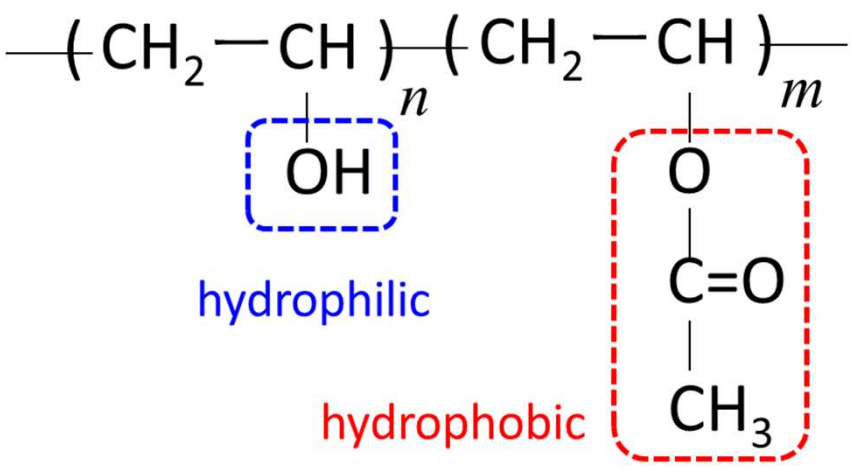


Effect of oil surface hydrophobicity on extraction



(PVA)

$$\text{hydrolyzed ratio} = \frac{n}{n+m} \times 100$$

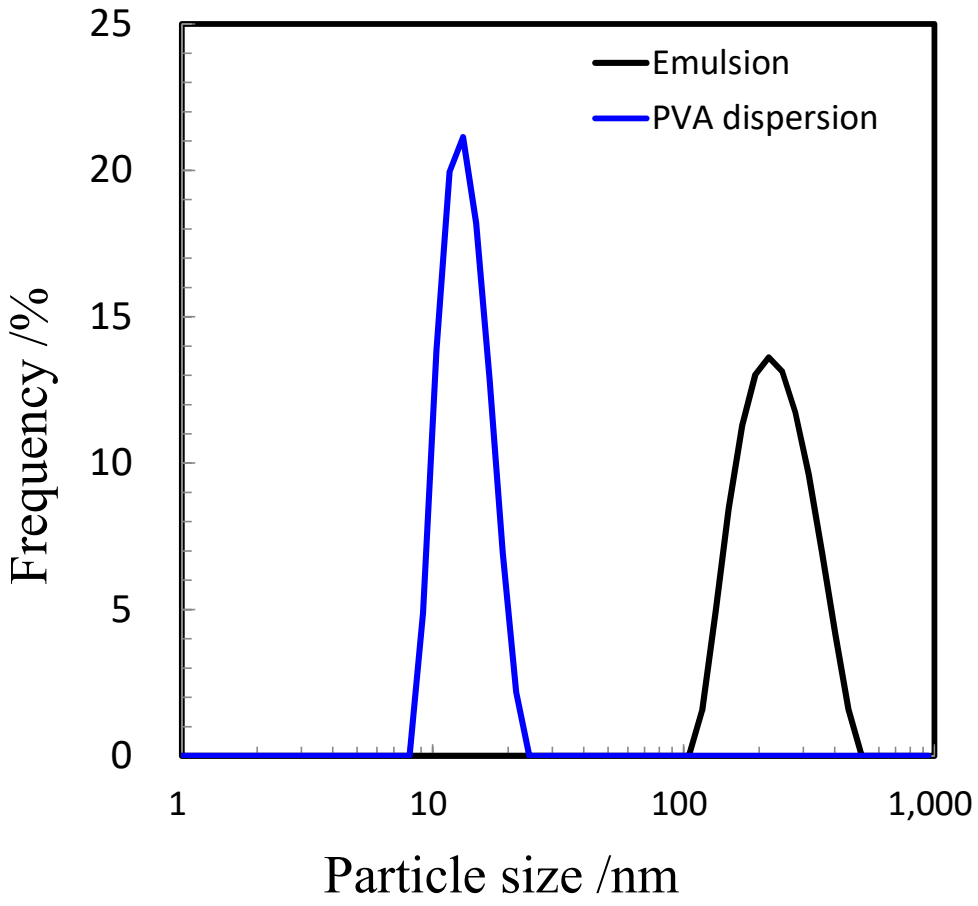


High hydrophobicity results in high extraction rate

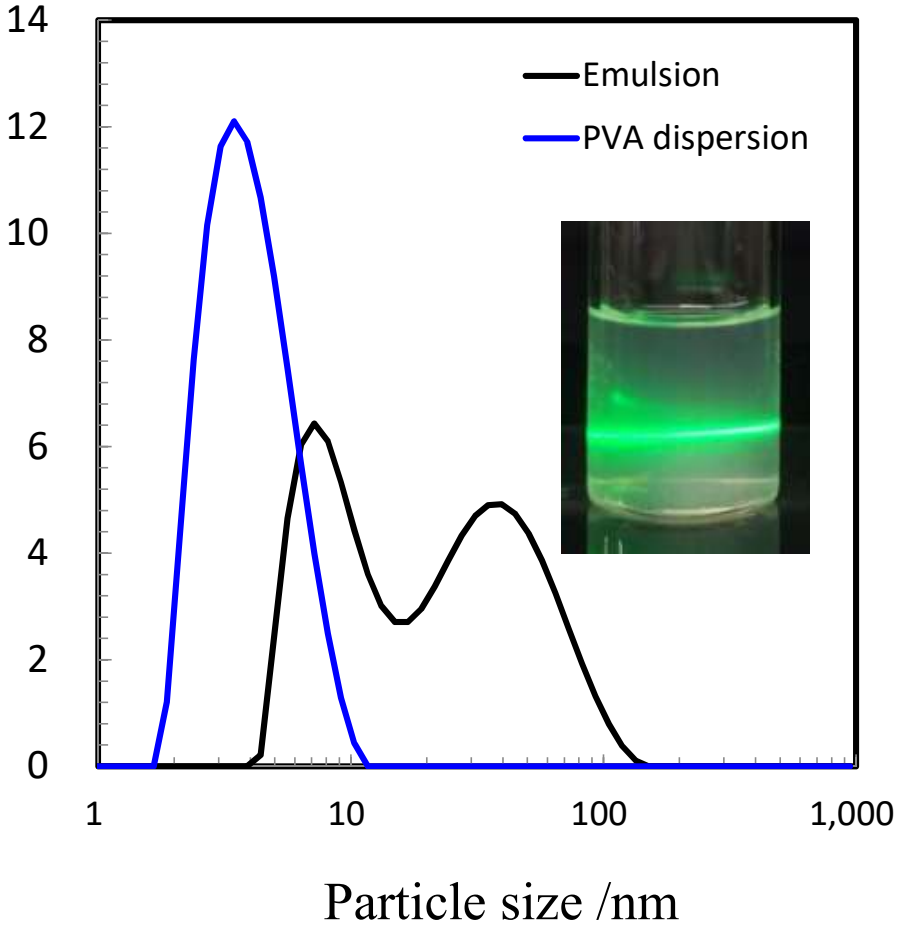
A-1 : Supercritical Extraction of emulsion 12

Effect of oil surface hydrophobicity on nanoparticle formation

PVA : 98 – 99 % hydrolyzed



PVA : 78 – 82 % hydrolyzed

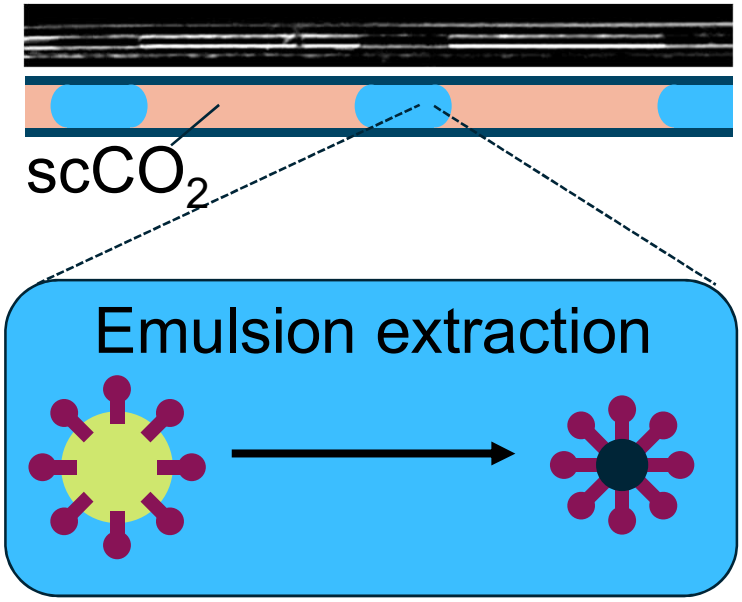


Y. Murakami, Y. Shimoyama, J. Supercrit. Fluids (2016)

Functionalized PVA nanoparticles with Chitosan

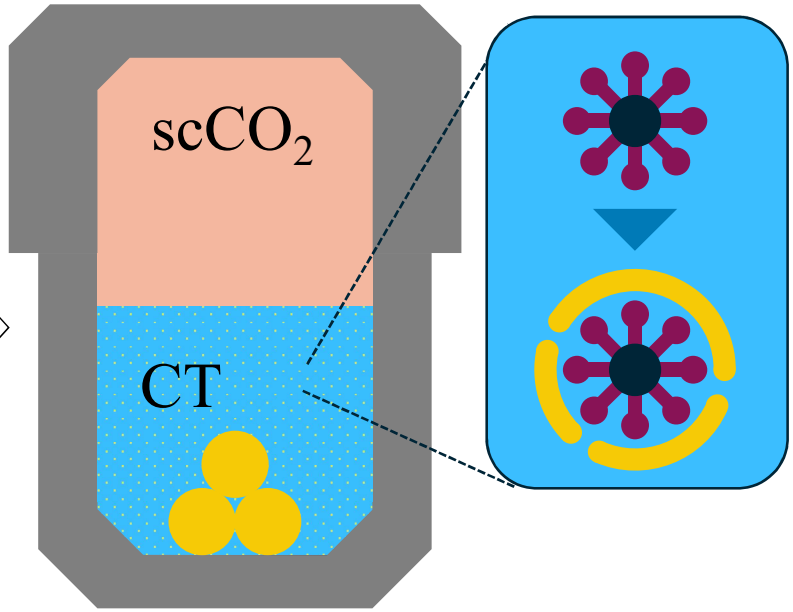
SFEE in microchannel

Segmented flow



Precipitation of IBP/PVA

Chitosan (CT) dissolution using supercritical CO_2

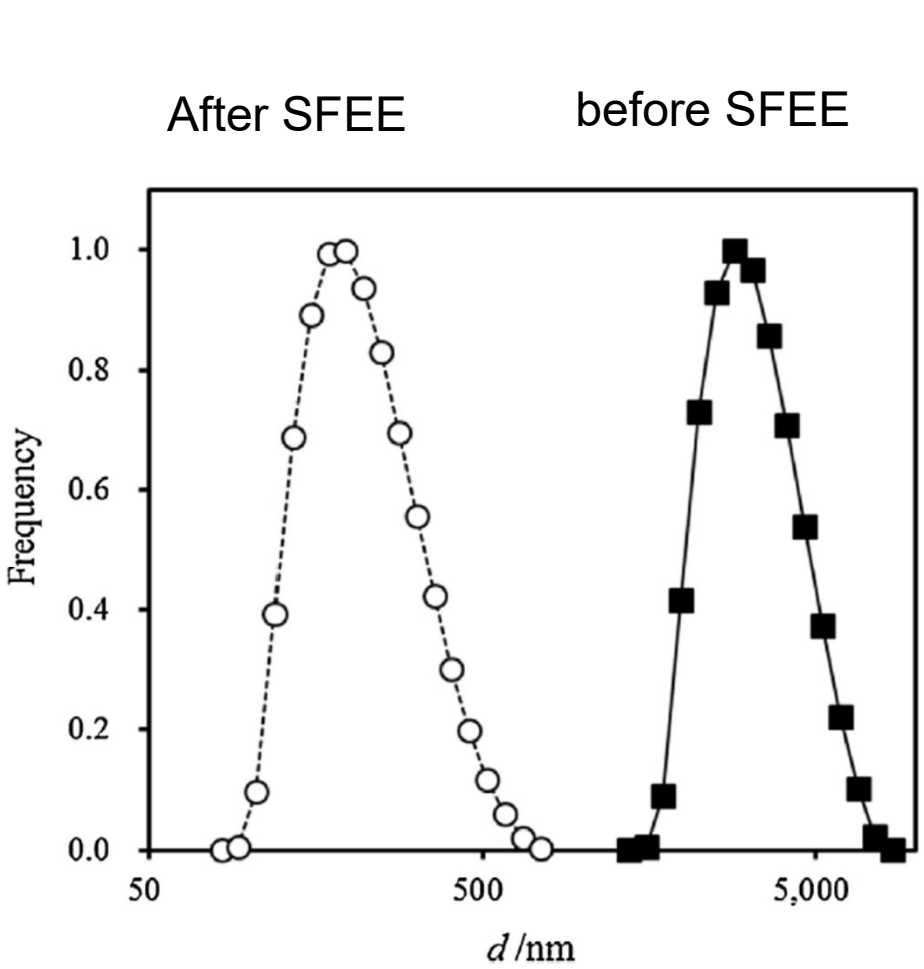


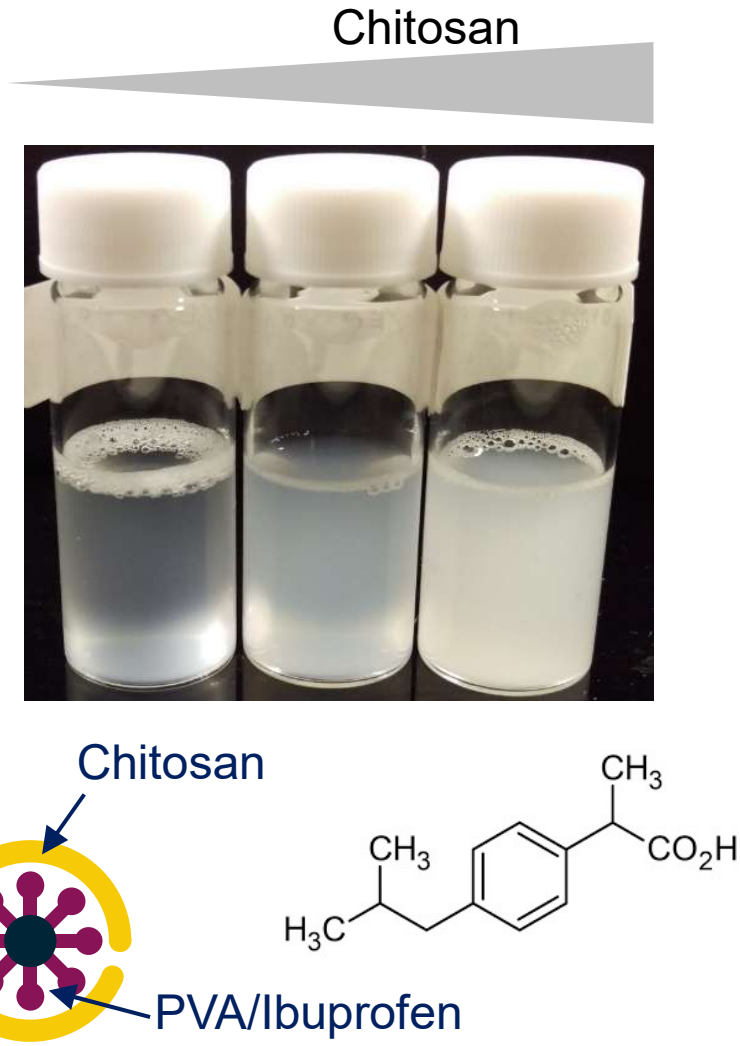
Functionalized by CT

Y. Murakami, Y. Shimoyama, J. Supercrit. Fluids (2017)

A-1 : Supercritical Extraction of emulsion 14

Functionalized PVA nanoparticles with Chitosan

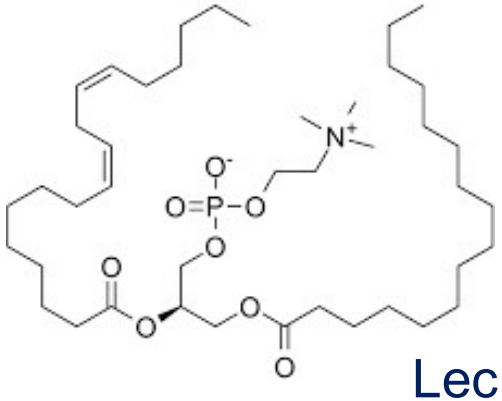




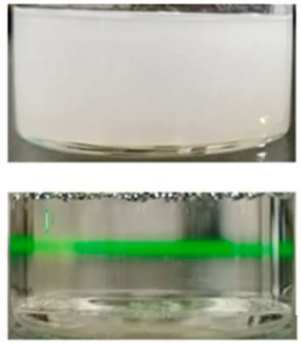
Y. Murakami, Y. Shimoyama, J. Supercrit. Fluids (2017)

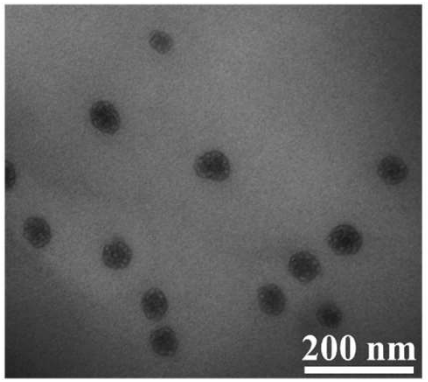
A-1 : Supercritical Extraction of emulsion

Lipid nanosuspension

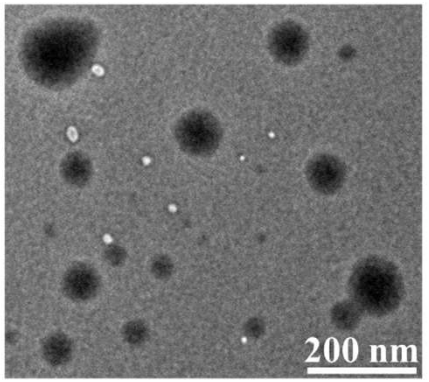


Lechitin

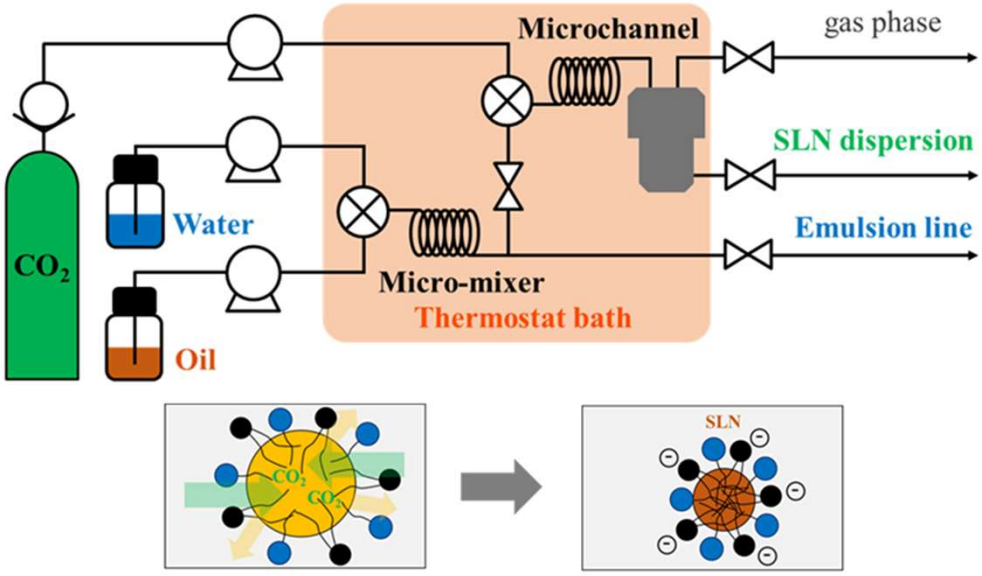


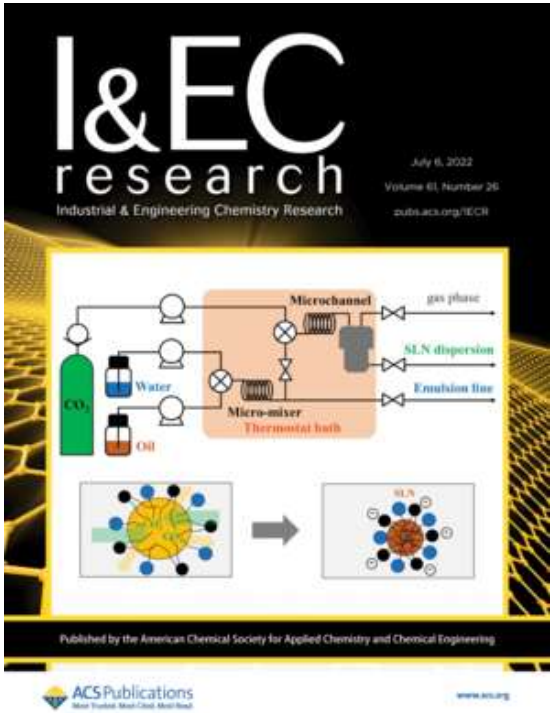


SFEE at 8.5 MPa



SFEE at 20.0 MPa



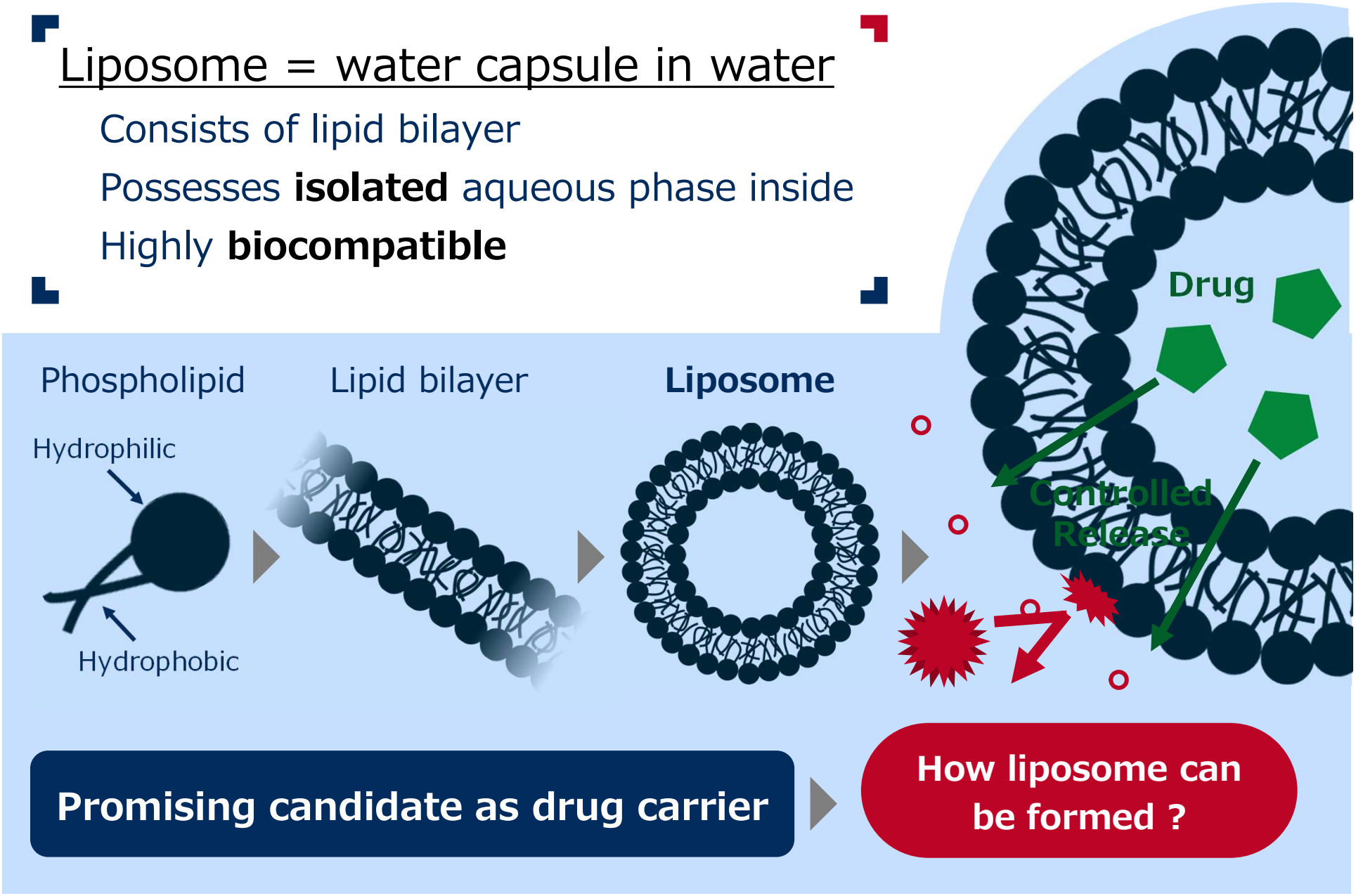


T. Wijakmatee, Y. Shimoyama, Y. Orita, Ind. Eng. Chem. Res. (2022)

A-2 : LipTube for liposome formation

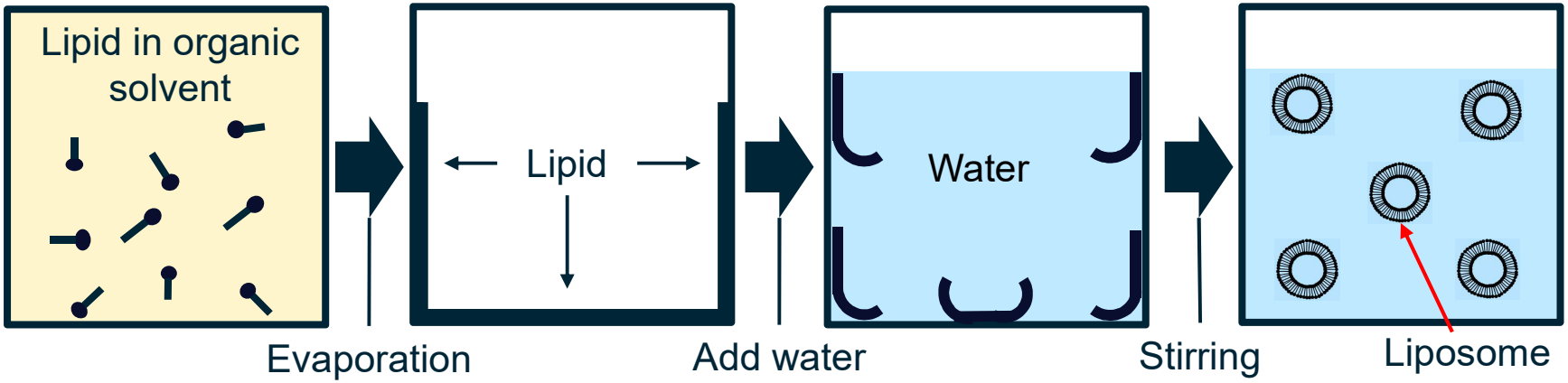
Liposome = water capsule in water

- Consists of lipid bilayer
- Possesses **isolated** aqueous phase inside
- Highly **biocompatible**

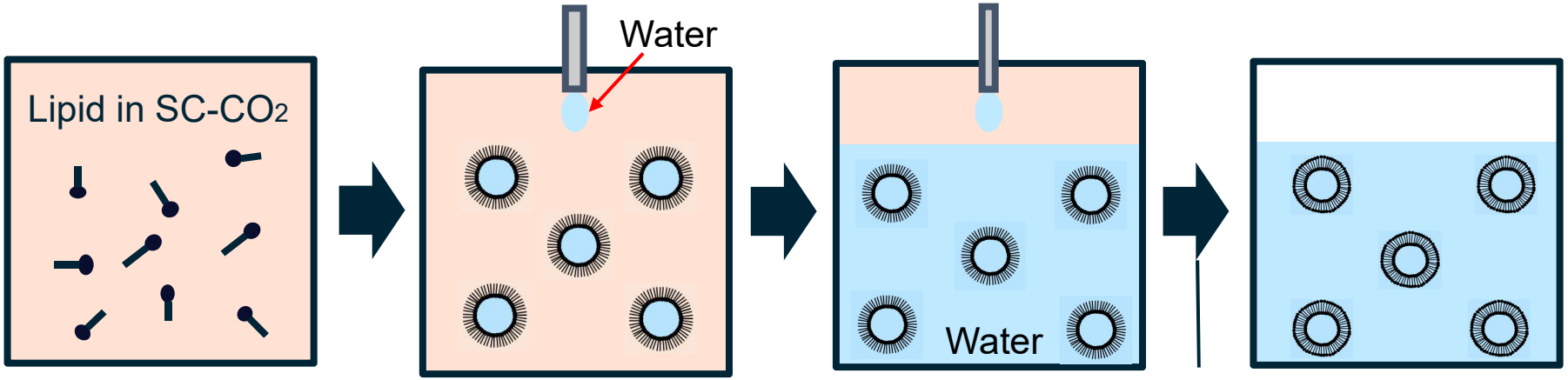


A-2 : LipTube for liposome formation

Bangham method: Chem. Phys. Lipid, 1 (1967) 225



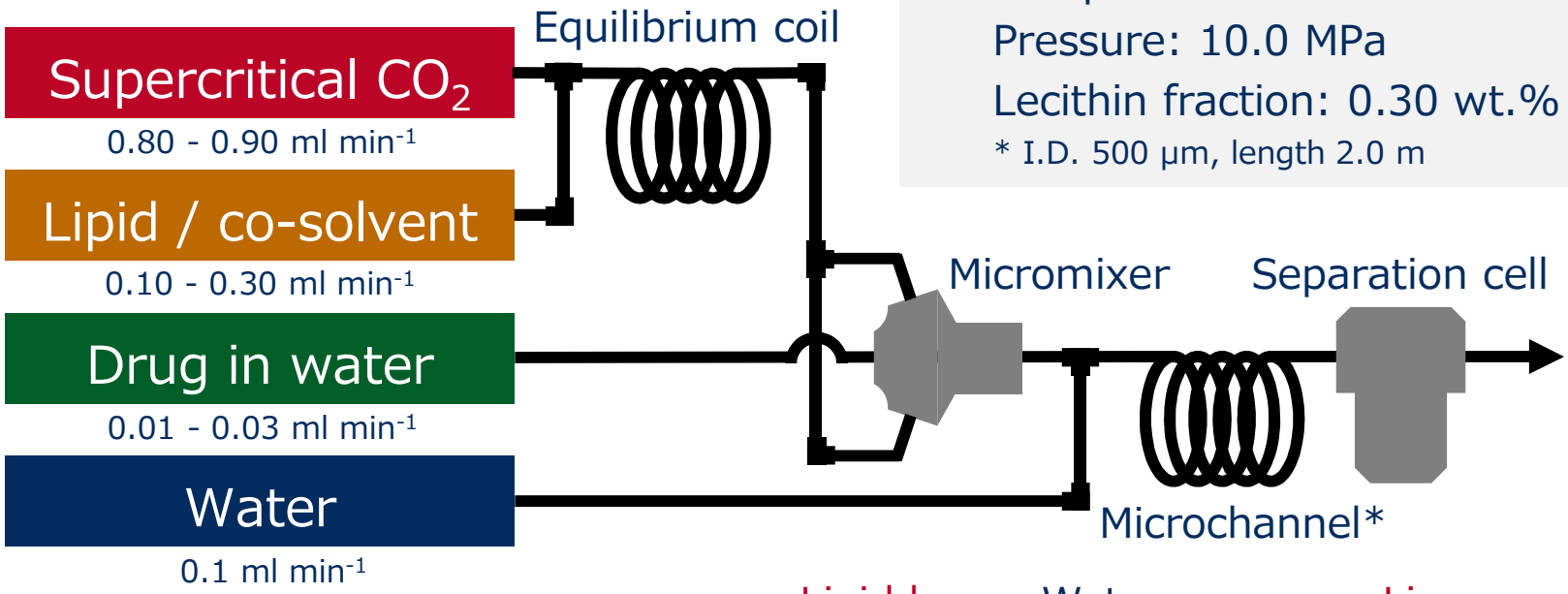
Supercritical reverse-phase inversion method: Langmiur, 22 (2006) 4054



Continuous operation on liposome production using $SCCO_2$:
SuperLip: Chem. Eng. J, 249 (2014) 3824

A-2 : LipTube for liposome formation

Apparatus



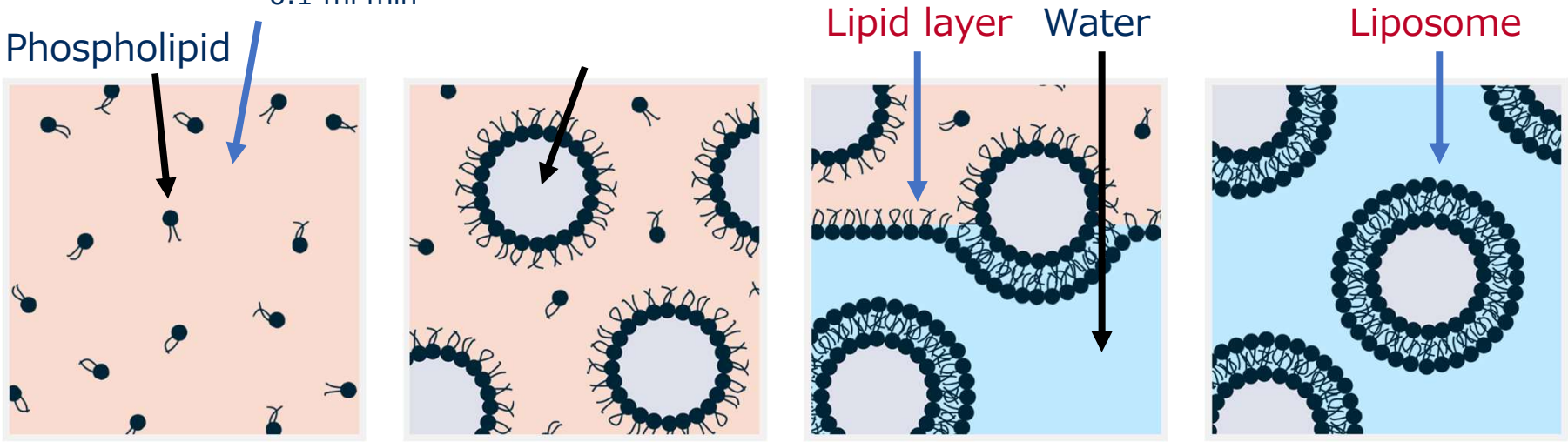
Conditions

Temperature: 313.0 K

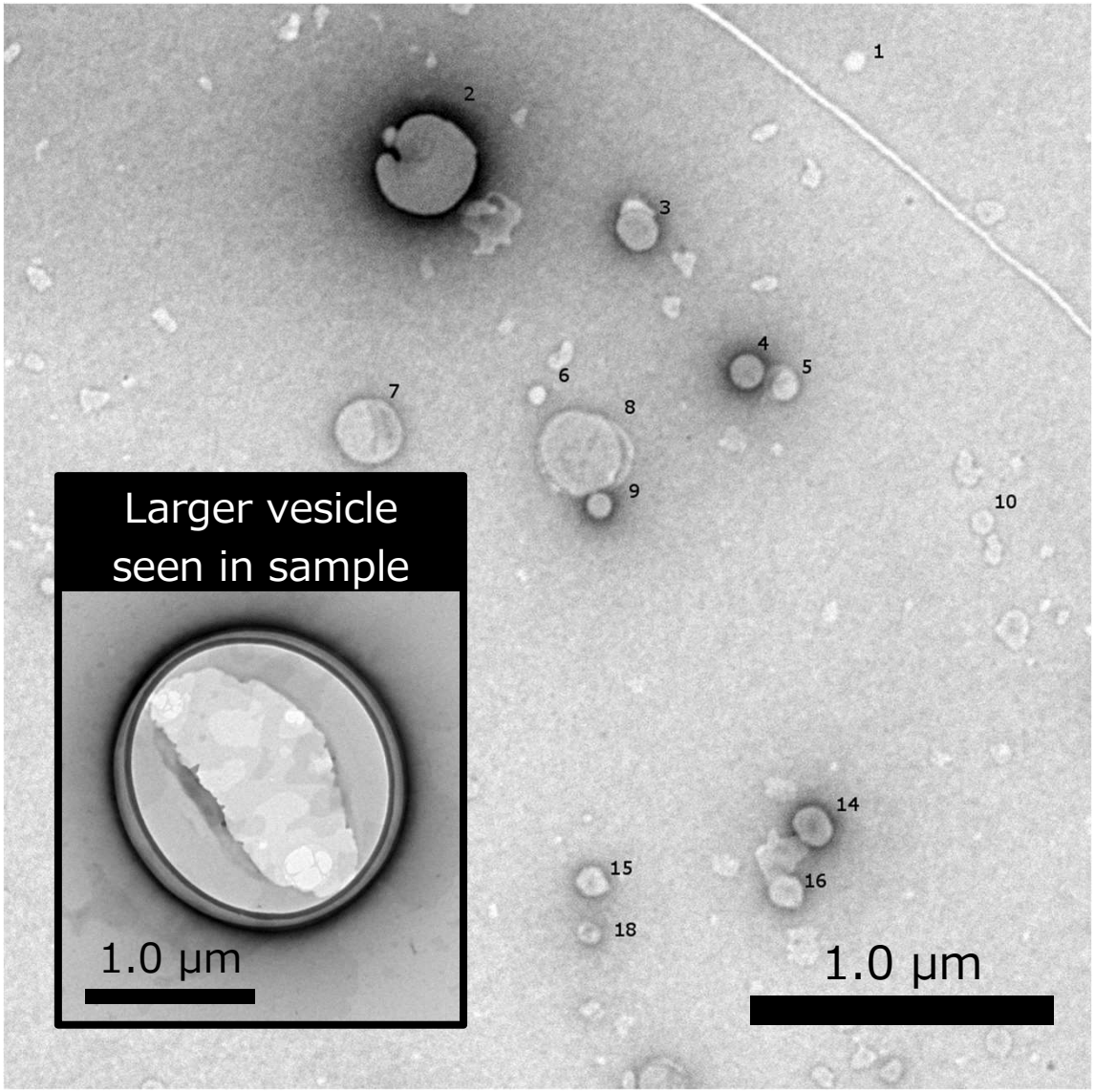
Pressure: 10.0 MPa

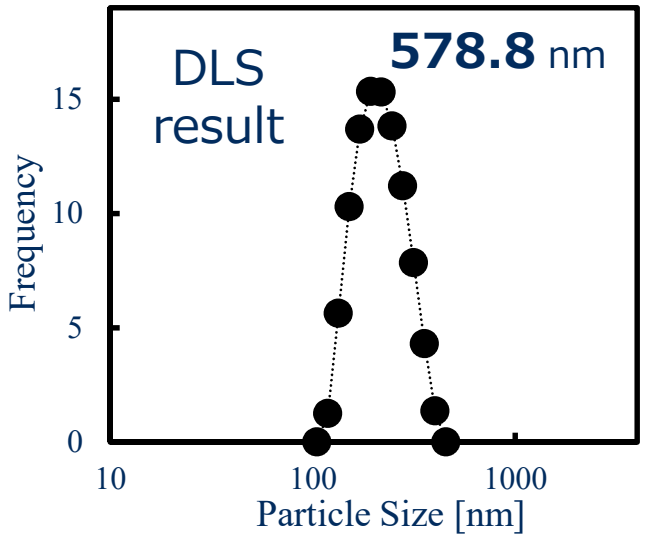
Lecithin fraction: 0.30 wt.%

* I.D. 500 μm, length 2.0 m



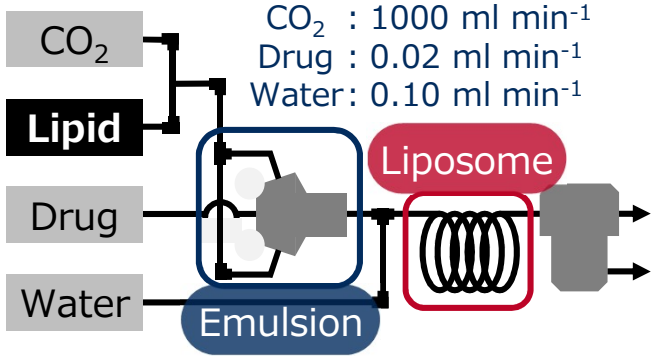
A-2 : LipTube for liposome formation





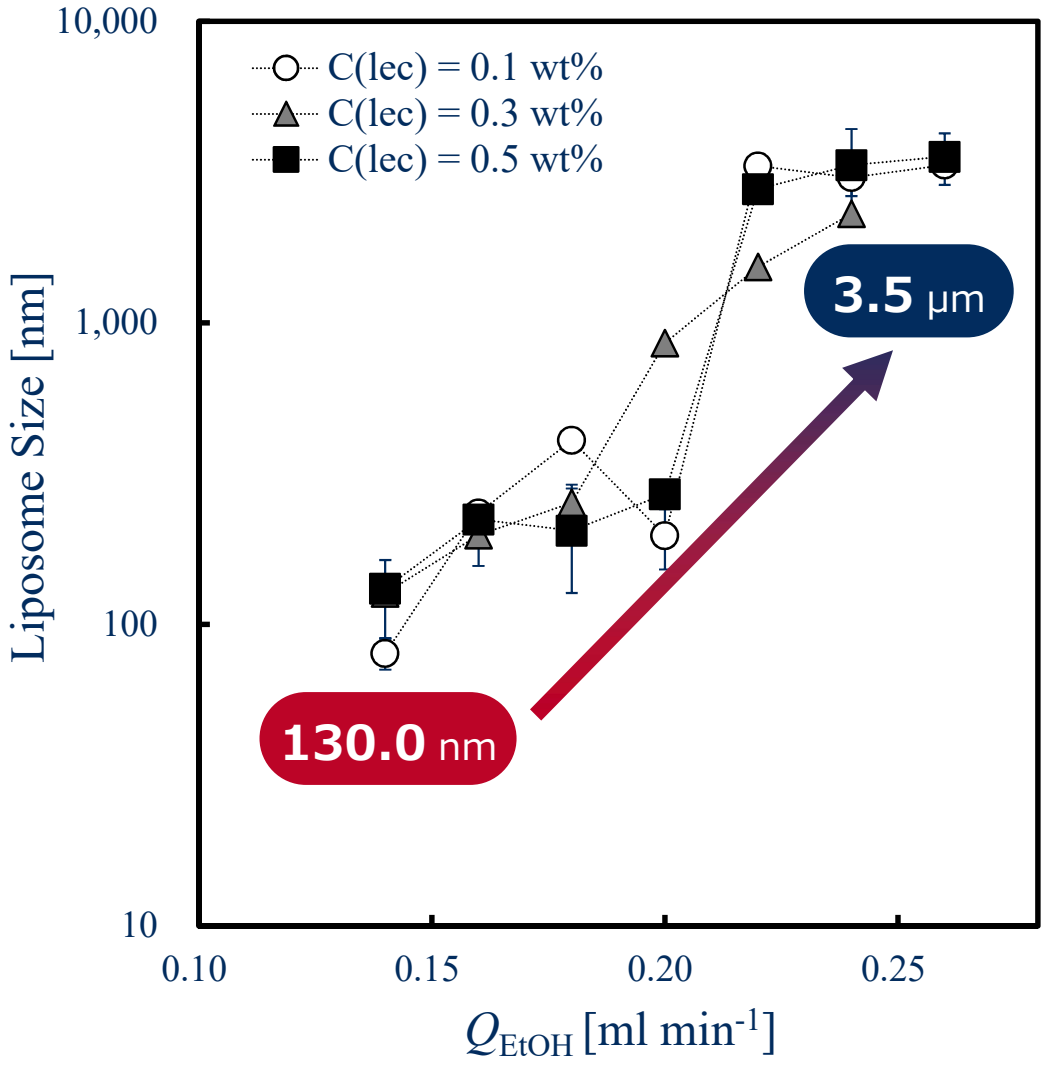
Conditions

Lipid: 0.5 wt% EtOH solution
0.22 ml min^{-1}



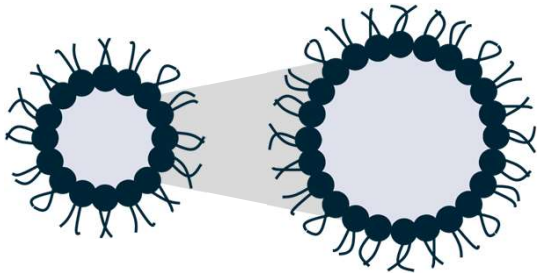
Y. Murakami, et al., Ind. Eng. Chem. Res. (2022)

A-2 : LipTube for liposome formation



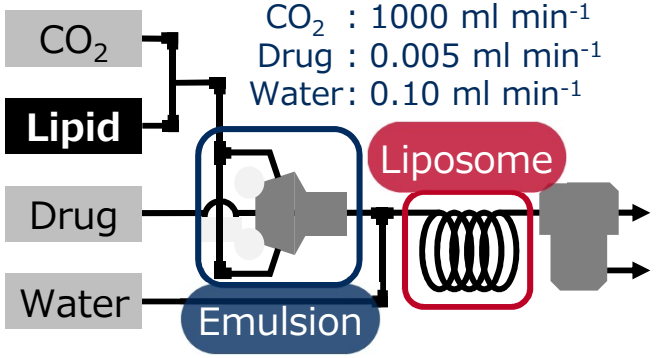
Ethanol Amount

small ↓ large ↑



Conditions

Lipid: EtOH solution
0.14 – 0.26 ml min^{-1}



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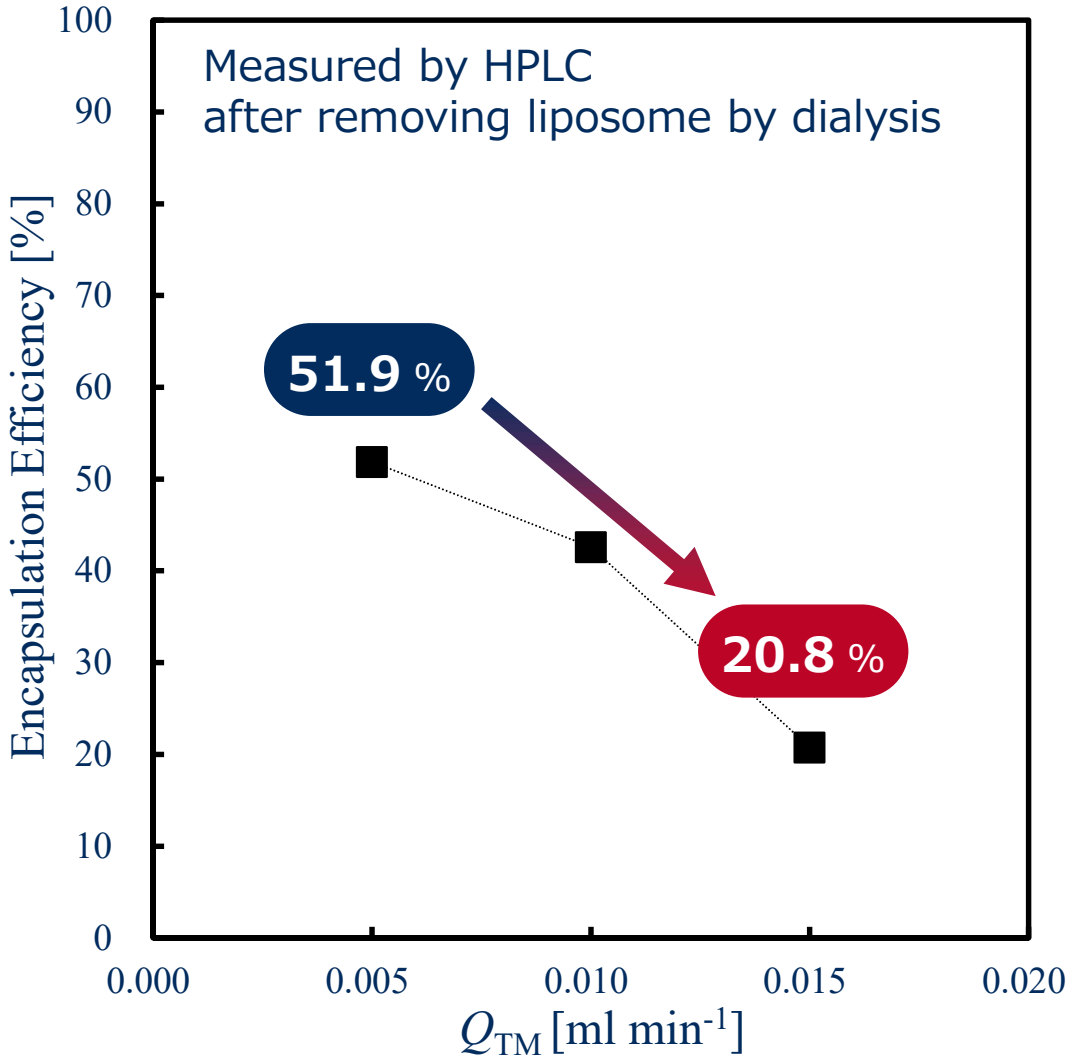
A-2 : LipTube for liposome formation

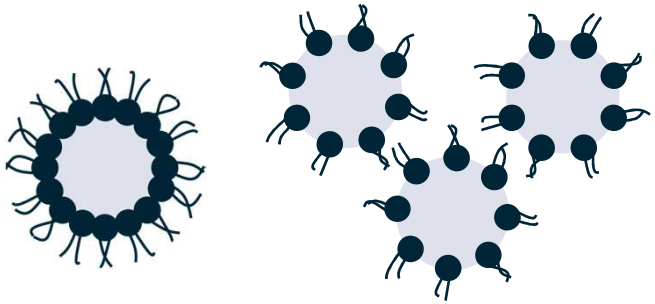


Drug aq. Amount

small ⬇ ⬆ **large**

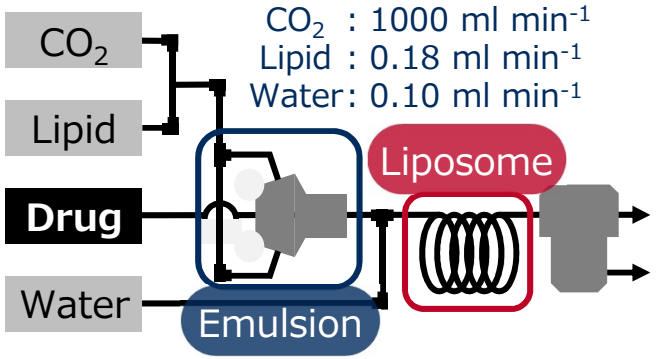
Stability of emulsion

high ⬆ ⬇ **low**



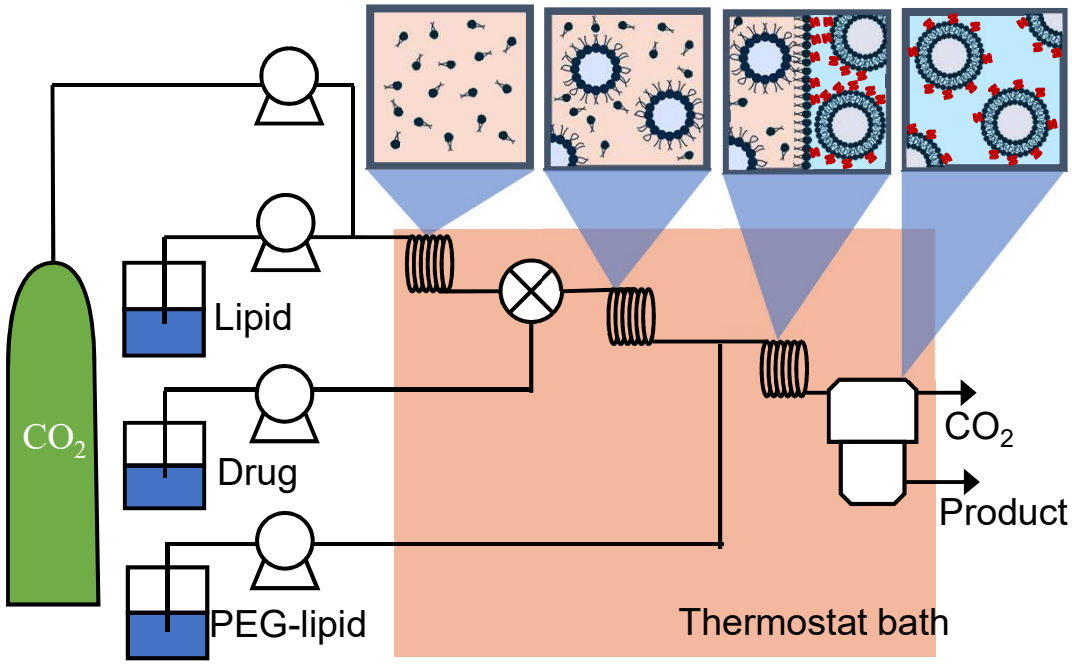
Conditions

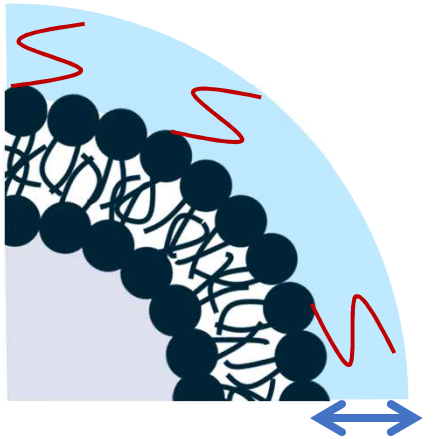
Drug: 0.005 – 0.015 ml min^{-1}

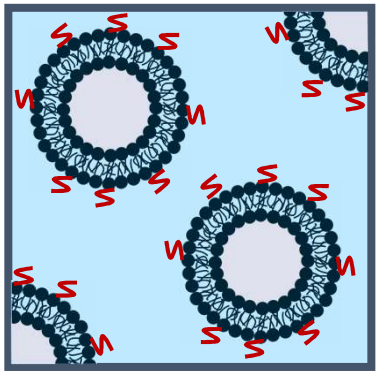


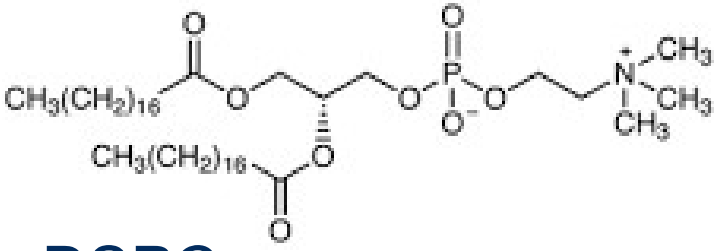
Y. Murakami, et al., Ind. Eng. Chem. Res. (2022)

PEGylated Liposome by LipTube process



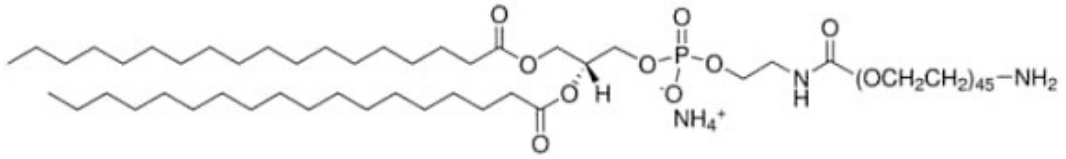






DSPC

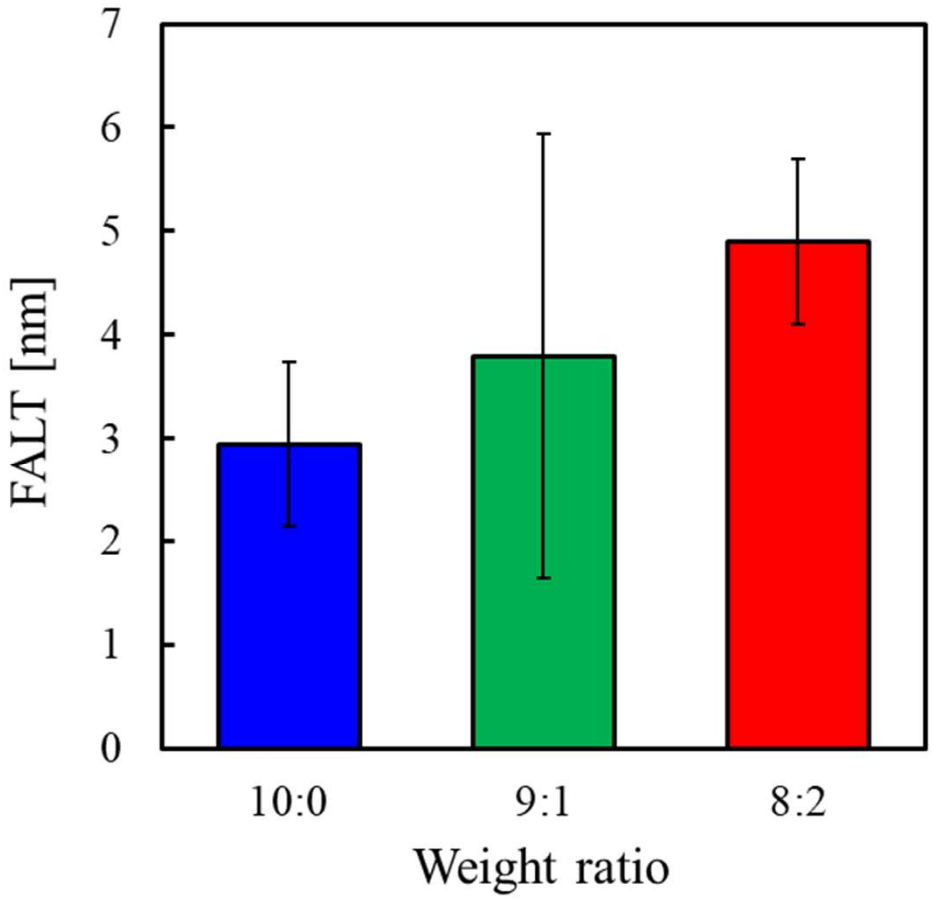
DSPE-PEG

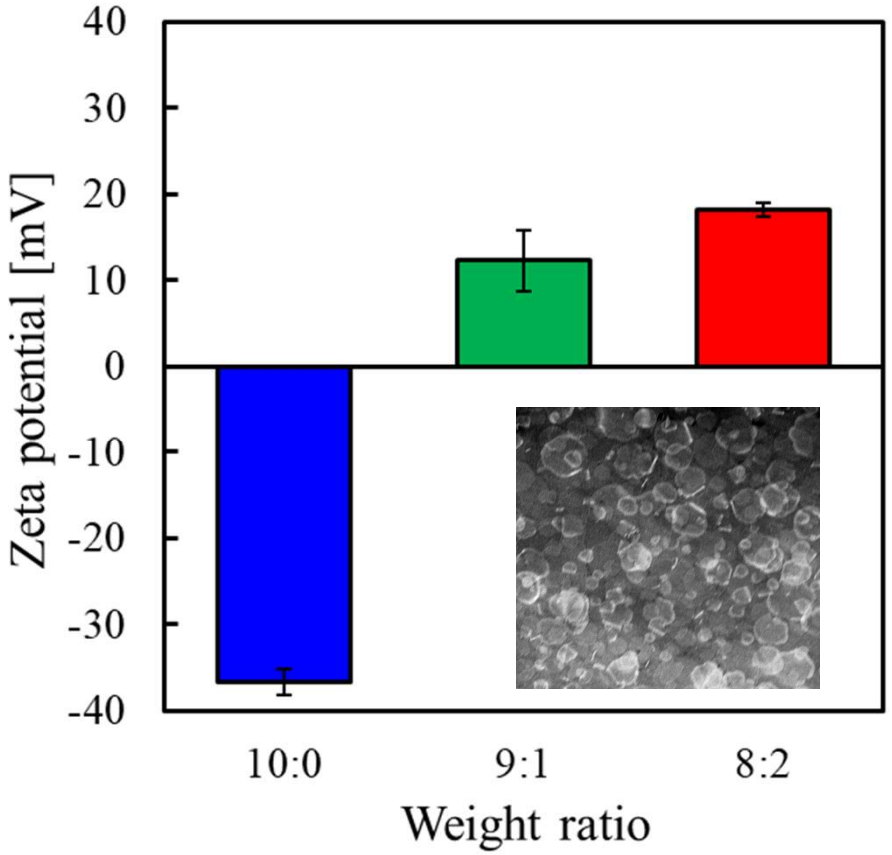


R. Akiyama, et al., J. Nanoparticle Res. (2023)

A-2 : LipTube for liposome formation

PEGylated Liposome by LipTube process





DSPC : DSPE-PEG

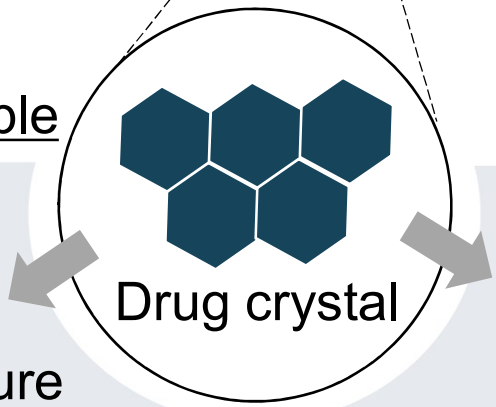
FALT : Fixed Aqueous Layer Thickness

R. Akiyama, et al., J. Nanoparticle Res. (2023)

Social Background

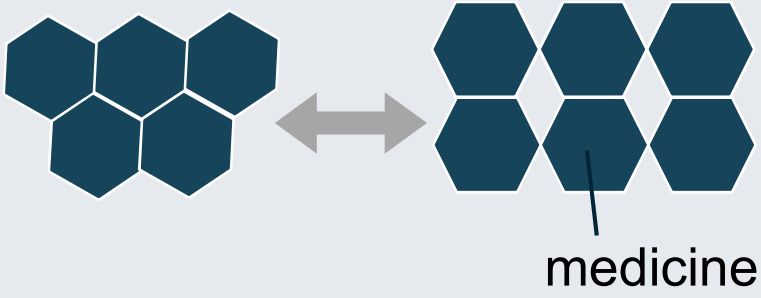
Low drug solubility
→ Effective to diseases
but stop development

Attempts to make drug soluble



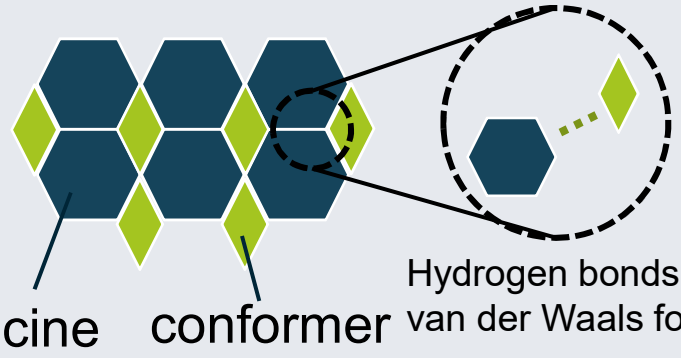
Polymorphous

Same molecular,
but different crystal structure



Cocrystal

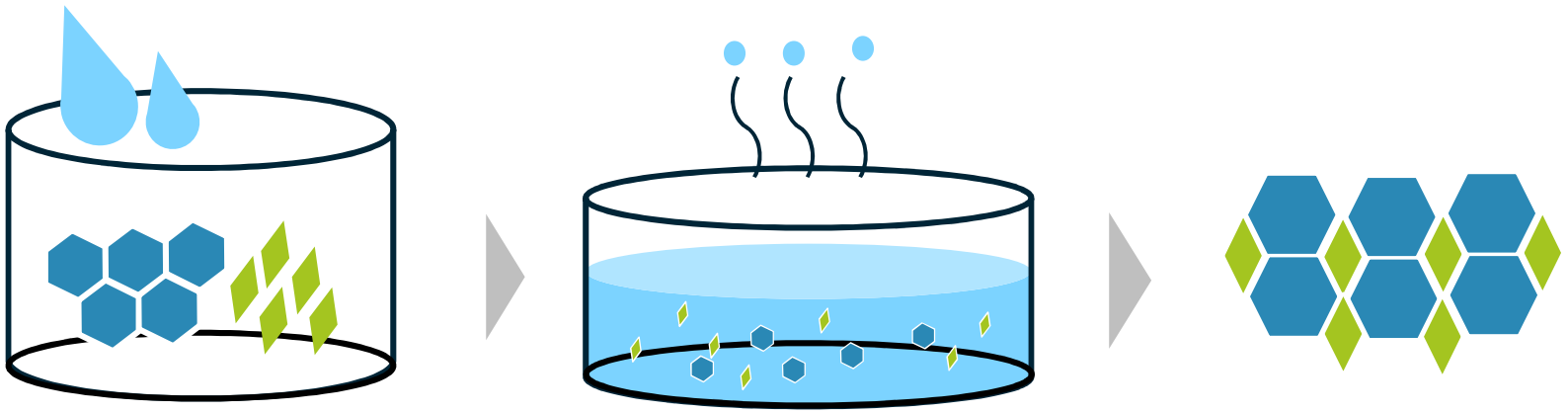
Multicomponent,
nonionic bond



Processing can Improve solubility, dissolution rate, bioavailability

** D.D. Bavishi et.al., Progress in Crystal Growth and Characterization of Materials 62 (2016) 1–8*

	API	Method	Characteristics	
			Solvent	Process
# 1	Norfloxacin-Isonicotinamid-chloroform	Chloroform solution evaporation	×	× 2steps
# 2	Nicotinamide-picric acid	Acetonitrile assisted grinding	△	× 2steps
# 3	Ciprofloxacin-Resorcinol	Toluene slurry crystallization	×	× 2steps



#1 Dissolution to solvent

#2 Evaporation at RT

*[1] Basavoju et al., Crystal Growth & Design, Vol. 6, No. 12, (2006) 2699-2708

	API	Method	Characteristics	
			Solvent	Process
# 1	Norfloxacin-Isonicotinamid-chloroform	Chloroform solution evaporation	×	× 2steps
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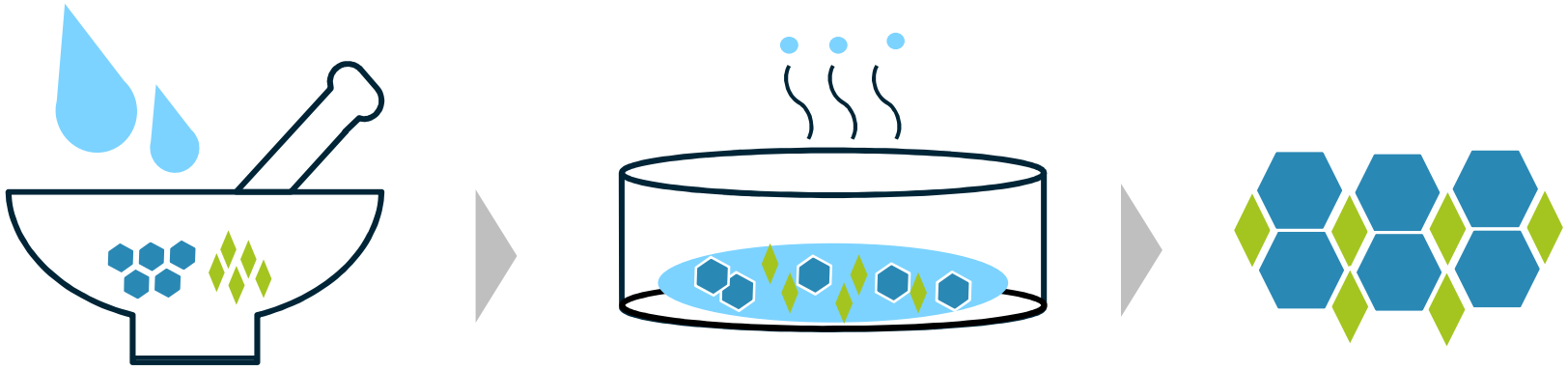


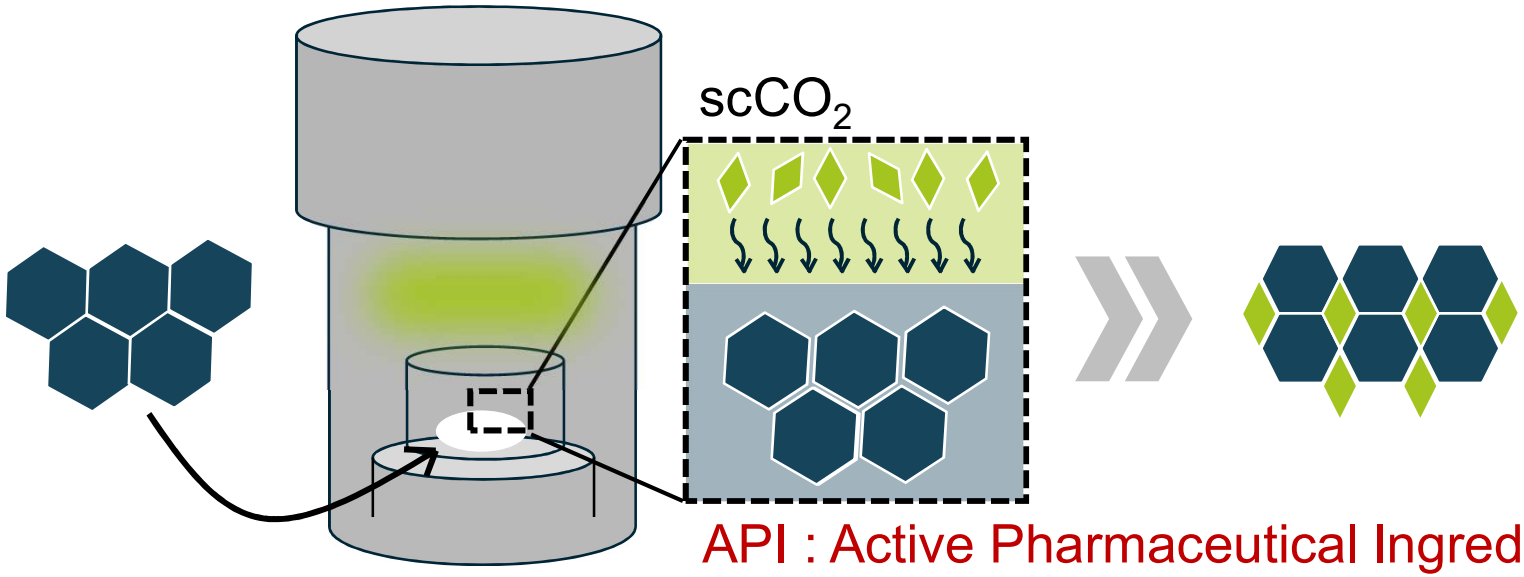
#1 Grinding

#2 Evaporation

*[2] U. Likhitha et al., Journal of Molecular Structure 1195 (2019) 827-838

CO_2 molecular crystal formation

Crystal phase transition driven by CO_2 uptake into crystal lattice in $scCO_2$



API : Active Pharmaceutical Ingredent

#1 Contact with $scCO_2$ → diffusion into crystal structure

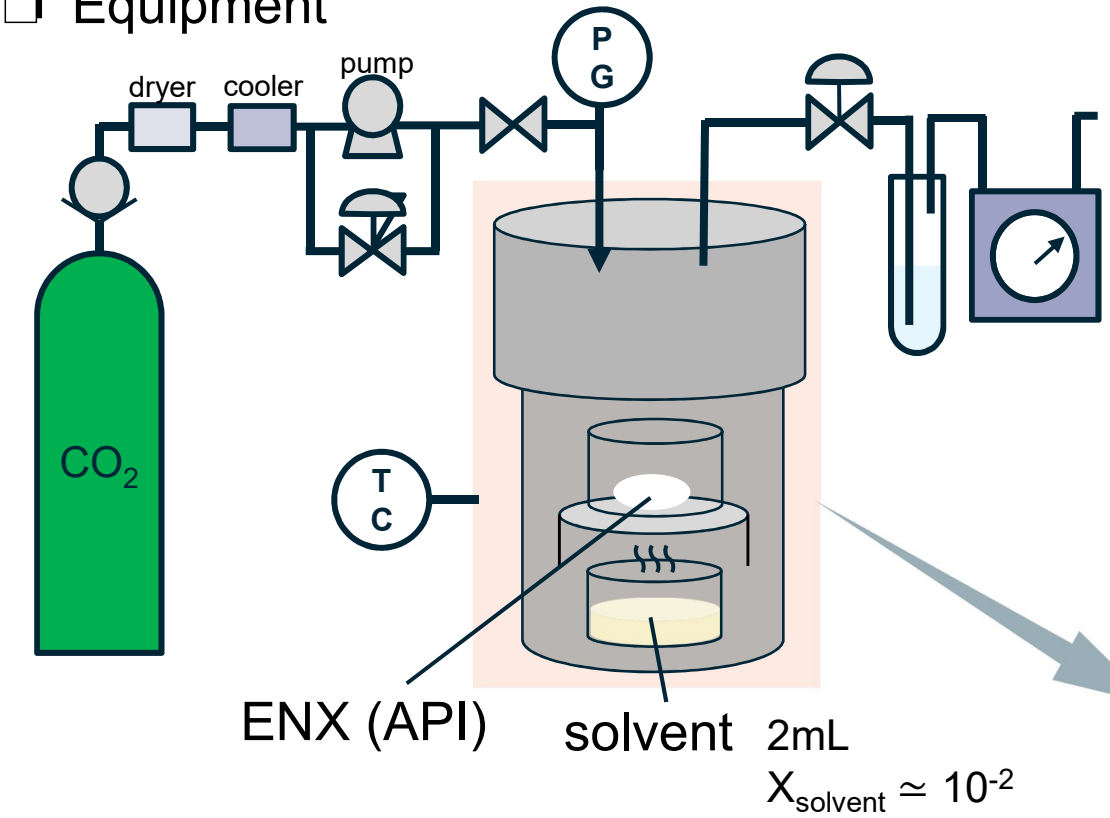
Advantage	Task
✓ **Increased solubility** … ENX : 2.5 times ✓ **Safe** … No solvent required ✓ **Easy** … 1step process	✓ **Unclear mechanism**

** Hao Yingquan et al., the 11th Intl. Conference on Sc. Fluids-Supergreen 2019*

* S. Akiyama et al., SCEJ Yokohama meeting C120 (2019)

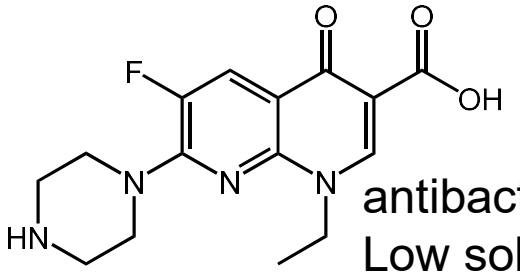
B : Pharmaceutical Crystal Engineering 28

❒ Equipment



❒ Used API

Enoxacin (ENX)



antibacterial
Low solubility

❒ Procedure

1. Put powder
2. Introduce CO_2
3. Wait for 2h
4. Take out

❒ Experimental Condition

Temperature	40 ℃	solvent	EtOH
Pressure	20 MPa		1-PrOH
ENX weight	60 mg		1-BtOH
Contact time	2h		Ethyl Acetate (EA)
Depressurize	0.1 MPa min^{-1}		Acetone (AC)

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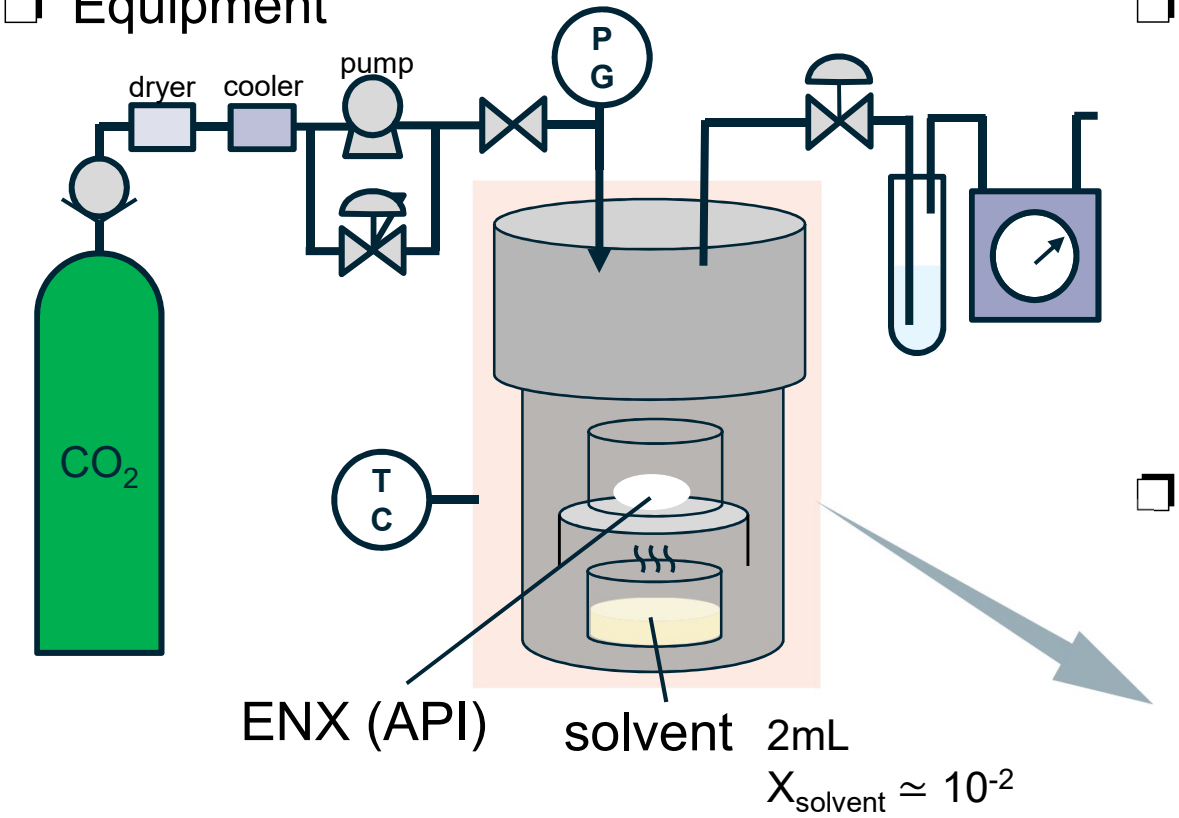
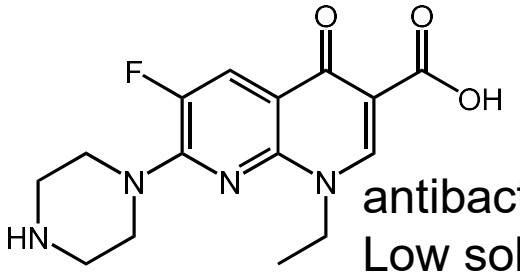
❒ Equipment



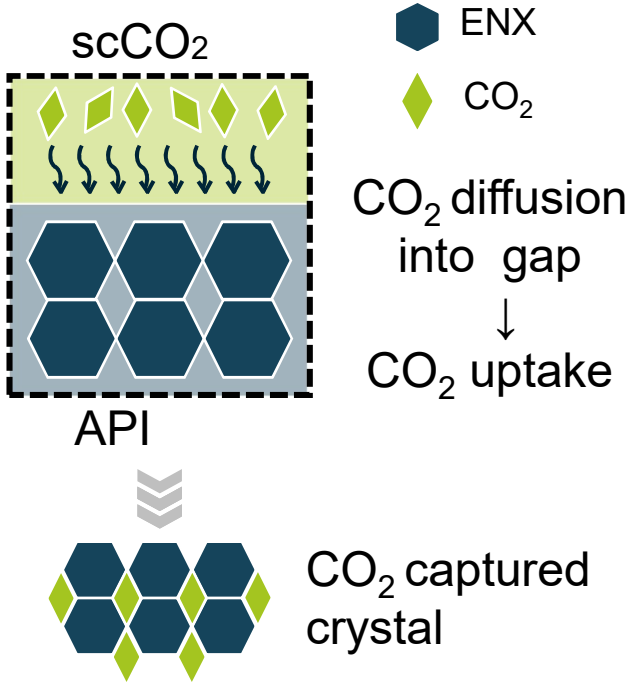
❒ Used API

Enoxacin (ENX)



antibacterial
Low solubility

❒ Image



❒ Experimental Condition

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Pressure	20 MPa		1-PrOH
ENX weight	60 mg		1-BtOH
Contact time	2h		Ethyl Acetate (EA)
Depressurize	0.1 MPa min^{-1}		Acetone (AC)

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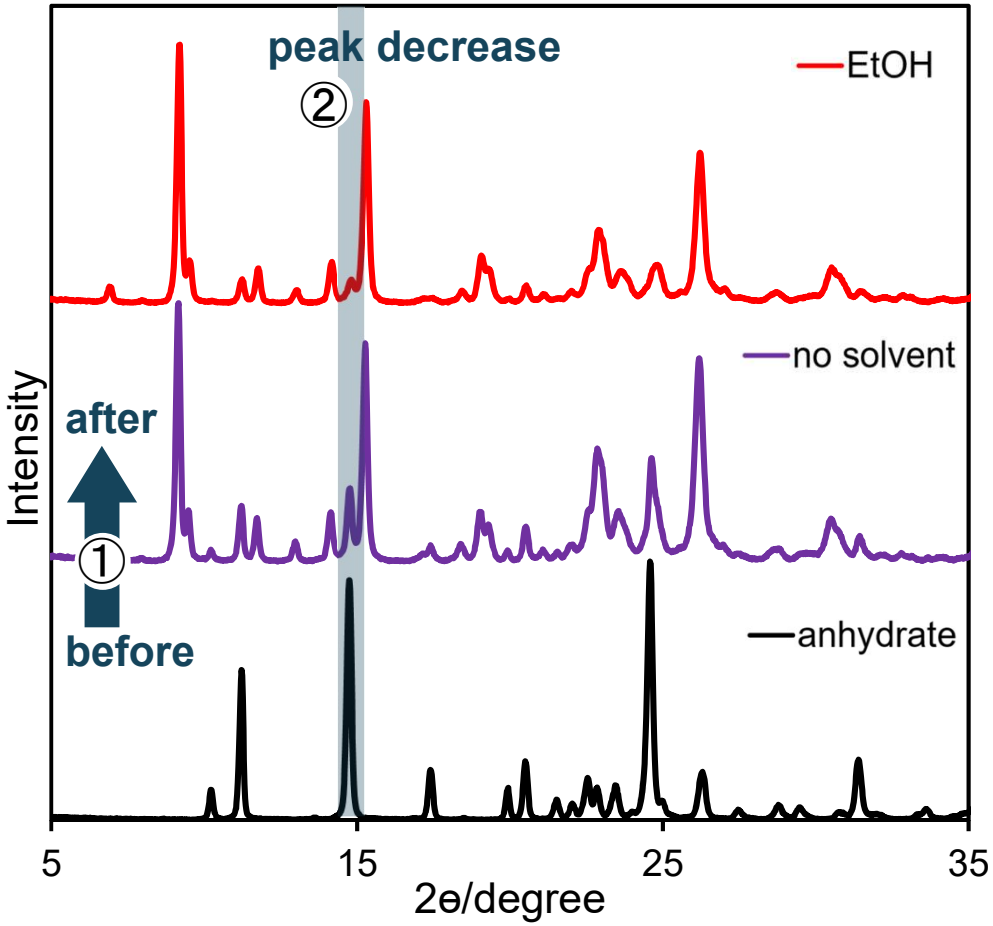
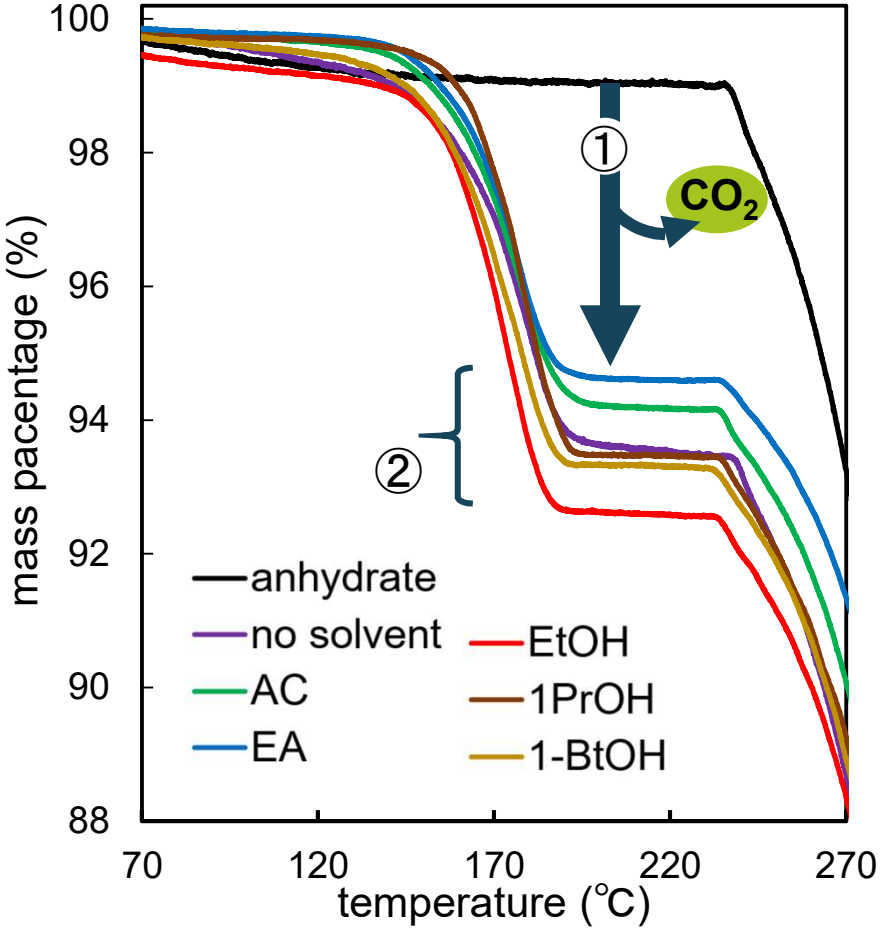
❒ Powder X-Ray Diffraction (XRD)



① crystal structure change
② solvent promotes phase transition
③ structure is independent of solvent type

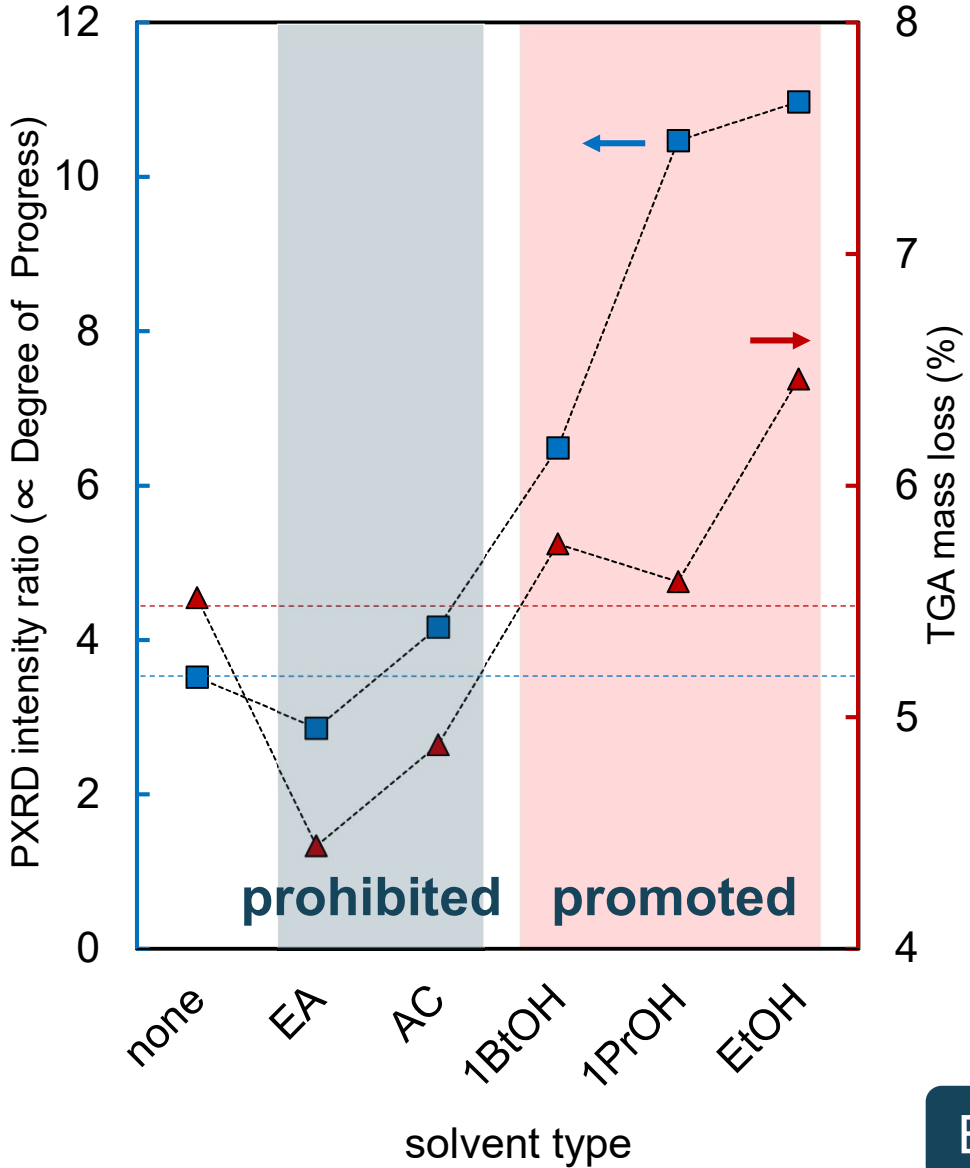
❒ Thermal Gravimetric Analysis (TGA)

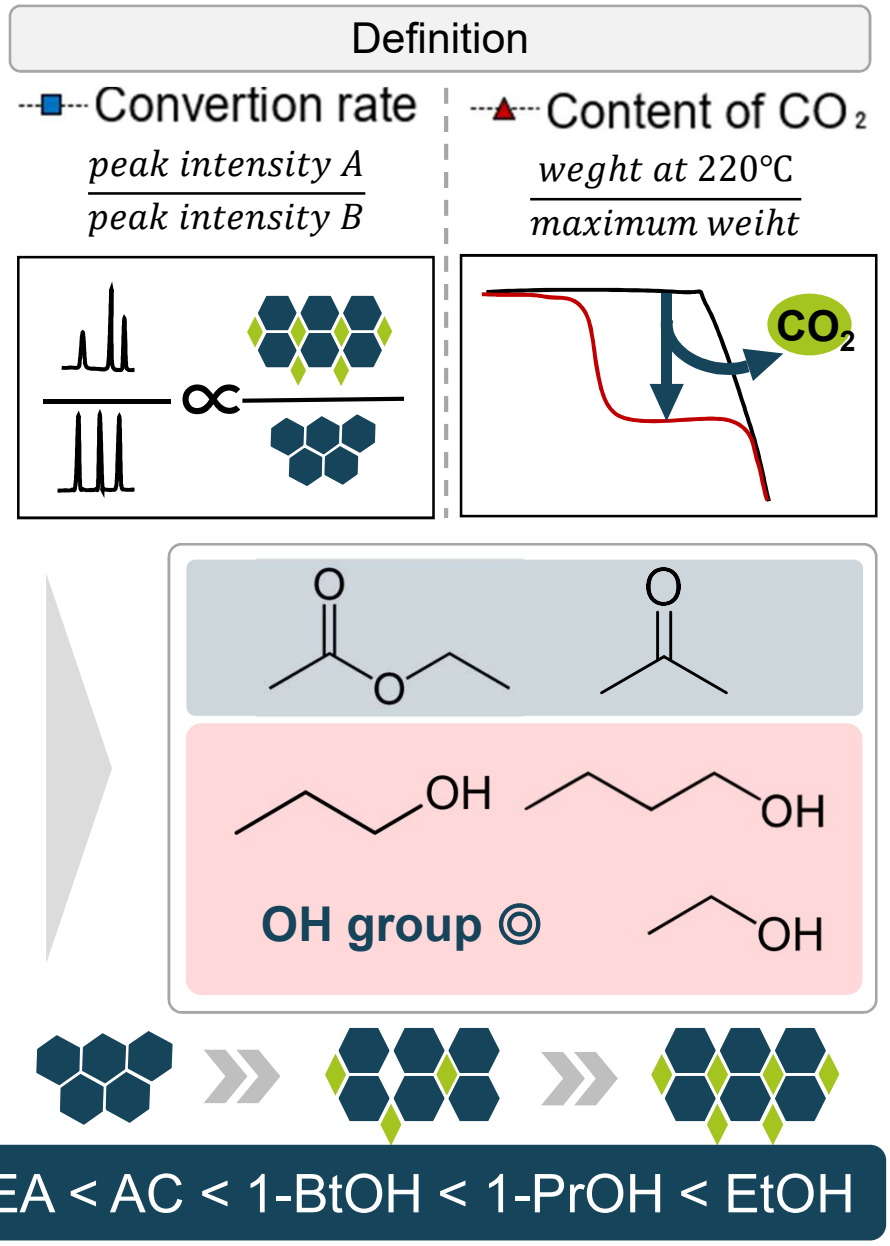


① mass loss by heating
→ CO_2 in crystal lattice
② solvent type

* S. Akiyama et al., SCEJ 51st fall meeting (2020)

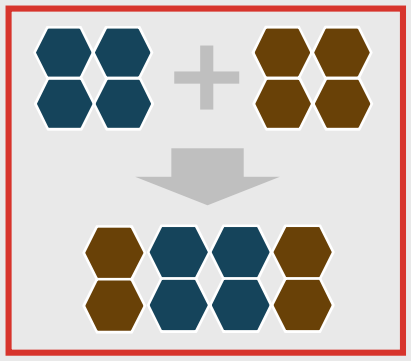
❒ Degree of progress for each solvent



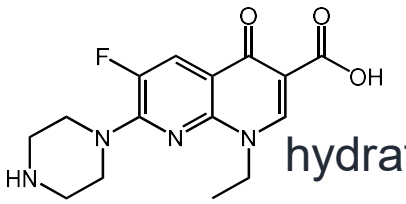


* S. Akiyama et al., SCEJ 51st fall meeting (2020)

CO_2 molecular crystal with various drugs

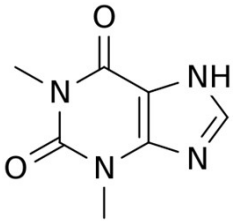


Enoxacin(ENX)

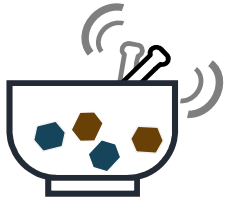


hydrate

Theophylline(THP)

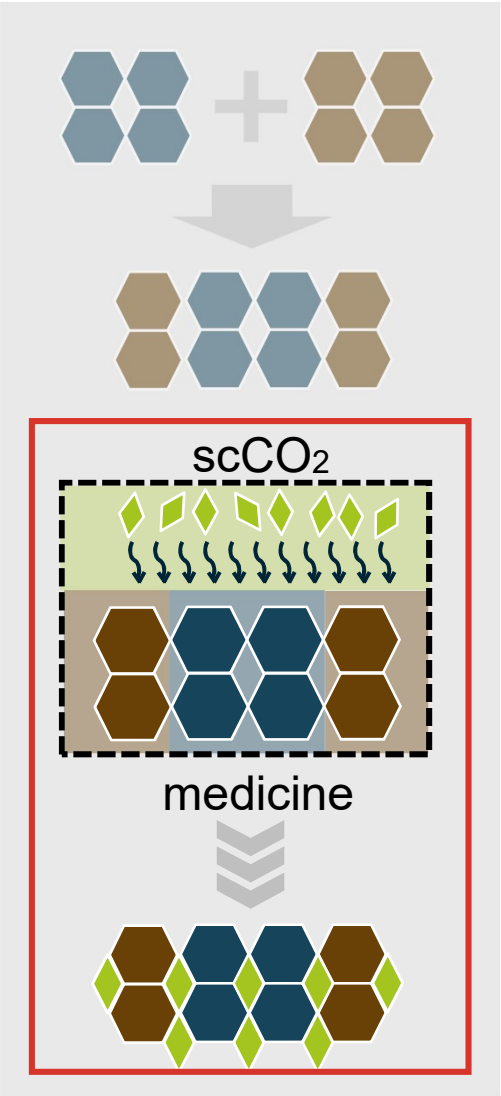


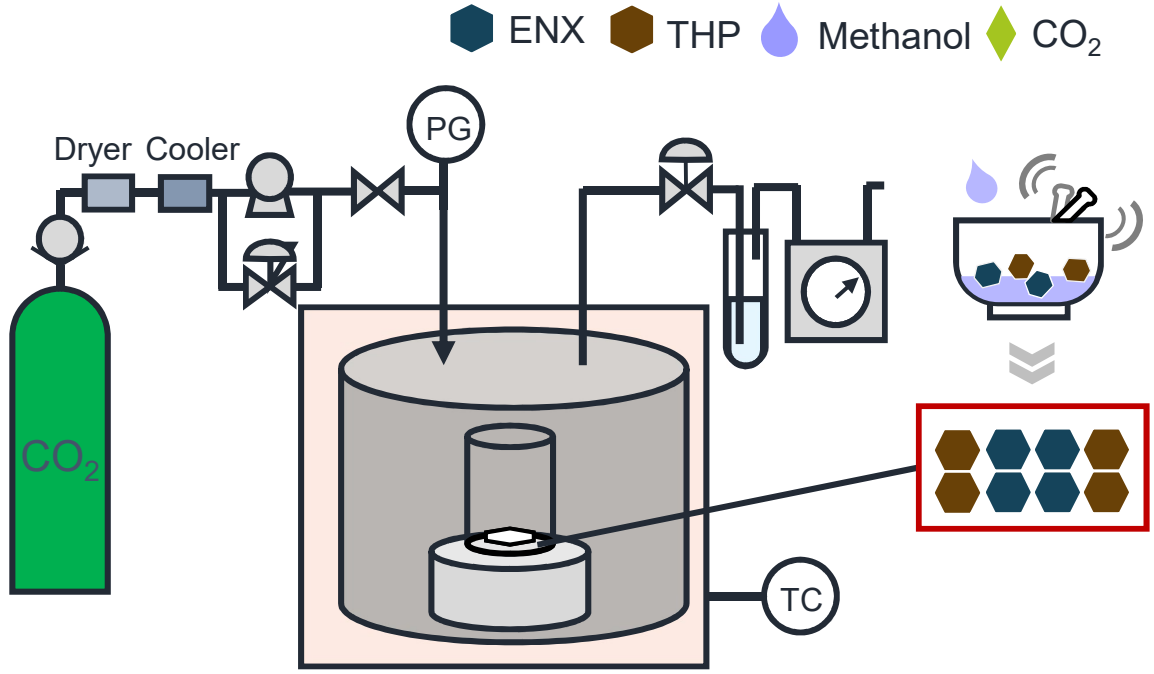
ENX THP Ethanol Methanol

Method	grinding	Liquid assist grinding
		
ENX hydrate, THP	0.3 mmol	1 mmol
Liquid	-	10 mL
Reaction time	1 h	2 h
Drying time	-	overnight

* M. Tanikoshi et al., SCEJ 52nd fall meeting (2021)

Setup and condition of CO_2-driven crystal





Conditions

Grinding time	2h	Stirring	200 rpm
Temperature	50 ℃	Reaction time	2 h
Pressure	20 MPa	flow rate	2 mL/min

* M. Tanikoshi et al., SCEJ 52nd fall meeting (2021)

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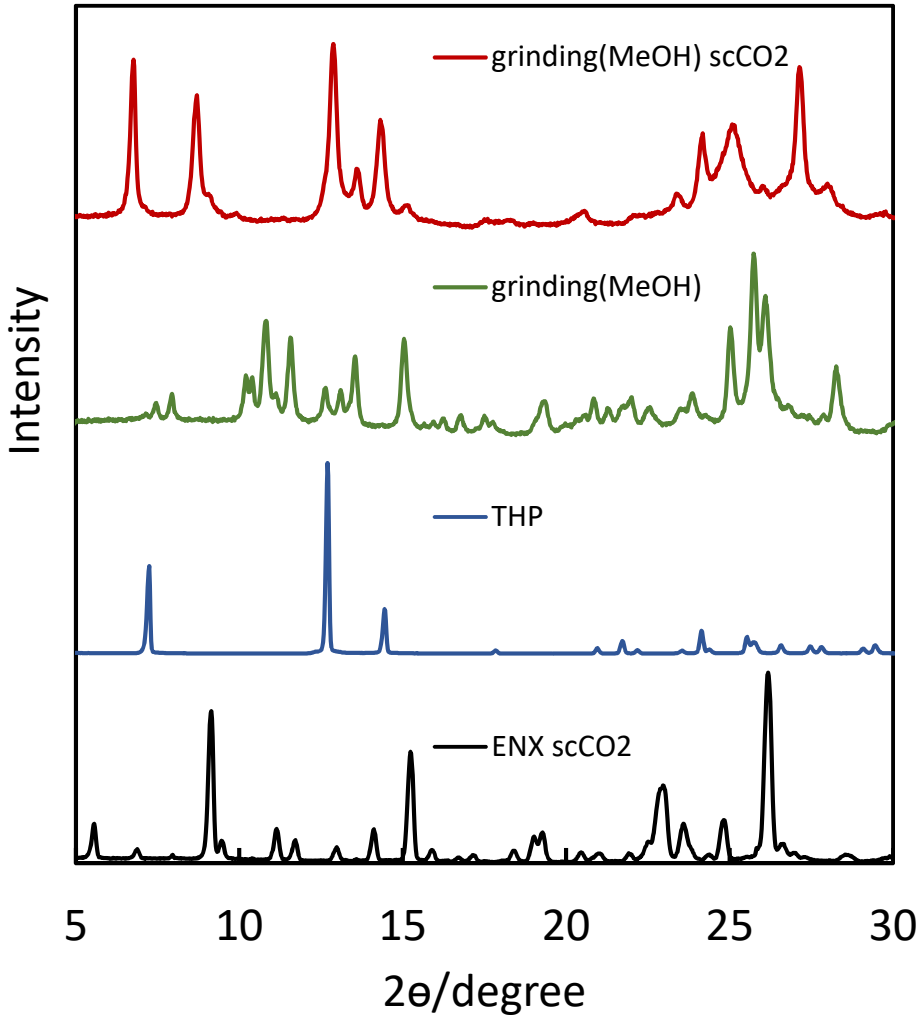
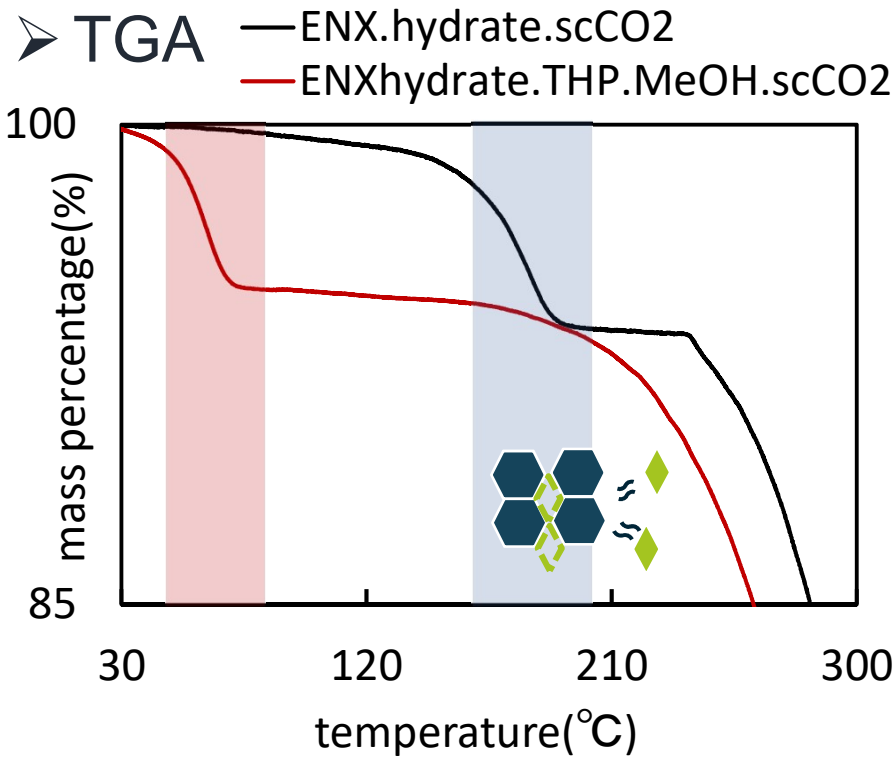
➢ PXRD



➢ TGA



crystal structure changed

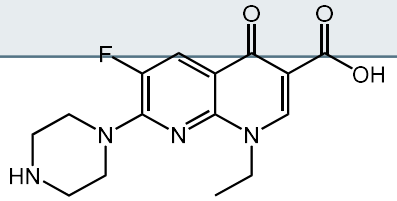
CO_2 used for crystal structure change

* M. Tanikoshi et al., SCEJ 52nd fall meeting (2021)

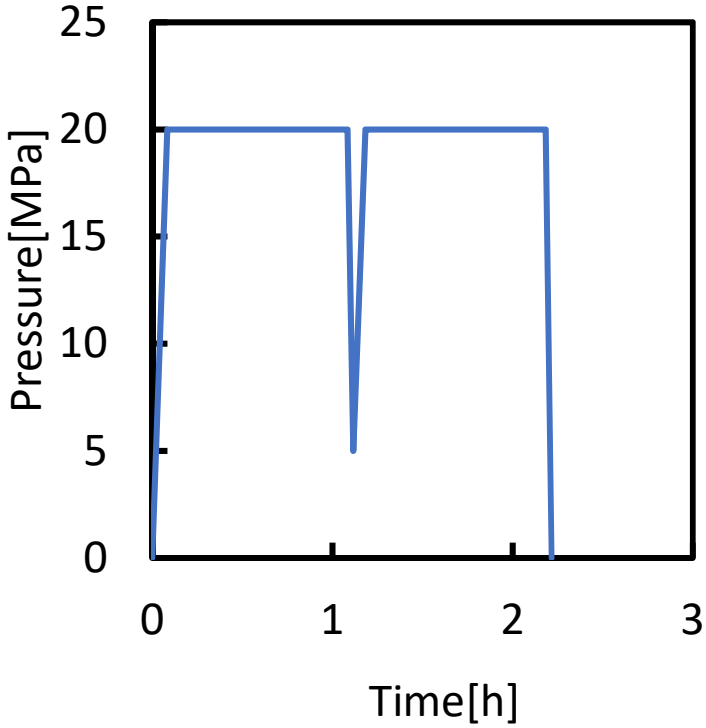
CO_2 molecular crystal of Enoxacin

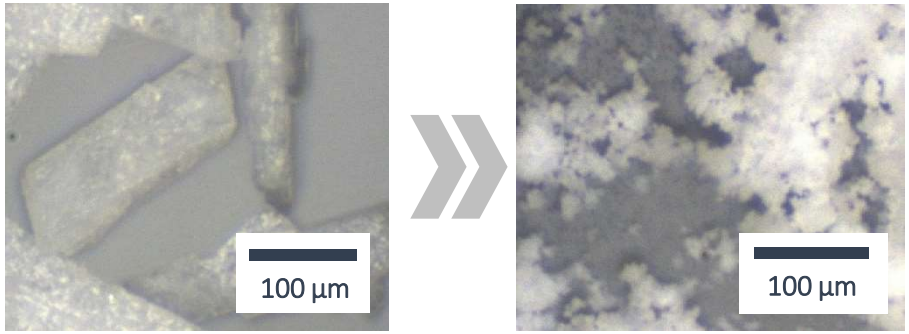
Atomization

Enoxacin(ENX)



Pressure swing





Advantage

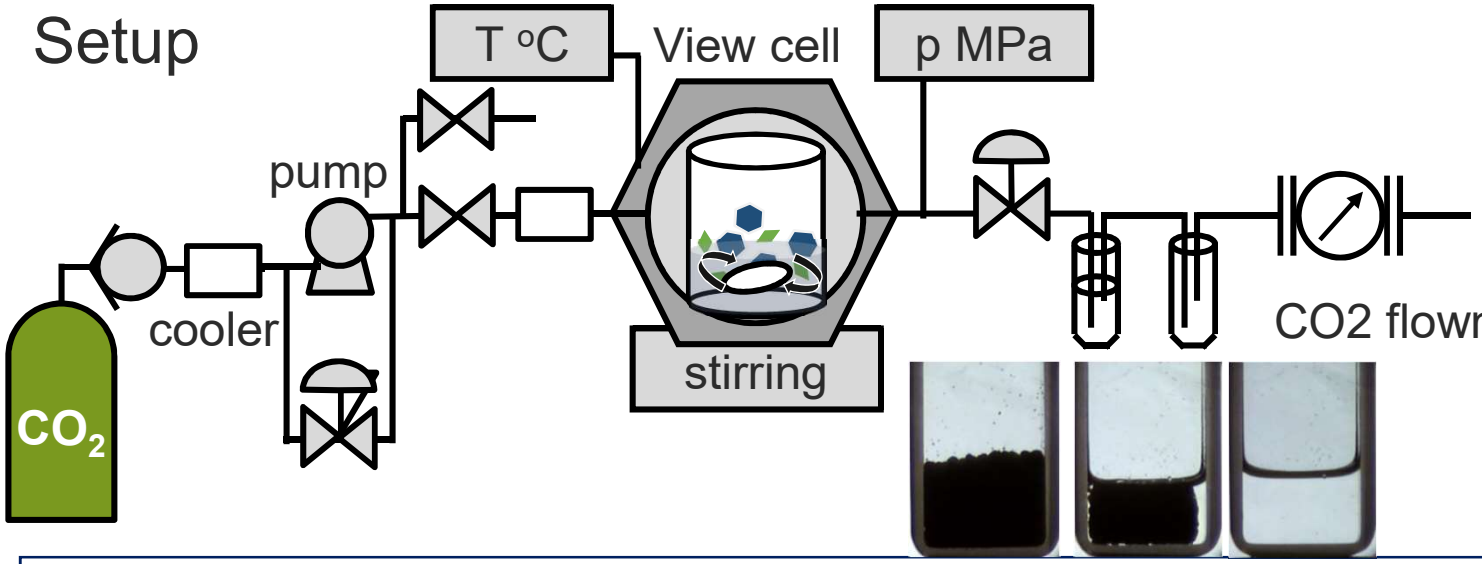
- ✓ **Safe** … No solvent required
- ✓ **Easy** … 1step process

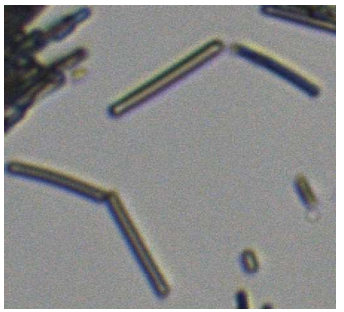
* M. Tanikoshi et al., SCEJ 53rd fall meeting (2022) coming soon…

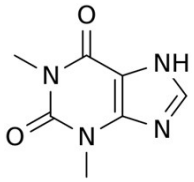
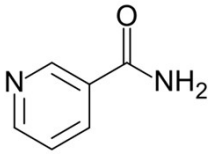
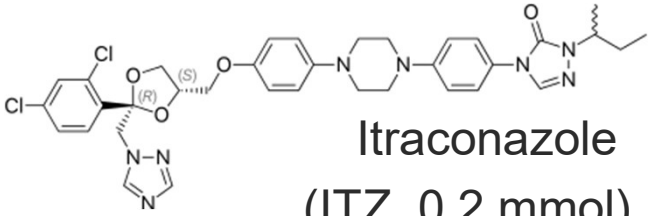
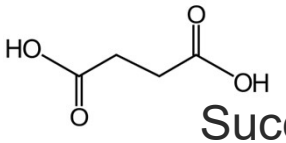
Lipid-mediated cocrystal formation

Supercritical CO_2

Setup



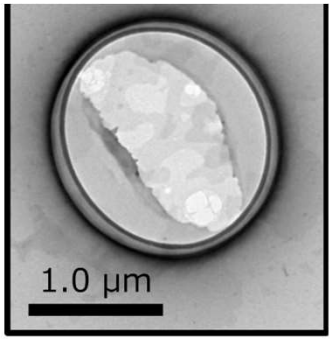


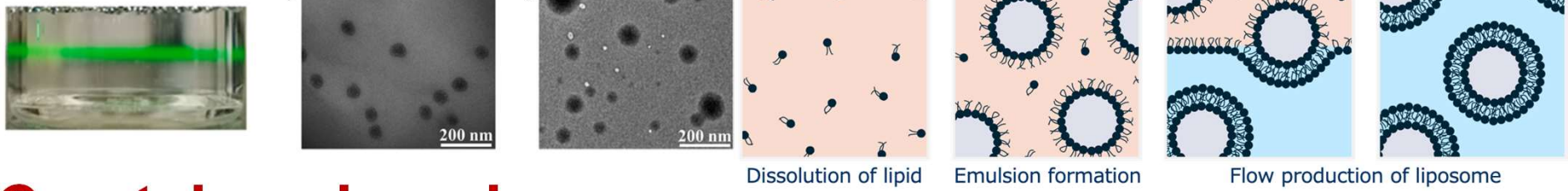
	drug	coformer
#1	 Theophylline (TPL, 1 mmol)	 Nicotinamide (NA, 1 mmol)
#2	 Itraconazole (ITZ, 0.2 mmol)	 Succinic acid (SUC, 0.1 mmol)

* Y. Tatsumi et al., Soc. Powder Tech. Spring meeting (2022)

Supercritical CO_2 applied for

Nanosuspension and Liposome





Crystal engineering