Strategic development of nano-drug delivery system for pharmacokinetic control

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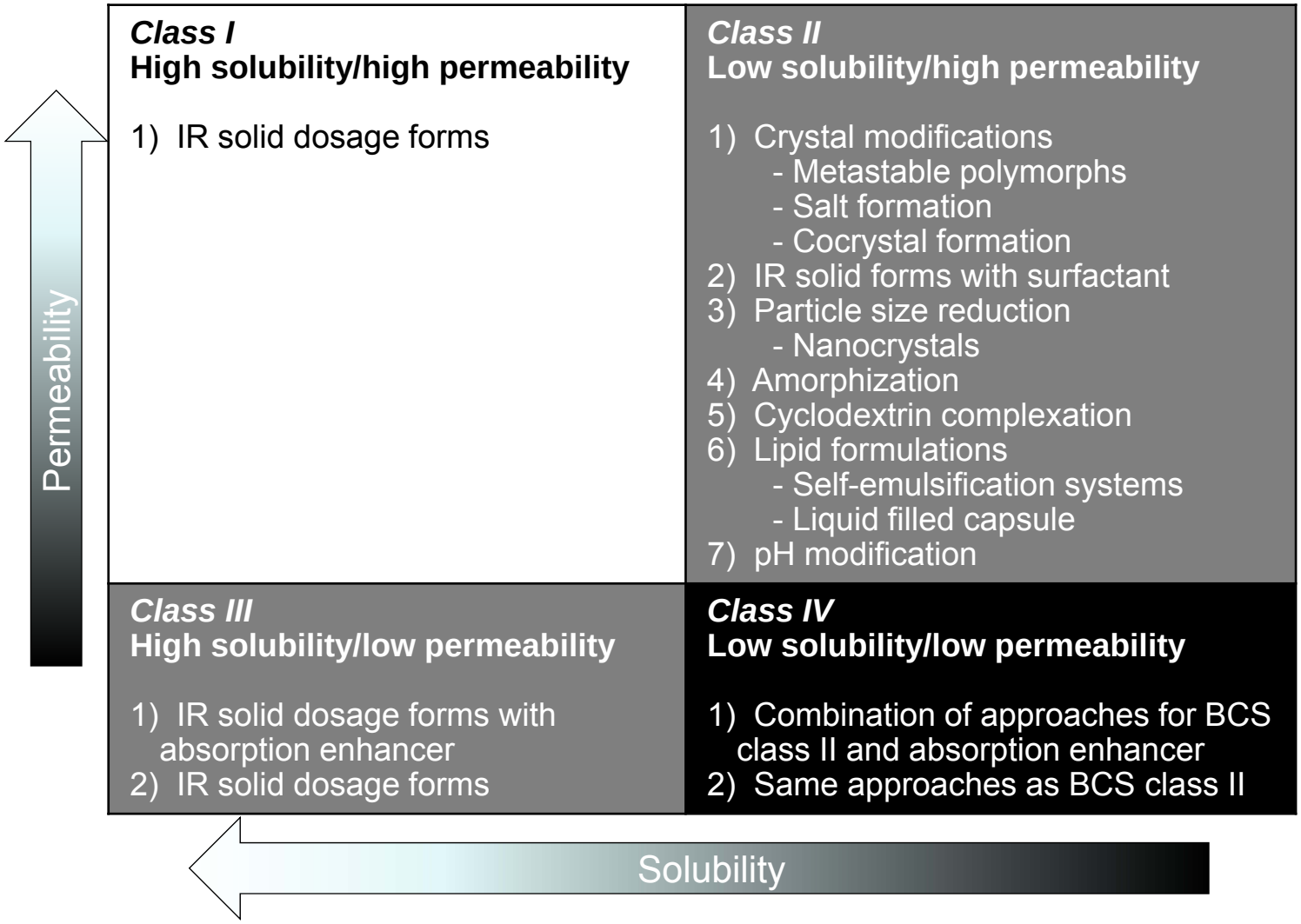
Scope of talks

1. Nano-drugs: PK and safety information
2. Nano-crystalline formulation
3. Self-micellizing solid dispersion system
4. Nano/microenvironmental pH-modifier approach
5. Pulmonary delivery to de-risk drugs
6. Summary

Biopharmaceutics classification system (BCS)

- Strategic formulation design based on molecular properties



Kawabata and Onoue, *Int. J. Pharm.*, **420:** 1-10 (2011)

Biopharmaceutical properties of nanodrugs

	Formulation system	Route	Observed PK/PD *in vivo*
Dendrimers			
Methotrexate	PEGylated polylysine dendrimer	i.v.	Prolonged systemic exposure
Piroxicam	Poly(amidoamine) dendrimer	i.v.	Prolonged systemic exposure
Engineered nanoparticles			
Diclofenac	SoluMatrix fine particle technology	Oral	Faster absorption and prompt pain relief
Fenofibrate	Nanocrystals	Oral	Improved oral bioavailability
Emulsion			
Cyclosporine A	Self-emulsifying DDS	Oral	Improved oral BA with low variability
	Inhalable dry emulsions	Pulmonary	Enhanced anti-inflammatory effects in lung
Liposomes			
Doxorubicin	Liposome, PEGylated liposome	i.v.	High distribution in neoplastic tissue
Paclitaxel	Liposome (PC/PG)	i.v.	Prolonged systemic exposure
Solid lipid nanoparticles			
Azidothymidine	Solid lipid nanoparticles	i.v.	Enhanced permeability and retention to brain
Diclofemac Na	Solid-in-oil nanosuspensions	Dermal	Increased percutaneous absorption
Micelles			
Paclitaxel	Block copolymeric micelles	i.v.	Increased BA, decreased clearance
Pilocarpine	Block copolymeric micelles	Ocular	Increased miotic activity
Polymeric nanoparticles			
Celecoxib	Ethylcellulose/caseinnanoparticles	Oral	Improved oral bioavailability
Docetaxel	PLA-PEG nanoparticles	i.v.	Extended half-life, enhanced antitumor effect
Glucagon	PLGA nanoparticles	Pulmonary	Extended half-life and enhanced BA

Onoue *et al*., *Int. J. Nanomed.*, **9:** 1025-37 (2014)

Biopharmaceutical and safety characteristics

Type of nanodrugs	Biopharmaceutical properties	Safety
Dendrimers	***Advantages*** High membrane permeability/solubility Controlled release/specific dug delivery ***Disadvantages*** Limited dosage routes	***Advantages*** Low immunogenicity ***Disadvantages*** Hemotoxicity
Engineered nanoparticles	***Advantages*** Improved systemic exposure High retention in mucosal layer Several dosage routes available ***Disadvantages*** Low sustained releasing potency	***Advantages*** Decreased gastric irritancy of NSAIDs ***Disadvantages*** Toxic risk due to high C_{max} Cytotoxic potential
Lipid nanosystems (Emulsion, liposome)	***Advantages*** Biodegradable and metabolized Prolonged/specific drug delivery Accumulation in tumor tissues ***Disadvantages*** Rapid clearance due to RES uptake Limited dosage route	***Advantages*** Low toxicity Low antigenicity ***Disadvantages*** Cytotoxicity depending on used surfactant
Micelles	***Advantages*** High membrane permeability/solubility Improved systemic exposure ***Disadvantages*** Low sustained releasing potency	***Advantages*** Low immunogenicity ***Disadvantages*** Toxic risk due to high C_{max} Cytotoxicity depending on used surfactant
Polymeric nanoparticles	***Advantages*** Stable *in vivo* drug release Long duration of action ***Disadvantages*** Need to avoid initial burst Limited dosage route	***Advantages*** Low immunogenicity ***Disadvantages*** Need to be removed surgically for nondegradable polymers

Onoue *et al*., *Int. J. Nanomed.*, **9:** 1025-37 (2014)

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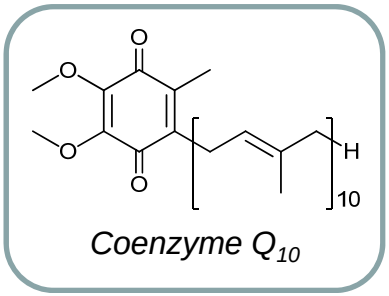
Nanocrystalline formulation

- Coenzyme Q_{10}

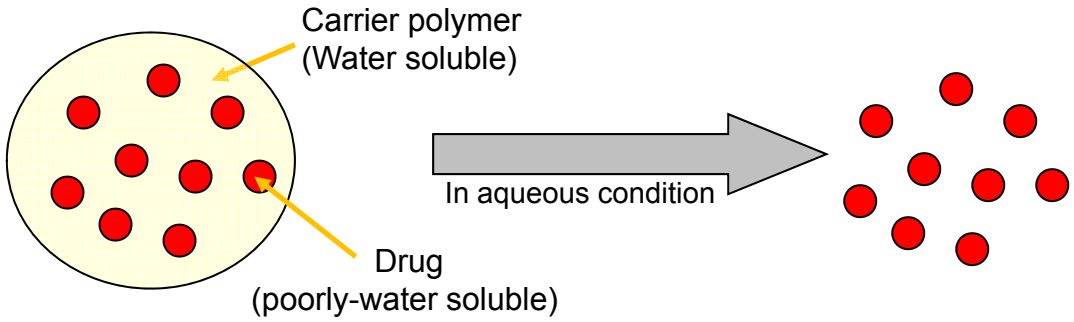
  Naturally occurring anti-oxidant
  - Poor solubility (＜4 ng/mL)
  - Low oral bioavailability (BA) (0.44%, Rat)
  - Low melting point (ca. 48℃)
  - Poor photostability



Coenzyme Q_{10}

- Solid dispersion (SD) system

  Distribution of active ingredients in molecular, amorphous, and/or nano/microcrystalline forms surrounded by inert carriers



W. L. Chiou and S. Riegelman, *J. Pharm. Sci.*, **60:** 1281-1302 (1971)

NCSD prepared with cold wet-milling

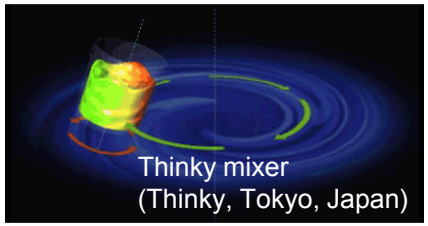
Preparation

(1) Cold wet-milling (-20℃, in EtOH)

Rotation/revolution mixer (custom-made NP-100 with cooling unit, Thinky Co., Ltd., Tokyo, Japan)

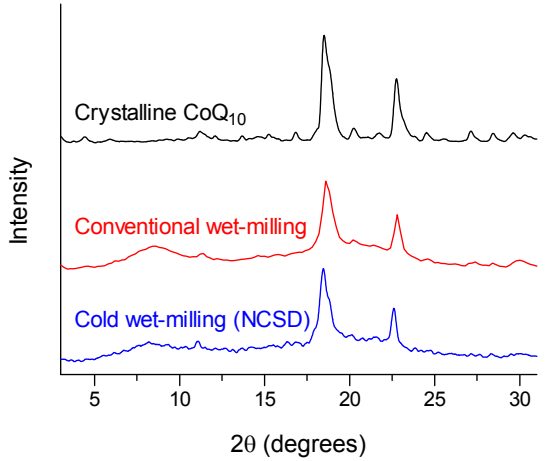
Zirconia balls (diameter, 0.1 mm)

(2) Freeze-drying

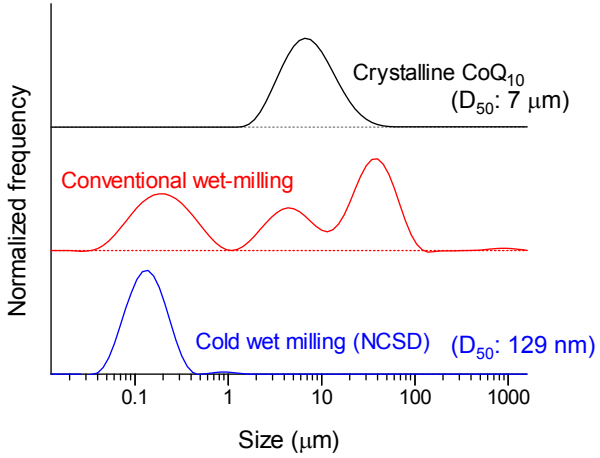


Onoue *et al.*,
J. Control. Release., **138:** 16-23 (2009)

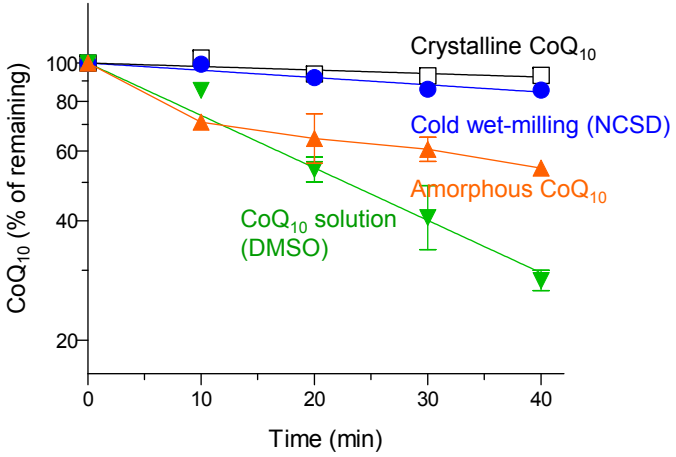
Powder X-ray diffraction



Particle size distribution



Photostability

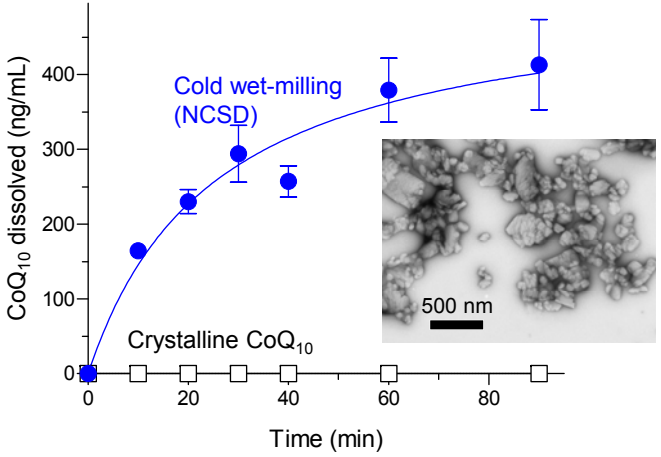


Exposed to the simulated sunlight (250 W/m^2).

Onoue *et al.*, *Eur. J. Pharm. Sci.*, **46:** 492-9 (2012); *Eur. J. Pharm. Sci.*, **53:** 118-25 (2014)

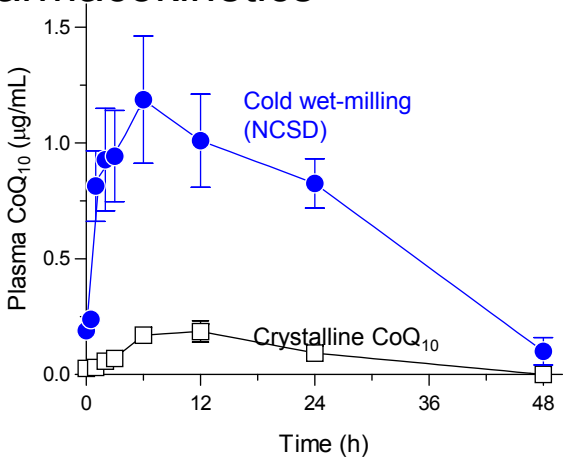
Pharmacokinetics and pharmacodynamics

Dissolution behavior



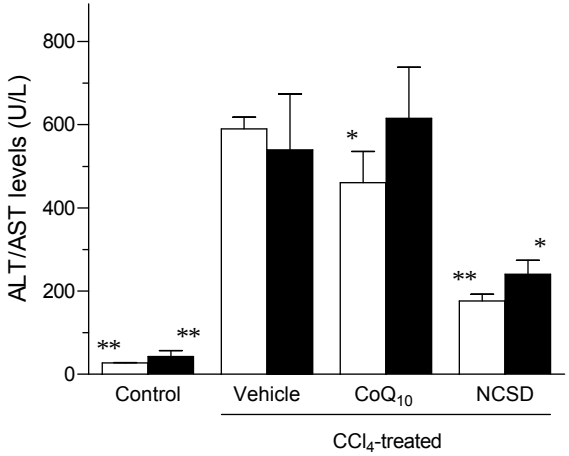
In distilled water (37℃, 100 rpm).

Pharmacokinetics



Oral administration of CoQ_{10} samples (100 mg CoQ_{10}/kg) in rats. (n=6).

Hepatoprotective effects



24 h after CCl_4 challenge with CoQ_{10} samples (100 mg CoQ_{10}/kg, twice) in rat.
Open, ALT; and filled, AST. $P<0.05$; $P<0.01$ vs CCl_4-treated rats with vehicle.

	C_{max} (mg/mL)	T_{max} (h)	K_{el} (h^{-1})	AUC_{0-inf} (mg·h/mL)	BA (%)
CoQ_{10}	0.22±0.042	8.3±1.7	0.049 ±0.024	5.1±0.60	0.28
NCSD	1.4±0.2 *	8.8±3.4	0.043 ±0.011	38±3.9 *	3.6 *

*, $P<0.01$ between crystalline CoQ_{10} and NCSD.

Onoue *et al.*, *Eur. J. Pharm. Sci.*, **53:** 118-25 (2014)

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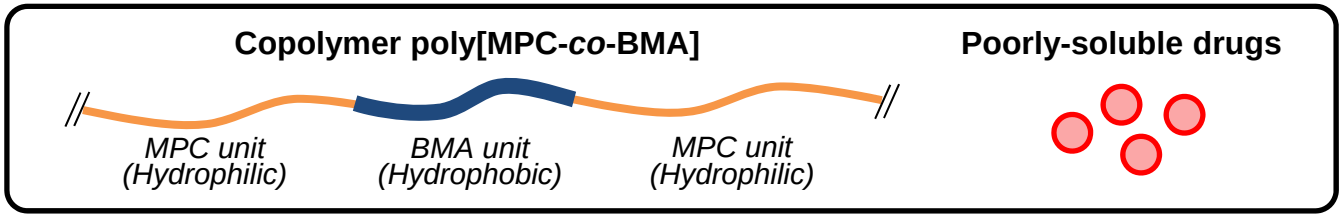
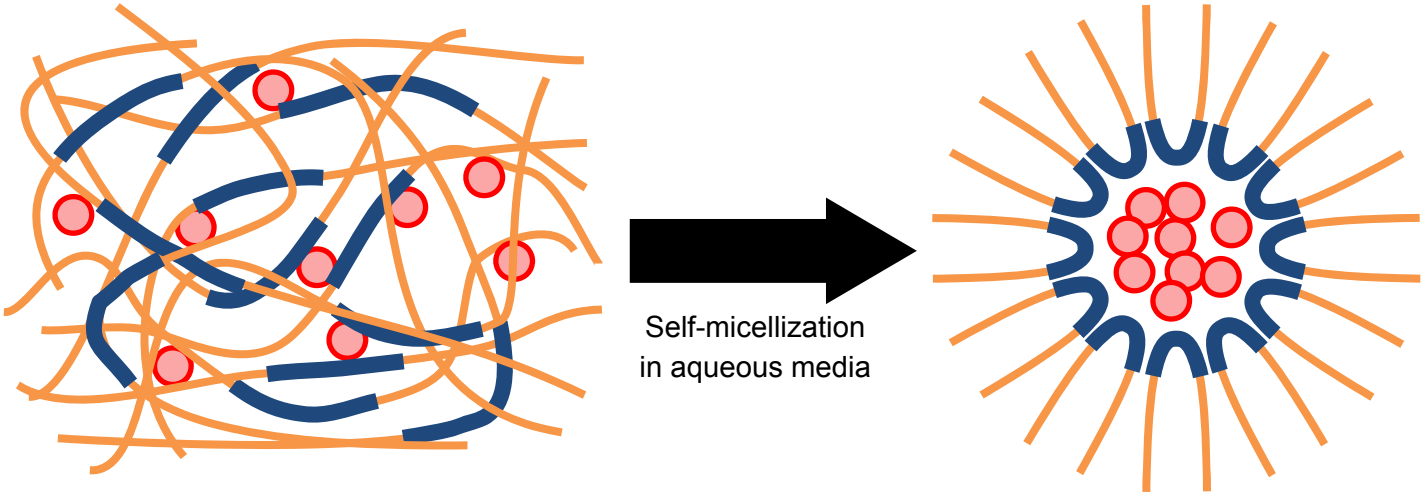
Self-micellizing solid dispersion (SMSD)

- Concept for SMSD

SD with poly[MPC-*co*-BMA] can form micelles spontaneously in aqueous medium, leading to improved dissolution of co-existing drugs.



MPC: 2-methacryloyloxyethyl phosphorylcholine; and BMA: *n*-butyl methacrylate

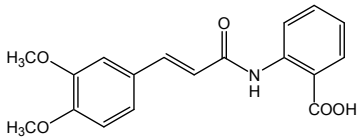


Self-micellizing solid dispersion (SMSD) **Micelle**

Onoue *et al*., *Int. J. Pharm*., **452:** 220-6 (2013); *Eur. J. Pharm. Sci.*, **62:** 16-22 (2014)

SMSD formulation of tranilast

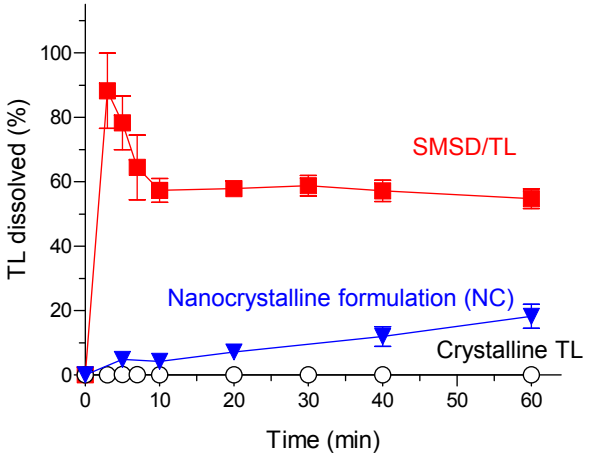
Tranilast (TL)



Tranilast (TL)

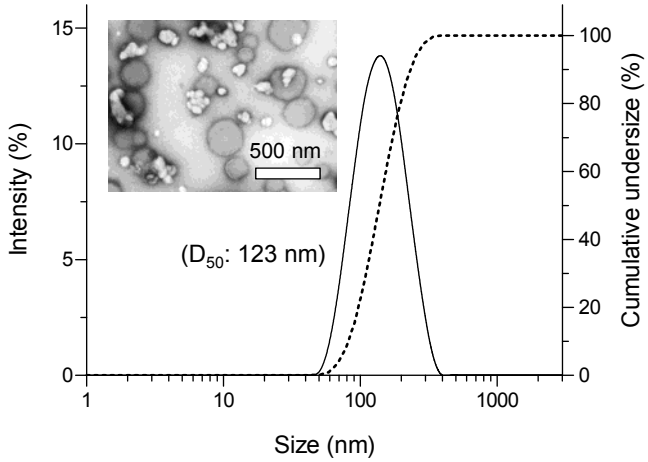
- Clinical usage
  - Bronchial asthma
  - Atopic dermatitis
  - Keloids and hypertrophic scar
- Physicochemical properties
  - Poor solubility in acidic condition (ca. 0.7 μg/mL in pH1.2)

Dissolution



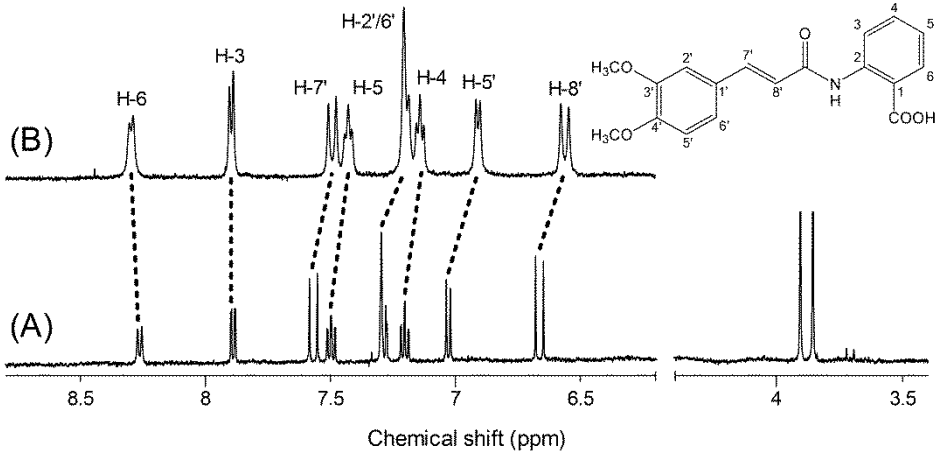
In acidic solution (pH1.2, 37°C, 50 rpm).

Particle size distribution



Onoue *et al*., *Int. J. Pharm*., **452:** 220-6 (2013)

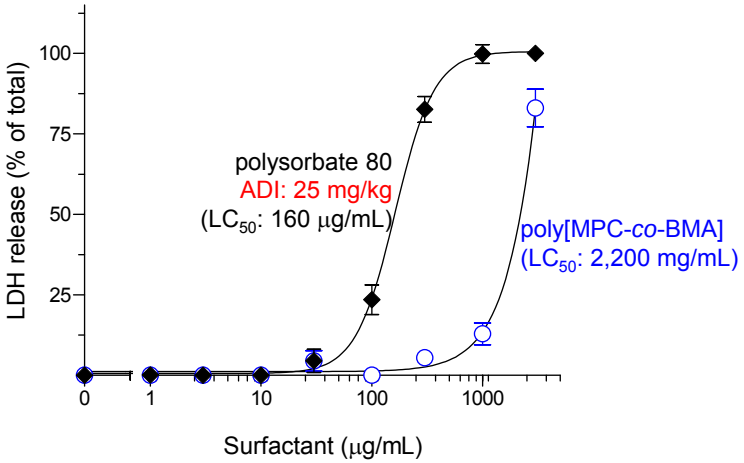
Interaction with polymer



^{1}H-NMR spectra (D_2O containing 100 mM NaPB, pH6.8).
(A) Full spectrum of TL and (B) aromatic proton peaks of SMSD/TL.

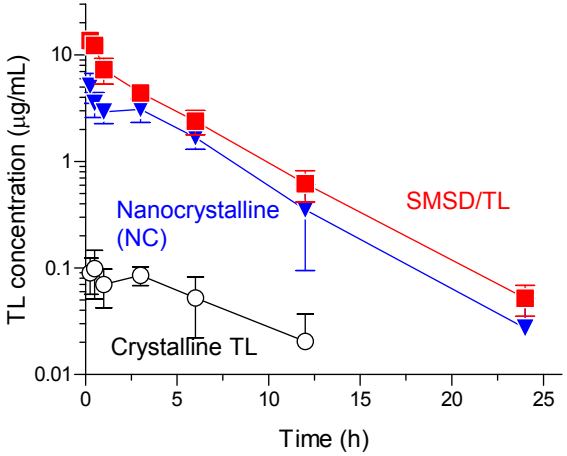
Safety and pharmacokinetics

In vitro cytotoxicity (IEC-6 cells)

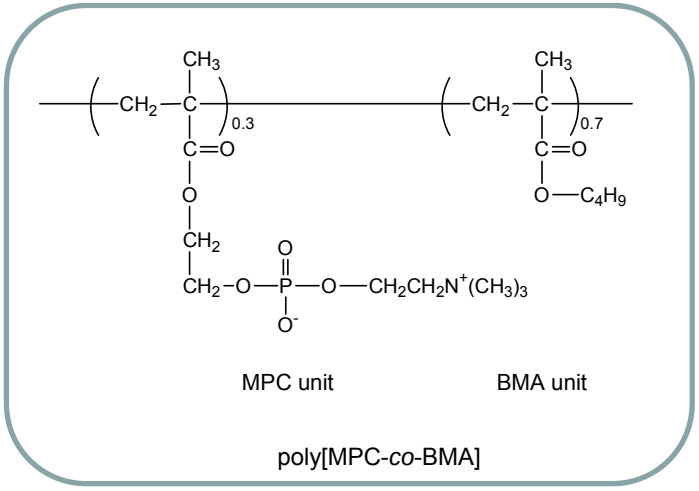


LDH leakage from rat intestinal IEC-6 cells incubated with polysorbate 80 or poly[MPC-*co*-BMA] for 24 h.

Pharmacokinetics



Oral administration of TL samples (10 mg TL/kg) in rats. (n=4-6).



	C_{max} (mg/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{0-inf} (mg·h/mL)	BA (%)
Crystalline TL (10 mg/kg)	0.1±0.0	1.8±0.7	2.9±0.7	0.8±0.4 (CV: 50%)	1.2
NC/TL (10 mg TL/kg)	6.0±1.3	2.5±1.1	2.2±0.5	24.8±2.4 (CV: 20%)	37.7
SMSD/TL (10 mg TL/kg)	11.9±1.58	0.38±0.1	3.3±0.3	41.2±3.2 (CV: 15%)	62.6

Onoue *et al*., *Int. J. Pharm*., **452:** 220-6 (2013); *Eur. J. Pharm. Sci.*, **62:** 16-22 (2014)

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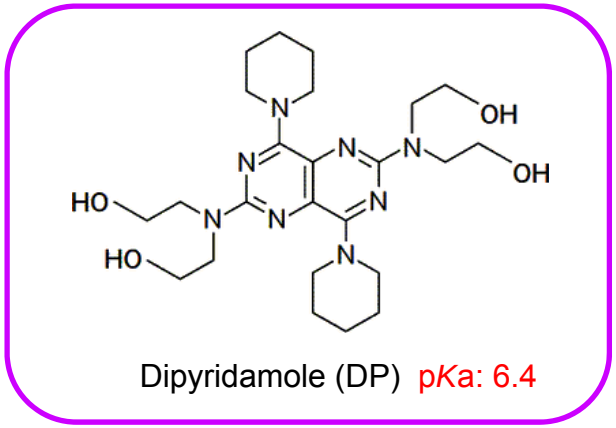
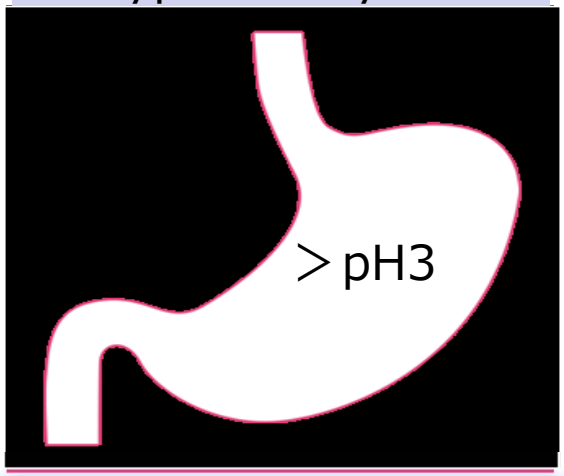
Nano/microenvironmental pH-modifier



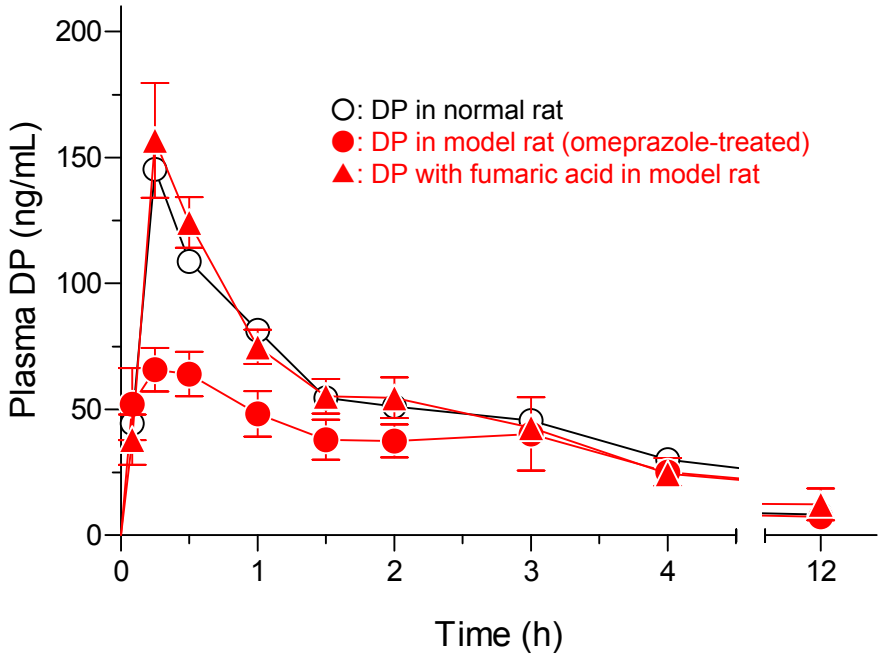
Dipyridamole (DP) p*K*a: 6.4

Hypochlorhydria



Solubility : low
oral BA : low

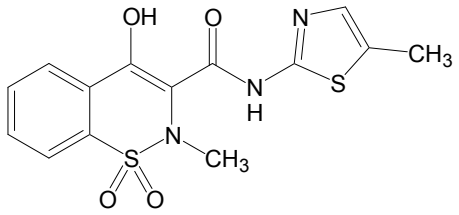
PK data on oral DP (10 mg/kg) in rats



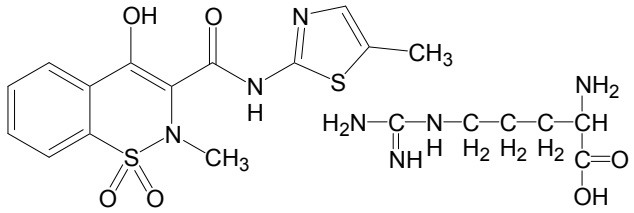
	C_{max} (ng/mL)	$T_{0.5}$ (h)	AUC_{0-3} (ng・h/mL)
Normal rat			
DP	145.3±19.9	2.5±0.5	209.7±29.9 (CV: 28.5%)
Model rat (omeprazole-treated)			
DP	68.8±9.9	3.5±1.0	130.3±23.5 (CV: 36.1%)
DP with fumaric acid	159.8±20.4	2.3±0.5	212.8±15.3 (CV: 14.4%)

Onoue *et al.*, *Int J Pharm,* **426:** 61 (2012); *Int J Pharm,* **434:** 148 (2012); *Drug Metab Pharmacokinet,* **28:** 383 (2013)

NSAIDs with nanoenvironmental pH-modifier

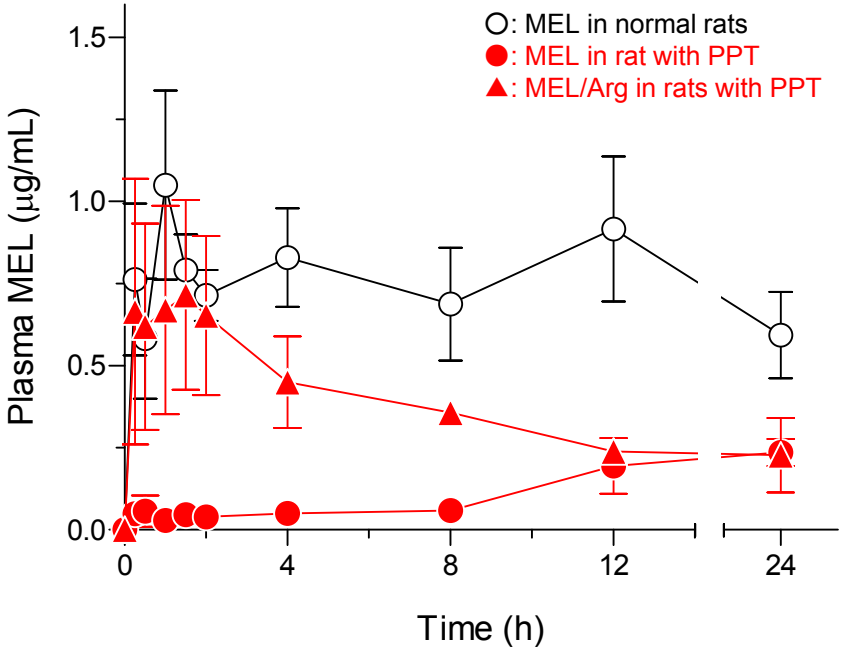


Meloxicam (MEL)



Meloxicam arginate (MEL/Arg)

PK data on oral MEL and MEL/Arg (1 mg/kg)



Orally-taken MEL or MEL/Arg (1.0 mg-MEL/kg) in rats treated with or without propantheline (PPT)

	MEL (Free)		MEL/Arg
	Normal rats	Rats treated with PPT	Rats treated with PPT
C_{max} (μg/mL)	1.1±0.3	0.3±0.1	0.9±0.3
T_{max} (h)	4.3±2.7	18.0±4.0	2.5±1.9
AUC (μg h/mL)			
0–4 h	3.1±0.2	0.2±0.1 (94%↓)	2.4±1.0 (22%↓)

Mean±SE (*n*=4).

Ochi and Onoue *et al.*, *Pharm Res*, **30:** 377 (2013)

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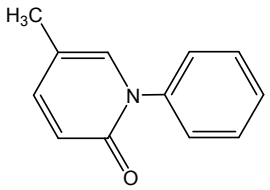
Inhalable pirfenidone formulation

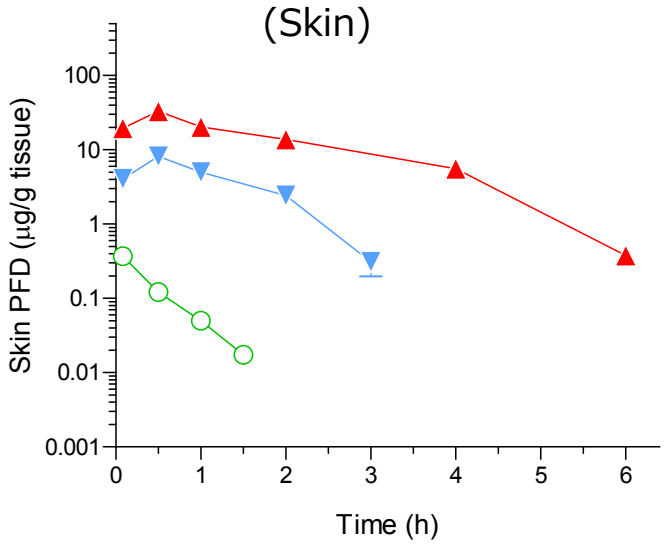


Pirfenidone (PFD)

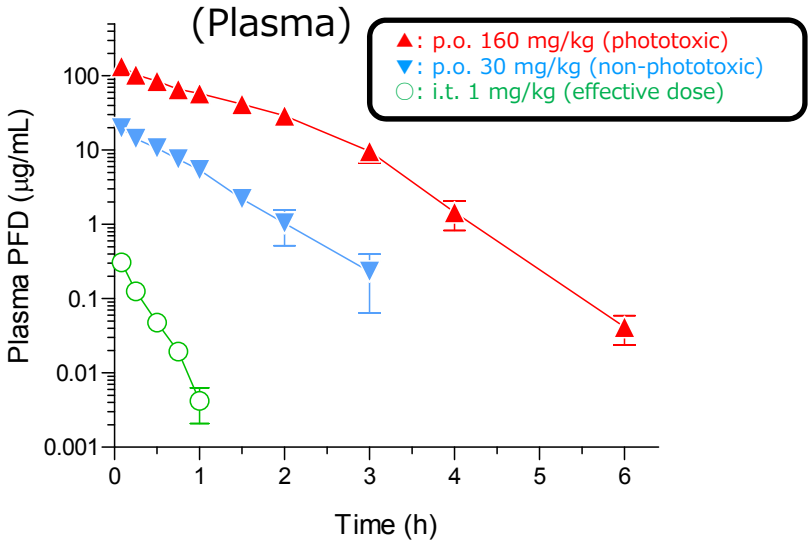
Pirfenidone (Pirespa®)

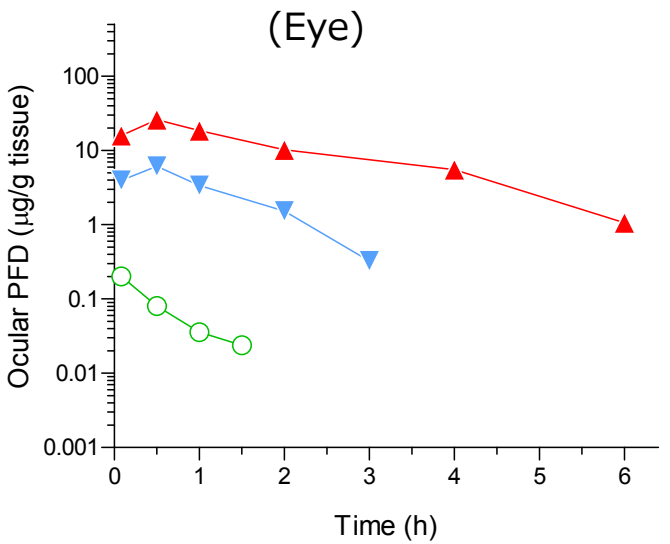
- The only drug for Idiopathic pulmonary fibrosis
- Severe systemic side-effects
  - Phototoxicity (52%)
  - Gastric dysfunction (37%)

What is suitable DDS to de-risk pirfenidone?



Pharmacokinetics of oral/inhaled pirfenidone





Onoue *et al.*, *Pharm Res*, **30:** 1586 (2013); *Eur J Pharm Sci*, **38:** 104 (2009); PCT/JP2012/073514

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Summary and future outlooks

1. Nanodrug systems could be a promising approach to obtain desirable drug-like properties by altering the biopharmaceutic and pharmacokinetic properties of new drug candidates.

2. A better understanding of the pharmacokinetics and safety on nanodrug systems is necessary to develop efficacious nano-DDS with high therapeutic potential and a wide safety margin.

3. Currently, nanodrugs are believed to be feasible and promising in cancer therapy. Other serious diseases would also be eventually treated effectively via nanotechnology upon further maturation of technology platform.

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