Hemi-porous Janus microparticles as a muco-adhesive enteral delivery system for BCS Class III drugs

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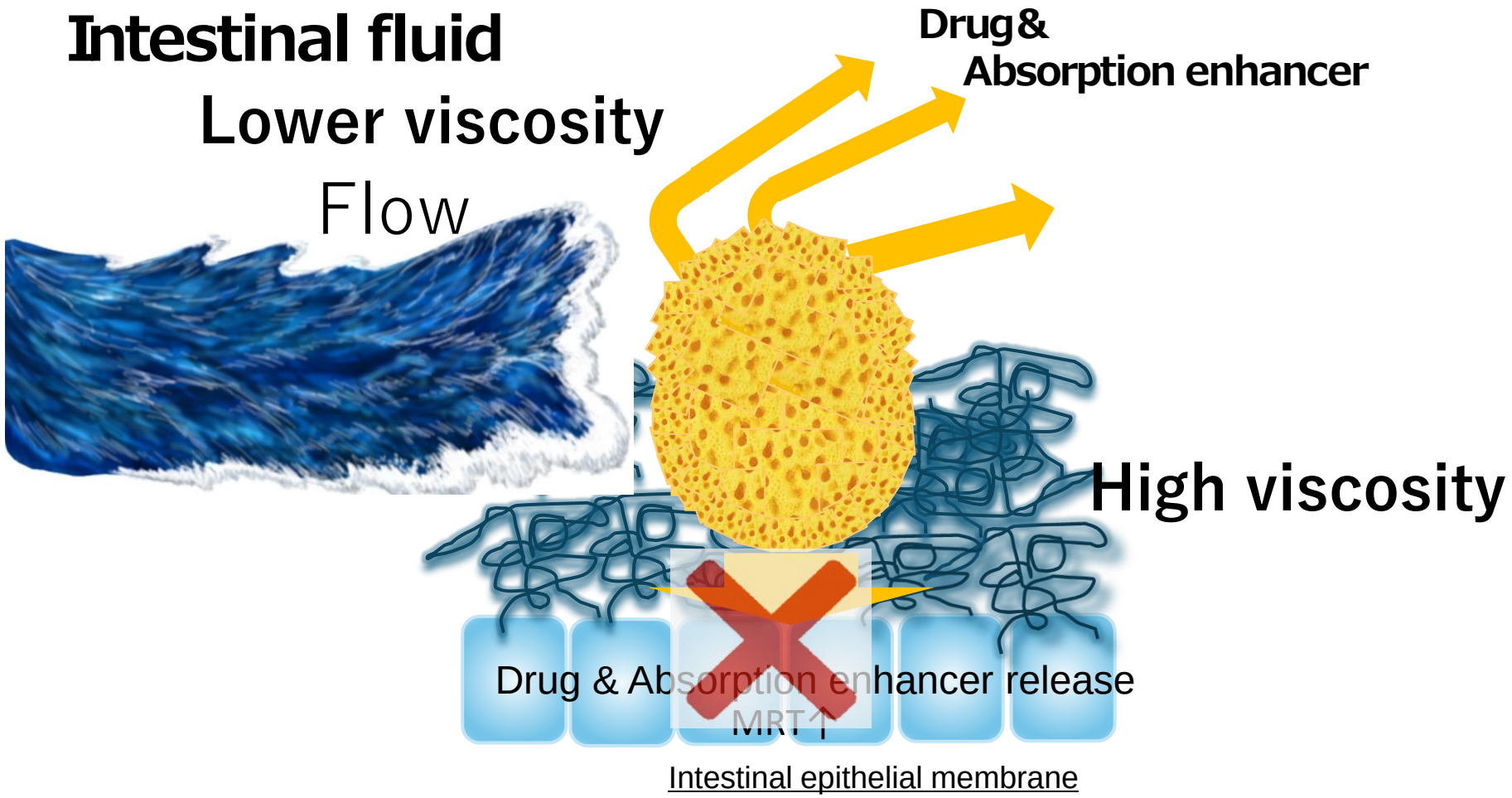
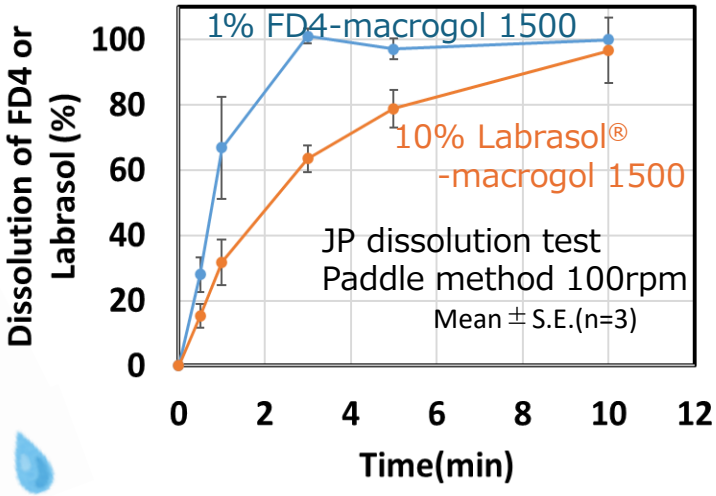
I have no financial relationships to disclose.

Are adhesive formulations effective for intestinal absorption of BCS class Ⅲ drugs ?



In vitro evaluation model for the dissolution of the formulation on mucosa

Disk-shaped formulation (ϕ4.5mm)



Artificial intestinal fluid
0.05%Tween80-
JP 2nd Fluid for dissolution test (pH6.8)
(1.03mL/min)

4.5mm

J.MAGNETIC RESONANCE IMAGING 32:345–351 (2010)

ϕ2.9 mm

Artificial mucosa

1.5% Carbopol 974
0.91% Mucin（Type Ⅱ）
7.02% BSA
2.5% egg yolk emulsion (pH6.8)

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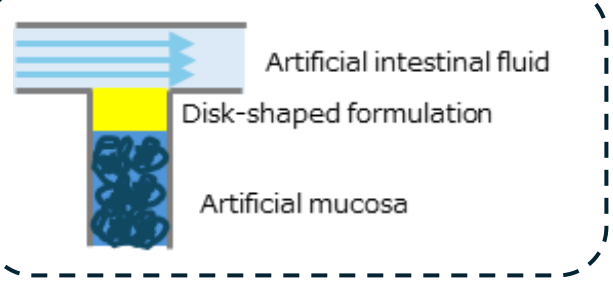
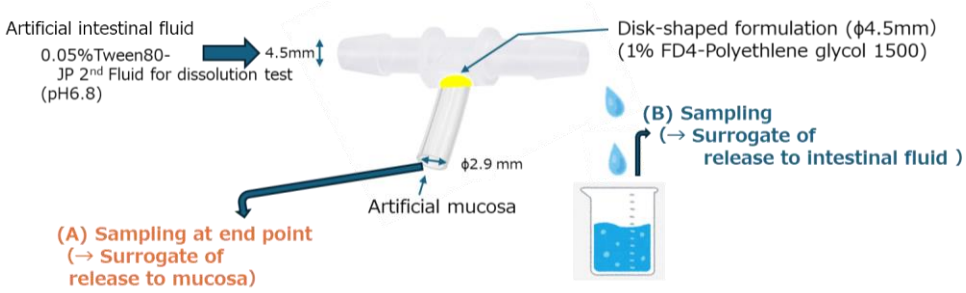
(A) Sampling at end point (→ Surrogate of release to mucosa)

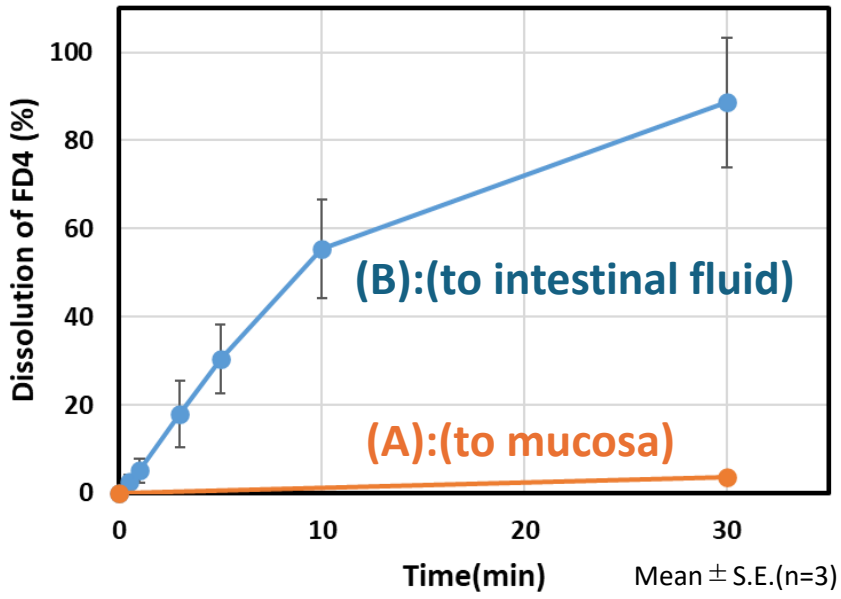
(B) Sampling (→ Surrogate of release to intestinal fluid)



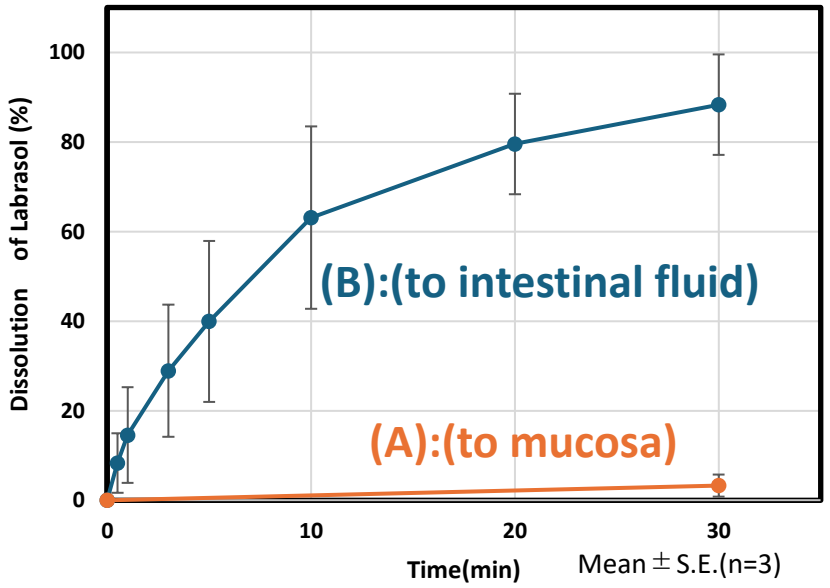
Drug is released to intestinal fluid, not mucosa!



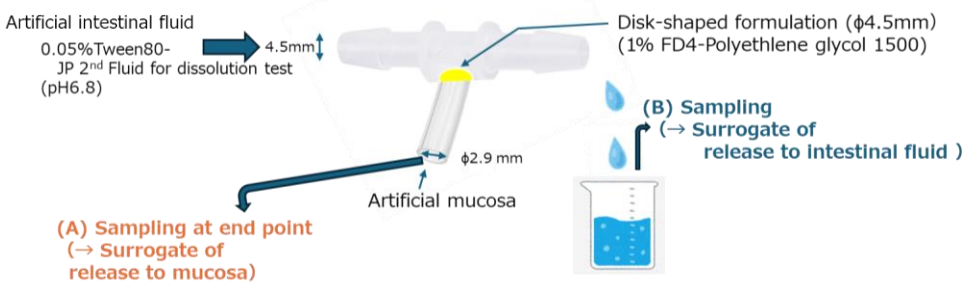
FD4 dissolution

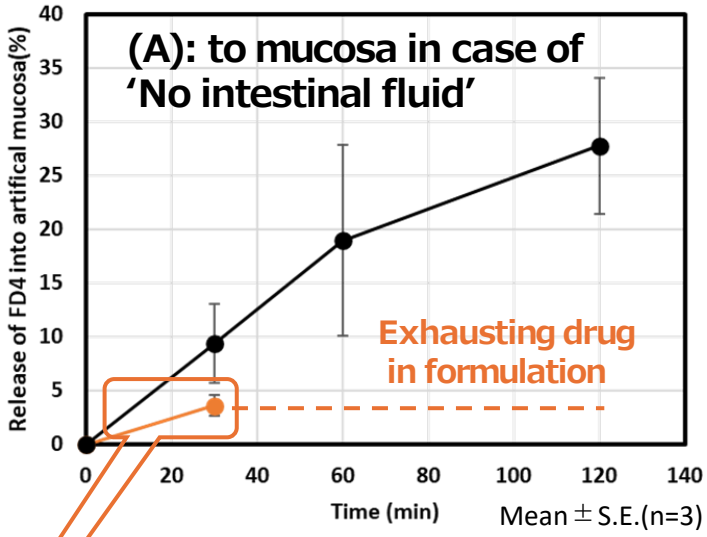


Labrasol ® dissolution

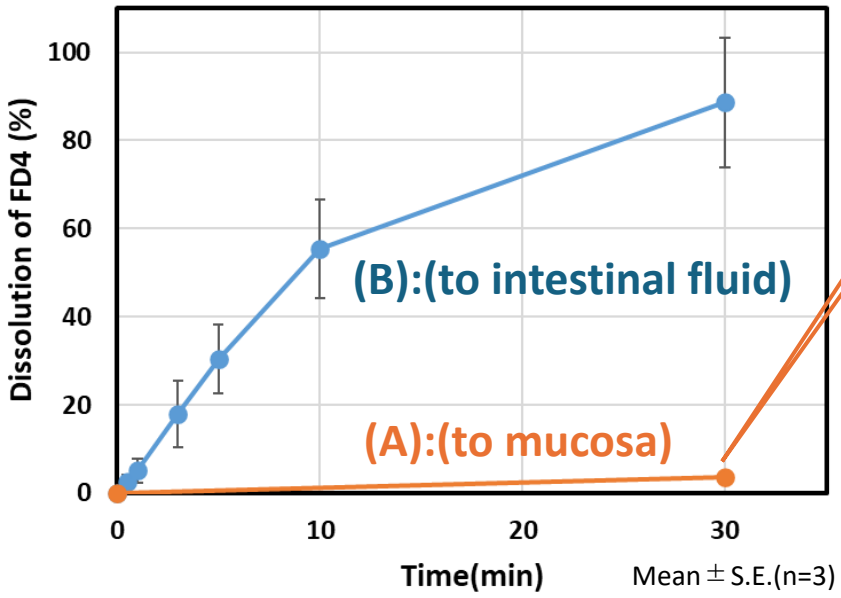


Drug is released to intestinal fluid, not mucosa!

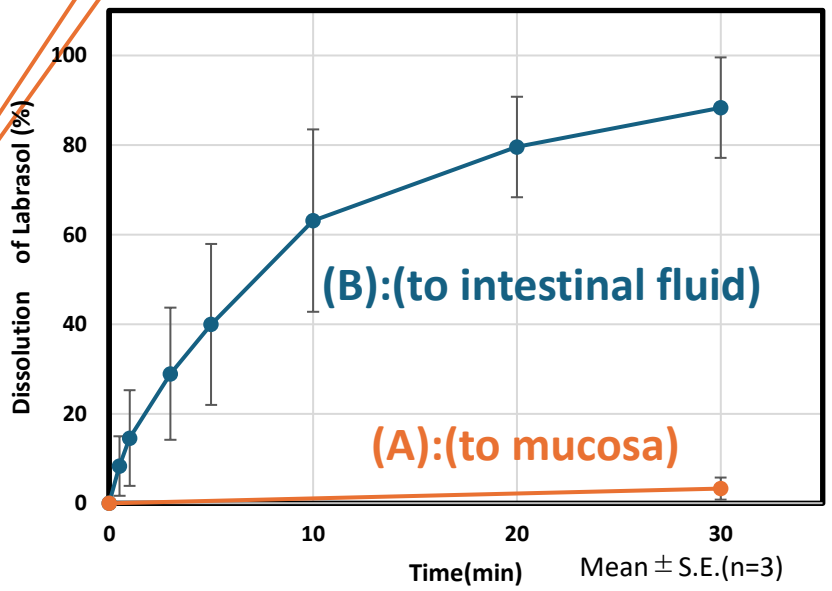




FD4 dissolution

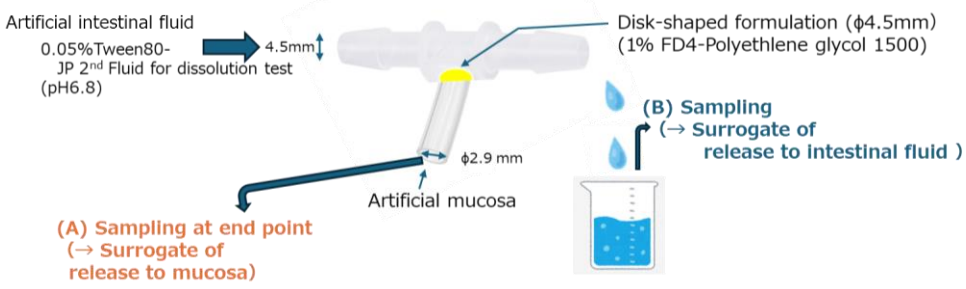


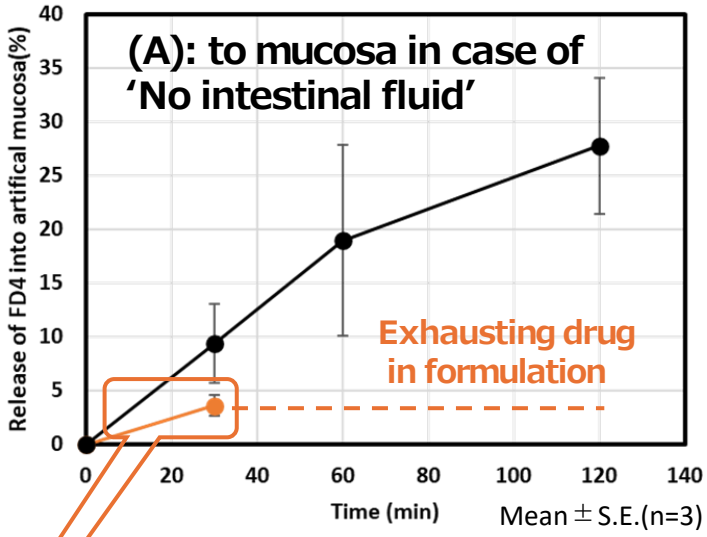
Labrasol® dissolution



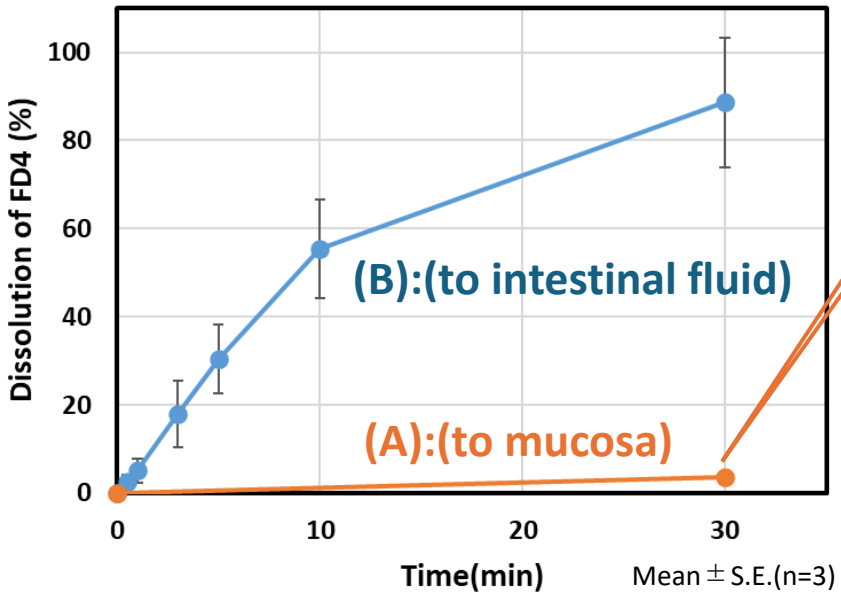
If the release to intestinal fluid stopped, the drug release to mucosa **prolonged** and **increased**.

Drug is released to intestinal fluid, not mucosa!

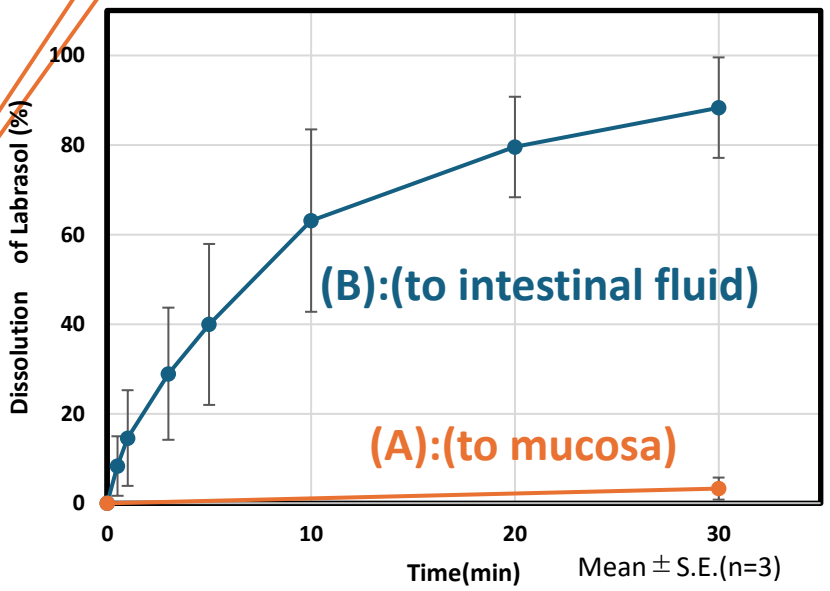




FD4 dissolution

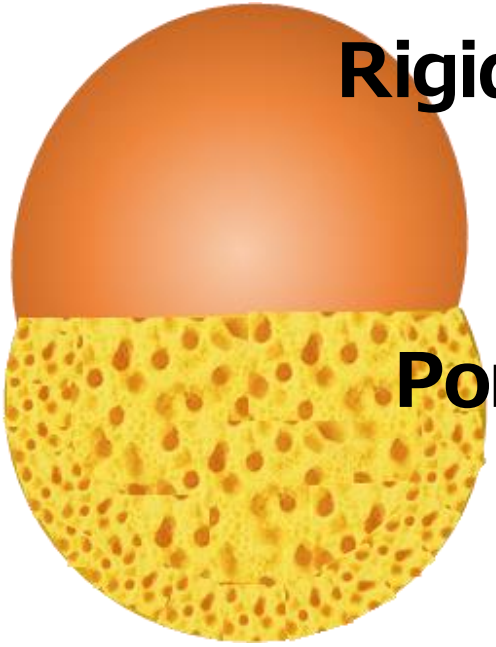


Labrasol ® dissolution



If the release to intestinal fluid stopped, the drug release to mucosa **prolonged** and **increased**.

One-directional release formulation:
Hemi-porous Janus microparticles



Rigid hemisphere

water repelling

Porous hemisphere

Impregnation

- Drug
- Absorption enhancer
- Enzyme inhibitor
- Muco-adhesive polymer

One directional release

Drug
Absorption enhancer
Enzyme inhibitor

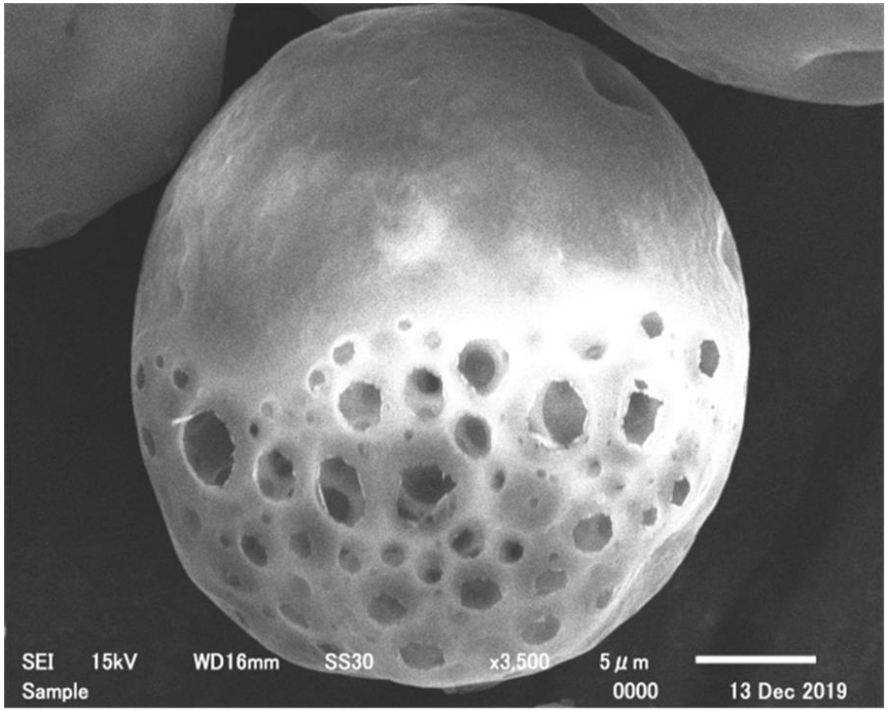
Size

10 ～100 μm

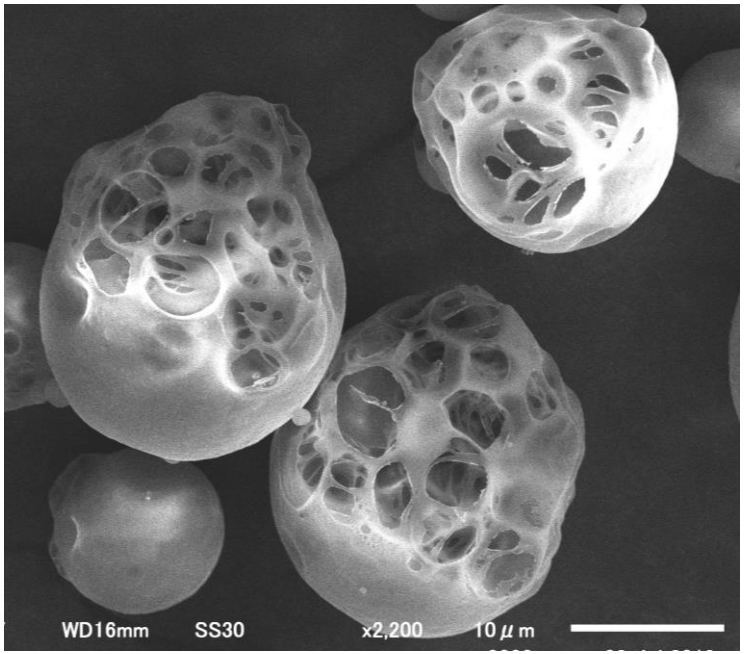
Composition

Ethyl cellulose
Hard-fat
Hypromellose phthalate（HPMCP）

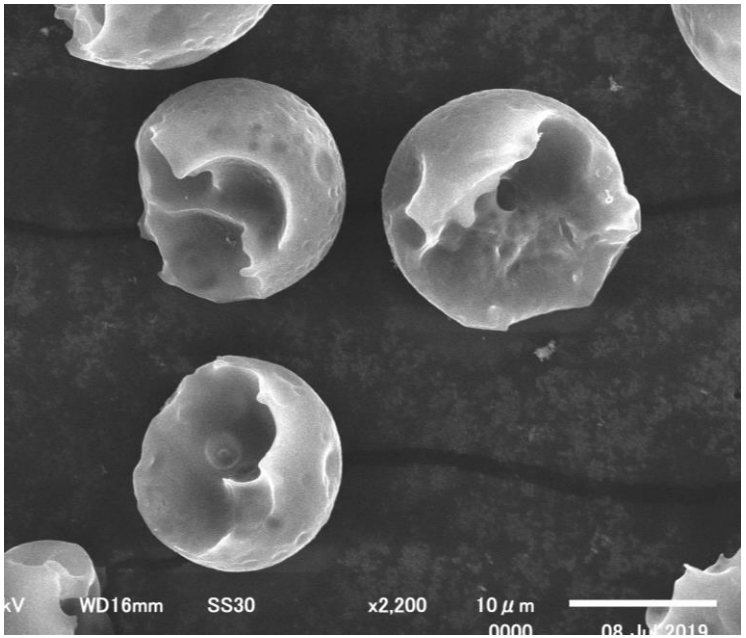
This is our formulation ‘hemi-porous Janus microparticles’.



What constitutes each hemisphere?



0.1M
Phosphate
buffer (pH8.0)



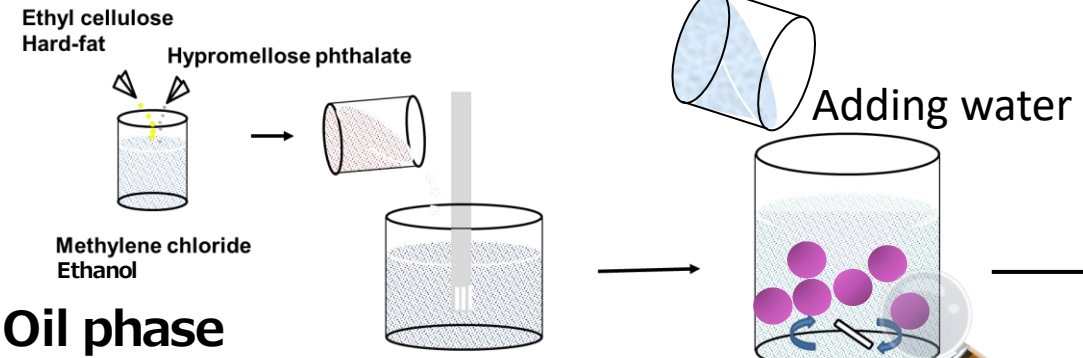
Porous hemisphere

→ Hypromellose phthalate

Rigid hemisphere

→ Blend of Ethyl cellulose and hard-fat

Preparation of hemi-porous Janus microparticles

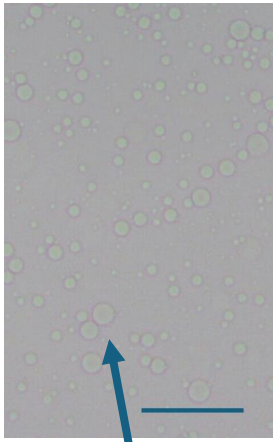


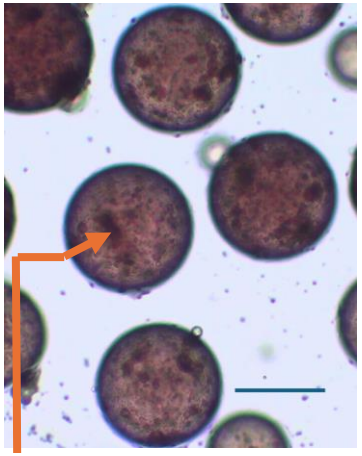
Oil phase

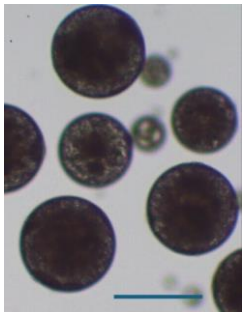
Emulsification (o/w emulsion)

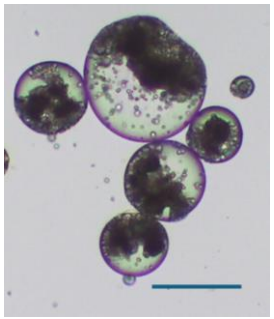
Partially solvent extraction

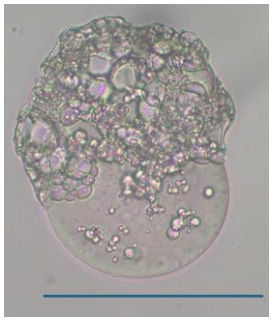
Solvent evaporation











Liquid

Coagulation

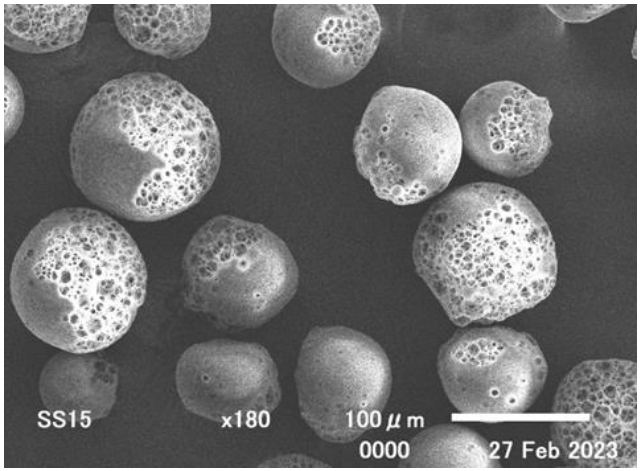
Migration

Swelling

Hypromellose phthalate phase

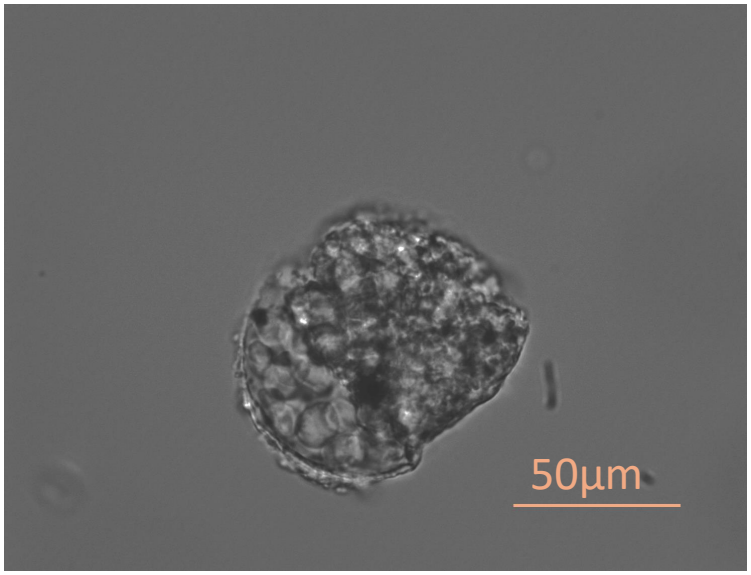
Blue bar (▬) indicates100μm.

Drug can be loaded only in a hemisphere

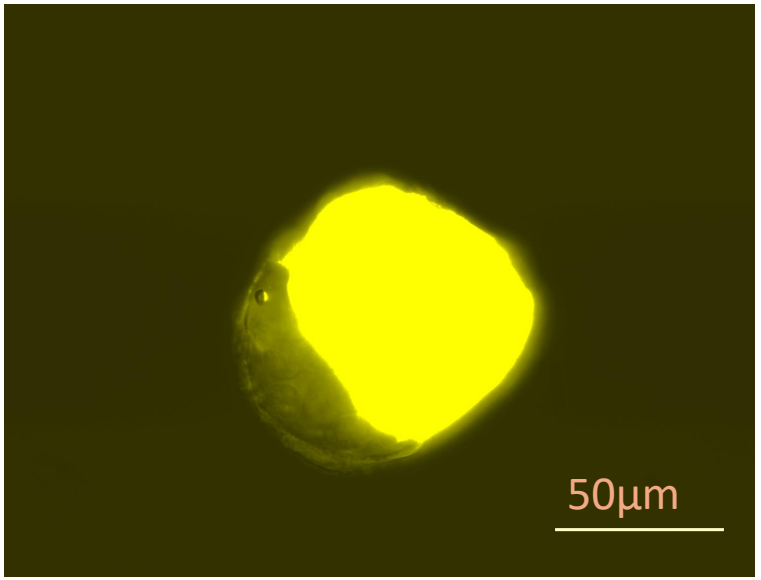


FD4 solution
Impregnating and drying

Optical



Fluorescent

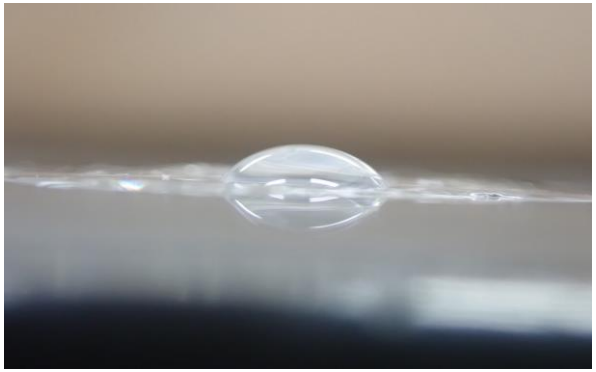


Surrogate evaluation of wettability of rigid and porous hemispheres

(A) Hypromellose phthalate film (Surrogate of porous hemisphere)

Contact angle: 53.7°

(B) Ethyl cellulose film



Contact angle: 60.3°

(C) Ethyl cellulose/hard fat film (Surrogate of rigid hemisphere)

Contact angle: 96.9°

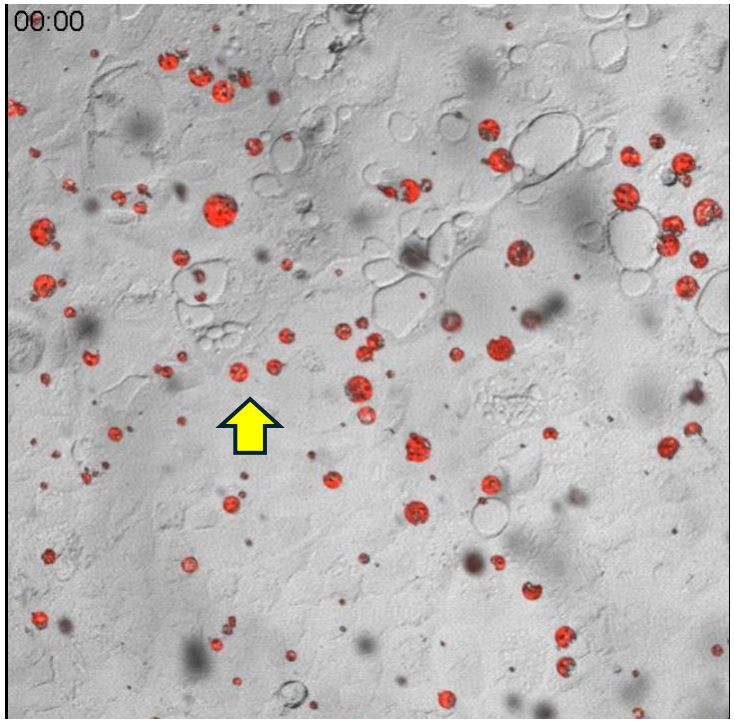
The difference in the wettability of the two hemispheres can be controlled by adding hard fat.

↓

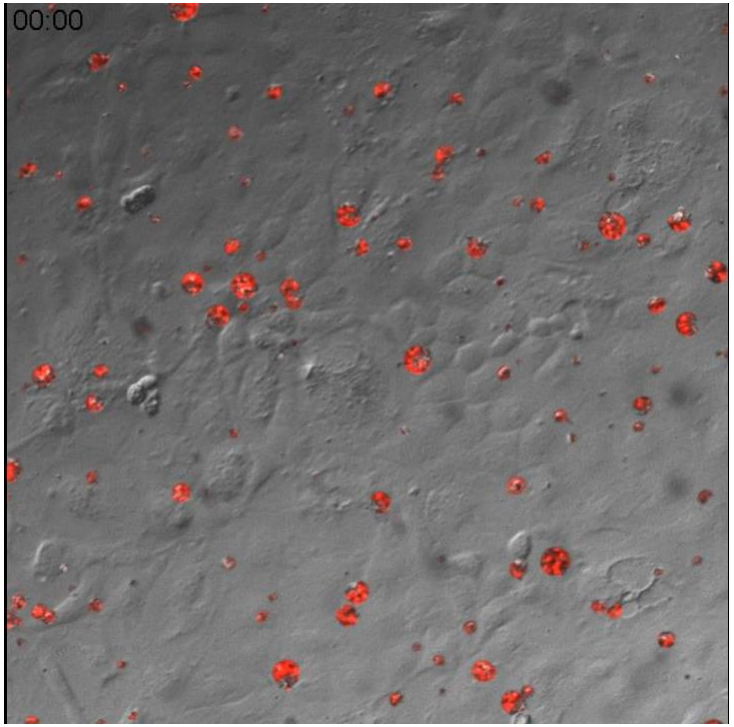
Increase the incorporation efficiency of drug aqueous solution in porous hemispheres

Muco-adhesive hemiporous microparticles attached Caco-2 membrane

(+) Muco-adhesive polymer

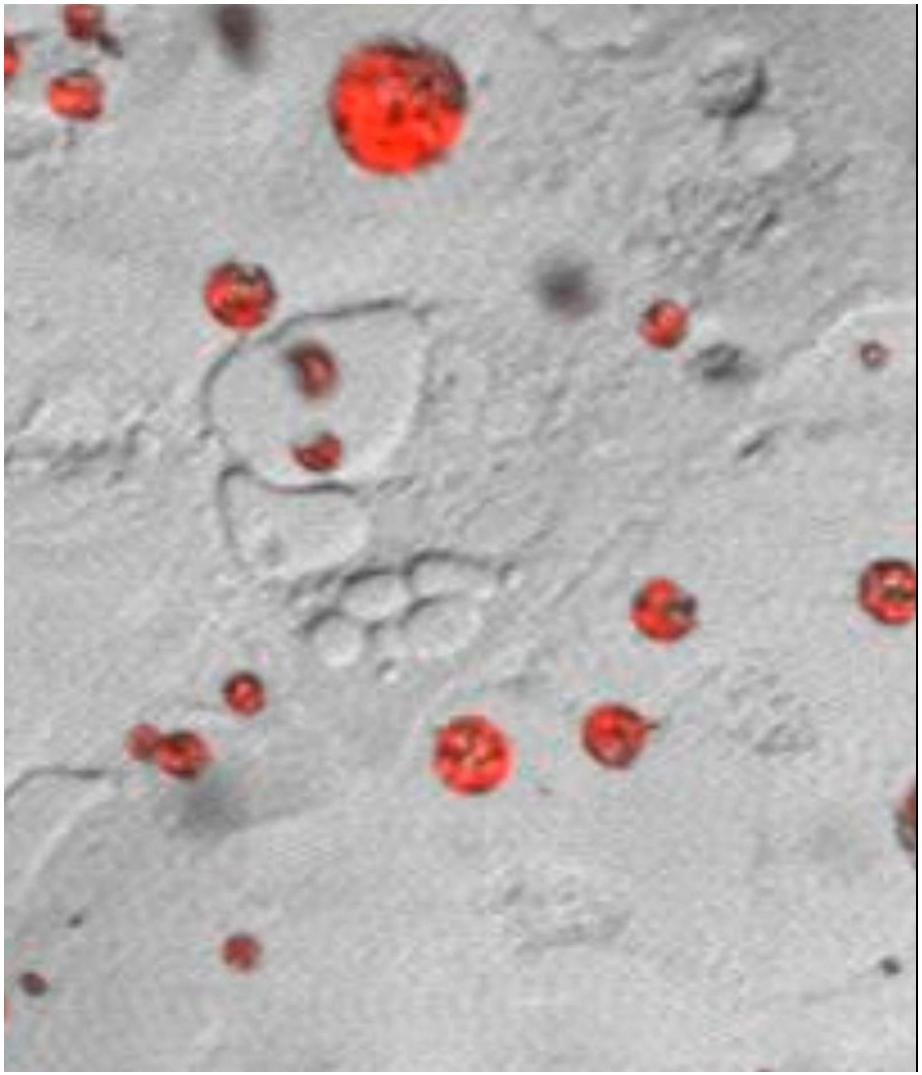


(-) Muco-adhesive polymer



Speed: ×1

Adhesive polymer: Carbopol® 934

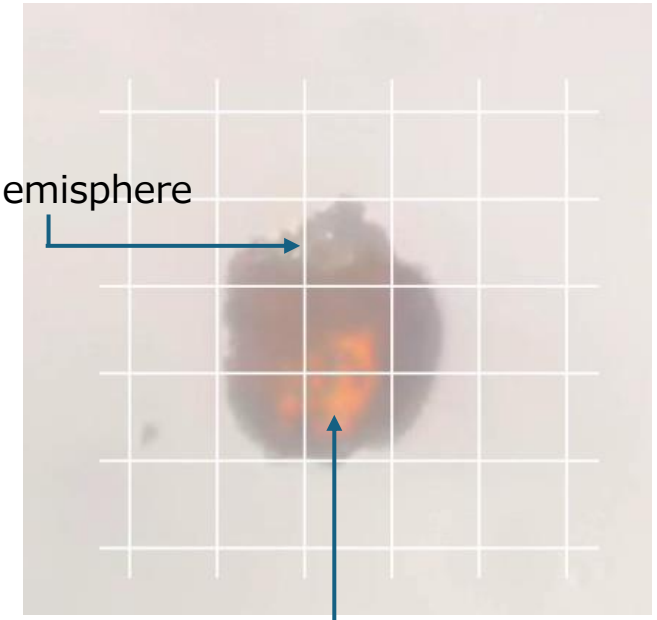


Speed: ×0.06

Adhesive polymer: Carbopol® 934

Porous hemisphere is transformed into a muco-adhesive portion under the intestinal pH condition (*in vitro*)

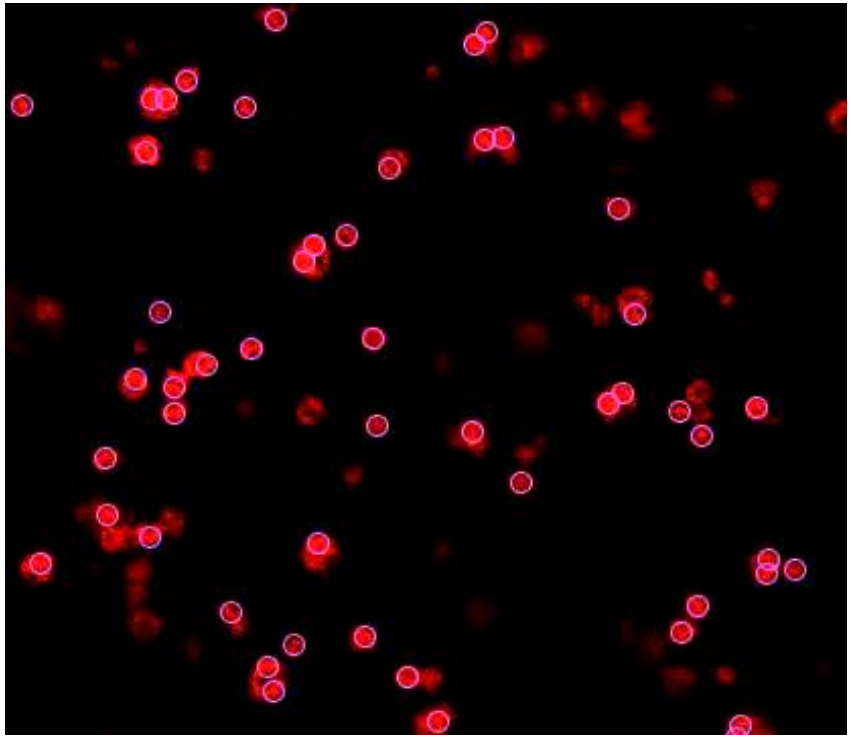
Just after the addition of 2nd fluid (pH6.8)



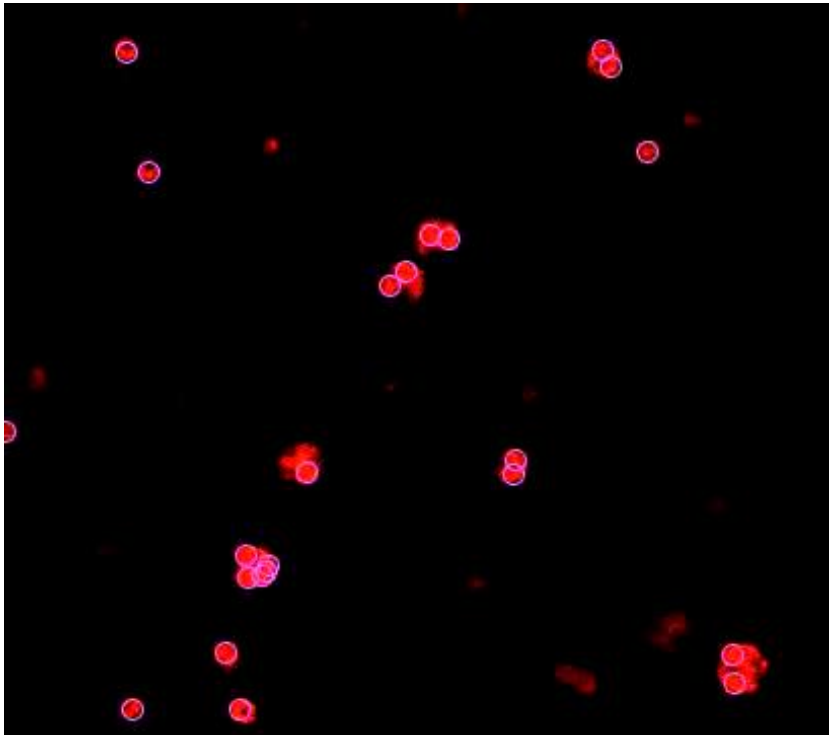
Adhesive polymer: Carbopol ® 934

Muco-adhesive hemiporous microparticles attached Caco-2-HT29MTX membrane

(+) Muco-adhesive polymer



(-) Muco-adhesive polymer

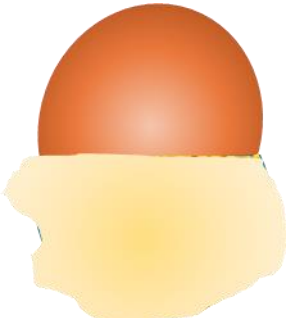


Speed: ×1

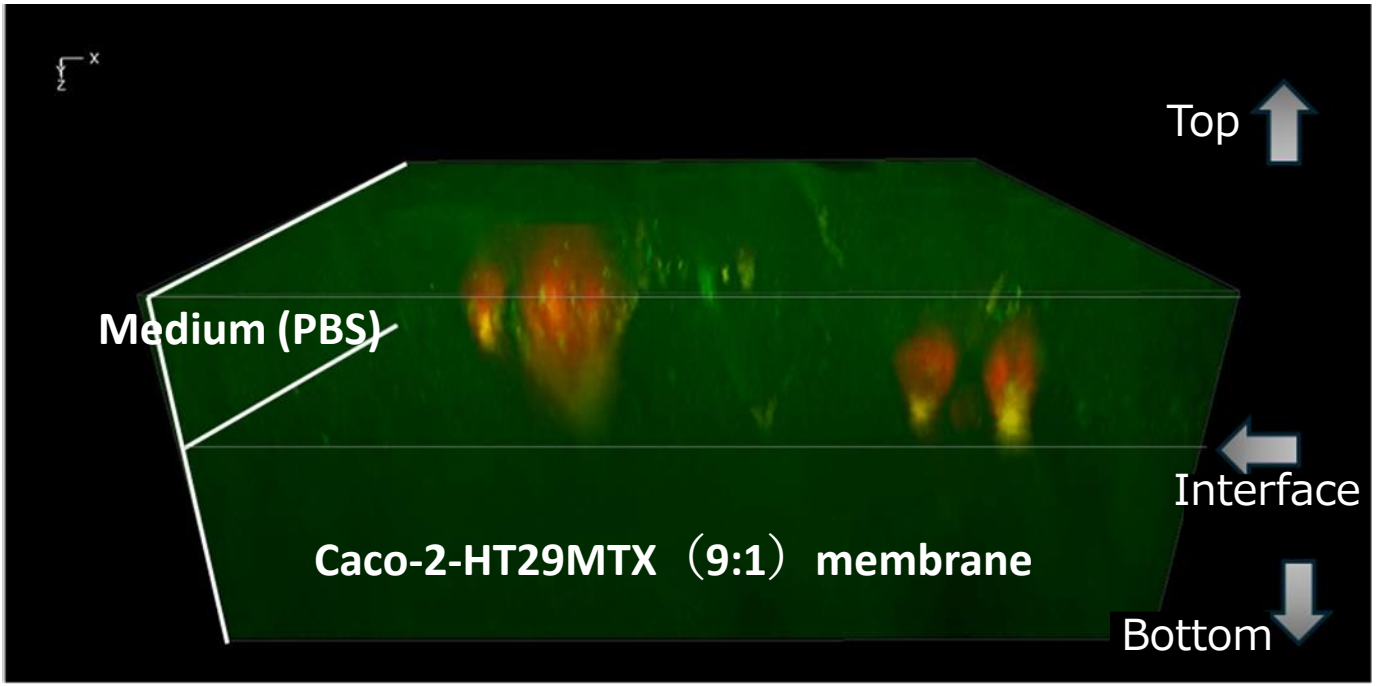
Adhesive polymer: Carbopol® 934

Muco-adhesive hemi-porous microparticles attached to mucus with the porous hemisphere oriented downwards and the rigid hemisphere facing upwards *in vitro* Caco-2-HT29MTX culture

Water-repelling rigid hemispheres
Nile red (red)



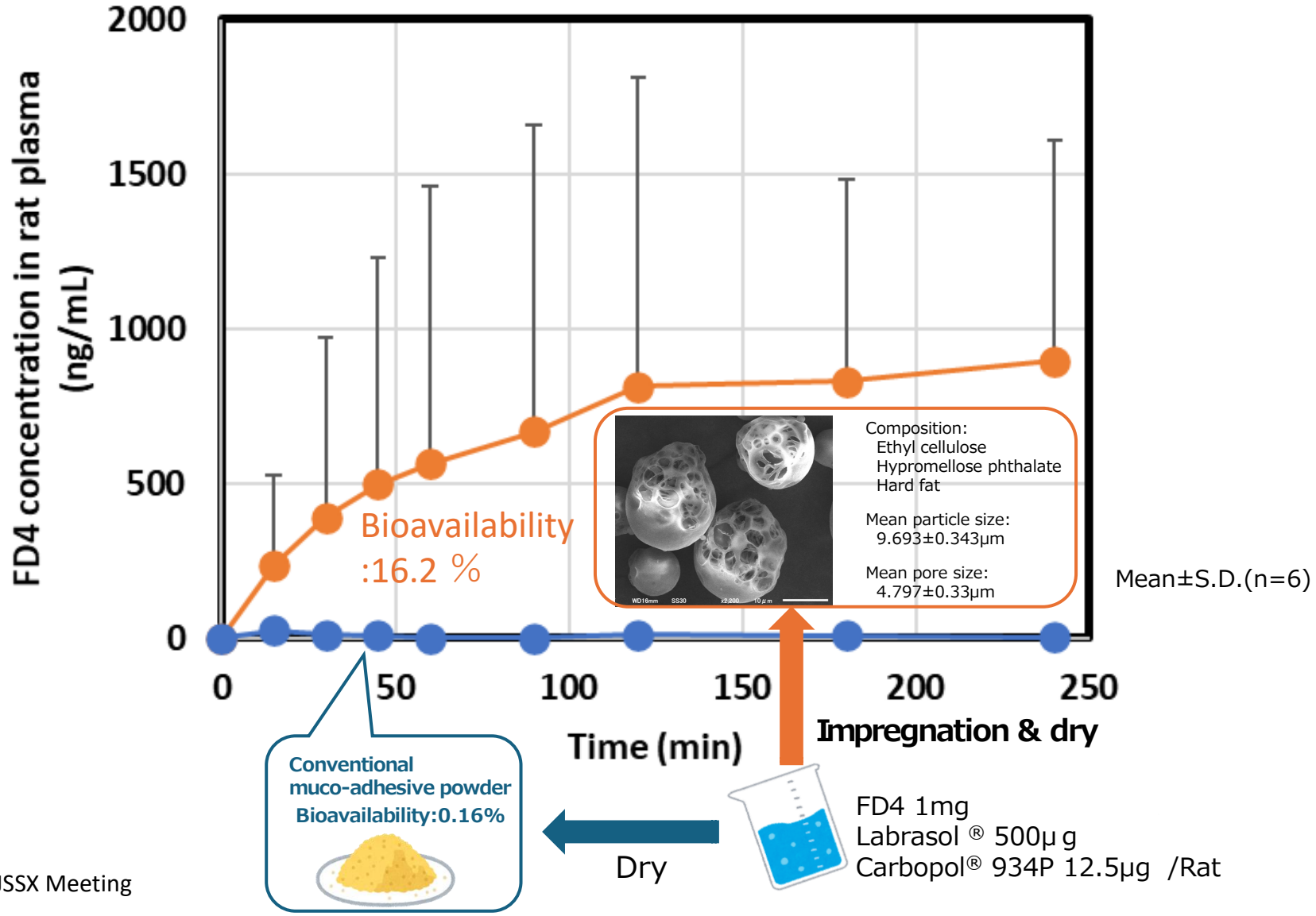
Muco-adhesive portion
FD4 (yellow)



24 h

Adhesive polymer: Carbopol ® 934

Rat jejunum absorption of FD4 were improved by the administration of FD4-muco-adhesive hemi-porous microparticles (Carbopol934)

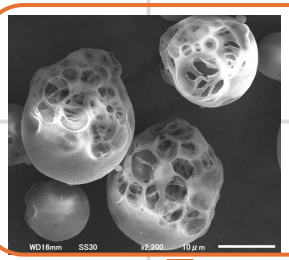


Rat jejunum absorption of FD4 were improved by the administration of FD4-muco-adhesive hemi-porous microparticles (Chitosan)

Impregnating

Drug:1mg FD4
Muco-adhesive polymer:
12.5μg Chitosan(200-600mPa･s)
Absorption enhancer:500μg Labrasol®/Rat

+Hemi-porous microparticles(1mg/rat)



Composition:
Ethyl cellulose
Hypromellose phthalate
Hard fat

Mean particle size:
9.693±0.343μm

Mean pore size:
4.797±0.33μm

drying

drying

Muco-adhesive hemi-porous microparticles

Conventional muco-adhesive powder

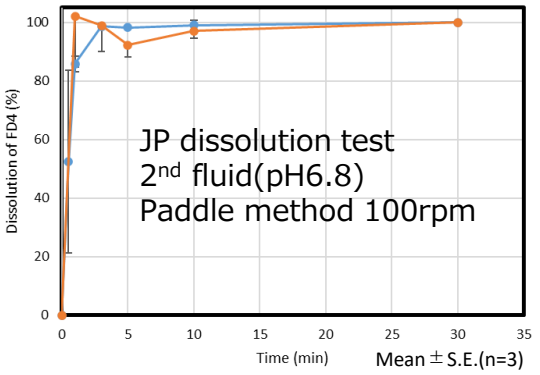
FD4 concentration in rat plasma (ng/mL)

2000
1500
1000
500
0

0 50 100 150 200 250

Time (min)

Mean ± S.D.(n=3)



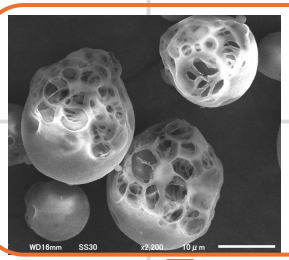
Mean ± S.E.(n=3)

Rat jejunum absorption of FD4 were improved by the administration of FD4-muco-adhesive hemi-porous microparticles

Drug:1mg FD4
Muco-adhesive polymer:
12.5μg Chitosan(200-600mPa･s)
Absorption enhancer: 500μg Labrasol®/Rat

Impregnating

+Hemi-porous microparticles(1mg/rat)



Composition:
Ethyl cellulose
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9.693±0.343μm

Mean pore size:
4.797±0.33μm

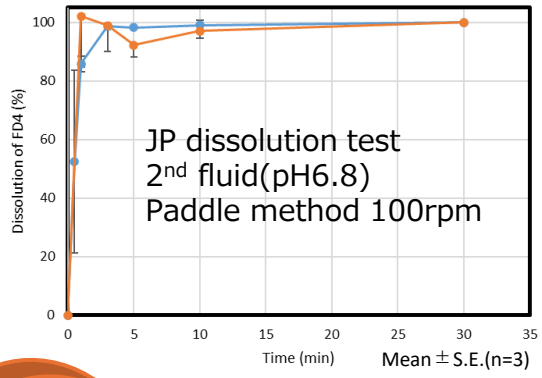
drying

drying

Muco-adhesive hemi-porous microparticles

Conventional muco-adhesive powder

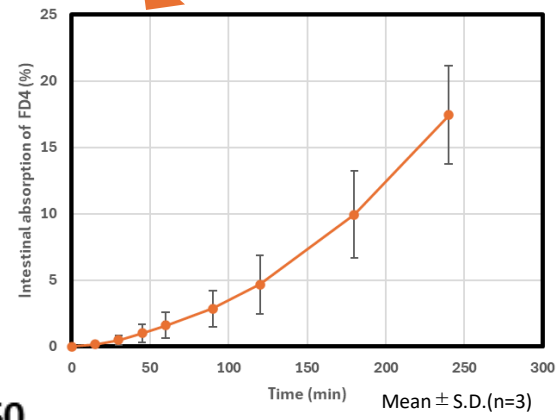
Mean ± S.D.(n=3)



JP dissolution test
2nd fluid(pH6.8)
Paddle method 100rpm

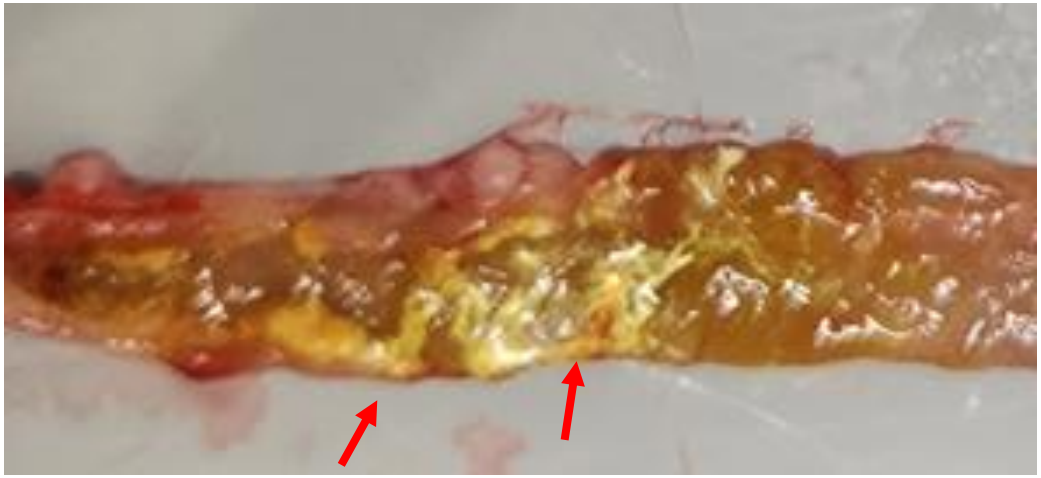
Mean ± S.E.(n=3)

Deconvolution



Mean ± S.D.(n=3)

FD4-muco-adhesive hemi-porous microparticles attached to rat jejunum



Undissolved FD4

240 min

・**Adhesion to jejunum**

・**Incomplete dissolution of FD4**

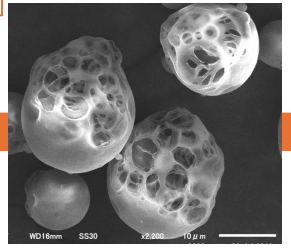
→ FD4 dissolved slowly in mucosa, which was the only direction of FD4 release.

6.6% relative bioavailability of insulin were achieved by the rat jejunum administration of insulin-muco-adhesive hemi-porous microparticles

Drug:2U insulin
Muco-adhesive polymer:
130 μg Chitosan(200-600mPa･s)
Enzyme inhibitor:1mg citric acid
Absorption enhancer:800μg Labrasol®/Rat

Impregnating

Hemi-porous microparticles (2mg/rat)



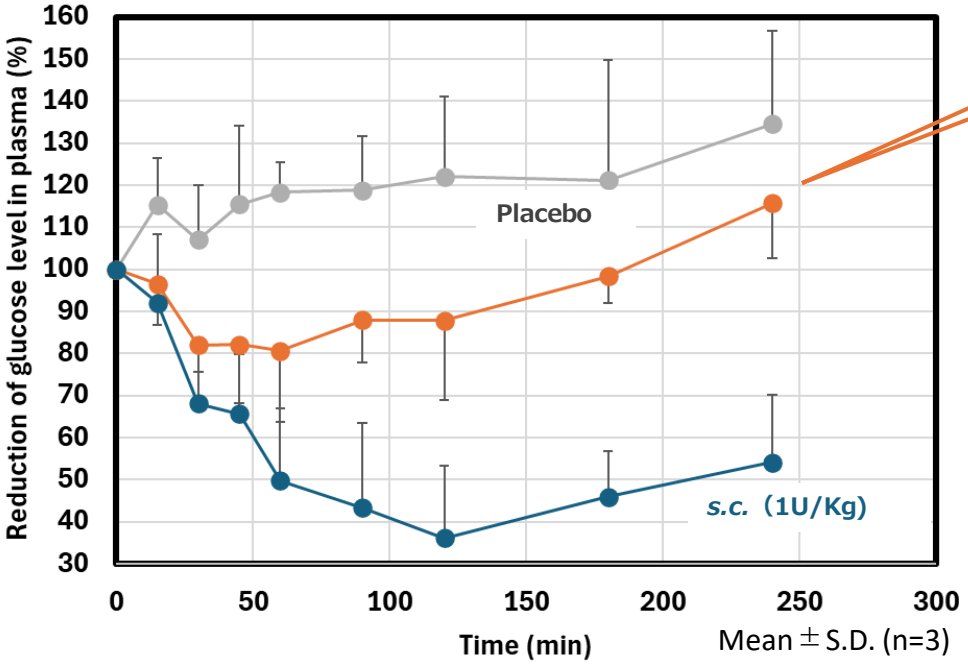
drying

Composition:
Ethyl cellulose
Hypromellose phthalate
Hard fat

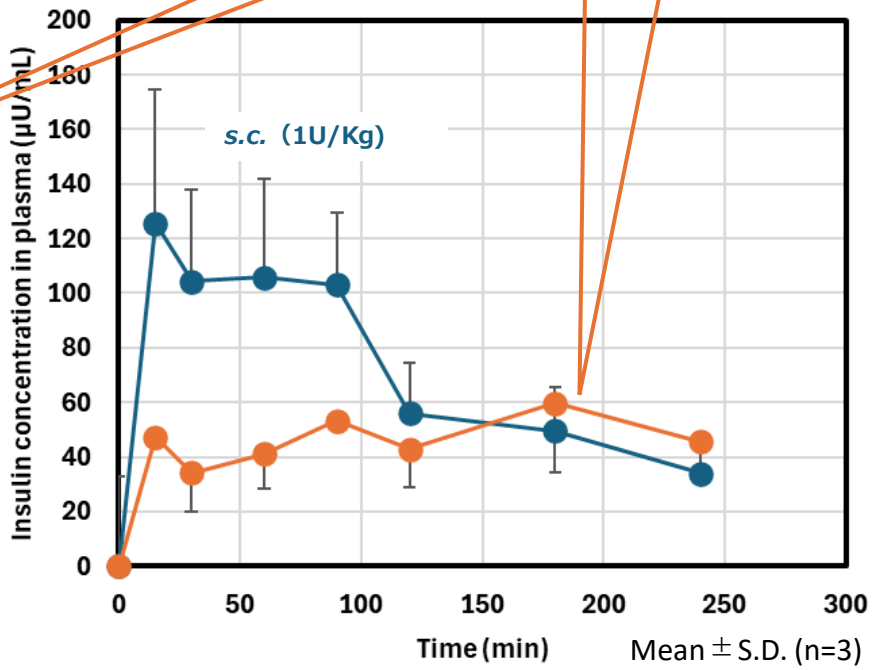
Mean particle size:
9.693±0.343μm

Mean pore size:
4.797±0.33μm

Muco-adhesive hemi-porous microparticles (Insulin 10U/Kg)



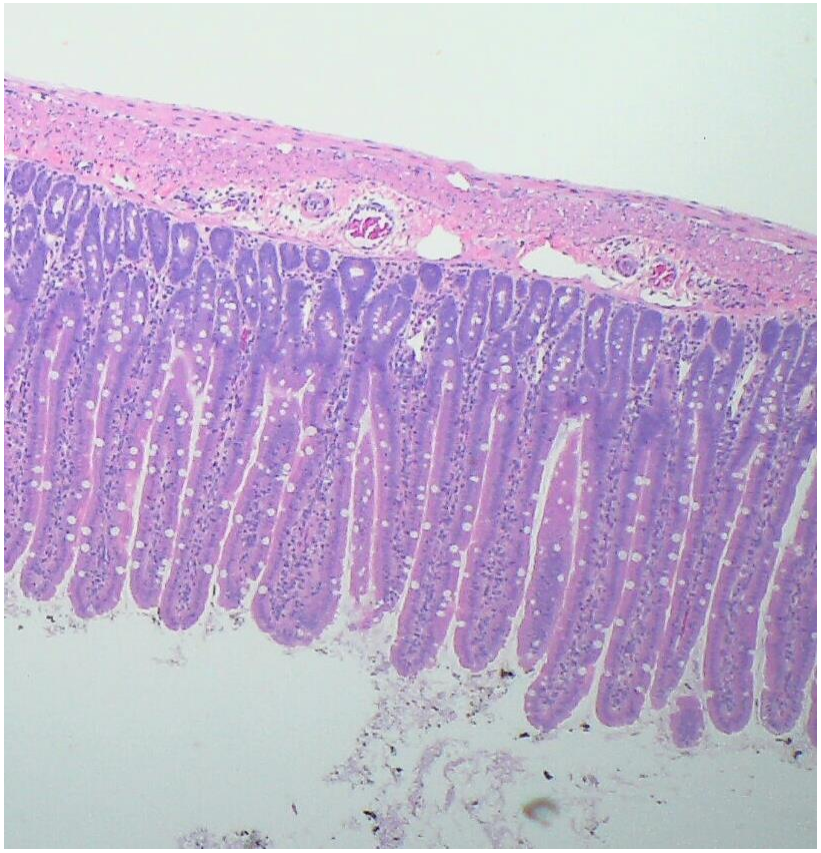
Mean ± S.D. (n=3)



Mean ± S.D. (n=3)

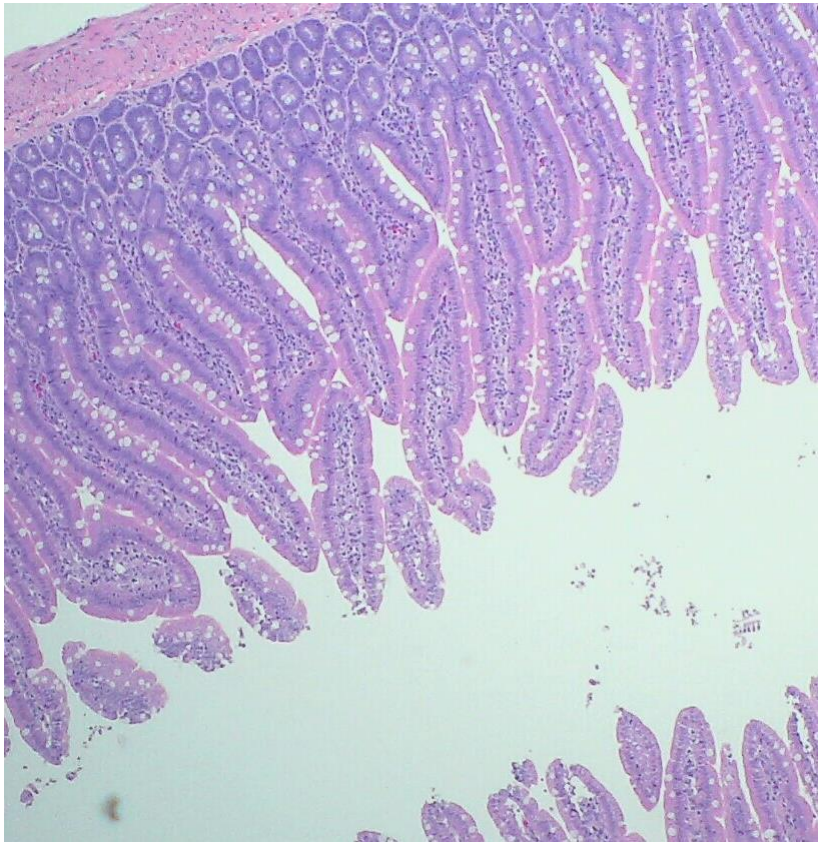
Histological analysis did not show pronounced local mucosal irritation

Insulin-muco-adhesive hemi-porous microparticles



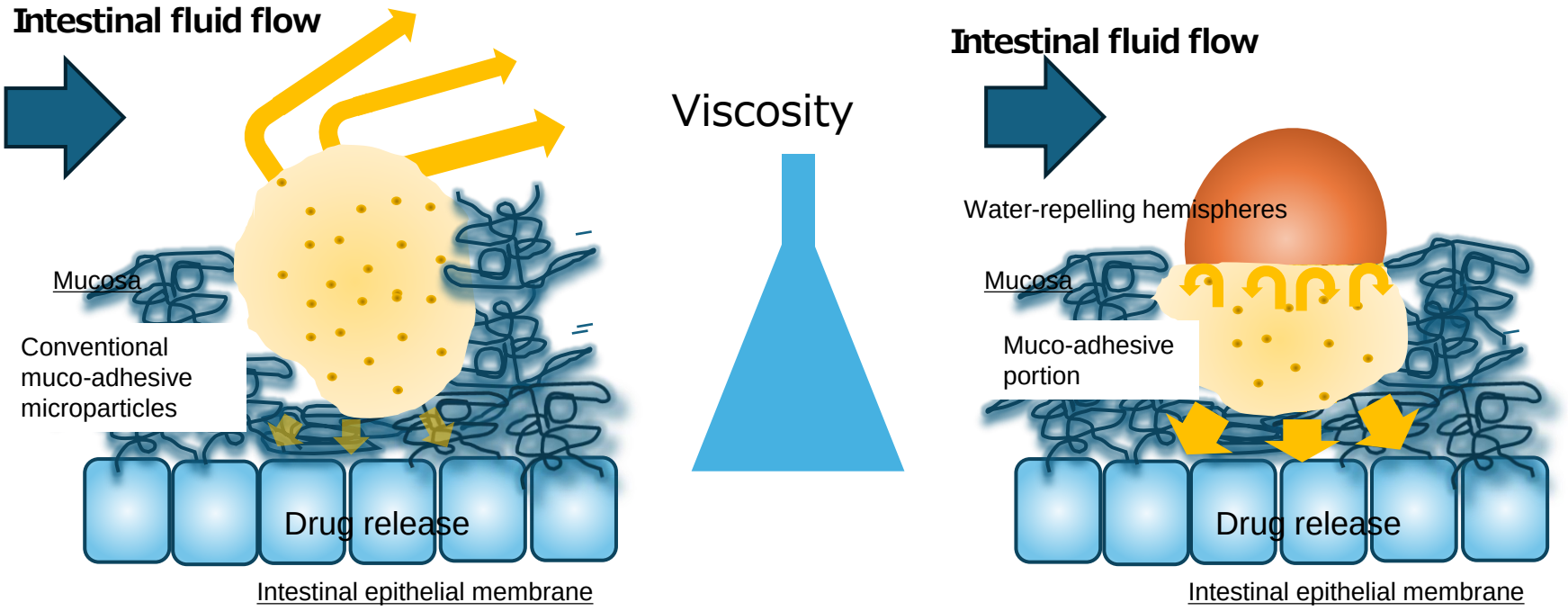
100μm

Control



100μm

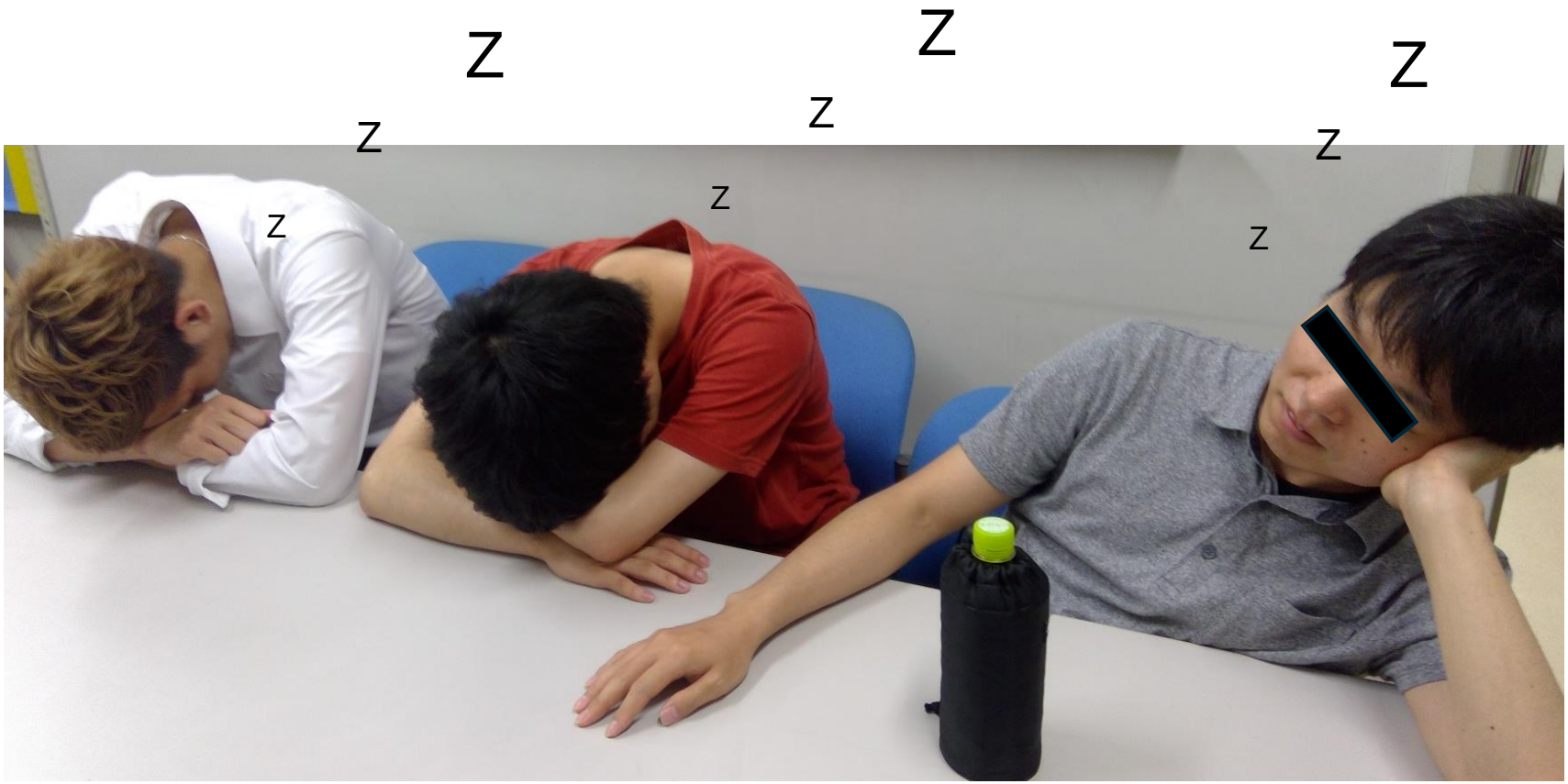
Conclusions



・A conventional formulation releases drugs and absorption enhancers mainly to the luminal side, and releases little to the high-viscosity mucosa.
・Drugs and absorption enhancers released to the luminal side are immediately diluted by the intestinal fluid. → **Bioavailability of BCS class 3 drugs was low.**

・ The oriented adhesion suppresses the release of drugs and absorption enhancers to the luminal side, and lead to the slow release of drug and absorption enhancer only to the mucosal side but keeping high concentrations of them in mucosa.
→ **Bioavailability of BCS class 3 drugs was improved.**

Merci pour votre attention!



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