Nanomedicine and Nanoscale Delivery IV

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PhD Candidate, MIT Chemical Engineering

CONTROLLED RELEASE SOCIETY
CRS 2024 Annual Meeting and Exposition
JULY 8-12, 2024 • BOLOGNA, ITALY

INTEGRATING
Delivery Science
ACROSS DISCIPLINES

Bottom-up templating of drug nanoparticles in core-shell hydrogel particles for versatile oral drug delivery

Lucas Attia, Liang-Hsun Chen, Patrick S. Doyle
MIT Department of Chemical Engineering

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Website: doylegroup.mit.edu/

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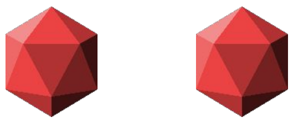
INTEGRATING Delivery Science ACROSS DISCIPLINES

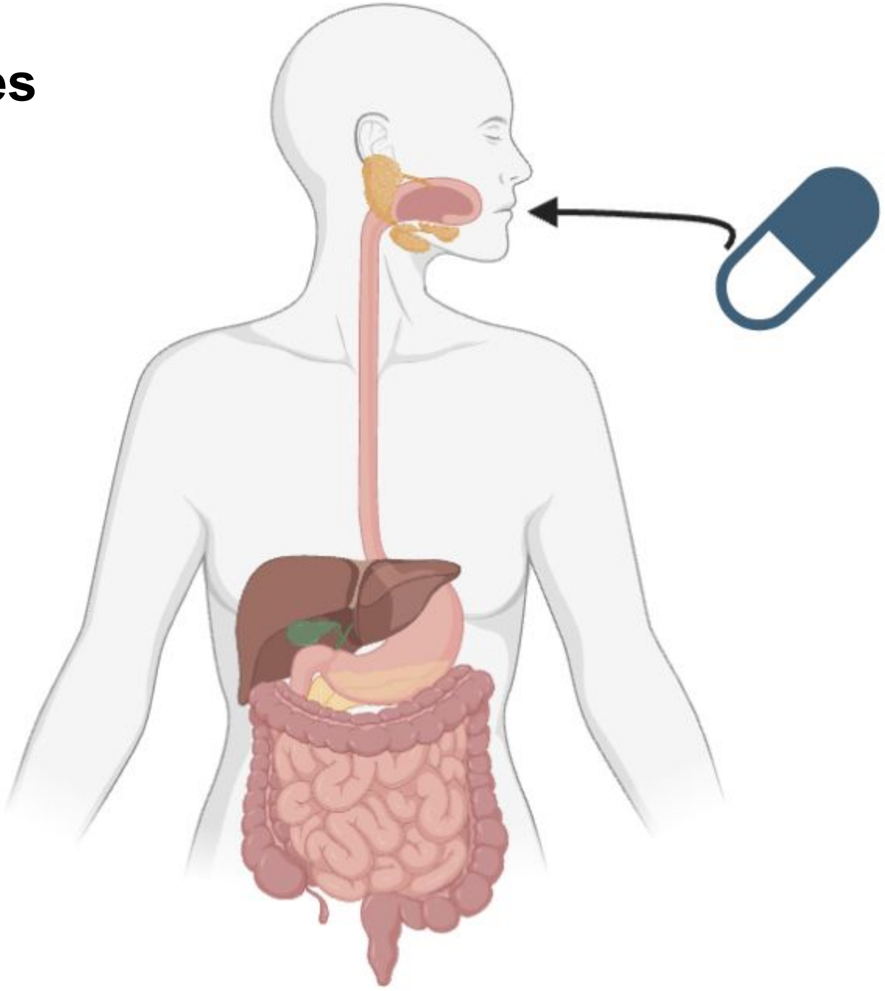
We address two challenges in oral formulation

Generating drug nanoparticles



$$O(L) \sim 0.1 - 1\ \mu m$$

- ✔ Improve drug dissolution
- ✔ Control crystal size distribution



Manufacturing core-shell carriers

- ✔ Control drug release
- ✔ Structure drugs in distinct layers

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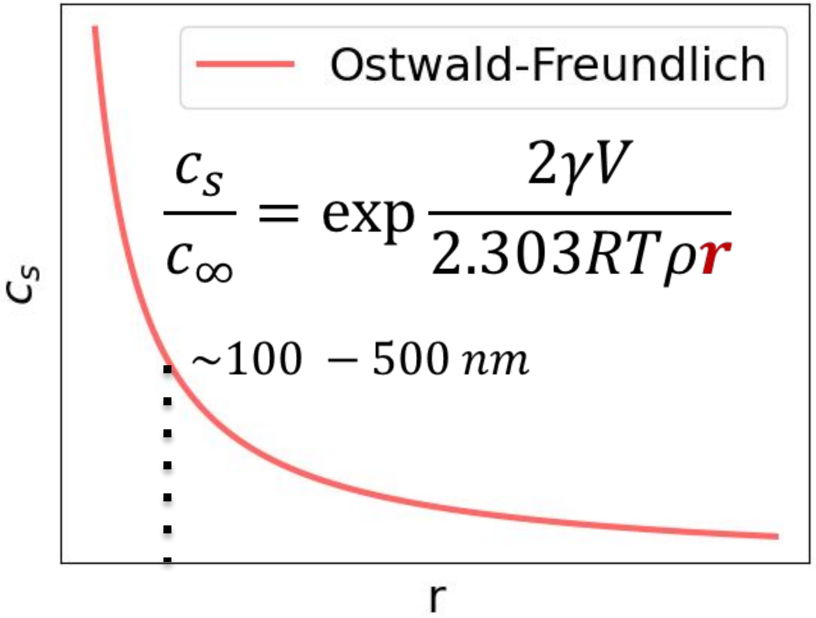
Nanosizing improves the oral bioavailability of hydrophobic APIs

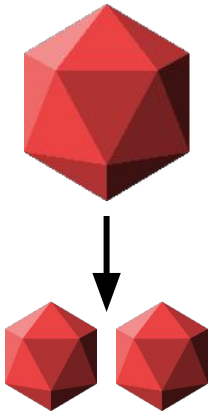
Thermodynamics



Nanosized API particles have increased **equilibrium solubility**

Nanosizing API

$\mathrm{r} \sim 1\ mm$



$r \sim 0.1 - 1\ \mu m$

Kinetics

Noyes-Whitney

$$\frac{\mathrm{dc}}{\mathrm{d}t} = \frac{D \times \mathbf{A}(c_s - c_x)}{h}$$

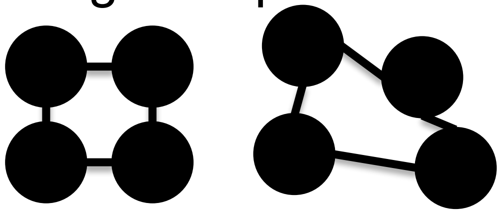
Nanosized API particles have faster **dissolution kinetics**

1. Padhye, *J Drug Deliv Sci Technol* (2021)

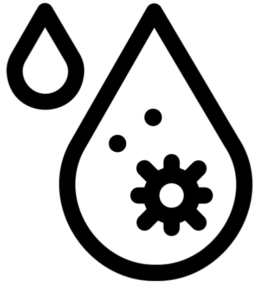
Conventional ‘top-down’ nanosizing is resource-intensive and difficult to control

Energy efficiency < 5 %

Drug amorphization

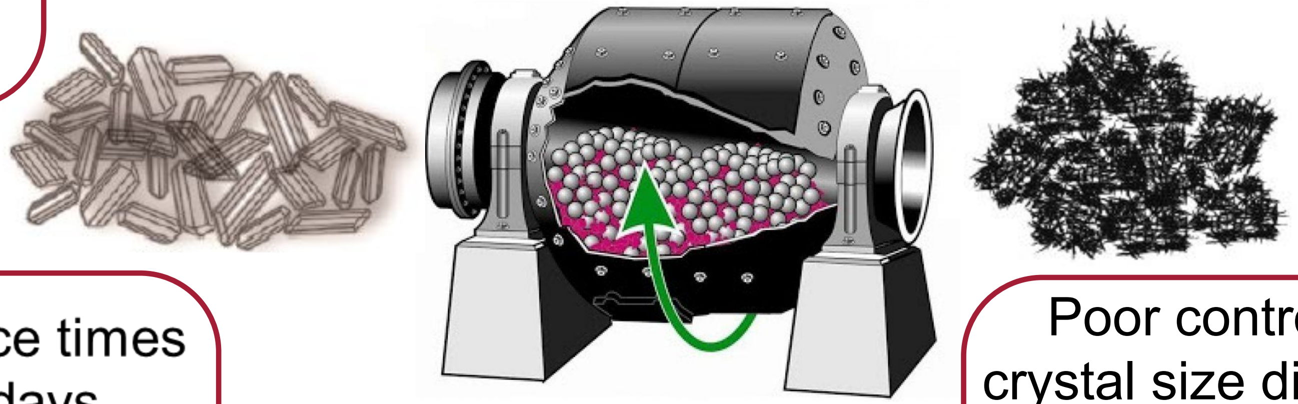


Contaminations from milling beads



$r \sim 1\ mm$

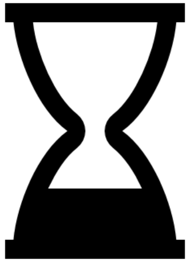
$r \sim 0.1 - 1\ \mu m$



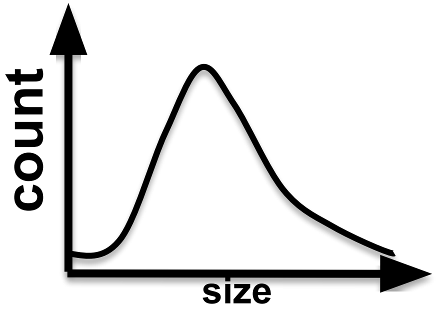
Media Mill

Long residence times

$\tau \sim 1 - 5$ days

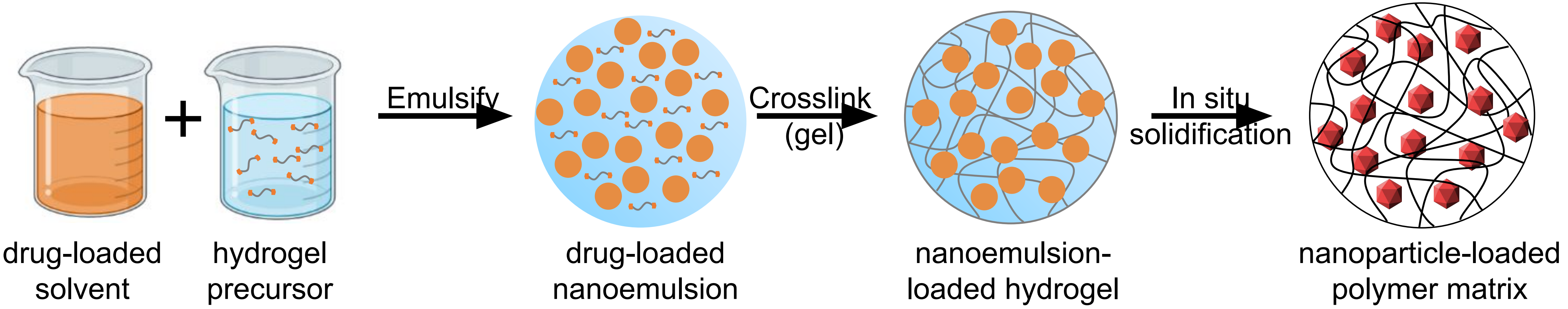


Poor control over crystal size distribution



1. Schenck. *Mol. Pharm* (2020)
2. Hansuld. *Int. J. Pharm* (2014)

Nanoemulsions template drug nanoparticles from the ‘bottom-up’



Eral. *Chem. Mater.* (2014)
Eral. *Cryst. Growth Des.* (2014)
Badruddoza. *Adv. Healthc. Mater.* (2016)
Badruddoza. *Adv. Ther.* (2018)

Domenech. *Chem. Mater.* (2020)
Chen. *Adv. Mater.* (2021)
Chen. *Chem. Mater.* (2022)
Attia. *Adv. Healthc. Mater.* (2023)

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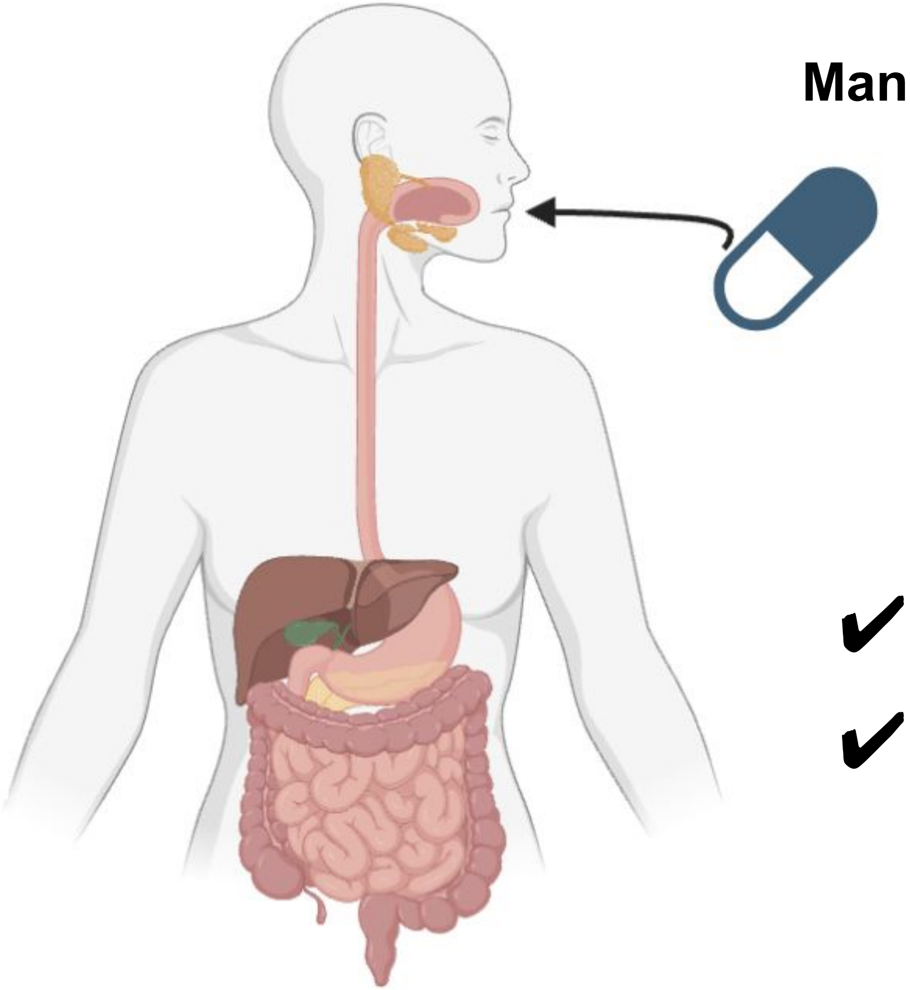
We address two challenges in oral formulation

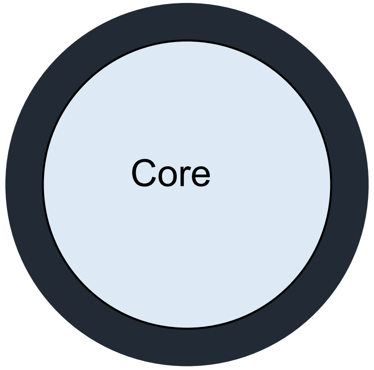
Generating drug nanoparticles

$O(L)\sim 0.1 - 1\ \mu m$

- ✔ Improve drug dissolution
- ✔ Control crystal size distribution



Manufacturing core-shell carriers



- ✔ Control drug release
- ✔ Structure drugs in distinct layers

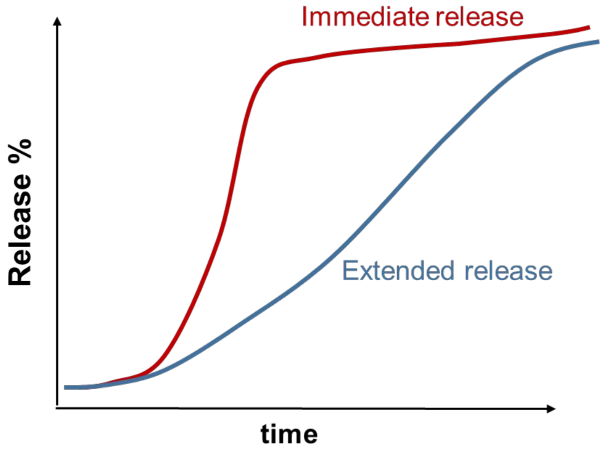
Various therapeutic applications require core-shell carriers

Intestinal and colonic targeting

Delzicol

McCoubrey. *J. Control. Release* (2023)

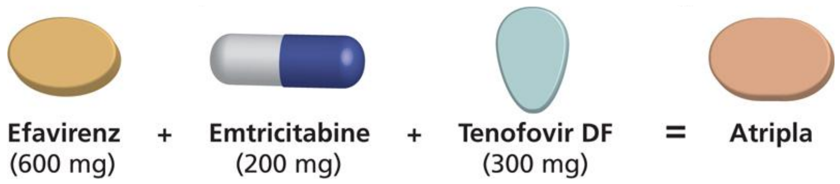
Sustained/Extended release



Carbamazepine

McHugh, *Nature Reviews Drug Discovery* (2023)

Combination drug products



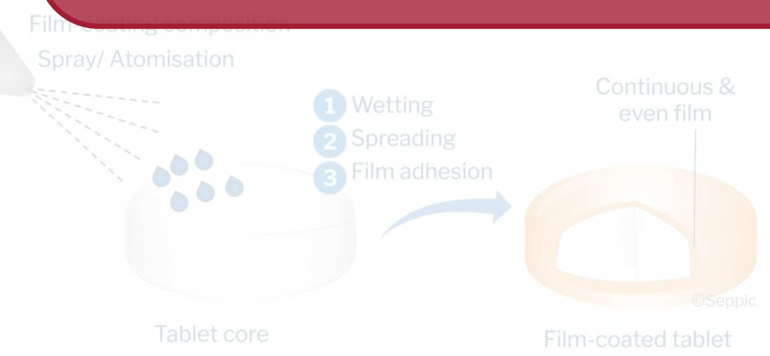
Atripla

Rabbani. *Am. J. Hypertens.* (2008)

Current core-shell carrier manufacturing platforms are limited

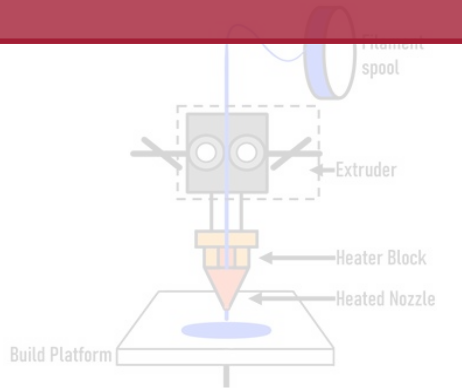
Platform | Additional unit operation | Organic solvent | Structure drugs in distinct layers | High processing temperature

1. **Manufacture core-shell particles with distinct polymeric layers**
2. **Template hydrophobic drug nanoparticles in each layer**
3. **Control release kinetics through formulation parameters**



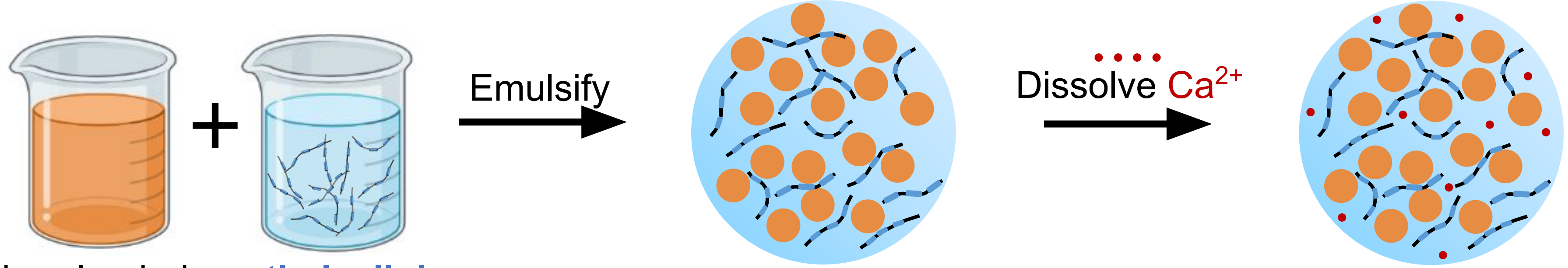
1. Film coating. *SEPPIC*

2. Windbergs. *JACS.* (2013



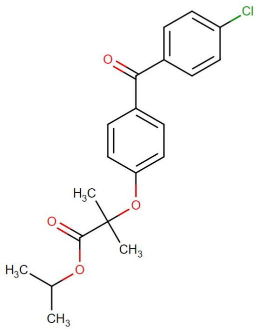
3. Parulski. *Adv. Drug Deliv. Rev.* (2021)

We combine thermogelling and ion-gelling capabilities

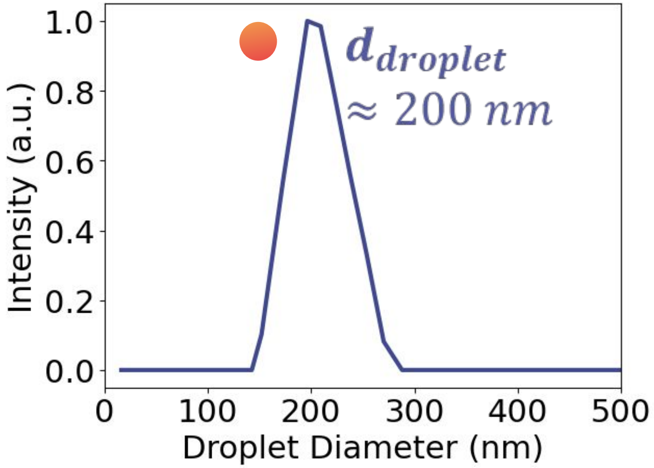


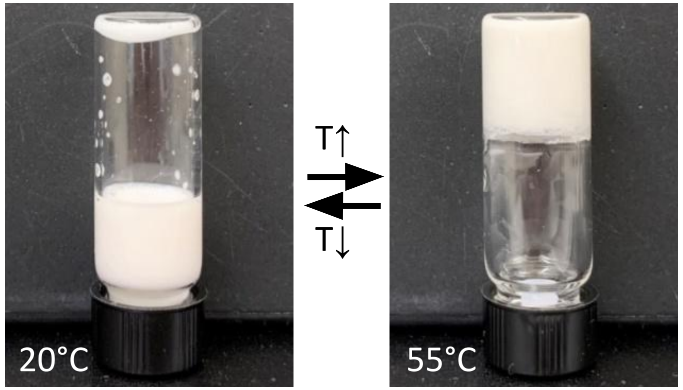
drug-loaded solvent + **methylcellulose** solution → **methylcellulose** nanoemulsion → Ca^{2+}-loaded **methylcellulose** nanoemulsion

Fenofibrate (FEN)[1]
0.3 µg mL^{-1} water



✔Low solubility
✔High permeability





Solution **Gel**

1. Tipduangta. *Cryst. Growth Des.* (2015)

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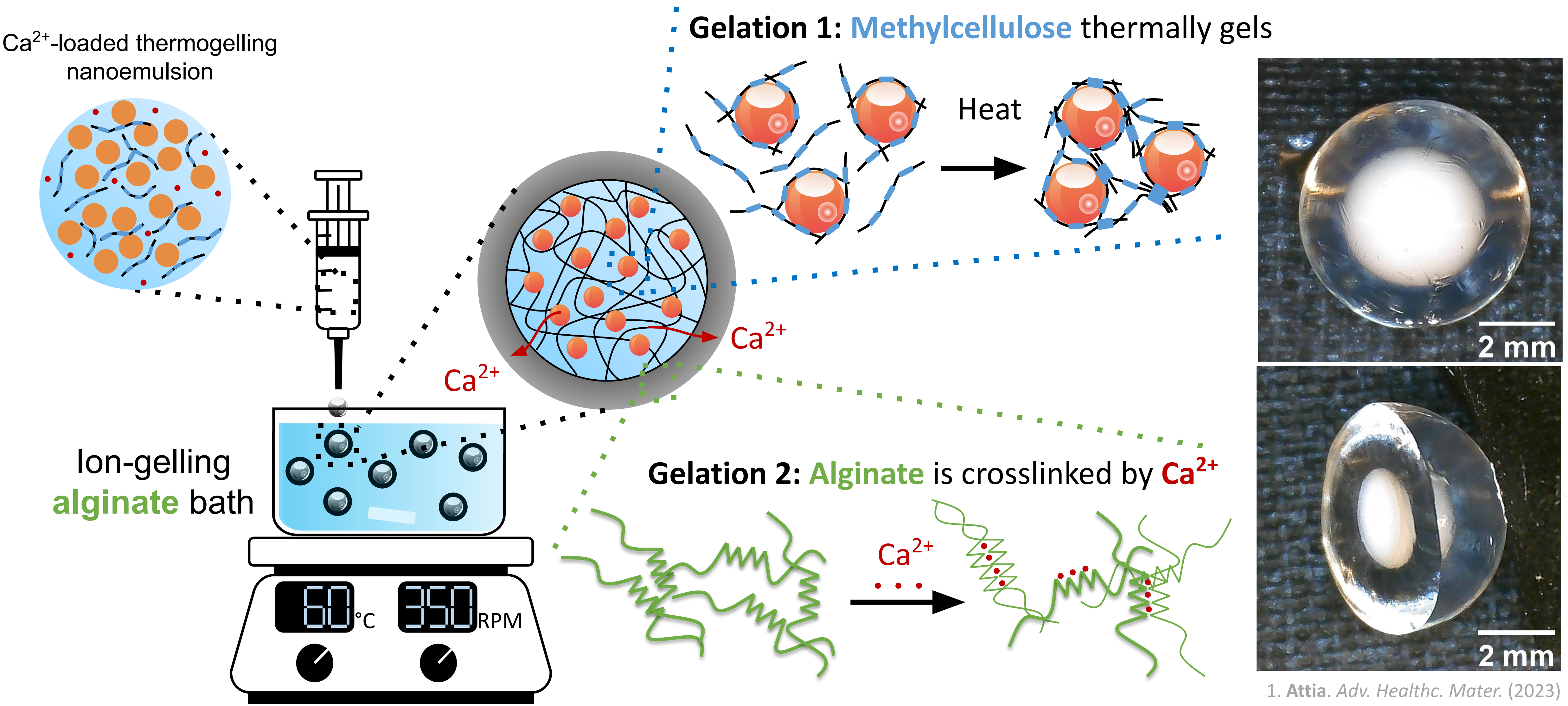
We exploit these orthogonal gelling mechanisms



1. **Attia**. *Adv. Healthc. Mater.* (2023)

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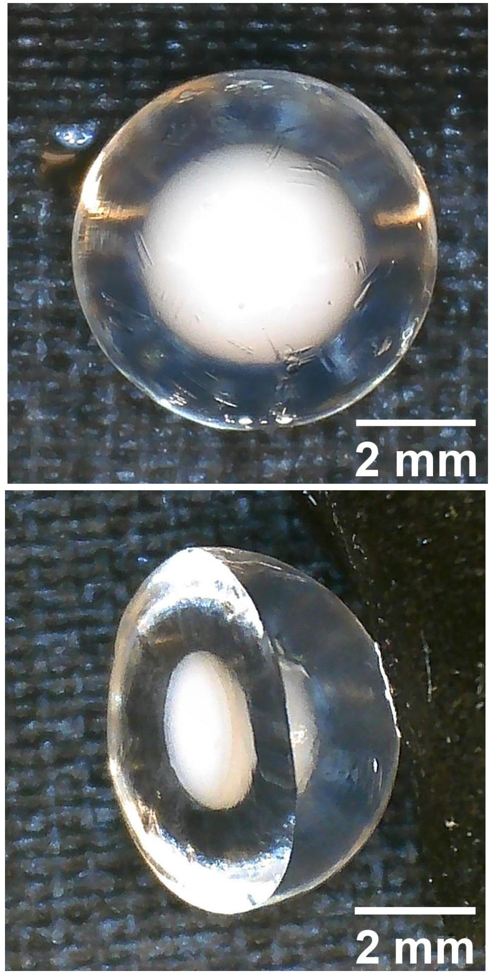
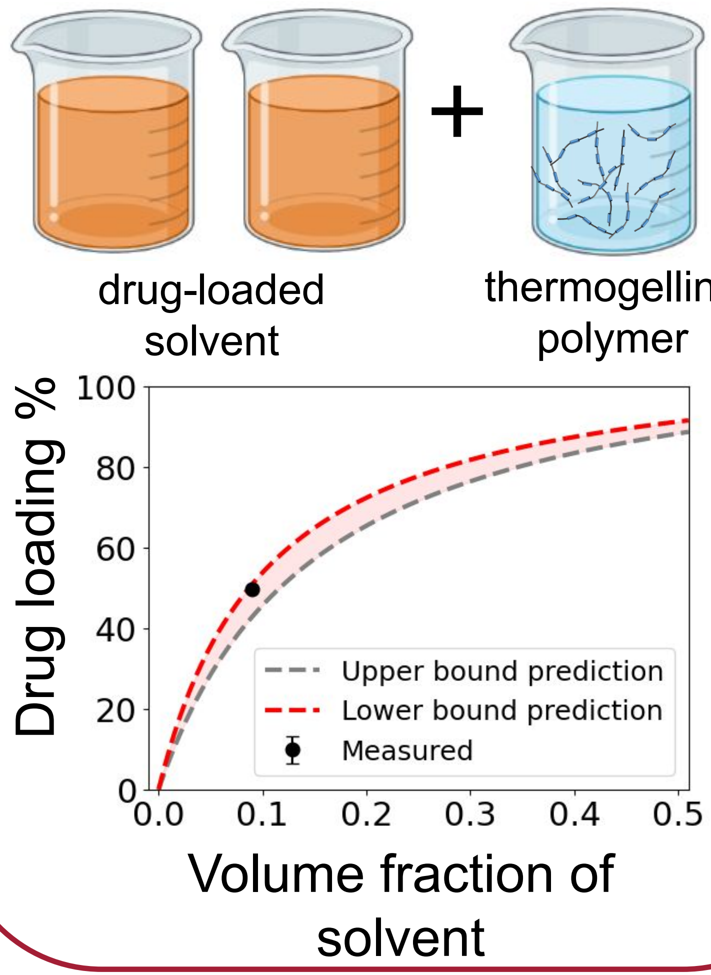
We exploit these orthogonal gelling mechanisms



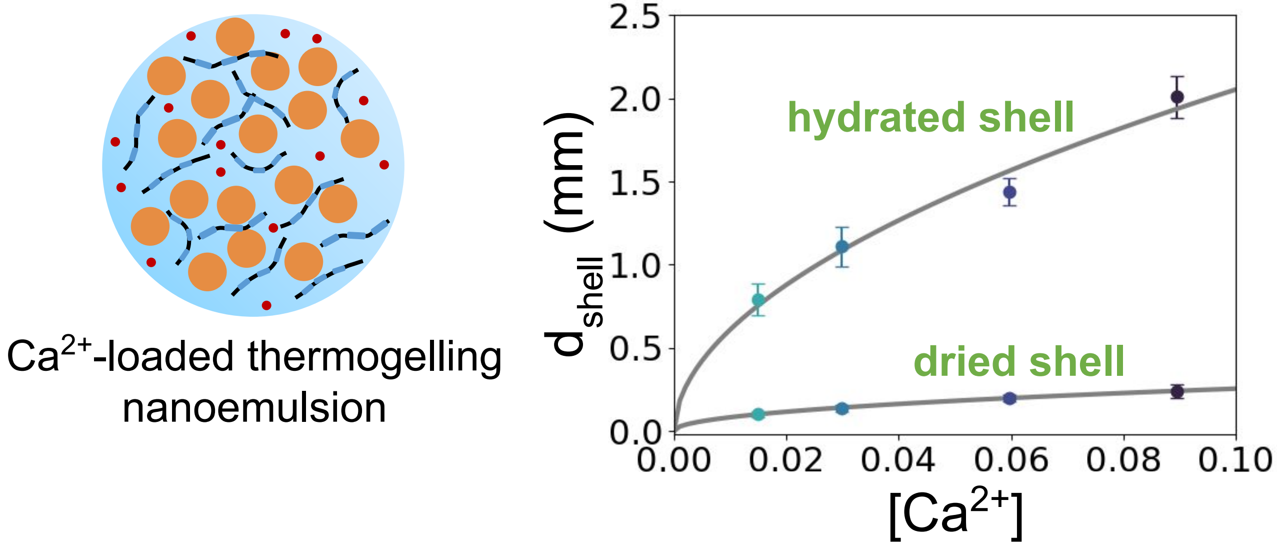
1. **Attia**. *Adv. Healthc. Mater.* (2023)

Formulation parameters control core-shell particle properties

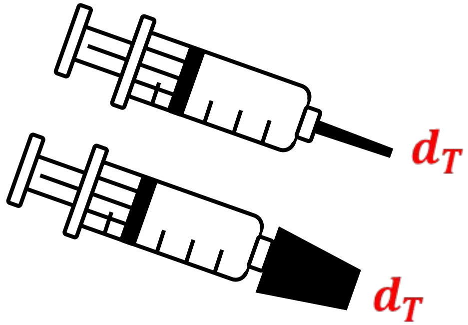
Volume fraction of solvent droplets controls drug loading



Salt concentration controls the alginate shell thickness



Dispensing tip size controls methylcellulose core radius



Tate's Design Law

$$r_{core} \propto \left(\frac{d_T \gamma_{NE}}{\rho_{NE} g}\right)^{\frac{1}{3}}$$

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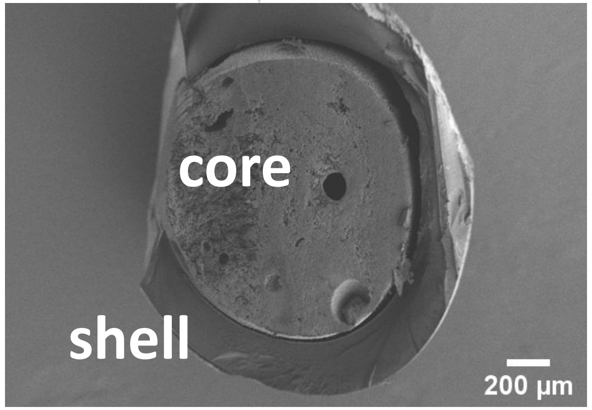
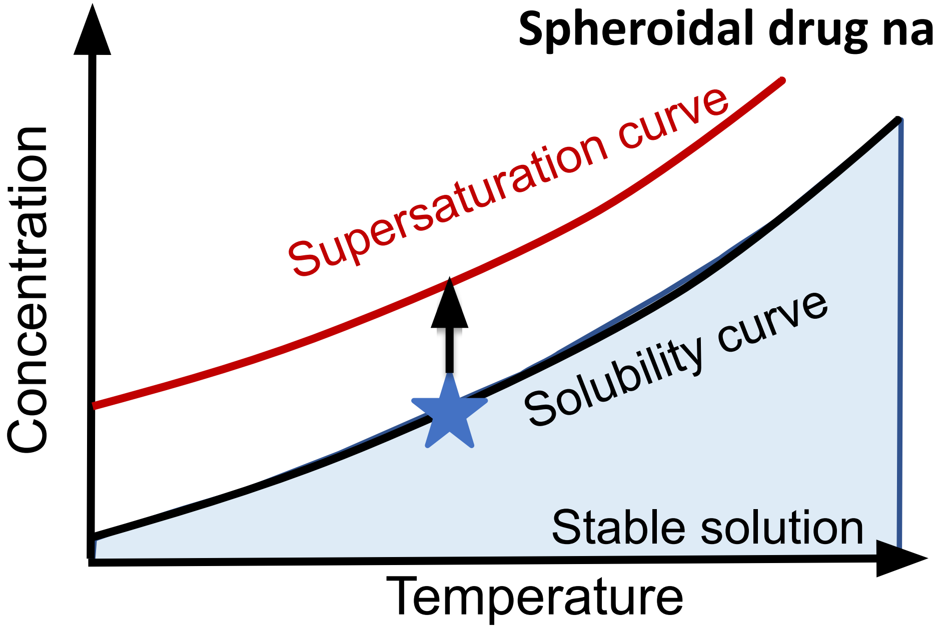
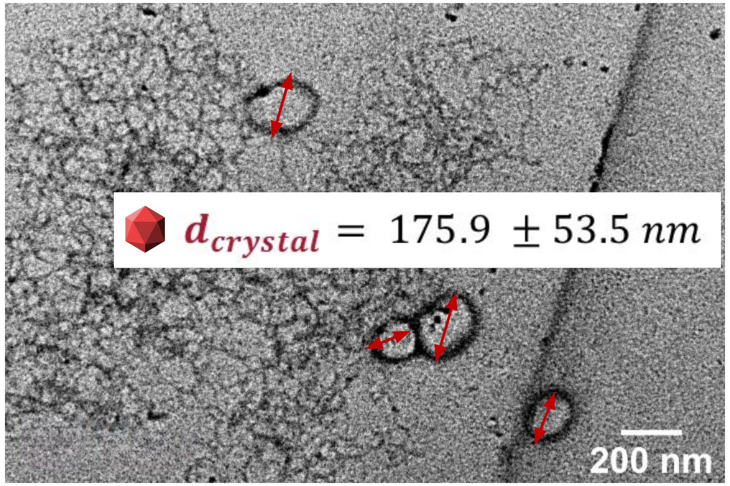
In situ crystallization templates drug nanoparticles

70 °C *Solvent extraction*





Spheroidal drug nanocrystals are templated

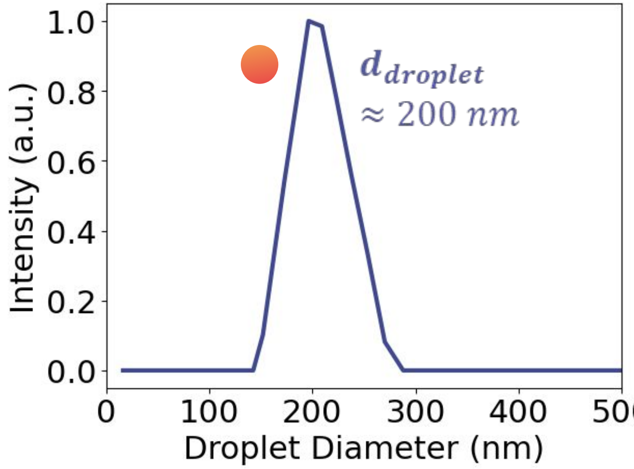


Nanodroplet size distribution controls crystal size

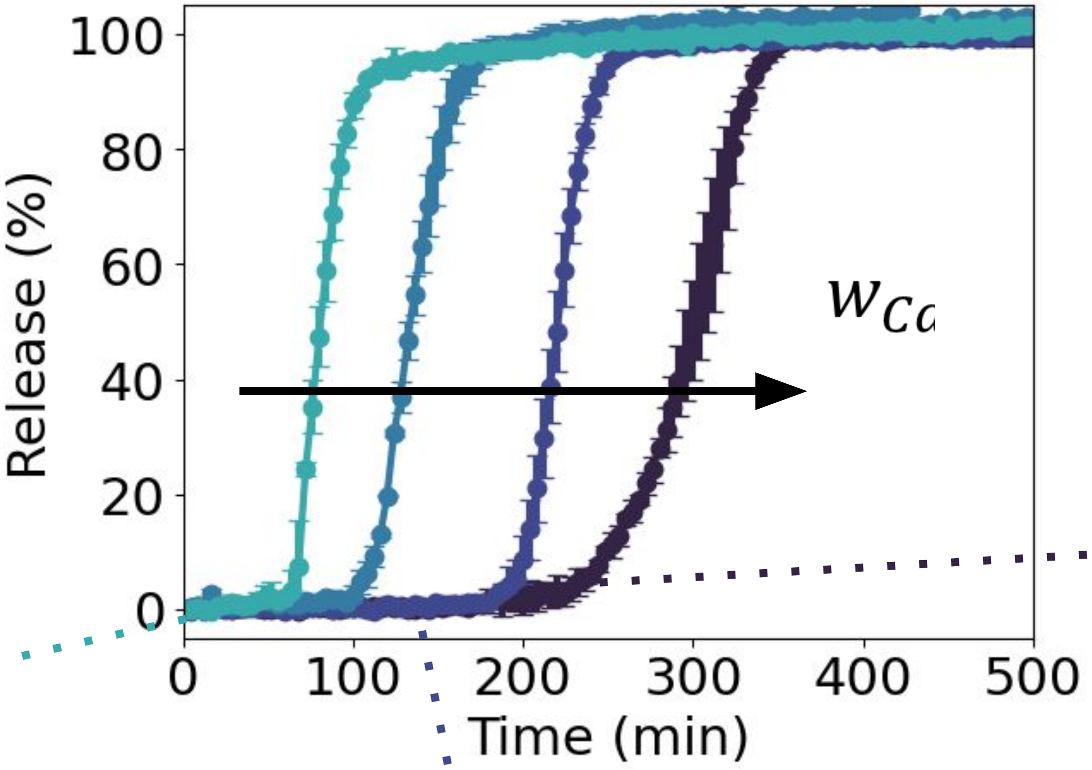
$$m_{drug,crystal} = m_{drug,droplet}$$

$$\frac{4}{3}\pi\left(\frac{\hat{d}_{crystal}}{2}\right)^3 \rho_{crystal} = \frac{4}{3}\pi\left(\frac{d_{droplet}}{2}\right)^3 C_{drug}$$

$$\hat{d}_{crystal} = \left(\frac{C_{drug}}{\rho_{crystal}}\right)^{\frac{1}{3}} d_{droplet} = 150\ nm$$

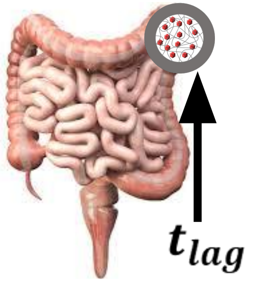


Increasing shell thickness accesses site-specific delayed release profiles



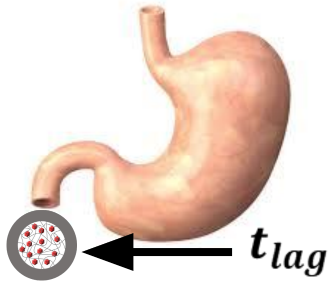
Colonic targeting[2]

$\tau_{large\ intestine} \sim 4 + hours$

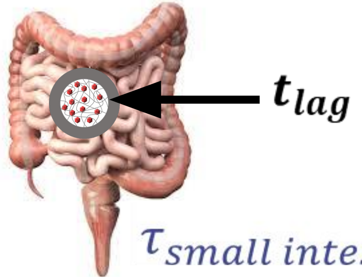


Enteric coating

$\tau_{stomach} \sim 1 - 2\ hours$



Intestinal targeting[1]

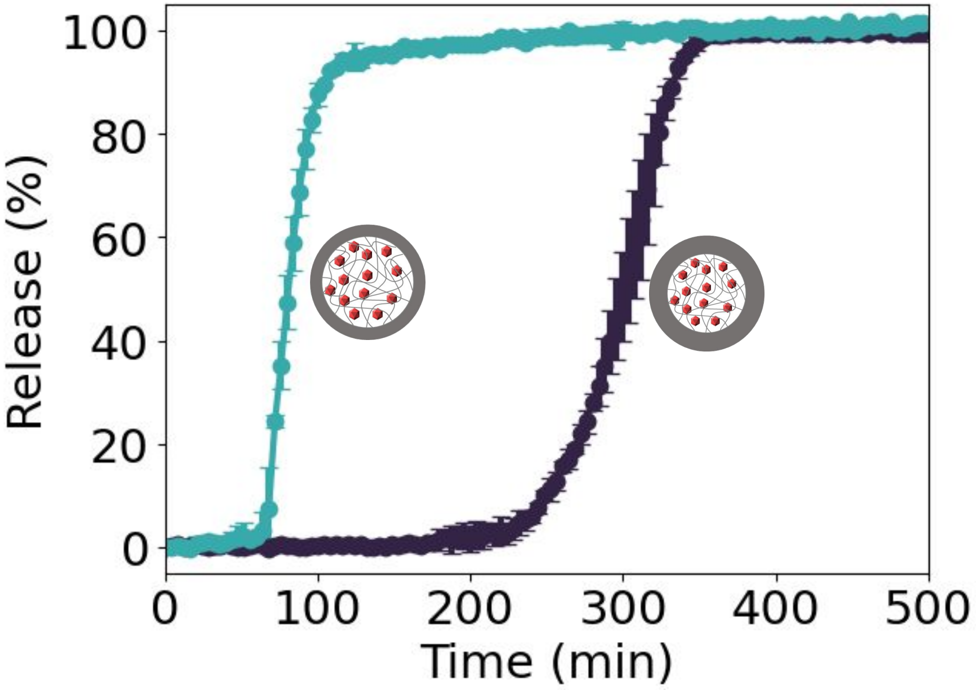


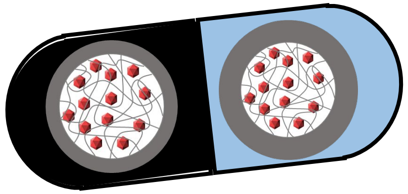
$\tau_{small\ intestine} \sim 3 - 5\ hours$

1. Hua, S., *Front. Pharmacol.* (2020)
2. Amidon S., *AAPS PharmSciTech* (2015)

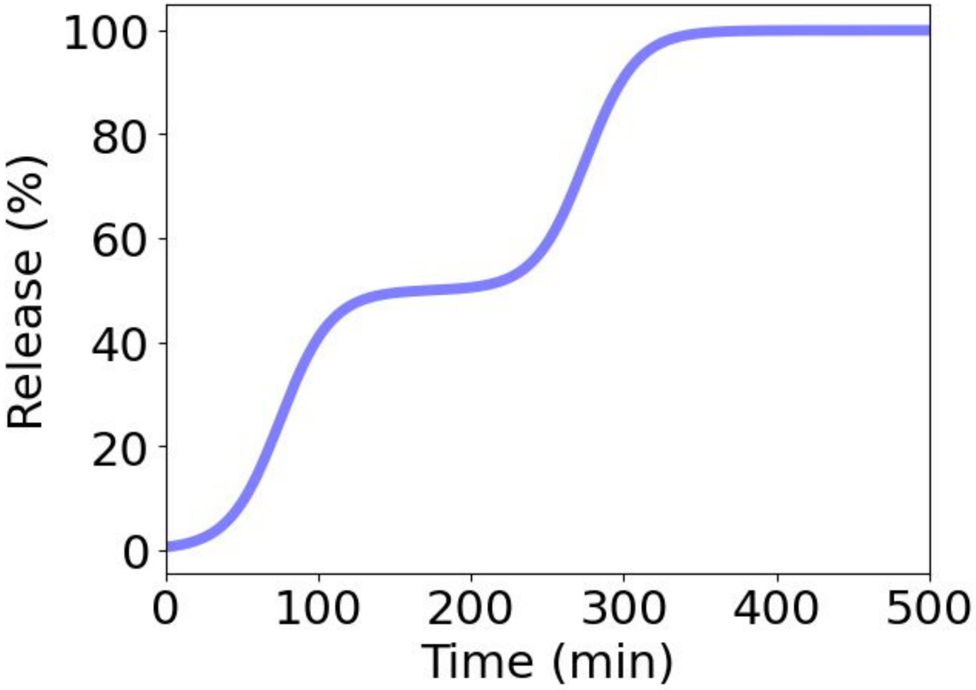
Combining particles with different lag times can sustain drug release

In vitro drug release results





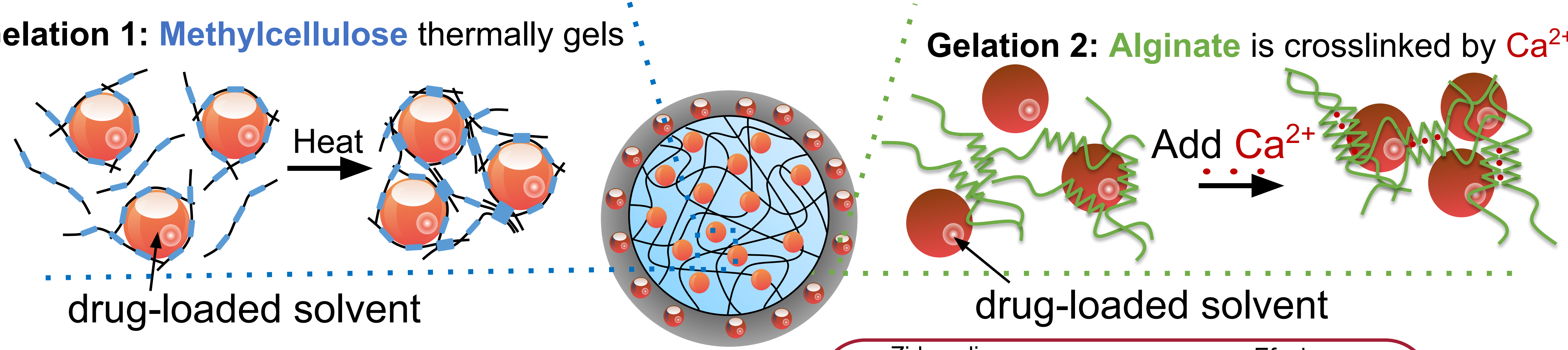
Simulated sustained release

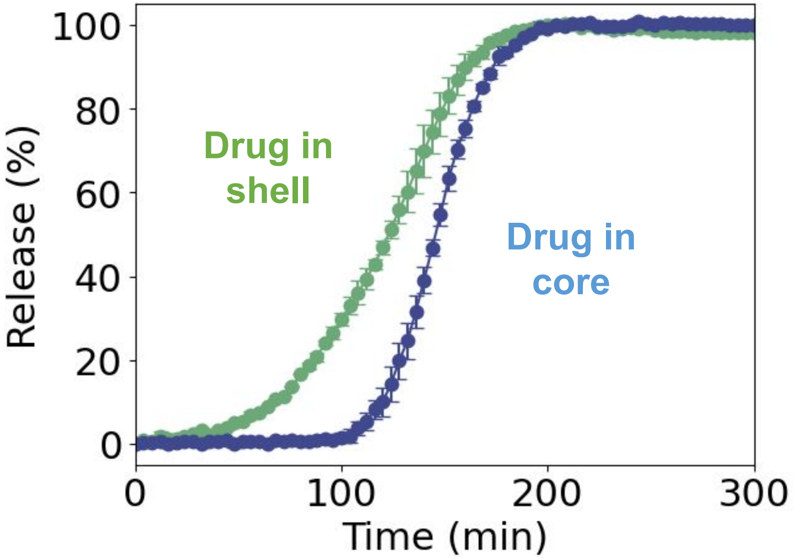


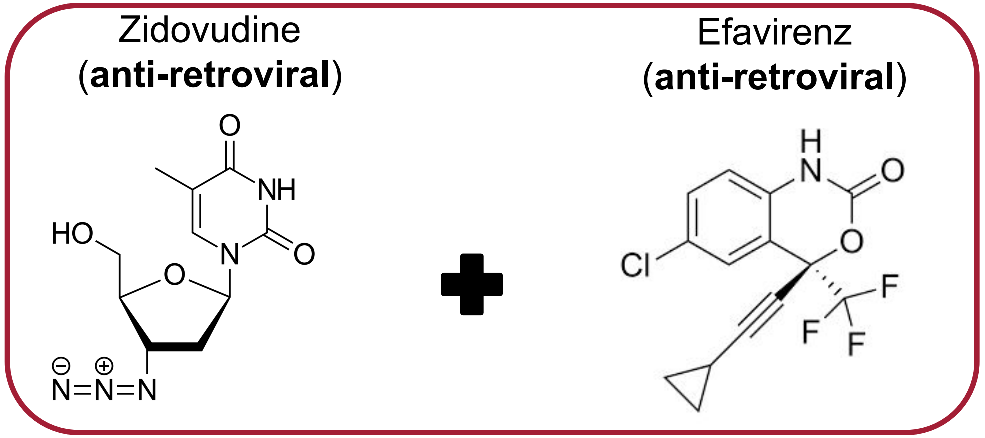
Our approach can structure drug nanoparticles in each gel layer

Gelation 1: **Methylcellulose** thermally gels

Gelation 2: **Alginate** is crosslinked by Ca^{2+}





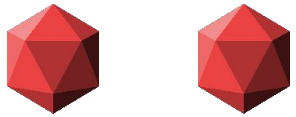


Example drug combination[1]

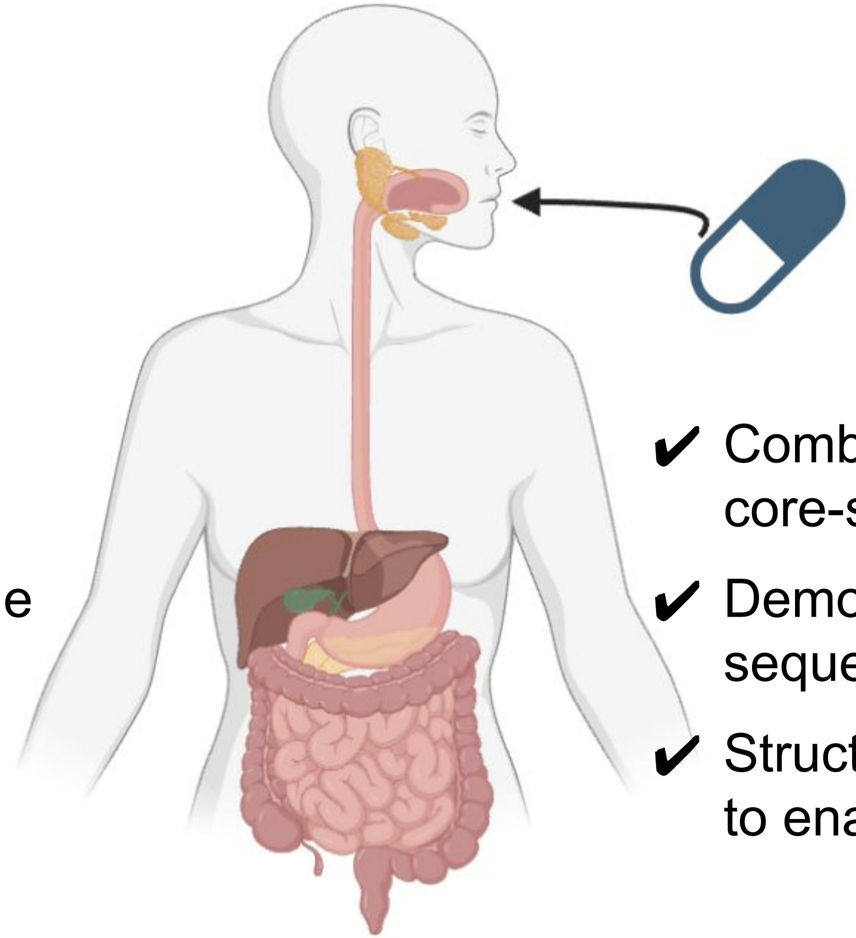
1. Gomes. *J. Braz. Chem. Soc.* (2013)

Summary

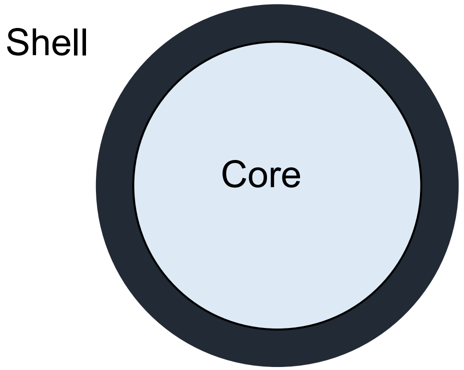
Generating drug nanoparticles



$$O(L) \sim 0.1 - 1\ \mu m$$



Manufacturing core-shell carriers



- ✔ Nanoemulsions template drug nanoparticles inside hydrogels
- ✔ Droplet size controls nanoparticle size
- ✔ Templated nanoparticles have improved drug dissolution

- ✔ Combined orthogonal gelations to build core-shell hydrogels in 1 step
- ✔ Demonstrated delayed, sustained, and sequential drug release
- ✔ Structured different drugs in each layer to enable new combination products

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Thank you! Questions?

Acknowledgments

<u>Doyle Group</u>
- Prof. Patrick Doyle
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- Amir Erfani

<u>Characterization</u>
- Yong Zhang
- Nicole Bohn

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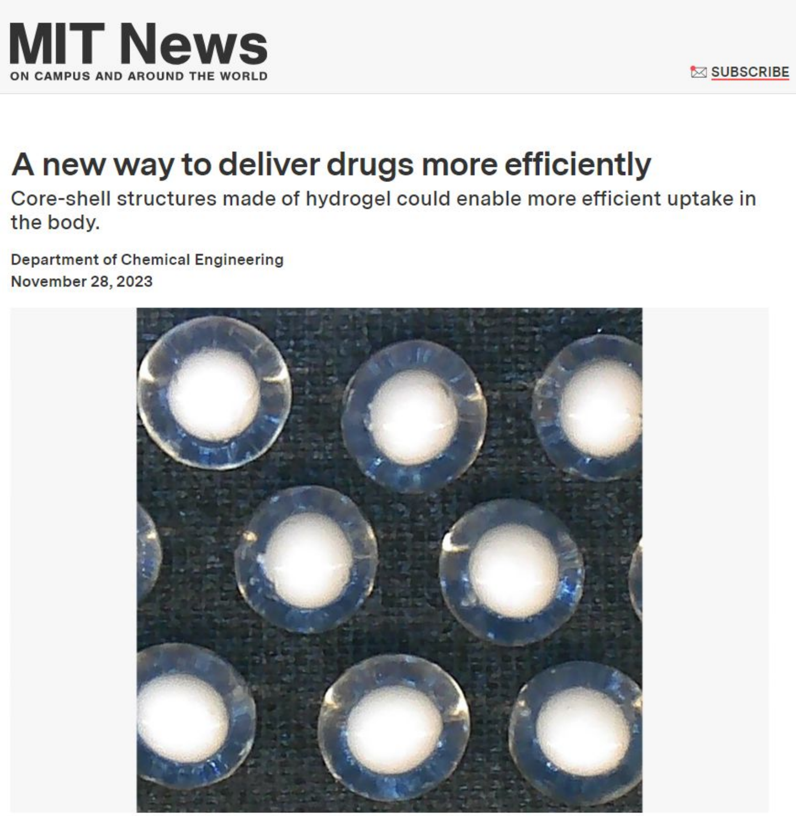
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A new way to deliver drugs more efficiently

Core-shell structures made of hydrogel could enable more efficient uptake in the body.

Department of Chemical Engineering
November 28, 2023

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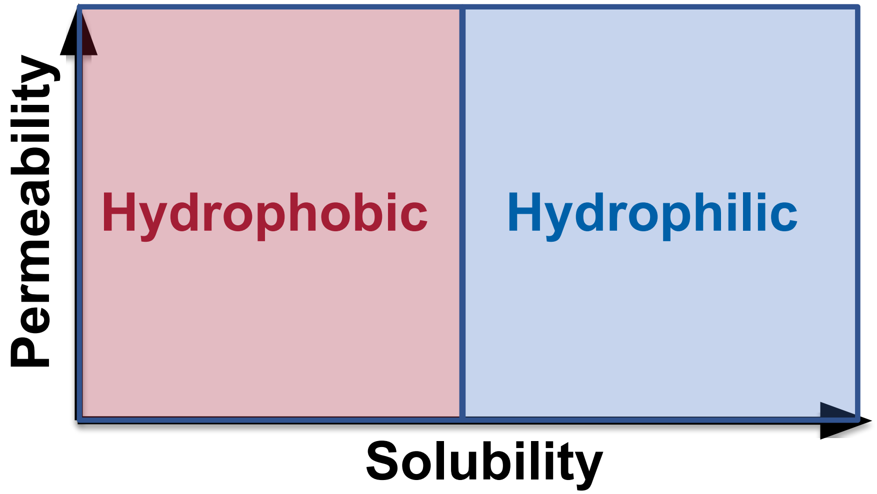
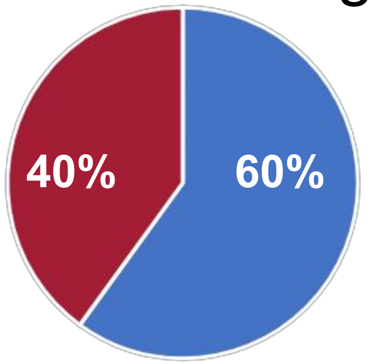
Hydrophobicity limits the oral delivery of small molecules

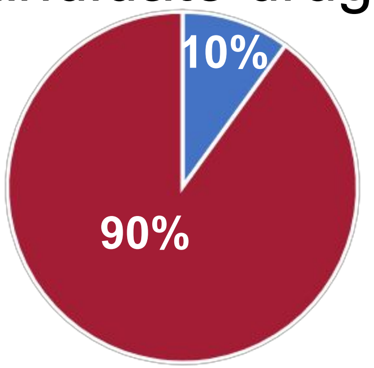
Most drug molecules are hydrophobic



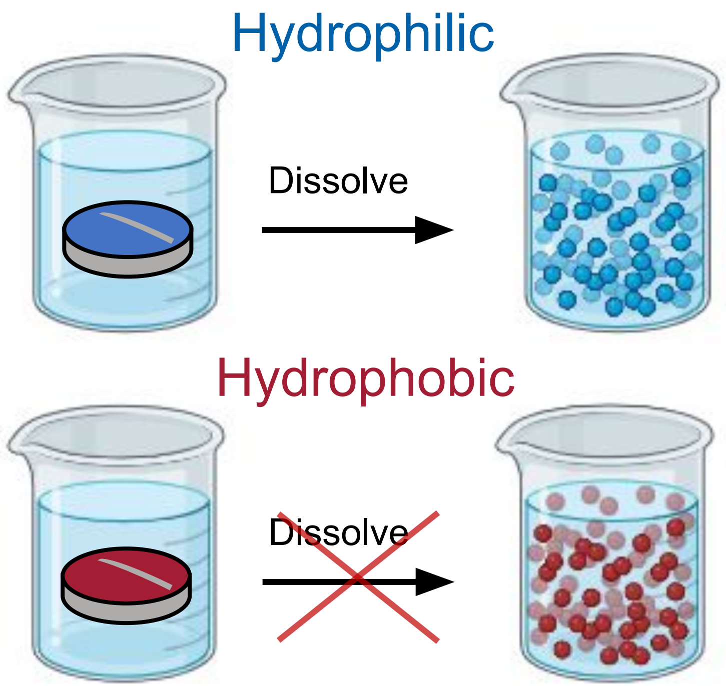
Marketed drugs



Candidate drugs[1]



Hydrophobic drugs have poor dissolution



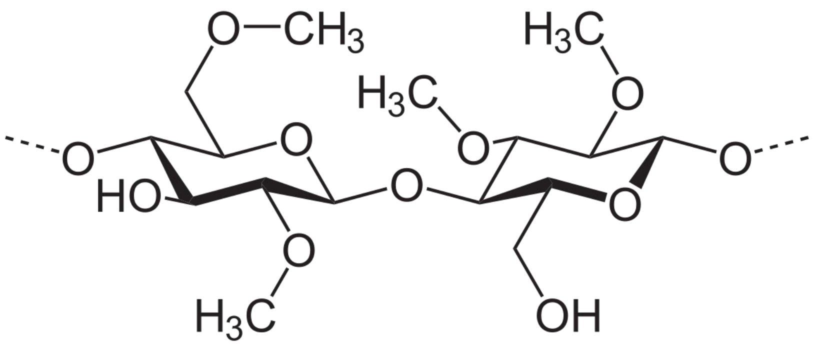
Causes **10-15 %** of clinical trial failures[2]

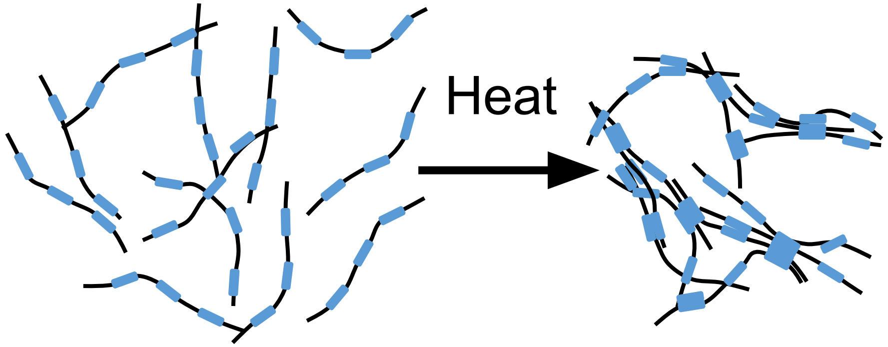
1. Alqahtani. *Front. Pharmacol.* (2021)
2. Brouwers. *J. Pharm. Sci.* (2009).

We use nature-derived polymers as model gelators

Methylcellulose (MC)

GRAS APPROVED

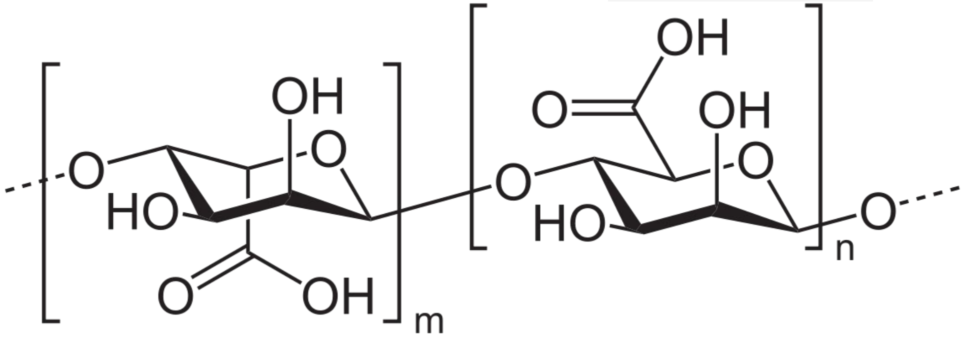


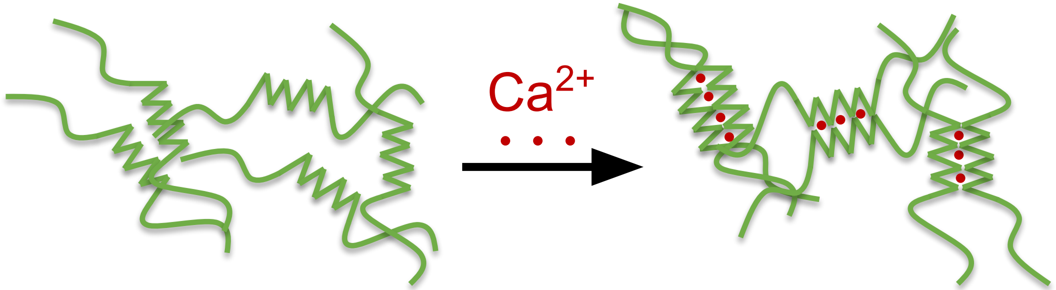


MC thermally gels[1]

Alginate

GRAS APPROVED





Alginate is ionically crosslinked[2] by Ca^{2+}

1. Chen. *Adv. Mater.* (2021)
2. Velings. *Polym. Gels Networks* (1995)

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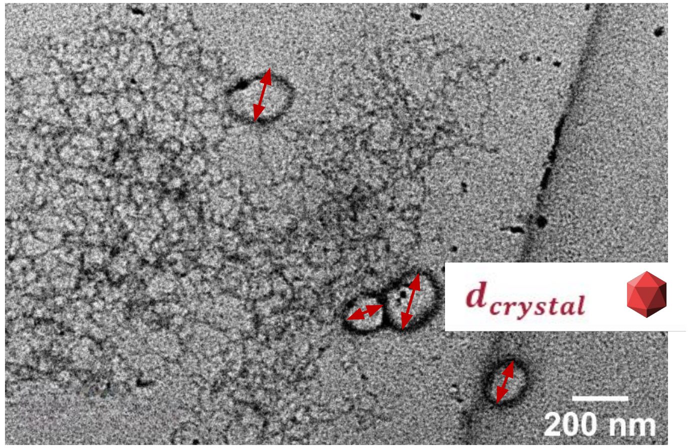
Nanodroplet size distribution controls nanoparticle size

Crystal size distribution



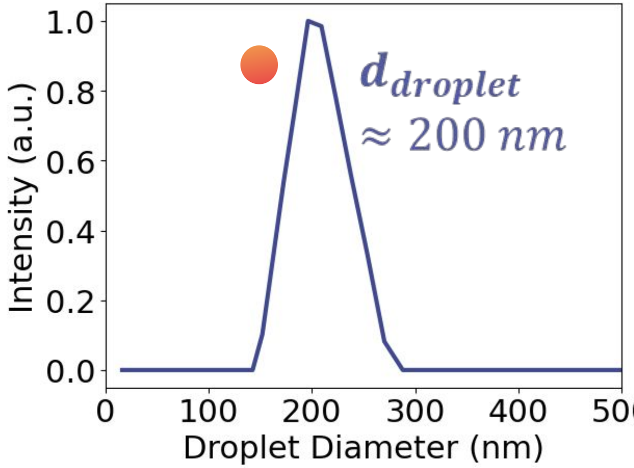
$d_{crystal} = 175.9 \pm 53.5\ nm$

$$m_{drug,crystal} = m_{drug,droplet}$$

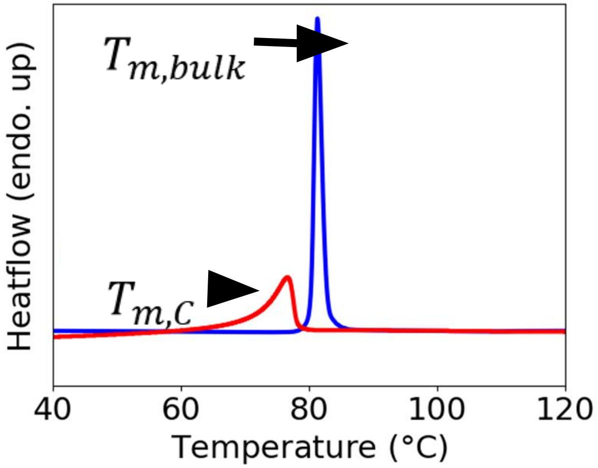
$$\frac{4}{3}\pi\left(\frac{\hat{d}_{crystal}}{2}\right)^3 \rho_{crystal} = \frac{4}{3}\pi\left(\frac{d_{droplet}}{2}\right)^3 C_{drug}$$

$$\hat{d}_{crystal} = \left(\frac{C_{drug}}{\rho_{crystal}}\right)^{\frac{1}{3}} d_{droplet} = 150\ nm$$

Nanodroplet size distribution



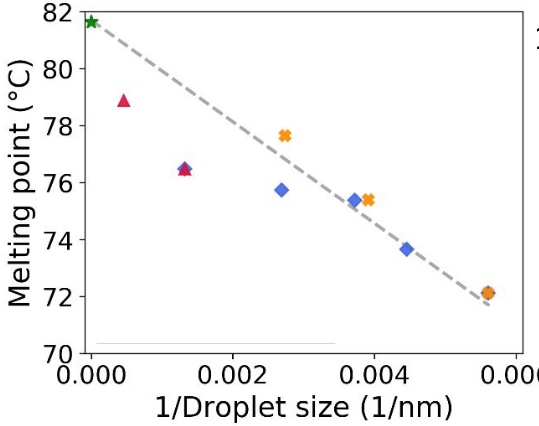
Melting point depression validates the relationship between droplet size and crystal size



Gibbs-Thompson Equation

$$T_{m,C} \sim \left(1 - \frac{K}{d_{crystal}}\right) T_{m,bulk}$$

$$T_{m,C} \sim \left(1 - \frac{K}{d_{droplet}}\right) T_{m,bulk}$$



[1,2]

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