Application of Mechanoresponsive polymer to Drug Delivery

2016.6.18

M1 Daiki Kuwana

Contents

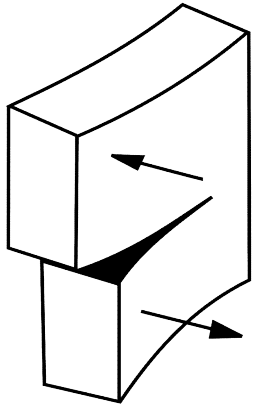
Contents

The word “mechanoresponsive”

- **Responsive to mechanical stimuli and inducing deformation**

compression

tension



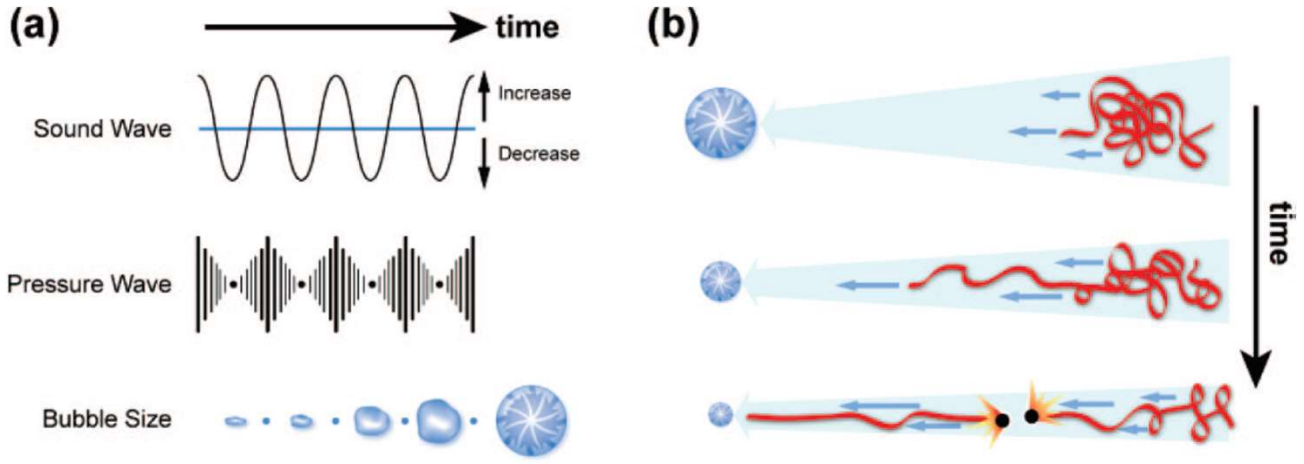
shear

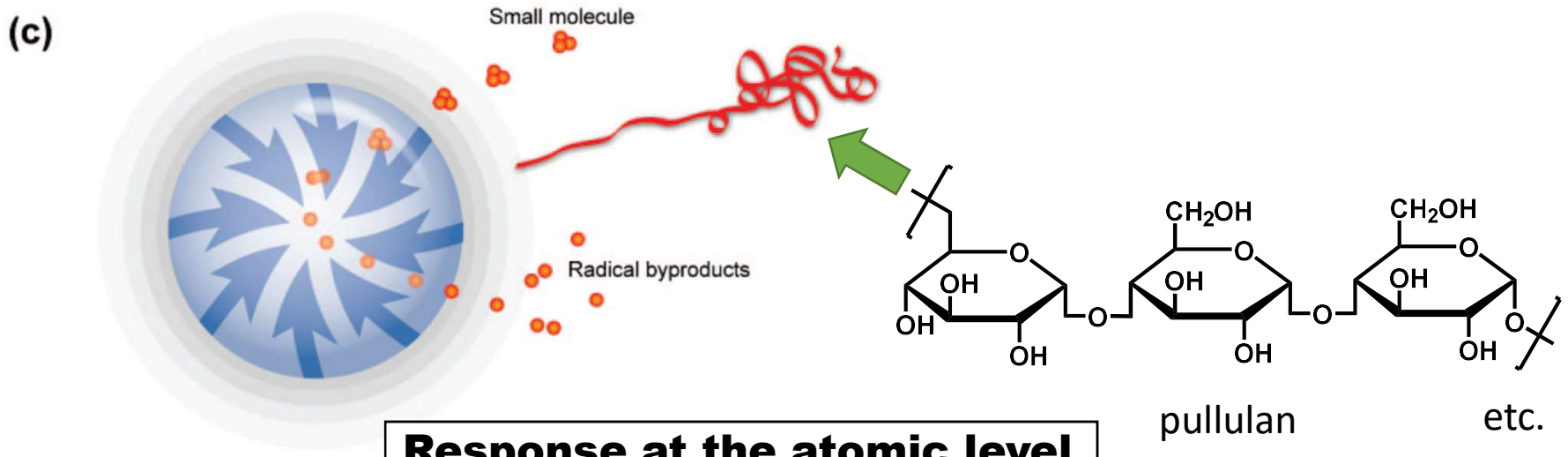
ultrasound

Responses at the

- **atomistic**
- **supramolecular**
- **micro/macroscopic level**

Example of mechanoresponsive materials (1)

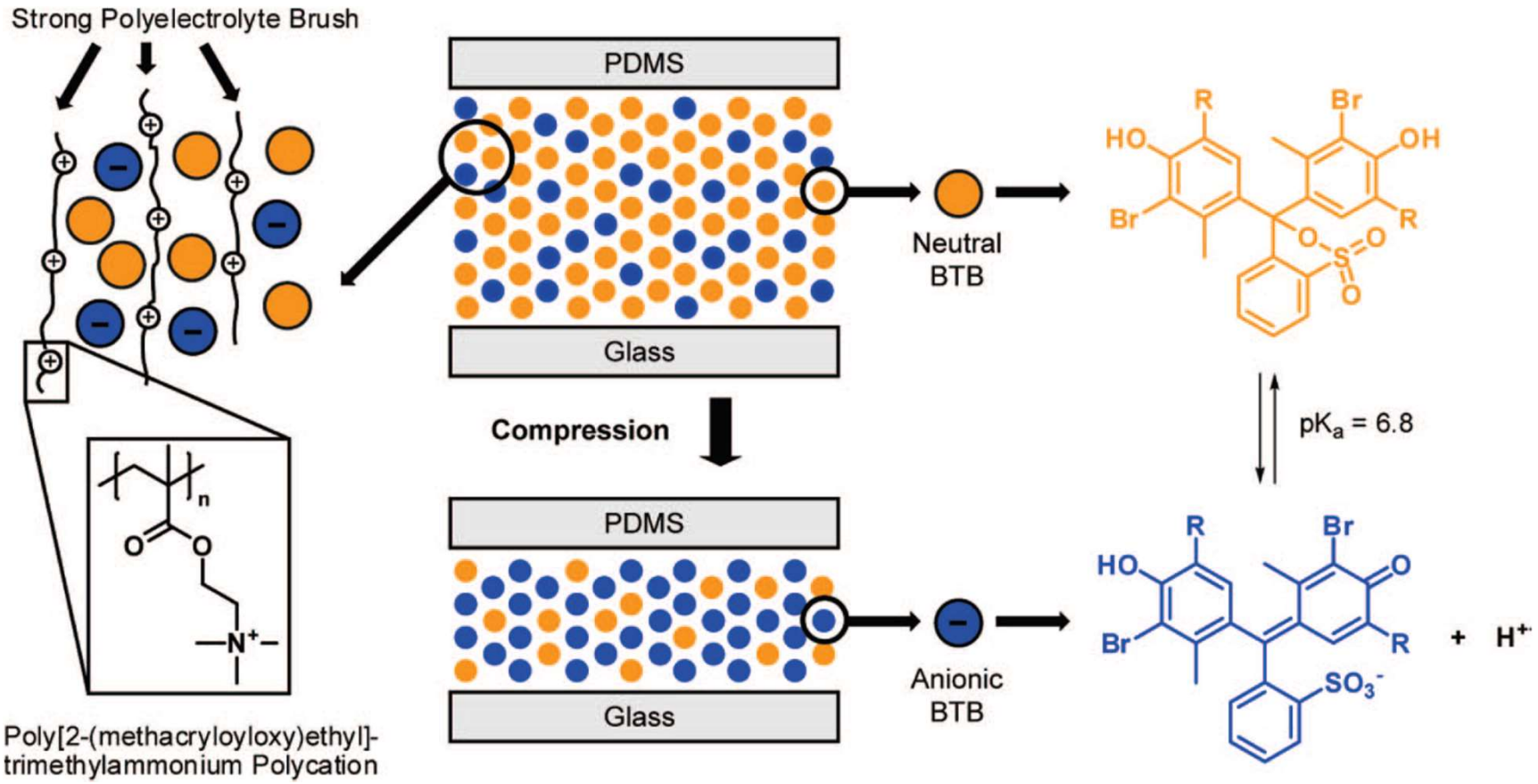




Response at the atomic level

Caruso, M. M.; Davis, D. A.; Shen, Q.; Odom, S. A.; Sottos, N. R.; White, S. R.; Moore, J. S. *Chem. Rev.* **2009,** *109,* 5759

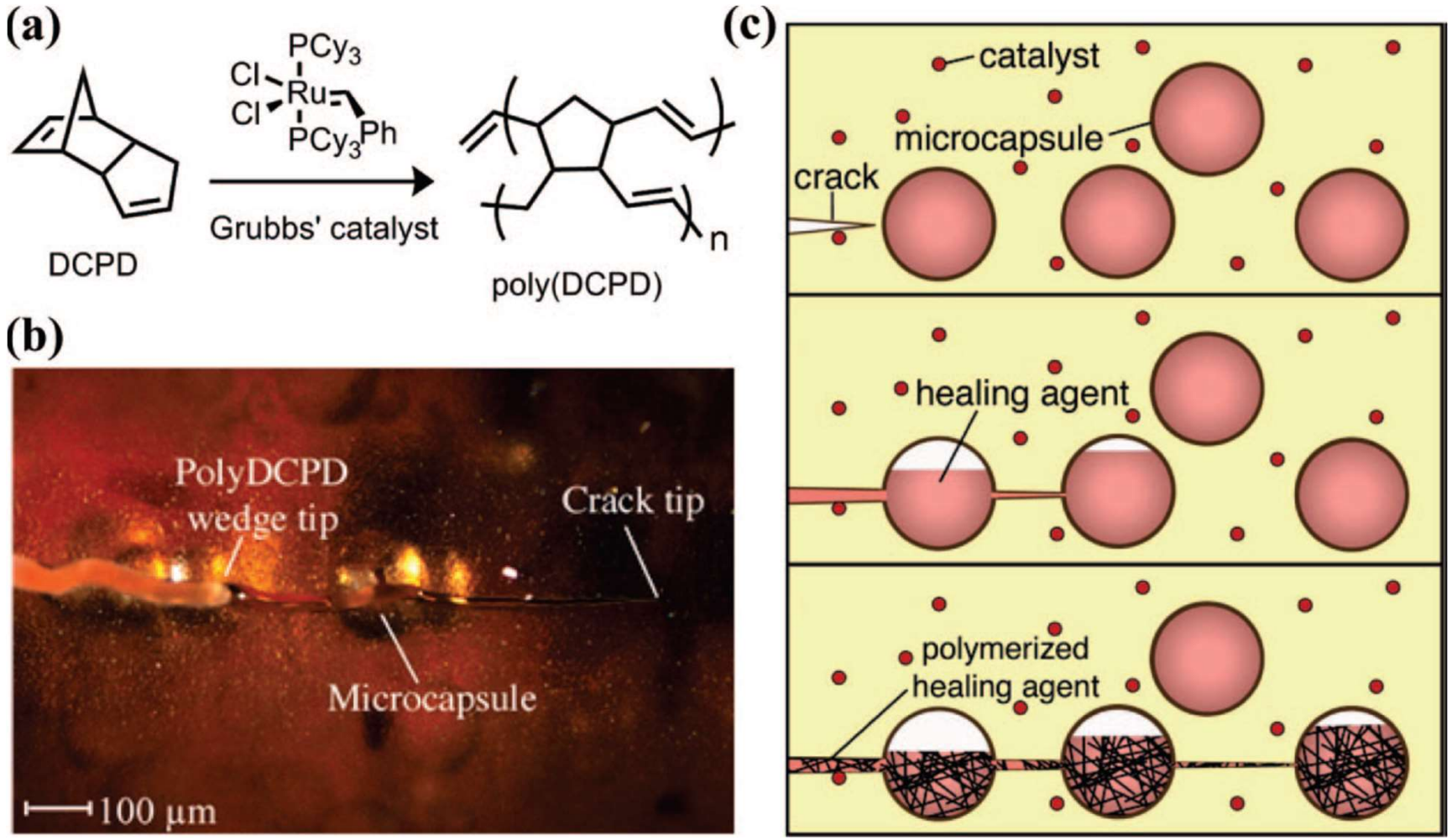
Example of mechanoresponsive materials (2)



Response at the supramolecular level

Caruso, M. M.; Davis, D. A.; Shen, Q.; Odom, S. A.; Sottos, N. R.; White, S. R.; Moore, J. S. *Chem. Rev.* **2009**, *109,* 5759

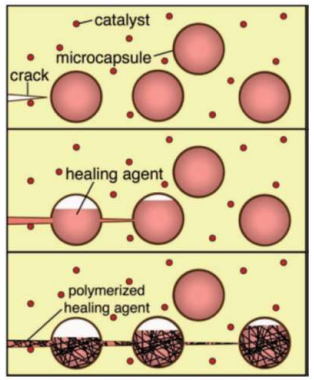
Example of mechanoresponsive materials (3)



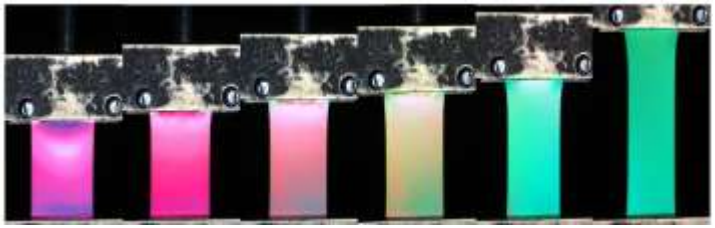
Response at the microscopic level

Caruso, M. M.; Davis, D. A.; Shen, Q.; Odom, S. A.; Sottos, N. R.; White, S. R.; Moore, J. S. *Chem. Rev.* **2009**, *109,* 5759

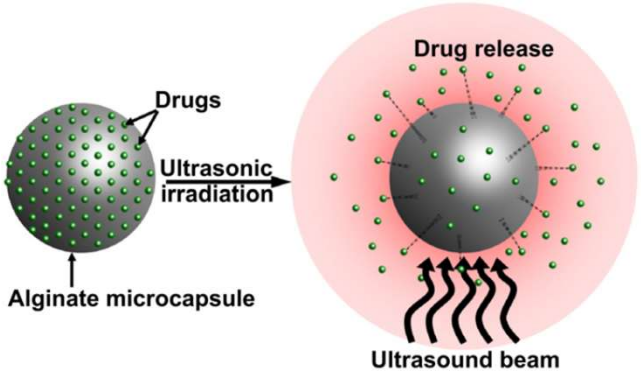
Application of mechanoresponsive materials



Self-healing assemblies



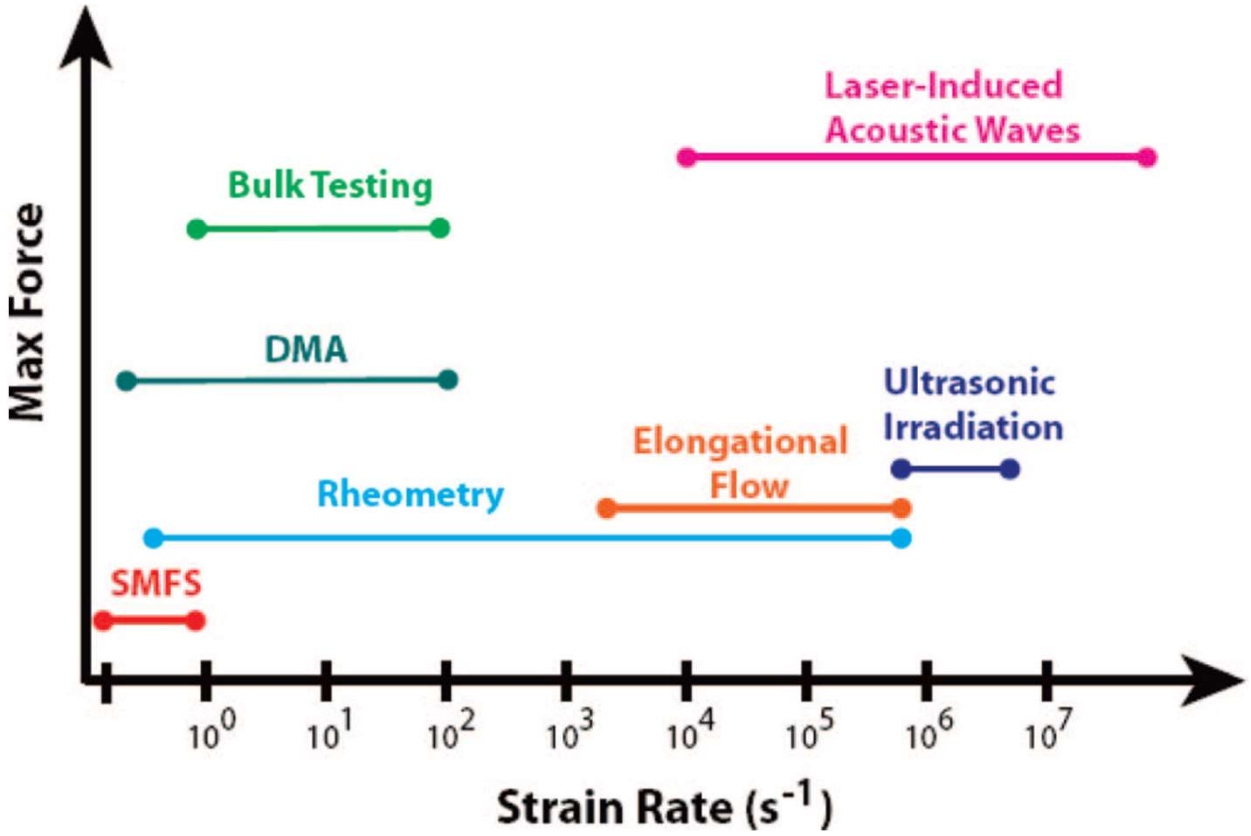
electronics



medicine

1) Caruso, M. M.; Davis, D. A.; Shen, Q.; Odom, S. A.; Sottos, N. R.; White, S. R.; Moore, J. S. *Chem. Rev.* **2009**, *109,* 5759
2) Schafer, C. G.; Gallei, M.; Zahn, J. T.; Engelhardt, J.; Hellmann, G. P.; Rehahn, M. *Chem. Mater.* **2013**, *25*, 2309
3) Wang, C. Y.; Yang, C. H.; Lin, Y. S.; Chen, C. H.; Huang, K. S. *Biomaterials* **2012**, *33*, 1547

Characterization of mechanochemical activity

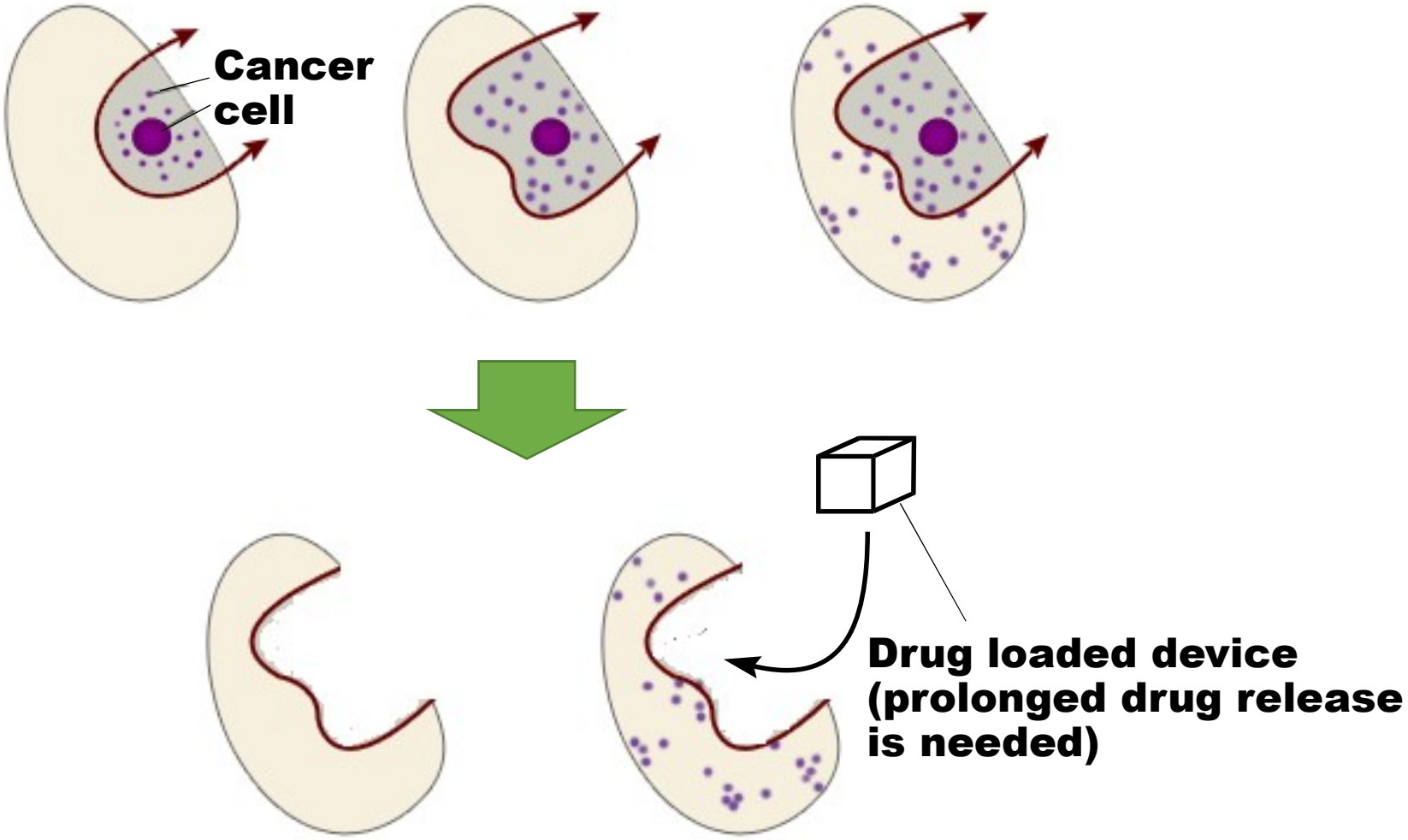


Caruso, M. M.; Davis, D. A.; Shen, Q.; Odom, S. A.; Sottos, N. R.; White, S. R.; Moore, J. S. *Chem. Rev.* **2009,** *109,* 5759

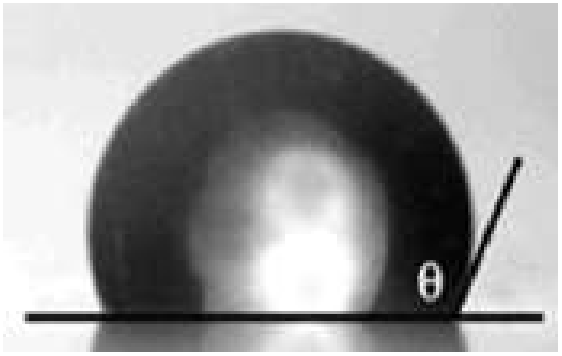
Contents

- 1. Mechanoresponsive polymer
- **2. DDS using polymer studied in Grinstaff group**
- **2-1. Previous study**
- 2-2. DDS using mechanoresponsive polymer (main paper)

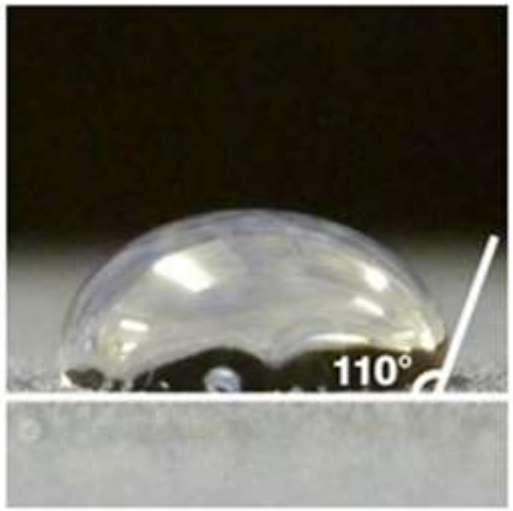
Suppression of cancer reccurence



“Super” hydrophobic



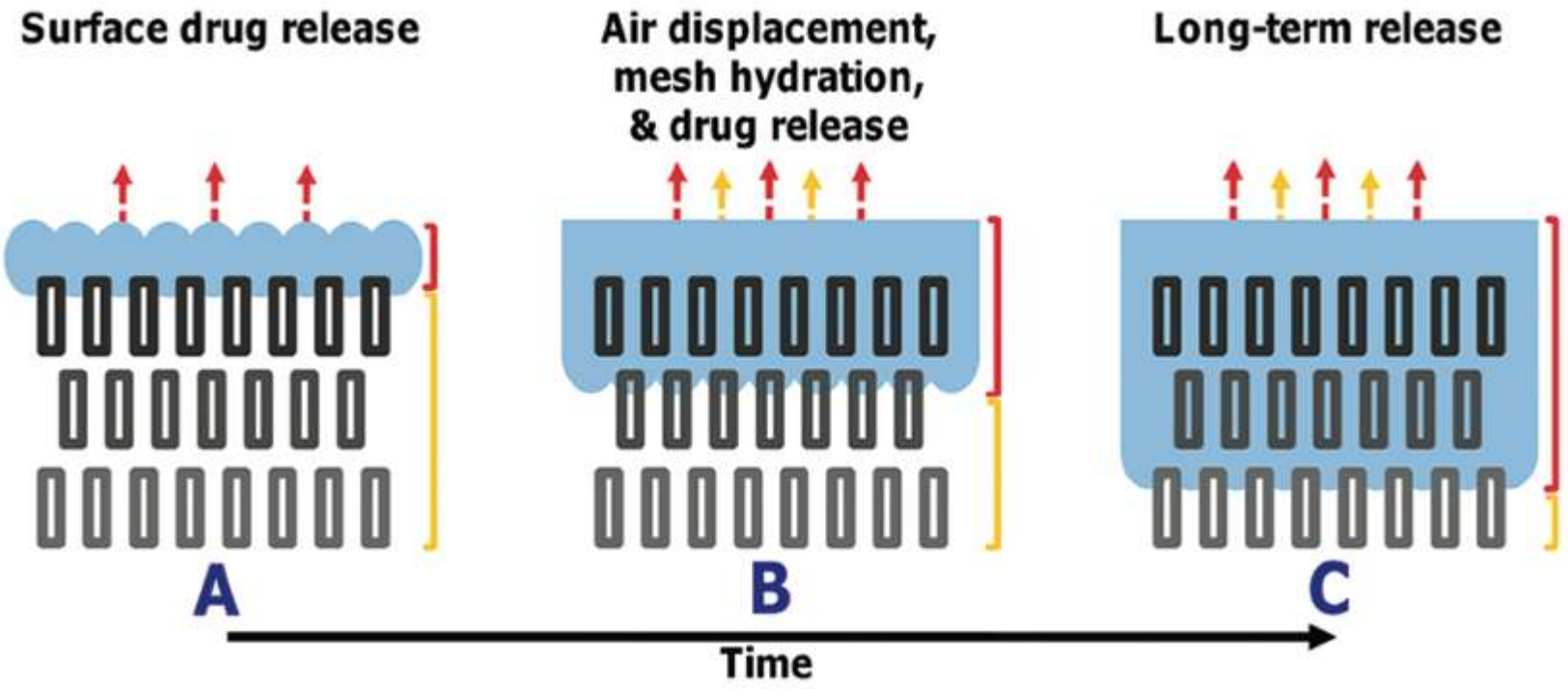
Θ = contact angle



Θ>90° : hydrohobic

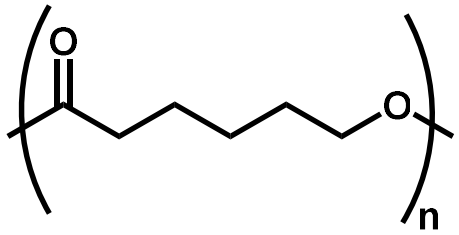
Θ>150° : superhydrophobic

Control drug release by hydrophobicity



Stefan, T.; Colson, Y. L.; Grinstaff, M. W. *J. Am. Chem. Soc.* **2012,** *134*, 2016

Polymer selection

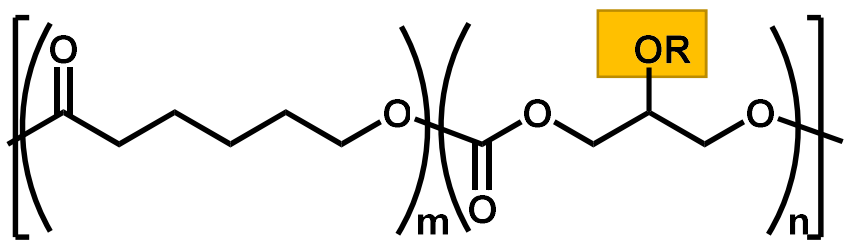


PCL

Slow degradation rate

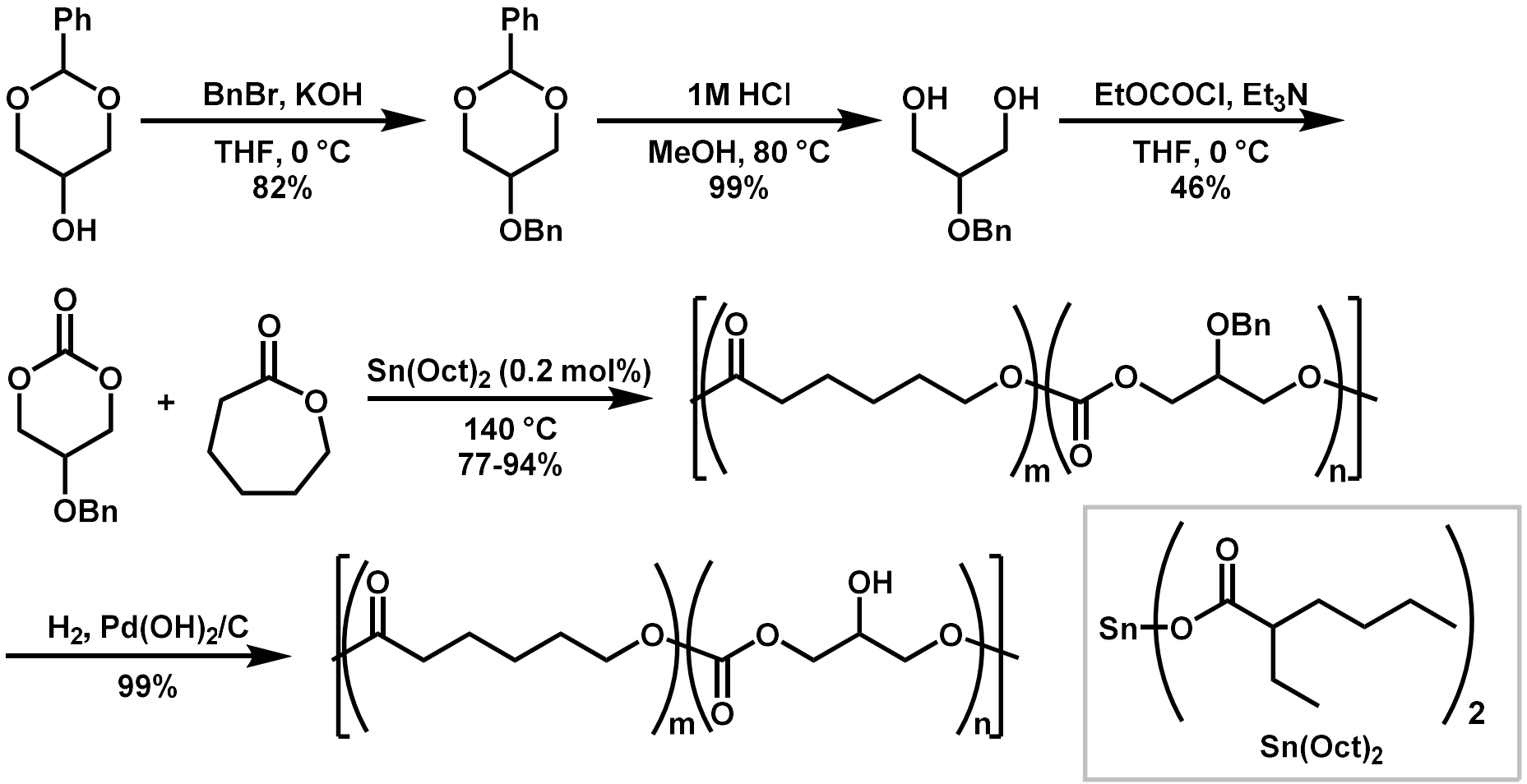
No space of functionalization

various functional group?



1) Liu, X. M.; Quan, L.; Tian, J.; Laquer, F. C.; Ciborowski, P.; Wang, D. *Biomacromolecules* **2010,** *11*, 2621
2) Wolinsky, J. B.; Yohe, S. T.; Colson, Y. L.; Grinstaff, M. W. *Biomol.* **2015,** *13,* 406

Synthesis of co-polymer



Wang, J.; Kaplan, J. A.; Colson, Y. L.; Grinstaff, M. W. *Angew. Chem. Int. Ed.* **2016,** *55*, 2796

Polymer scope

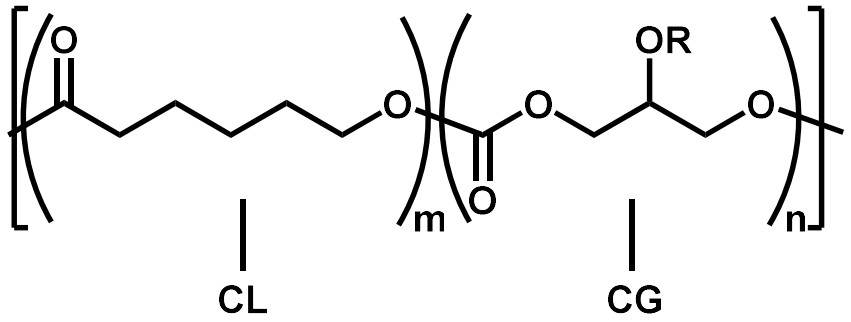
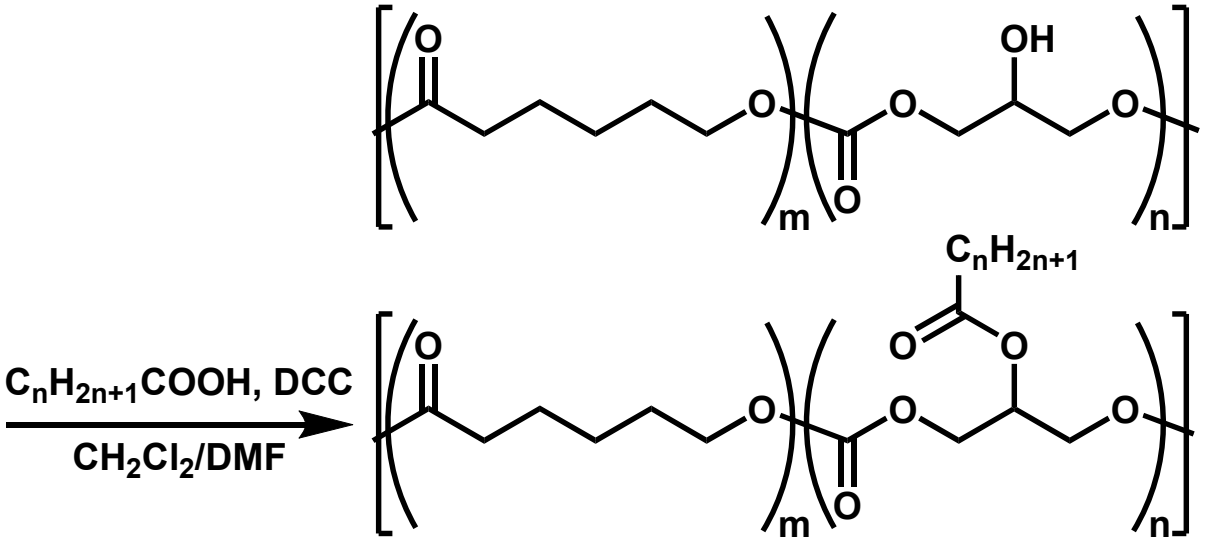


Table 1. Composition, Molecular Weight, and Thermal Data of Copolymers[a]

polymer	yield (%)	mol wt M_n(theor)	mol wt M_n(SEC)	M_w/M_n
CL-CG-100−0	77	57 000	22 700	1.47
CL-CG-90−10-Bn	87	61 700	13 300	1.67
CL-CG-90−10-OH	99	57 200	12 200	1.67
CL-CG-80−20-Bn	92	66 400	10 200	1.96
CL-CG-80−20-OH	99	57 400	8600	1.96
CL-CG-80−20-C_6-OH	86	68 800	10 100	1.91
CL-CG-80−20-C_5-CO_2H	83	70 200	10 400	1.96
CL-CG-80−20-C_6-NH_2	85	68 700	10 100	1.94
CL-CG-70−30-Bn	94	71 100	9300	1.78
CL-CG-60−40-Bn	79	75 800	7900	1.94
CL-CG-0−100-Bn	42	104 000	3600	3.16

Wolinsky, J. B.; Ray, W. C.; Colson, Y. L.; Grinstaff, M. W. *Macromolecules.* **2007,** *40*, 7065

Addition of natural fatty acids



n=12 : lauric acid
n=14 : myristic acid
n=16 : palmitic acid
n=18 : stearic acid

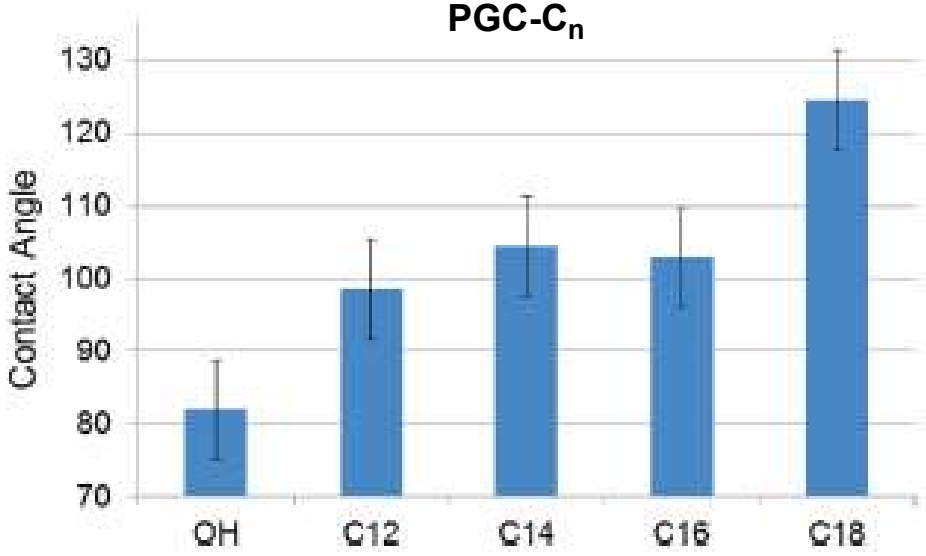


Figure 4. Static contact angle measurements from polymer cast films ($n = 3$).

Wolinsky, J. B.; Yohe, S. T.; Colson, Y. L.; Grinstaff, M. W. *Biomol.* **2015,** *13,* 406

Formation of drug loaded mesh

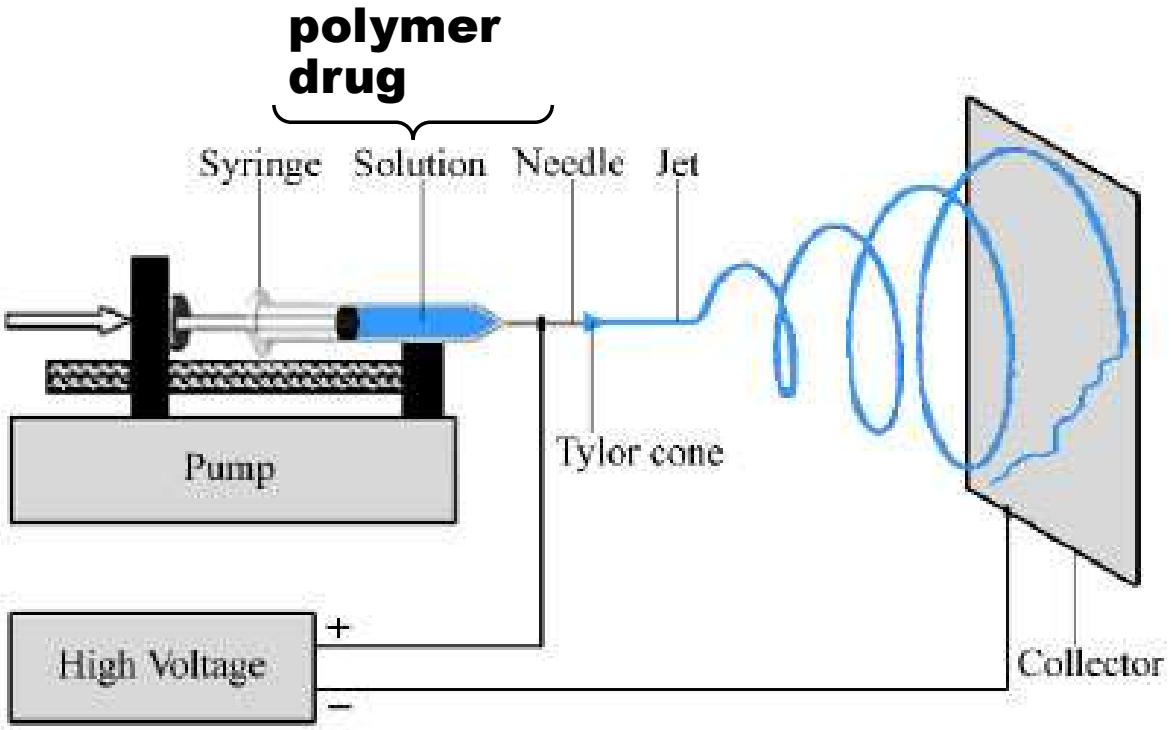


Figure 1: Electrospinning setup

Drug release experiment

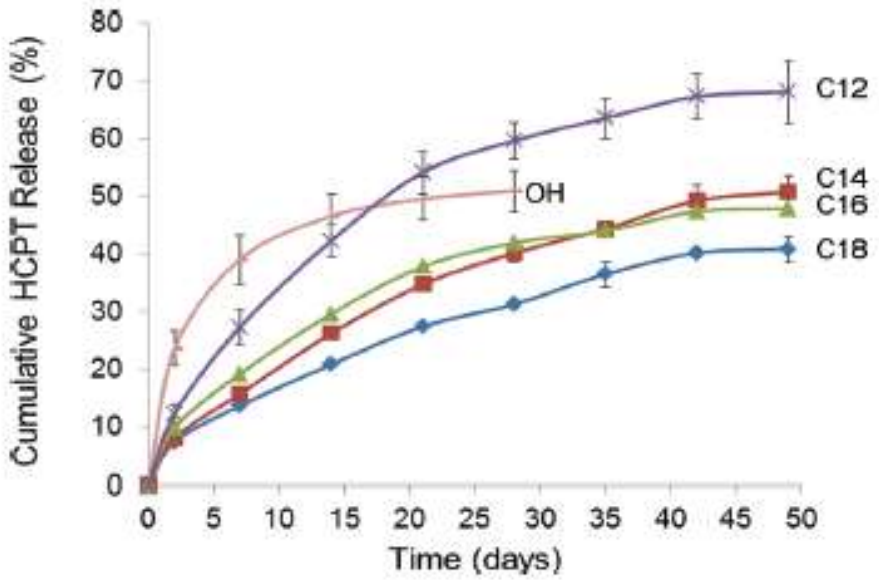


Figure 5. Cumulative release of 10-hydroxycamptothecin from drug-loaded films in PBS at 37 °C (n = 3).

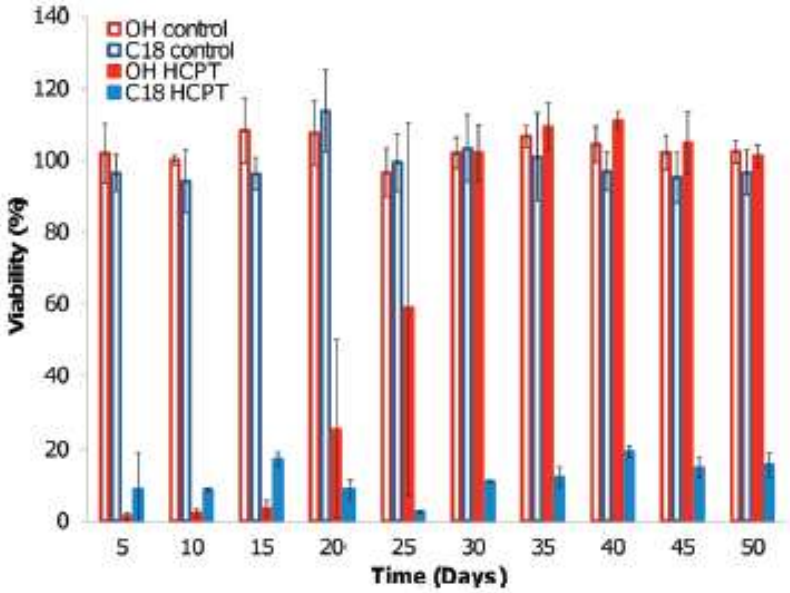
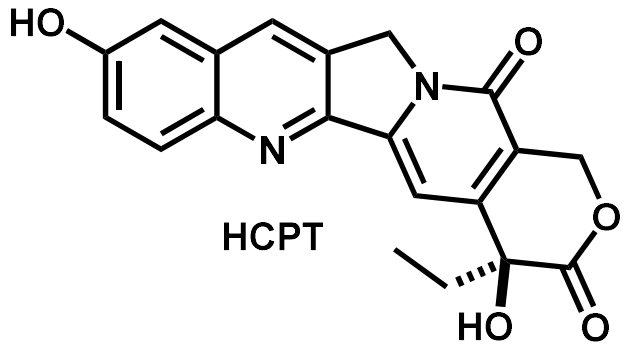


Figure 6. Antiproliferative efficacy of HCPT-loaded and unloaded PCG-OH and PCG-C18 films exposed to A549 human nonsmall cell lung cancer cells over 24 h intervals (n = 3).



HCPT

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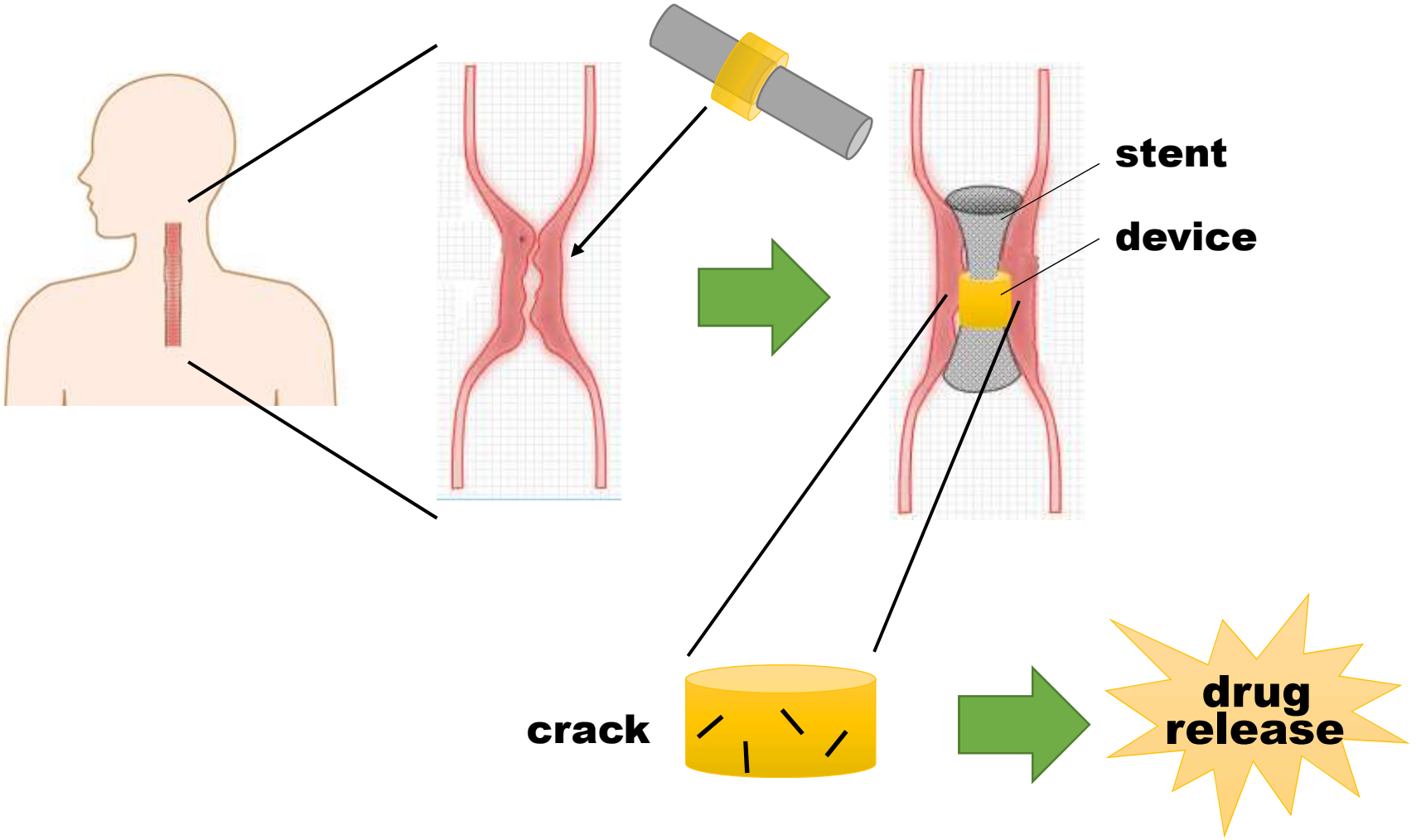
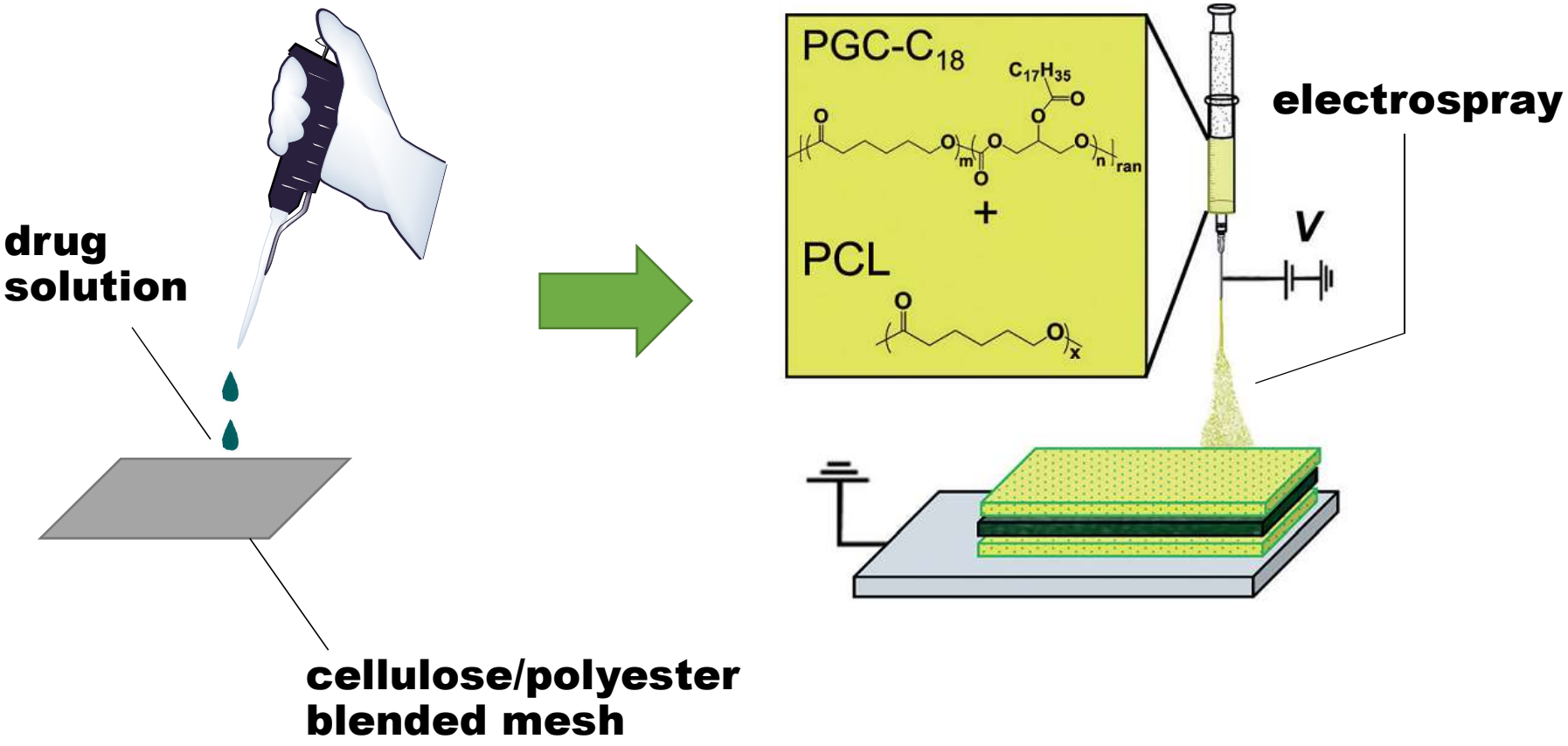
Concept



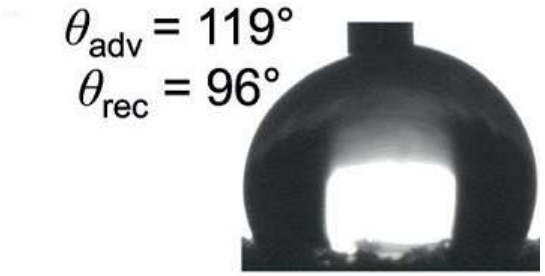
Wang, J.; Kaplan, J. A.; Colson, Y. L.; Grinstaff, M. W. *Angew. Chem. Int. Ed.* **2016,** *55*, 2796

Fabrication of device



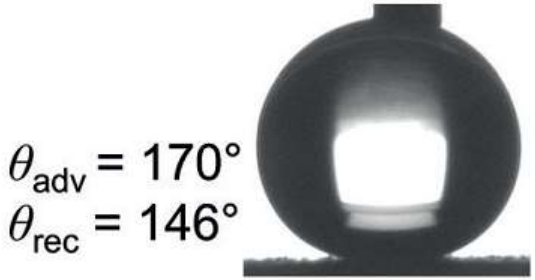
Wang, J.; Kaplan, J. A.; Colson, Y. L.; Grinstaff, M. W. *Angew. Chem. Int. Ed.* **2016,** *55*, 2796

Hydrophobicity of device



PCL

hydrophobic

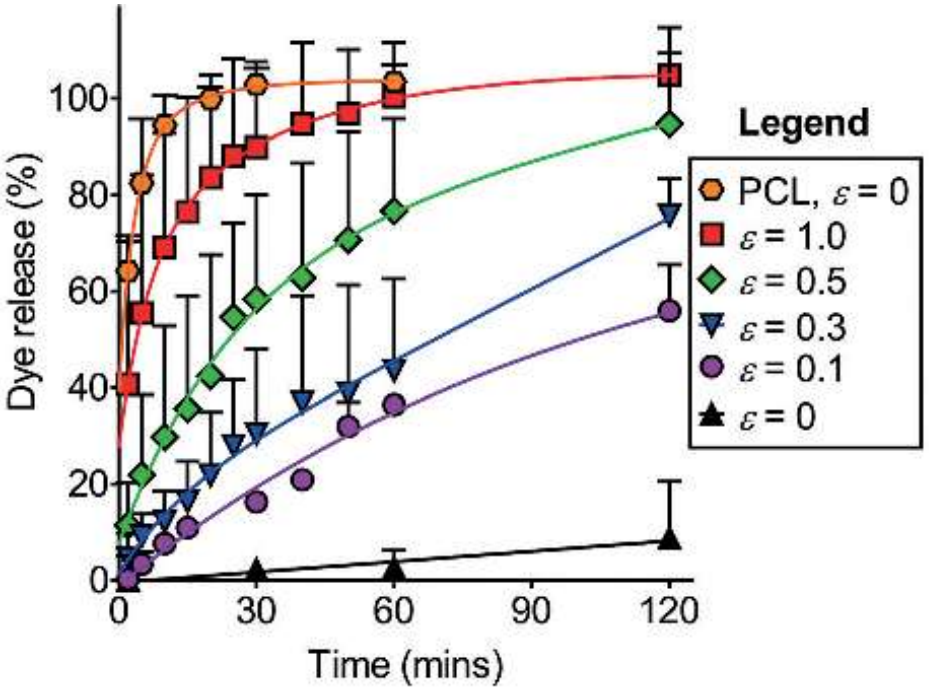


PCL:PGC-C18 = 1:1

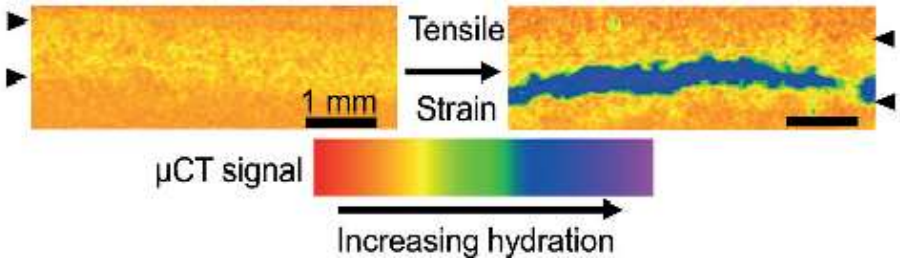
superhydrophobic

Wang, J.; Kaplan, J. A.; Colson, Y. L.; Grinstaff, M. W. *Angew. Chem. Int. Ed.* **2016,** *55*, 2796

Drug release under tension



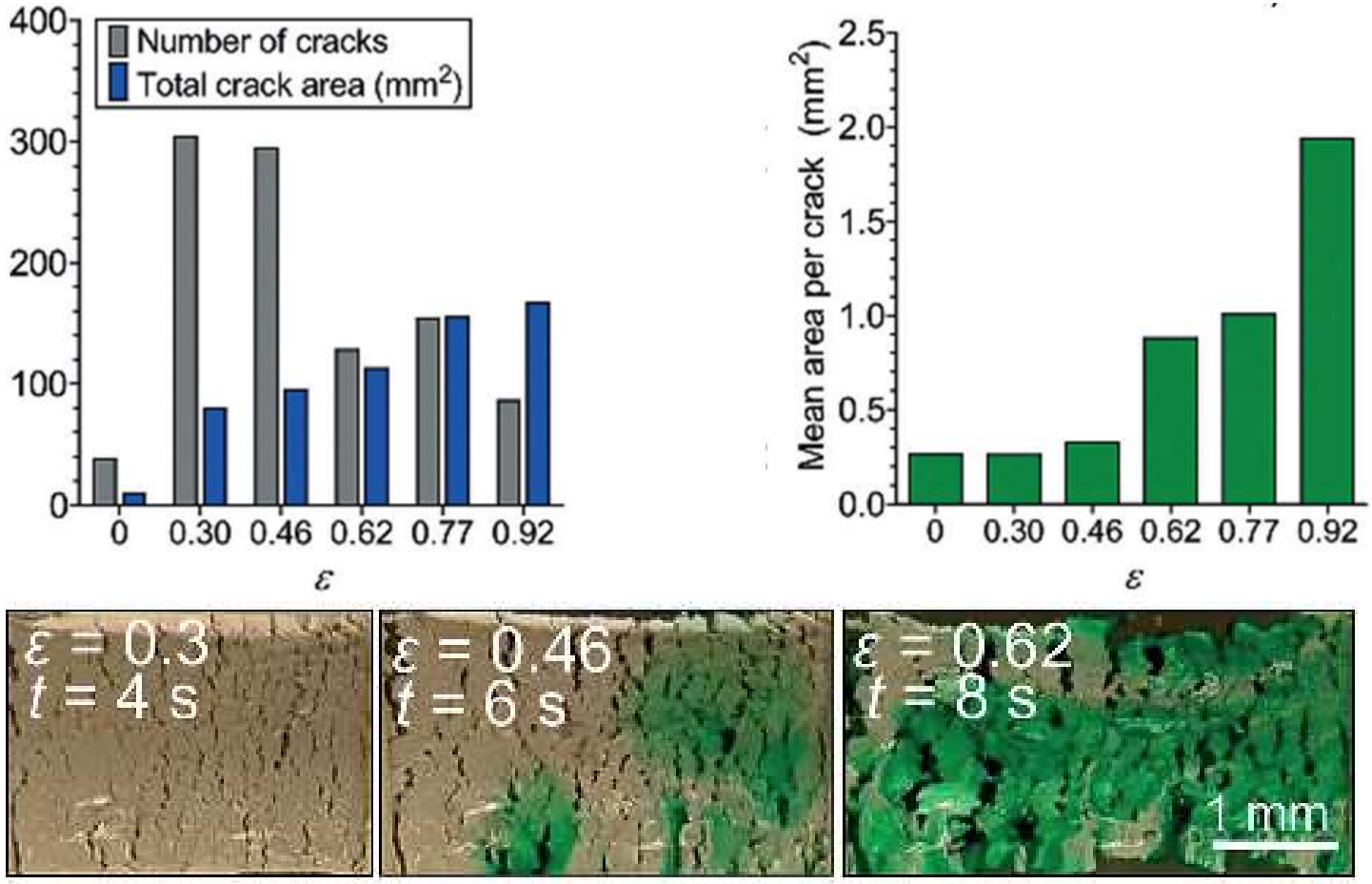
(ε : The degree of strain)



Blue color = hydration
= Crack appearance

1) Subrahmanyam, C .; Kulatheeswaran, R.; Ward, R. S. *J. Nat. Prod.* **1999,** *62.* 257-260
2) Shin, J.; Park, M.; Fenical, W. *Tetrahedron* **1989,** 41, 1633-1638

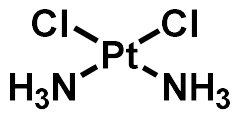
Mechanism of drug release



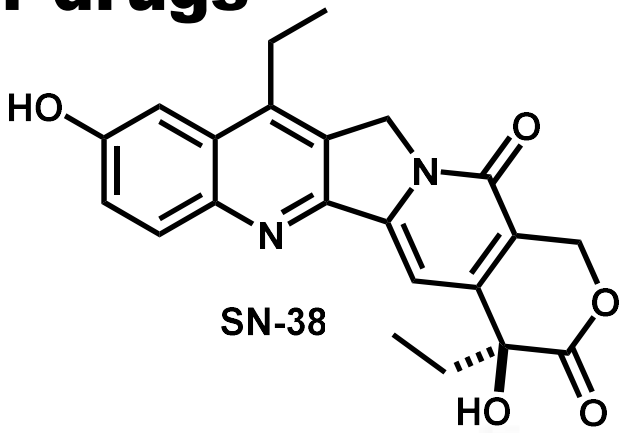
Crack formation **Crack propagation**

Wang, J.; Kaplan, J. A.; Colson, Y. L.; Grinstaff, M. W. *Angew. Chem. Int. Ed.* **2016,** *55*, 2796

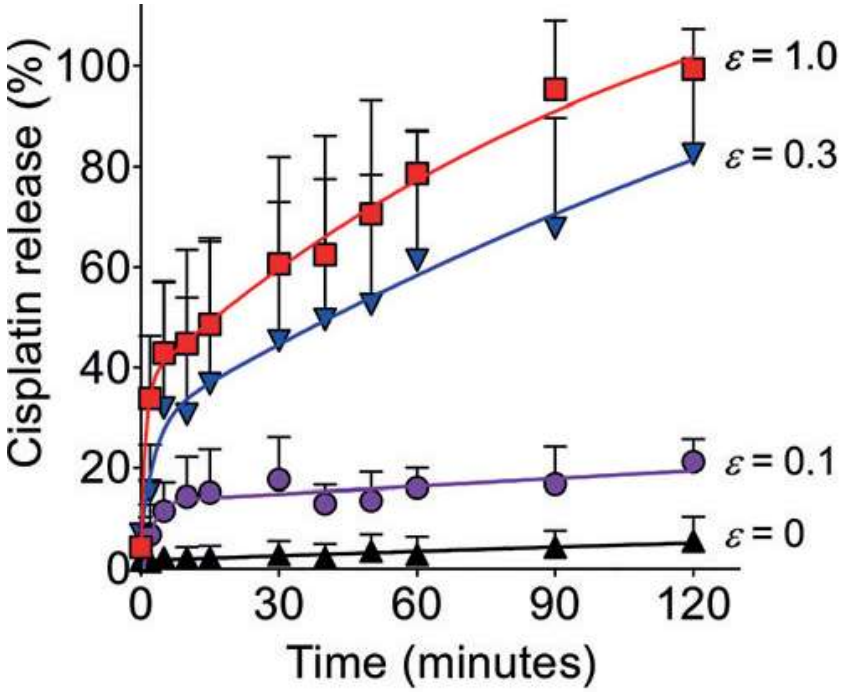
Delivery of anti-cancer drugs

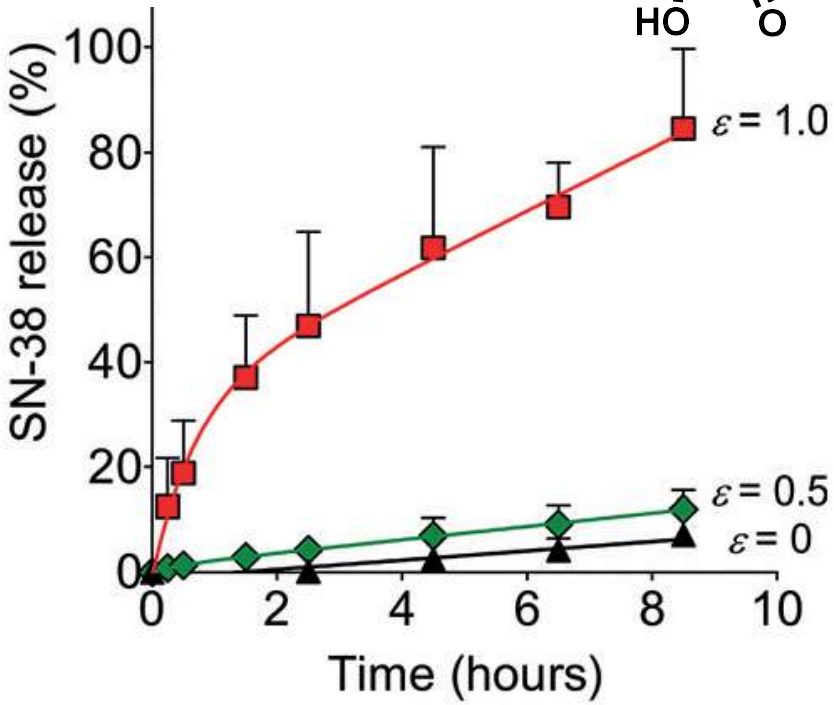


cisplatin



SN-38

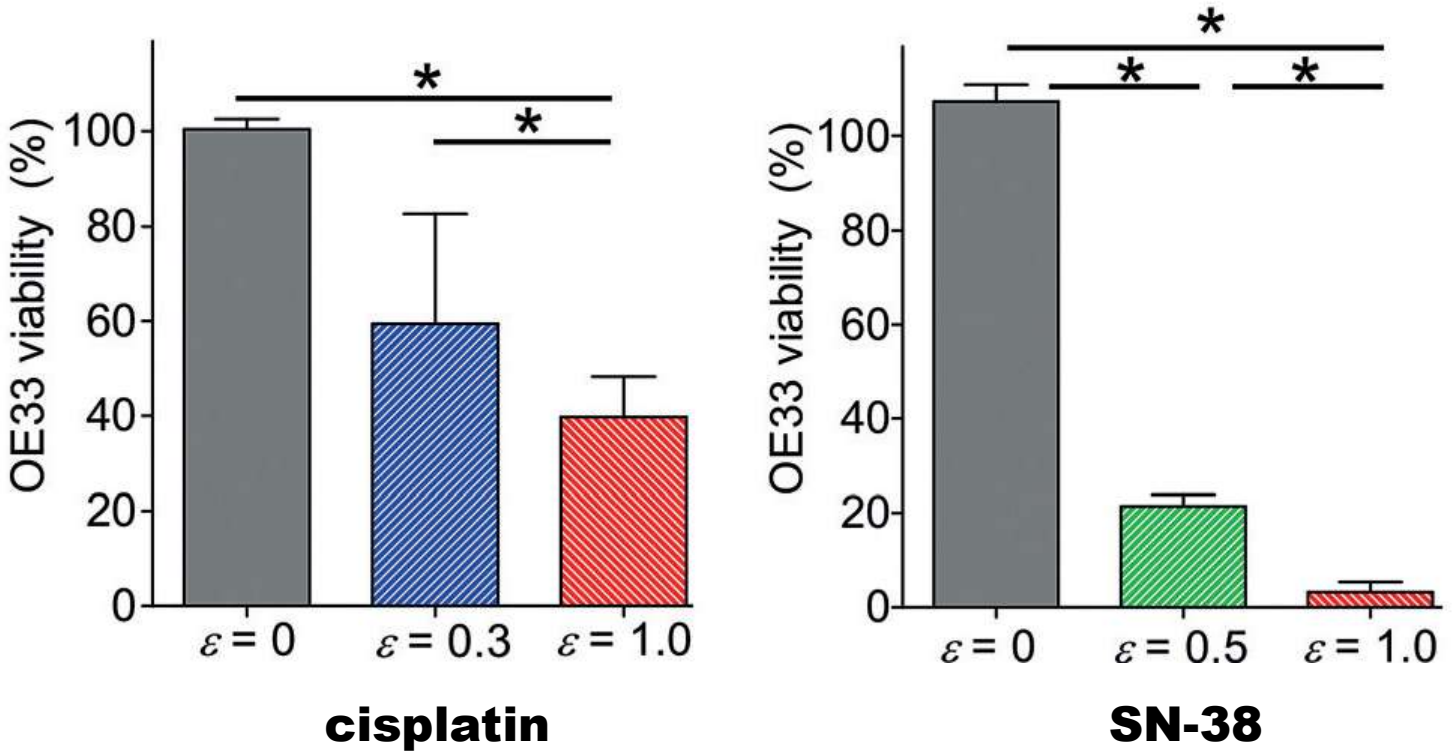




Drug release can be controlled by tension.

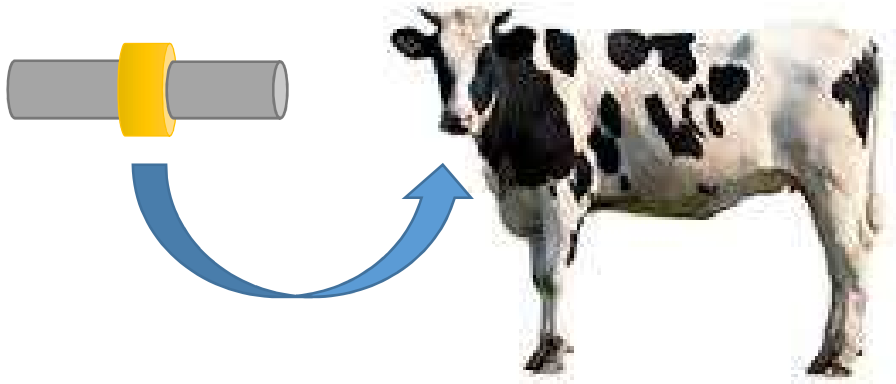
Wang, J.; Kaplan, J. A.; Colson, Y. L.; Grinstaff, M. W. *Angew. Chem. Int. Ed.* **2016,** *55*, 2796

In vitro experiment

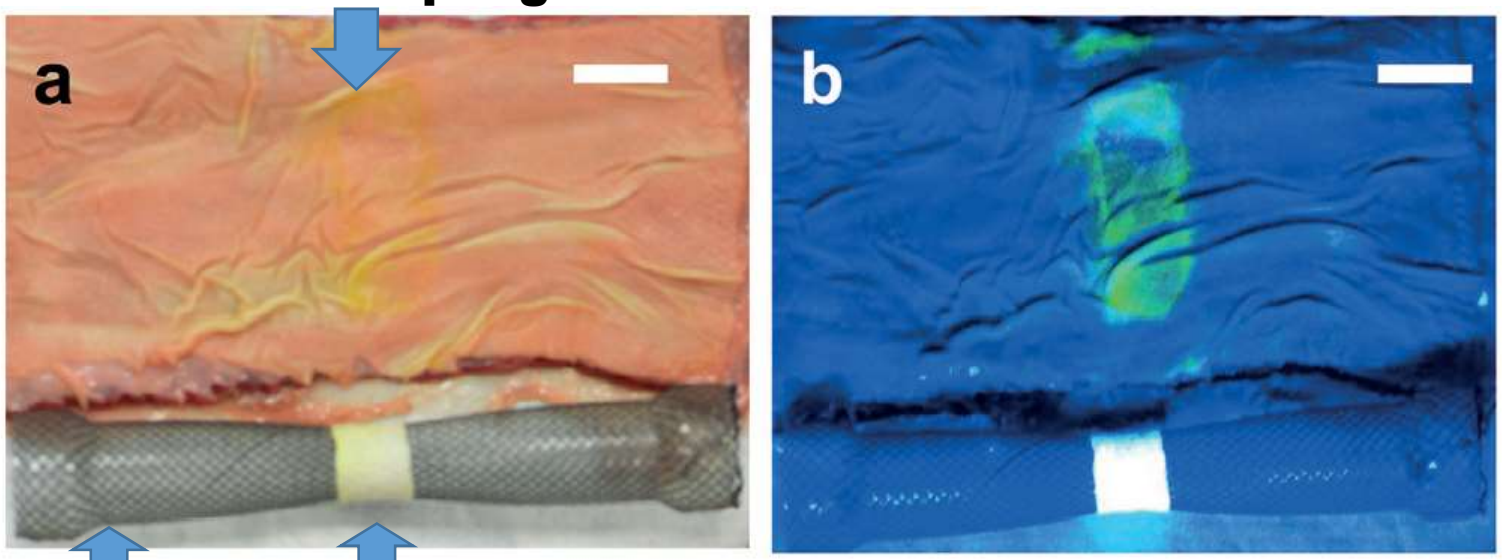


Wang, J.; Kaplan, J. A.; Colson, Y. L.; Grinstaff, M. W. *Angew. Chem. Int. Ed.* **2016,** *55*, 2796

Ex vivo experiment (1)



bovine esophagus

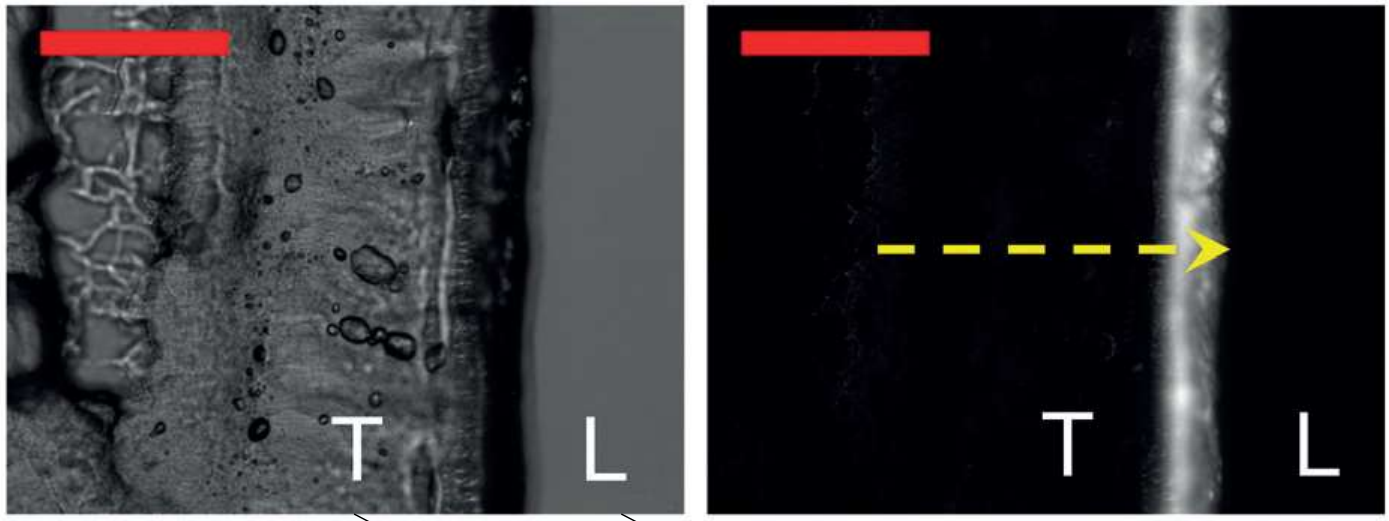


stent **device**

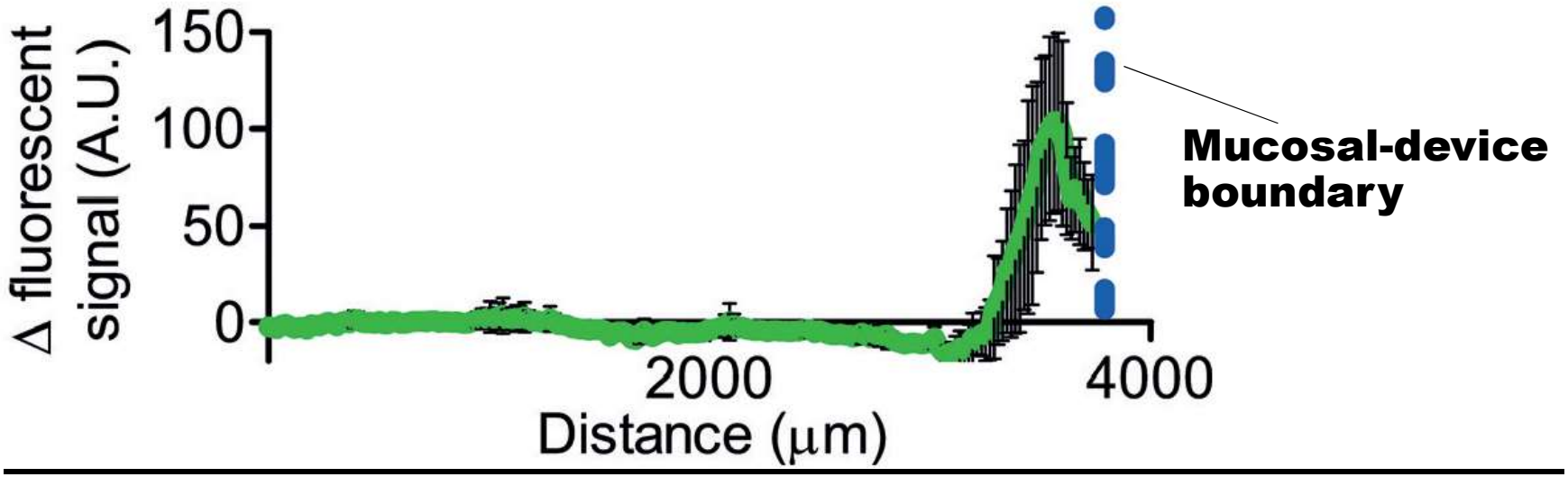
(a. white, b. UV light)

Wang, J.; Kaplan, J. A.; Colson, Y. L.; Grinstaff, M. W. *Angew. Chem. Int. Ed.* **2016,** *55*, 2796

Ex vivo experiment (2)



tissue **lumen** **left: bright, right: fluorescent**



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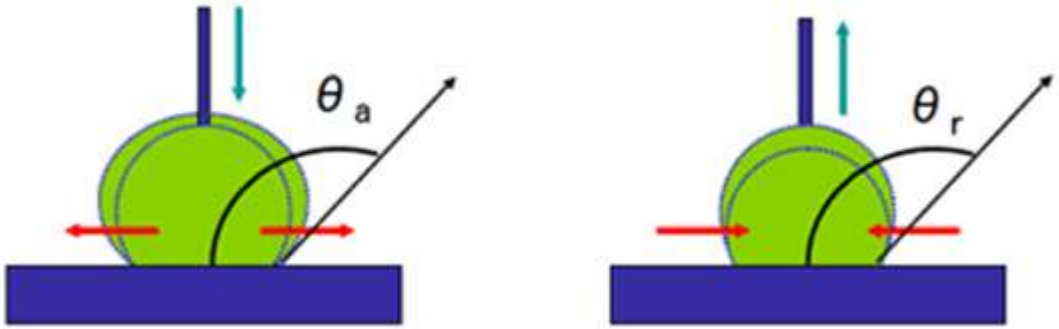
Summary

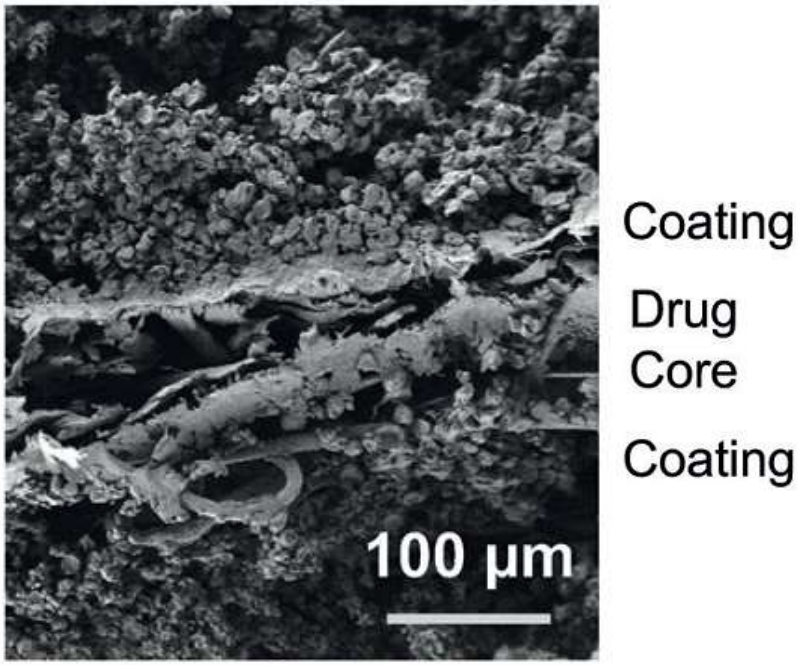
- **There are polymers which respond mechanical stimuli and change formation.**
- **Drug delivering device which used mechanoresponsive polymer was fablicated.**
- **Crack propagation is applied to DDS with help of superhydrohobicity.**

Appendix

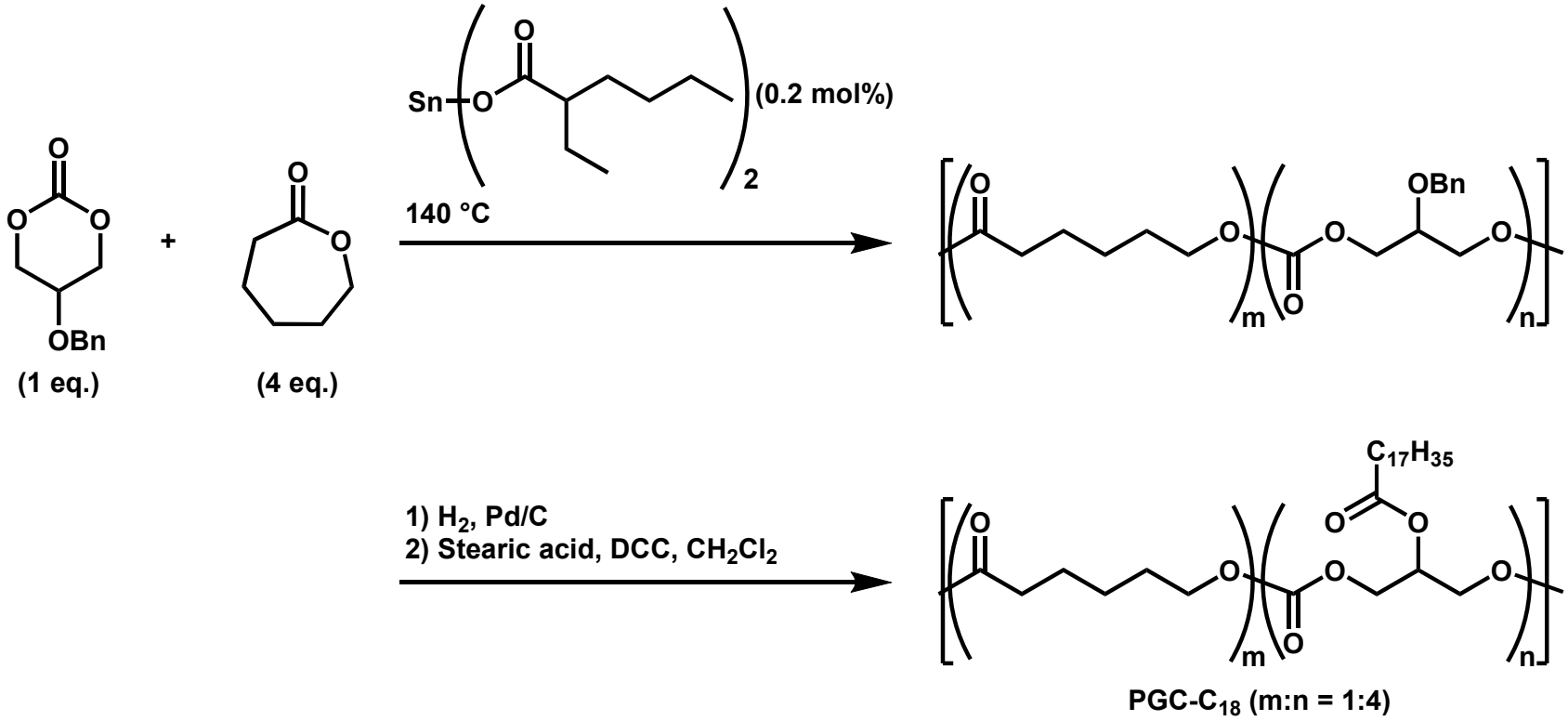
Advancing/reversing contact angle



SEM image of device



Synthesis of PGC-C18



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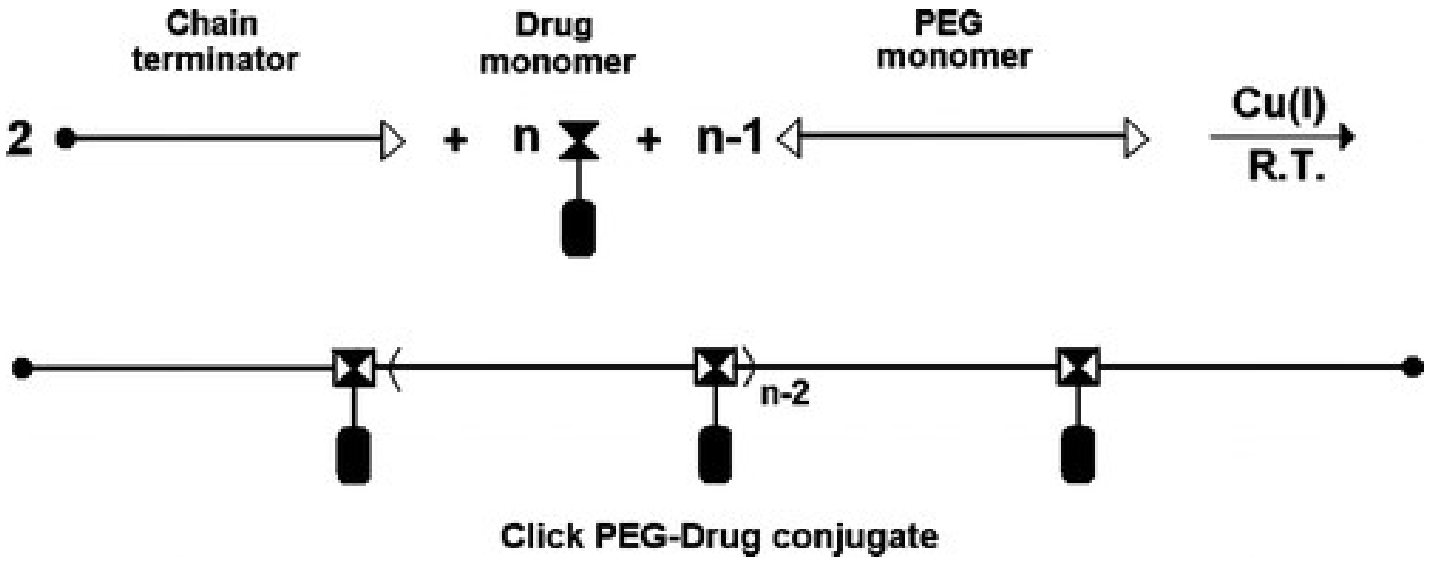
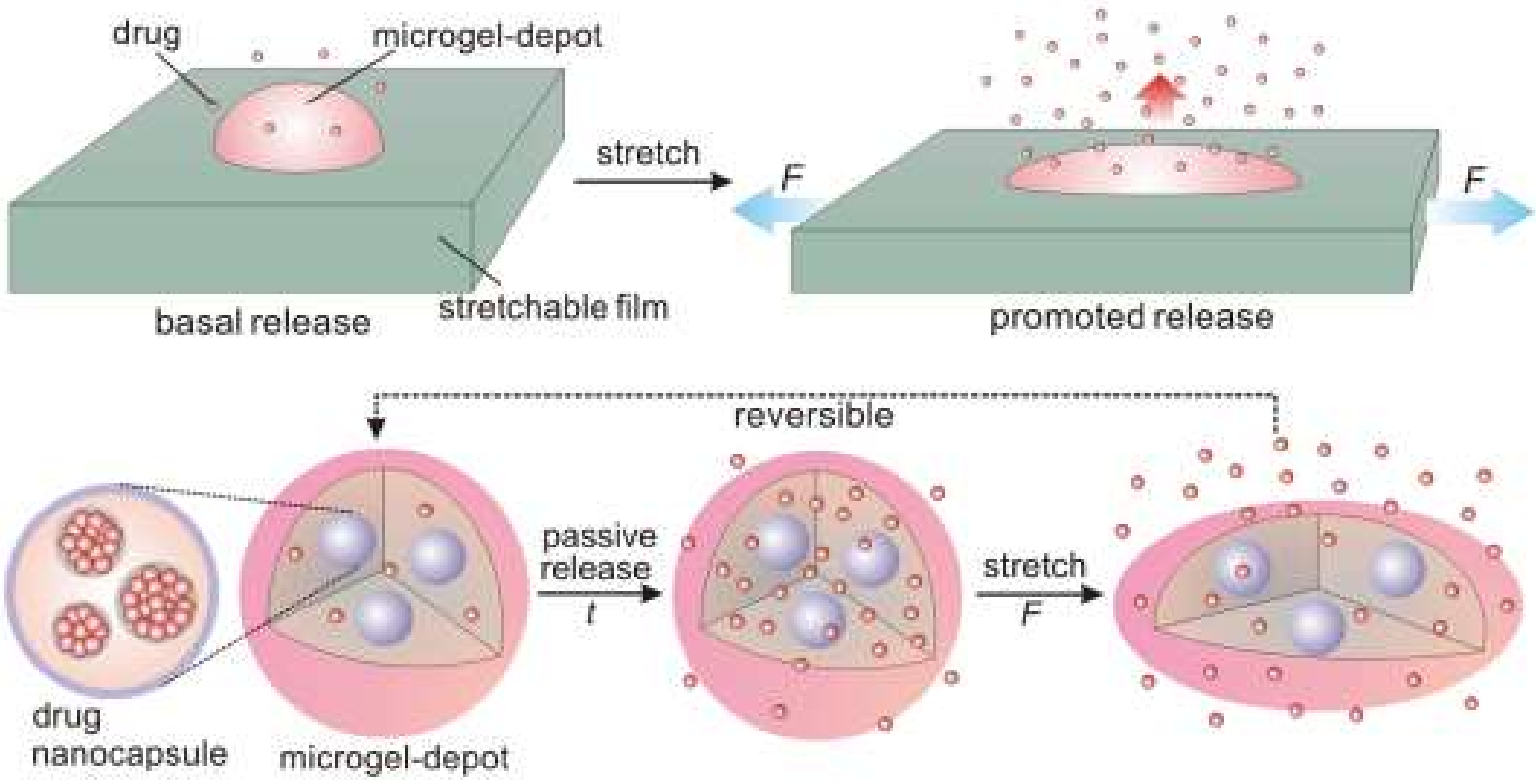
DDS using polymer



Covalent bonds with drugs
High concentration is dosed at once

1) Liu, X. M.; Quan, L.; Tian, J.; Laquer, F. C.; Ciborowski, P.; Wang, D. *Biomacromolecules* **2010,** *11*, 2621
2) Wolinsky, J. B.; Yohe, S. T.; Colson, Y. L.; Grinstaff, M. W. *Biomol.* **2015,** *13,* 406

Stimuli-responsive drug delivery



Di, J.; Yao, S.; Ye, Y.; Cui, Z.; Yu, J.; Ghosh, T. K.; Zhu, Y.; Gu, Z. *ACS Nano.* **2015,** *9,* 9407