Design of Smart Nanocapsules and Gel Particles Using W/O Emulsions for Drug Delivery Carriers

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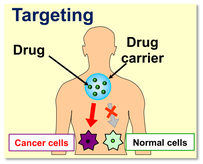
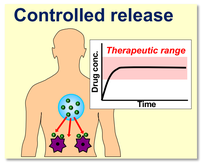
Introduction

Drug Delivery System (DDS)





Requirements

- ✓ Stimuli-responsive drug release
- ✓ High drug loading efficiency
- ✓ Good biocompatibility
- ✓ Good stability in physiological condition

DDS carriers

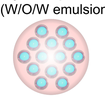
Liposomes

- Allen, T.M. *et al. Adv. Drug Deliv. Rev.* **2013**, *65*, 36.

Gel particles

- Akiyoshi, K. *et al. Bioconjugate Chem.* **2008**, *19*, 882.
- Jiang, S. *et al. PNAS* **2015**, *39* 12046.

Polymer particles (W/O/W emulsion)



- Nakashima, T. *et al. Adv. Drug Deliv. Rev.* **2000**, *45*, 47.
- Zhou, S. *et al. J. Controlled Release* **2001**, *75*, 27.

Polymer capsules

- Zetterlund, P.B. *et al. Biomacromolecules* **2015**, *16*, *2144*.
- Lu, Y.F. *et al. Nat. Nanotech.* **2010**, *5*, 48.

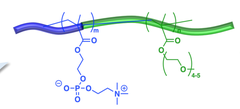
W/O Emulsion Formation by Water-soluble Emulsifier

Design of water-soluble block copolymer emulsifier

Poly(methacryloyloxyethyl phosphorylcholine) (PMPC)

- ✓ Biocompatible polymer
- ✓ Soluble in water and alcohol

Hydrophilic



PMPC-*b*-POEGMA

Poly[oligo(ethylene glycol) methacrylate] (POEGMA)

- ✓ Biocompatible polymer
- ✓ Soluble in both water and various organic solvents
- ✓ Distribution into chloroform in a water chloroform mixture

Amphiphilic

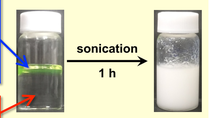
Preparation of W/O emulsion

Water phase

PMPC-*b*-POEGMA
Fluorescein
Phosphate buffer soln.
(pH 7.4, 20 mM: PB)

Oil phase

Chloroform



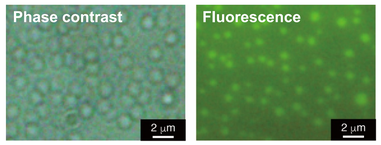
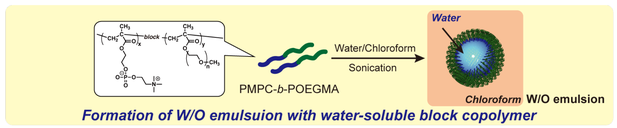


Fig. Phase contrast and fluorescence images of W/O emulsions after sonication for 1 h. The W/O emulsions were prepared using an aqueous fluorescein solution (5 mg/mL) as a water dispersed phase in the presence of PMPC-*b*-POEGMA (10 % (w/v) relative to the dispersed phase).

PMPC-b-POEGMA stabilized a water-chloroform interface to form W/O emulsions.

Nakaura, H.; Kawamura, A.; Miyata, T. *Langmuir* **2019**, *35*, 1413-1420.

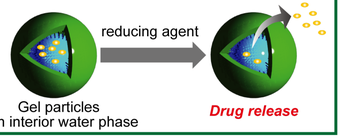
In this study



Formation of W/O emulsuion with water-soluble block copolymer

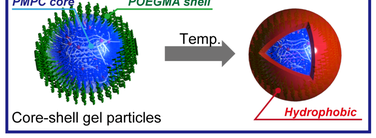
RAFT Polymn. at a surface of emulsion

Reductively responsive gel capsules



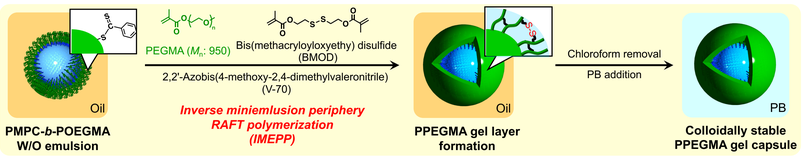
RAFT polymn. in the water dispersed phase

Temp.-responsive core-shell gel particles



Smart gel capsules and particles having potential application for DDS carriers were prepared by using W/O emulsion stabilized with water soluble PMPC-b-POEGMA.

Preparation of Amphiphilic Gel Capsules



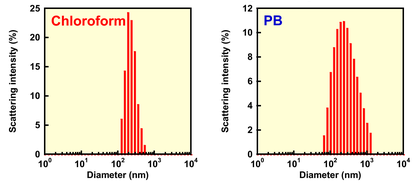
Preparation condition

Table. Synthetic conditions and cumulant diameters of gel capsules.

PEGMA : BMOD : PMPC-*b*-POEGMA : V-70 (mol/mol)	Cumulant diameter (nm)[a]	
	Chloroform	Water
500 : 100 : 1 : 0.5	234	217

[a] determined by dynamic light scattering measurements.

Size distributions of gel capsules



Colloidally stable amphiphilic gel capsules were successfully prepared by amphiphilic gel layer formation at the surface of W/O emulsion.

Cellular Uptake and Cytotoxicity of Gel Capsules

Cellular uptake

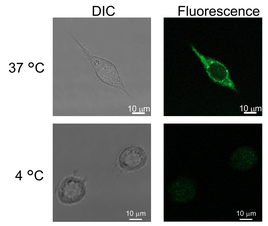


Fig. Confocal laser scanning microscopy images of the L929 cells incubated with Fluorescein conjugated gel capsules at 37 and 4 °C (0.1 mg/mL).

Cytotoxicity (WST-8 assay)

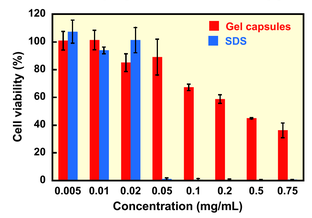


Fig. Viability of L929 cells treated with gel capsules (●) and sodium dodecyl sulfate (SDS) (●). Viability was expressed as the percentage to the untreated control cells. The data were presented as averages of three experiments ± SD.

Gel capsules were taken up by cells via endocytosis with low toxicity.

Reductively Responsive Drug Release

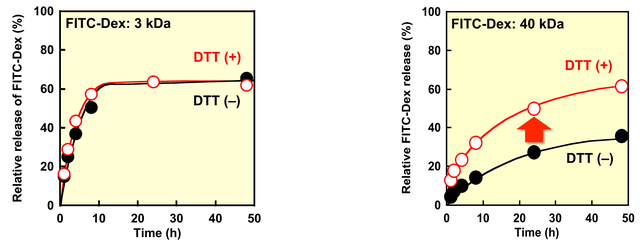
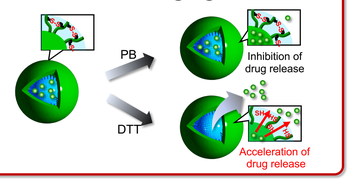
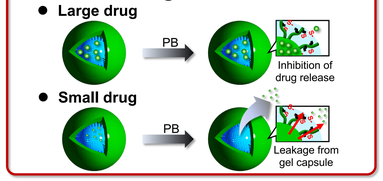


Fig. Release of FITC-Dex (M_w of 3 and 40 kDa) from gel capsules in 20 mM PB with (○) and without 10 mM of DTT (●) at 25 °C.

Effect of reducing agent



Effect of drug size



FITC-Dex release was enhanced under reducing environment owing to the decrease in the cross-linking density of gel capsule layer.

Synthesis of Emulsifier for Core-shell Gel Particle

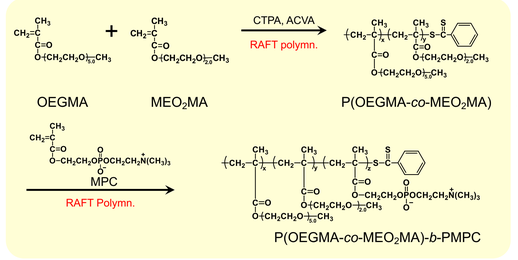


Table. Characterization of P(OEGMA-*co*-MEO_2MA)-*b*-PMPC by ^1H NMR and GPC

Degree of polymerization			M_n	M_w	$Đ$*
POEGMA	$PMEO_2MA$	PMPC	(×10³)*	(×10³)*	
28	93	17	8.9	9.7	1.1

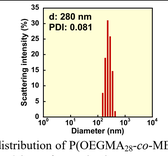
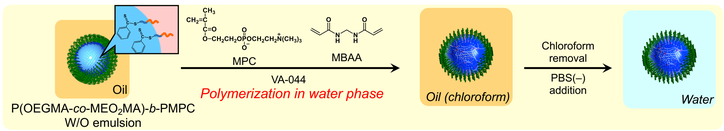


Fig. Size distribution of P(OEGMA$_{28}$-*co*-MEO_2MA_{93})-*b*-$PMPC_{17}$ emulsions after sonication.

Preparation of Core-shell Gel Particles



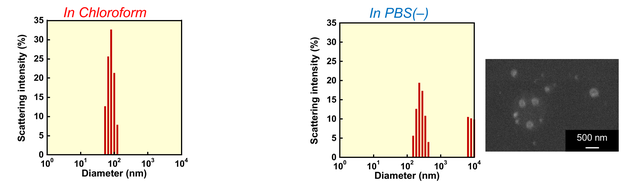


Fig. Size distribution of PMPC gel particles in chloroform.

Fig. Size distribution and SEM image of PMPC gel particles in PBS(-).

Colloidally stable PMPC gel particles were successfully prepared by inverse miniemulsion RAFT polymerization in the water droplet of W/O emulsion.

Preparation of Core-shell Gel Particles

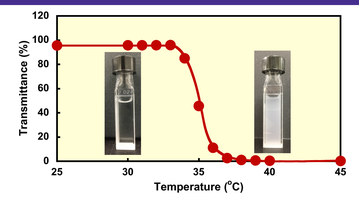
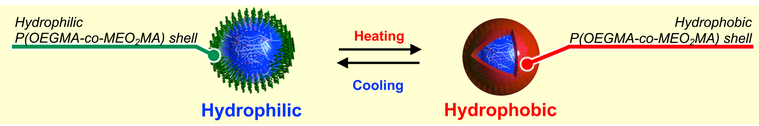


Fig. Change in transmittance (650 nm) of the PMPC gel particle dispersion as a function of temperature.



Core-shell gel particles dispersion became turbid owing to the phase transition of P(OEGMA-co-MEO_2MA) shell

Summary

- ✓ The water dispersible gel capsules were obtained by the amphiphilic gel layer formation on the surface of W/O emulsion.
- ✓ The drug release from gel capsules enhanced in response to a reducing environment owing to the decrease in crosslinking density resulting from the dissociation of disulfide cross-links.
- ✓ Temperature-responsive core-shell gel particles having hydrophilic PMPC core were successfully prepared by inverse miniemulsion RAFT polymerization.

Nakaura, H.; Kawamura, A.; Miyata, T. *Langmuir* **2019**, *35*, 1413-1420.
Sasaoka, M.; Kawamura, A.; Miyata, T. *in preparation*.