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研究課題名(和文) Novel nanomaterials and hybrid soft contact lens for removing fluorouracil from the tear of cancer patients

研究課題名(英文) Novel nanomaterials and hybrid soft contact lens for removing fluorouracil from the tear of cancer patients

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交付決定額(研究期間全体)：(直接経費) 3,400,000円

研究成果の概要(和文)：本研究は、がん患者におけるフルオロウラシル(5-FU)治療を受ける際、目への副作用を軽減するため涙液中の5-FUを吸着できるナノ材料および複合化コンタクトレンズ(CL)の製造を目指す。各種親疎水性や気孔率を有するメラミンナノ粒子を製造し、疎水性ナノ空間における水素結合力によって高い5-FU吸着能力を確認した。一方、メラミン残基をナノチューブの中空空間に導入すると、中空空間の親疎水性にかかわらず吸着効果は確認されなかった。ナノ材料と高分子材料の複合化を検討し、ナノ材料による高分子ゲルの物理強度や徐放性向上にも確認し、CL応用への用途開発の指針を示した。研究期間中、計4報の国際誌を発表した。

研究成果の学術的意義や社会的意義

5-FU治療を受けているがん患者のQOLを向上するため、涙液中極めた低い濃度の5-FUを吸着取り除くことが極めて重要な手段。本研究は、メラミンナノ粒子やメラミン残基修飾したナノチューブを設計合成し、5-FUの吸着性及びコンタクトレンズ(CL)との複合性を検討した。疎水性ナノ空間を有するメラミンナノ粒子は高い5-FU吸着能力を示している一方、メラミン残基修飾したナノチューブでの5-FU吸着は確認できなかった。ナノ材料と高分子材料の複合化を検討し、ナノ材料による高分子ゲルの物理強度や徐放性向上にも確認し、CL応用への用途開発の指針を示した。研究期間中、計4報の国際誌を発表した。

研究成果の概要(英文)：In this research, nanomaterials containing melamine units were designed and synthesized for the absorption of excess 5-FU in the patient tears for relieving its side effects. Melamine-nanoparticles which showed hydrophobic nanocavity and high porosity were effective in absorbing about 50% of 5-FU at a concentration of 200 ng/mL; However, the melamine-nanoparticles were poorly dispersible in CL monomers. Self-assembled nanotubes were finely dispersed in CL monomers and formed clear hybrid CL, and the hybrid hydrogel showed increased mechanical strength and sustained released property. However, introducing melamine units into the nanotube nanospace did not observe any 5-FU absorption. As research achievements, the related results have been published in four peer-reviewed international papers.

研究分野：ナノバイオ材料

キーワード：フルオロウラシル メラミンナノ粒子 ナノチューブ 複合化コンタクトレンズ

1. 研究開始当初の背景

One of the most significant ocular side effects of fluorouracil (5-FU), excessive lacrimation, has dramatically decreased the QOL of patients who receive 5-FU treatment. Wearing contact lenses to absorb and remove excess 5-FU from the patient tears can provide a novel approach for resolving this problem. Therefore, the design of nanomaterials that can selectively absorb 5-FU and compatible with contact lens are the key issue in this research proposal.

2. 研究の目的

The aims of this research proposal are to design such (1) 5-FU absorbing nanomaterials and (2) hybridize the nanomaterials with contact lens.

(1) Melamine-nanoparticles (MNP) containing different alkyl chain length were synthesized and evaluated for their 5-FU absorbing efficiencies (Fig. 1A). Since the hydrogen bonding between 5-FU and melamine unit depends significantly on the microenvironments, MNP having different nanocavity characteristics will be synthesized and optimized for high 5-FU absorption.

Self-assembled nanotubes are nanocapsules having cylindrical nanochannels connected with open-ends, which allow small molecules diffusing into the nanochannels. The melamine units will be chemically conjugated on the inner surface of nanochannels for 5-FU absorption (Fig. 1B). Importantly, the nanotubes can be specifically designed at a size less than 20 nm, which may guarantee a high dispersibility and transparency of the consequent hybrid contact lens.

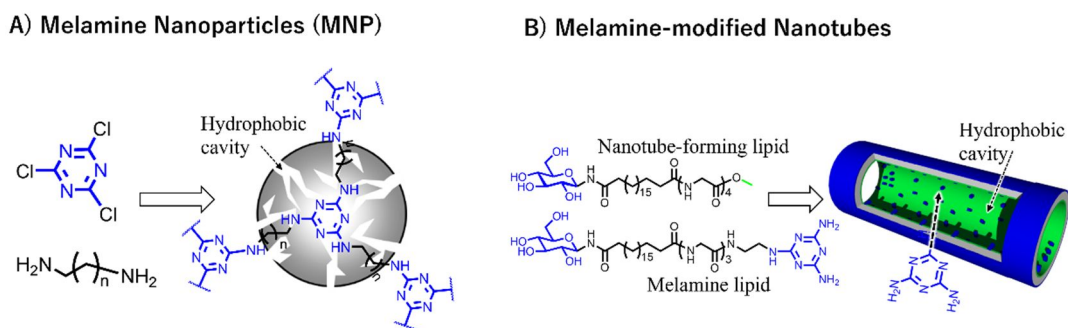


Figure 1 Melamine-containing nanomaterials

(2) Provided these nanomaterials can absorb 5-FU in water, they will be fabricated into hybrid contact lens prototypes to confirm their absorption capability in gel state (Fig. 2). Further the hybridization of nanotube with hydrogel is an important issue to explore their biomedical applications.

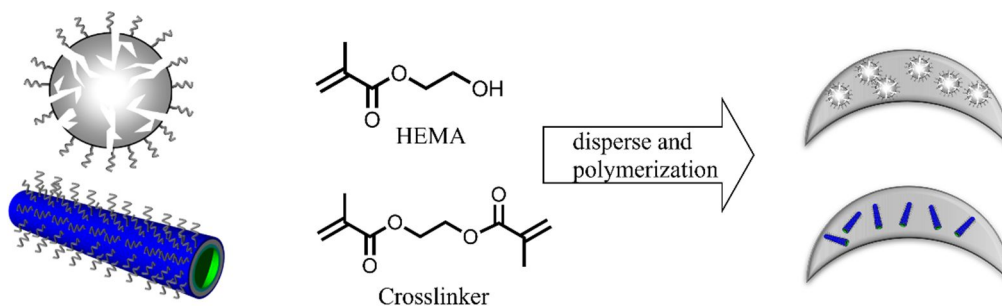


Figure 2 Hybridization of nanomaterials with hydrogel

3. 研究の方法

MNP was simply synthesized by one-pot crosslinking of the cyanuric chloride with diamine linker, with an aim of achieving nanoparticles less than 100 nm and large porosity. Melamine-modified nanotubes were constructed from the nanotube-forming lipid and melamine lipids, by a routine co-assembly method as established in my laboratory. The MNP and nanotubes dispersions will be incubated with 5-FU solution at different ratios, and the 5-FU amount in the residue after specific incubation time was measured by HPLC analysis.

For hybridization, nanotubes were surface-modified with methacrylate group and then crosslinked with lens monomer HEMA or polyethylene glycol dimethacrylate to form hybrid hydrogels (Fig. 3). Mechanical strength of the hybrid hydrogels was evaluated rheological study.

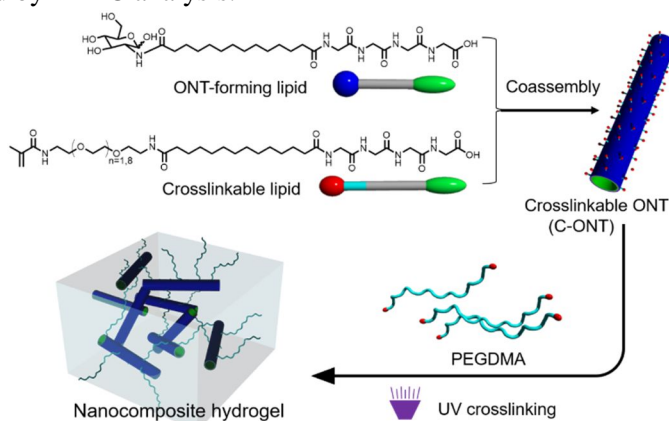


Figure 3 Nanotubes hybrid hydrogel

4. 研究成果

(1) Melamine-nanoparticles (MNP) containing different alkyl chain length were synthesized and evaluated for their 5-FU absorption efficiencies. It was found that MNP containing long alkyl chain, which has been proved to have high porosity and highly hydrophobic nanocavity, showed excellent 5-FU absorbing capability at a concentration of 250 ng/mL (Fig. 4). For example, at a melamine to 5-FU ratio of 1600, the most hydrophobic MNP (MNP-C12) showed about 80% absorption while hydrophilic MNP-C6O2 only showed about 10% absorption. This result suggested that hydrophobic nanocavity was more favorable for the hydrogen bonding formation between melamine and 5-FU. However, at low 5-FU concentration such as 20 ng/mL which is near the lacrimation condition, all the MNPs did not show any absorption capability. Further, the dispersion of MNPs in HEMA were quite white and turbid, preventing its application in contact lens. Melamine-modified nanotubes were also fabricated by co-assembly method, and the melamine group were anchored on the inner surface of nanotube nanochannels, which can be tuned as hydrophilic or hydrophobic. However, no absorption phenomenon was observed in the melamine-modified nanotubes even at high concentration. One plausible reason can be the low modification density of melamine groups in nanotubes.

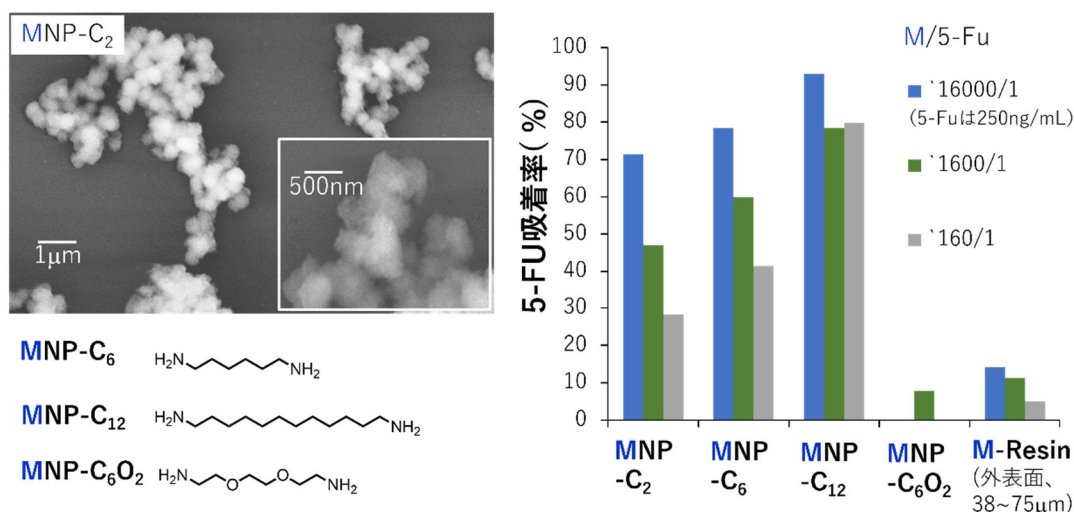


Figure 4 Melamine nanoparticles and their 5-FU absorption

(2) Nanotubes without or with methacrylate crosslinking group were finely dispersible in HEMA or polyethylene glycol dimethacrylate as semi-clear solution (Fig. 5). After polymerization, clear contact lens having 98% transparency were achieved. The methacrylate crosslinking group on nanotube surface greatly improved the mechanical strength of hybrid hydrogel and contact lens (Fig. 6).

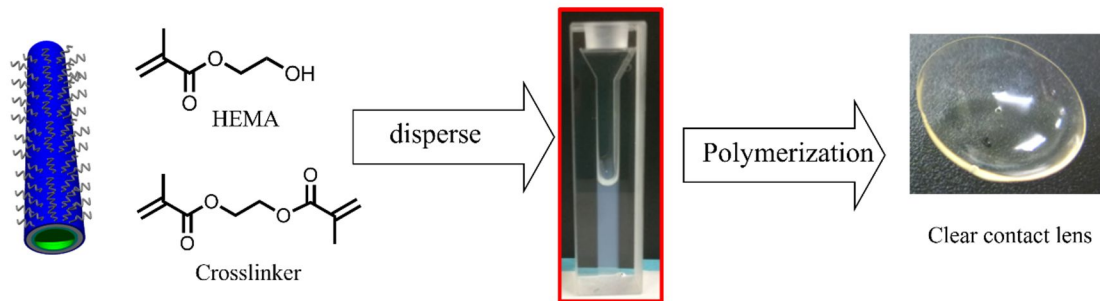


Figure 5 Nanotubes hybrid contact lens

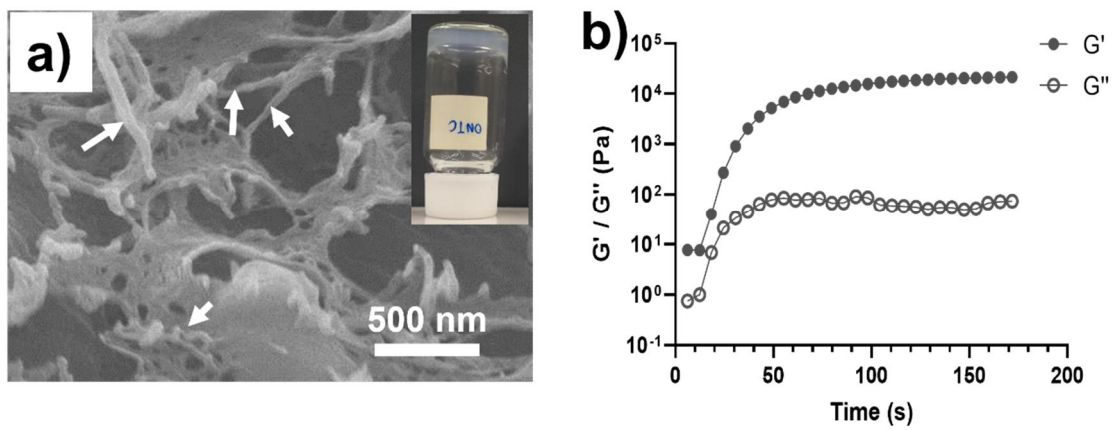


Figure 6 SEM of nanotubes hybrid hydrogel and its rheological behavior

5. 主な発表論文等

〔雑誌論文〕 計4件（うち査読付論文 4件/うち国際共著 2件/うちオープンアクセス 0件）

1. 著者名 Shimizu Toshimi, Ding Wuxiao, Kameta Naohiro	4. 巻 120
2. 論文標題 Soft-Matter Nanotubes: A Platform for Diverse Functions and Applications	5. 発行年 2020年
3. 雑誌名 Chemical Reviews	6. 最初と最後の頁 2347 ~ 2407
掲載論文のDOI (デジタルオブジェクト識別子) 10.1021/acs.chemrev.9b00509	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 -
1. 著者名 Wu Dongwei, Ding Wuxiao, Kameta Naohiro	4. 巻 242
2. 論文標題 Selective construction of single-walled asymmetrical nanotube by platinum (II)-coordination/dissociation	5. 発行年 2019年
3. 雑誌名 Materials Letters	6. 最初と最後の頁 107 ~ 110
掲載論文のDOI (デジタルオブジェクト識別子) 10.1016/j.matlet.2019.01.107	査読の有無 有
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1. 著者名 Ding Wuxiao, Kameta Naohiro, Oyane Ayako	4. 巻 50
2. 論文標題 Reactive Oxygen Species (ROS)-responsive Organic Nanotubes	5. 発行年 2021年
3. 雑誌名 Chemistry Letters	6. 最初と最後の頁 1743 ~ 1746
掲載論文のDOI (デジタルオブジェクト識別子) 10.1246/cl.210413	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 -
1. 著者名 Wu Dongwei, Ding Wuxiao, Kameta Naohiro	4. 巻 54
2. 論文標題 Functionalized organic nanotubes with highly tunable crosslinking site density for mechanical enhancement and pH-controlled drug release of nanocomposite hydrogels	5. 発行年 2021年
3. 雑誌名 Polymer Journal	6. 最初と最後の頁 67 ~ 78
掲載論文のDOI (デジタルオブジェクト識別子) 10.1038/s41428-021-00556-1	査読の有無 有
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〔学会発表〕 計0件

〔図書〕 計0件

〔産業財産権〕

〔その他〕

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6. 研究組織

	氏名 (ローマ字氏名) (研究者番号)	所属研究機関・部局・職 (機関番号)	備考
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7. 科研費を使用して開催した国際研究集会

〔国際研究集会〕 計0件

8. 本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関
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