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		(脂質集合体形成能を有する両親媒性高分子の合成と評価に関する研究)				
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### 論文の内容の要旨

Liposomes (vesicles) are microscopic spheres with an aqueous core surrounded by one or more outer shell(s) consisting of lipids, surfactants, or block copolymers arranged in a bilayer configuration. They are of great interest for applications from drug delivery and controlled release to separations and sensing. However, administration of the dispersed liposome particles to a specific site in the body still remains a problem. In this thesis, we explore the immobilization of liposomes within gel matrix via the anchoring of the hydrophobic moieties of the polymer into the liposome bilayers. Systematic investigations were carried out on this physically-crosslinked liposome gel network on the following aspects: (a) dynamic rheological behaviour of the liposome gel, especially, in the aspect of its recovery ability upon either mechanical deformation or temperature change; (b) the in vitro degradation behaviour of liposome gel, especially in comparison with rheological studies; (c) change of liposome bilayer microenvironment before and after the addition of amphiphilic polymer. These studies could be useful for the future biomedical application.

Firstly, self-assembled liposome gel from liposome and cholesterol-end capped polyethylene glycol, was systematically investigated by rheological method, especially in the aspect of its recovery ability upon either mechanical deformation or temperature change. The liposome gel was found to have rheological behaviour similar to that of Maxwell model. The dynamic shear modulus of the liposome gel was dependent on both the liposome concentration and the polymer concentration. At low liposome concentration range (5-20 mM), dynamic shear modulus decreased considerably with the liposome concentration, implying the decrease of effective cross-linking density inside gel network due to the addition of liposome. The liposome gel network had a fast, self-healing ability even after high deformation, and the injectability of the gel was confirmed by injection experiment in vitro. The liposome gel also exhibited temperature stimuli responsive behaviour and thermo-reversibility. Dynamic light scattering studies proved that the particle size of liposome remained almost unchanged before and after the addition of the polymer.

Secondly, the in vitro degradation behaviour of self-assembled liposome gel was investigated, especially in comparison with rheological studies. The plateau modulus of the liposome gel, an important value to reflect the

effective cross-linking density among the network, was dependent on both the liposome concentration and the polymer concentration. When the liposome gels were exposed to an aqueous solution, they first showed a period of swelling phase due to adsorption of water and then a dissolution phase began, leading to the full degradation of the network. The liposome gel with higher plateau modulus (i.e. higher effective cross-linking density) was found to degrade more slowly, indicating that the degradation behaviour of the gel was closely related with the rheological properties. In order to study the gel degradation mechanism more directly, dextran blue-loaded liposome gel was prepared. In the initial period of the liposome gel exposure to the aqueous solution, the dextran blue release was of Fickian diffusion transport behaviour. After that period, the release mechanism was found to be of Super Case II transport, which was gel matrix relaxation controlled.

Finally, in order to investigate how the incorporation of the cholesterol end groups of cholesterol-end capped polyethylene glycol affects the microenvironment of liposome bilayer, two kinds of molecular probes, namely Nile Red and pinacyanol chloride, were used. Their UV-Visible and fluorescence spectrum were recorded before and after the addition of the polymer. Shifts of the maximum absorbance ( $\lambda_{\max}$ ) of Nile Red shows that the bilayer microenvironment around Nile Red is becoming more polar with increasing polymer concentration while shifts of  $\lambda_{\max}$  of pinacyanol chloride indicates that the surrounding environment of Pinacyanol chloride is becoming more apolar with addition of polymer. Effect of temperature and composition of liposome were also studied. With the increase of temperature, the bilayer microenvironment became more apolar. With the increase of dimethyldioctadecylammonium bromide (DODAB) fraction in liposome, it became easier for the cholesterol end groups to embed into the bilayer, while cholesterol fraction in liposome helps to stabilize the bilayer structure and impedes the cholesterol end groups' penetration into the bilayer.

## 審査の結果の要旨

脂質集合体であるリポソームを物理的に架橋することにより得られるリポソームゲルをレオロジーの観点から検討している。第2章では、両末端にアミド結合を介してコレステリル基を導入したポリエチレングリコールを合成し、合成脂質により調製したリポソーム溶液に添加することにより、リポソームゲルが得られることを明らかにした。また、シェアストレスのオン-オフによりリポソームゲルがゾル-ゲル転移を示すことを示した点は、興味深い。この特性を利用して、リポソームゲルはインジェクタブルゲルとして有用であることを実証している。また、第3章では、リポソームゲルの分解性について評価を行っている。直接的な分解性の評価として、デキストランブルーを内包したリポソームゲルを調製し、徐放性を評価することにより分解性過程を明らかにした。第4章では、両末端にコレステリル基を導入したポリエチレングリコールを低分子プローブである Nile Red と pinacyanol chloride 存在下でリポソームに添加することによる微小環境変化について検討を行っている。Nile Red と pinacyanol chloride の最大波長変化を追跡することで、脂質二分子膜の極性変化が生じることを明らかにしている。

第2章から第4章までの研究において、既に国際誌に2報受理(2報とも掲載済み)および1報は、投稿中であることから、研究成果を着実にまとめており、博士(工学)の学位論文として評価に値する。

平成24年2月10日、数理物質科学研究科学学位論文審査委員会において審査委員の全員出席のもと、著者に論文について説明を求め、関連事項につき質疑応答を行った。その結果、審査委員全員によって、合格と判定された。

上記の論文審査ならびに最終試験の結果に基づき、著者は博士(工学)の学位を受けるに十分な資格を有するものと認める。