Preparation of liposome for thermotherapy and Drug Release Control

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Abstract: Currently, the side effect of anticancer drugs is serious problem for cancer patients. Drug Delivery System by using liposome could be reduce the side effect. We prepare a liposome which can release the inclusion by warming. Therefore, we control release of the inclusion in liposome by warming and ultrasonic irradiation.

Key-Words: *Drug Delivery System, temperature-sensitive liposome, ultrasonic irradiation*

1. Introduction

As one of cancer treatment, many cancer patients use pharmacotherapy by anticancer drugs because it is effective in a wide range of cancer. But, the side effect may occur to the patient by anticancer drugs, and physical, mental burden is a social problem. Therefore, the method of Drug Delivery System (DDS) for controlling the drug distribution in the body has been important. Nanocapsule called liposome composed of lipids is expected as drug delivery vehicle of DDS. Drug-containing liposome is administered to the body and the drug is released in the affected part, it is possible to obtain a high effect with less drug. However, liposome have been used in clinical practice is less and have been made studies to have a variety of functions to liposome for example an improvement of secured stability in the blood, and targeting to cancer cells [1].

In such studies, there is a temperature-sensitive liposome can release the contained drug by warming. It is able to obtain a high effect while reducing the side effect by combination with hyperthermia to heat the cancer cell more than 42℃. However, there is a possibility that the side effect will cause to patients to leak the contained substance at 37℃ a body temperature and many researchers try to control the release temperature by chemical approach up till now.

Therefore, we aimed preparation of liposome, which doesn't leak the inclusions at body temperature but release the inclusions at warm range 39~42℃ used in hyperthermia, and control the release of inclusions by adding the ultrasound at the same time.

2. Principle of release of temperature sensitive liposome's inclusion

Liposome is a vesicle composed of lipid bilayer, such as represented in Figure1 and lipid bilayer become one of the state of crystalline phase or gel phase or liquid crystal phase by temperature. The state of the hydrocarbon chains and the film surface is the solid phase at low temperature crystal phase or gel phase. In contrast, liquid crystal phase becomes the main chain of the hydrocarbon chain is a state of flux, and membrane permeability of liquid crystal phase is higher than the other phases. Temperature-sensitive liposome that utilizes this phenomenon, and it is possible to release the inclusion by gel-liquid crystal phase transition by warming.

In addition, the previous study has been found a liposome to be released many more inclusion by combination of warming and ultrasonic irradiation (Figure2) [2].

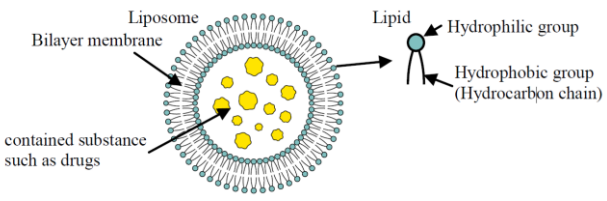

Figure 1 Structure of the liposome

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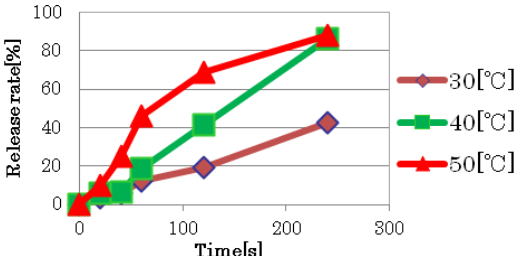

Figure 2 Emission rate of the inclusion when adding warming and ultrasonic irradiation

3. Preparation of temperature-sensitive liposome

Liposome prepared in this study is composed of DPPC, DSPC, Cholesterol, and DPPE-PEG2000. DPPC and DSPC is a typical phospholipids, gel-liquid crystal phase transition temperature of DPPC is about 41℃, DSPC is about 55℃. Therefore, the high stability liposome in blood is provided by reacting the DPPE-PEG2000 by crosslinking reaction. The liposome was prepared by freeze-thaw method, it contain the calcein which is a fluorescent agent at high concentrations. Adjustment of the particle size using the Extruder fitted with a polycarbonate film, we prepared the liposome of particle diameter is 200nm by using polycarbonate membrane which is 200nm pore size.

4. Release of the inclusion by warming

4.1 Experimental condition

We used the temperature-sensitive liposome composed of DPPC, Cholesterol and PEG. It was warmed for 10 minutes in a Thermostatic Bath shown in Figure3, the temperature-sensitive liposome was gel-liquid crystal phase transition.

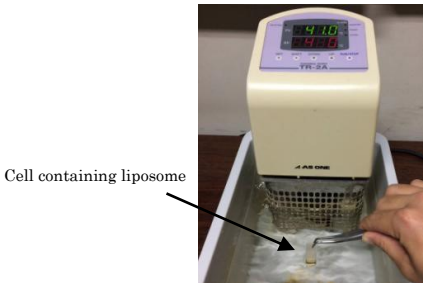

Figure 3 Warming step

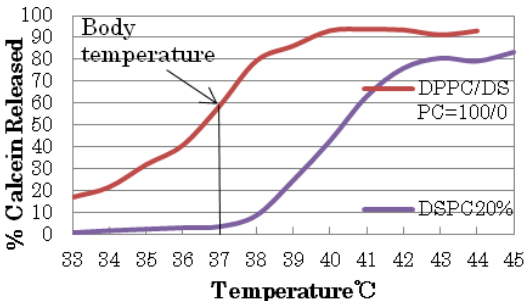

Figure 4 Inclusion release rate

4.2 Result

Release rate of inclusion was remained as shown in Figure 4(a).This liposome leak 60% of the inclusion at the body temperature. Thus, it can't be used in combination with hyperthermia. Therefore, we had prepared the liposome, which is gel-liquid crystal phase transition temperature is higher by adding a small amount of DSPC. We had prepared the liposome from DPPC and DSPC (DPPC:DSPC=4:1(Molar concentration ratio)). Release rate of inclusion was remained as shown in Figure 4(b).

5. Conclusion

Gel-liquid crystal phase transition temperature is increased by the 20% blended DSPC. Furthermore, the leakage rate of the inclusion was only 4% at the body temperature. But, the inclusion release rate of this liposome was lower at 39~42℃ for clinically heatable temperature range. It is expected to compensate by a combination of heating and ultrasonic irradiation.

References:

[1] Mitsuru Hashida, Drug Delivery System, Kagakudojin, 1995,p.5.

[2] Yushi Matsumoto, Studies on the controlled release of the inclusion of liposomes by heating and ultrasonic irradiation, 2013, p.27~29.