pH AND TEMPERATURE SENSITIVE BIODEGRADABLE BLOCK COPOLYMER HYDROGELS AND MICELLES FOR BIOMEDICAL APPLICATIONS

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1. INTRODUCTION

The stimuli-sensitive hydrogels and micelles have attracted considerable attention as intelligent materials in the biochemical and biomedical field, since they can environmental changes and induce structural changes by themselves.[1] Among the stimuli-sensitive materials, the block copolymer hydrogels composed of poly(ethylene glycol)(PEG) as hydrophilic part and biodegradable polyester as hydrophobic part, such as poly(L-lactic acid)(PLLA), poly(D,L-lactic acid)(PDLLA), poly(D,L-lactic acid-co-glycolic acid)(PLGA) were studied as controlled-release drug carriers, because the hydrogels need not to be removed by surgical treatment owing to their biodegradability after injecting to body. Kim and coworkers reported the PLGA-PEG-PLGA block copolymer hydrogel has been used as an injectable drug delivery system, owing to its remaining in the gel form for a long time in the body. [2]

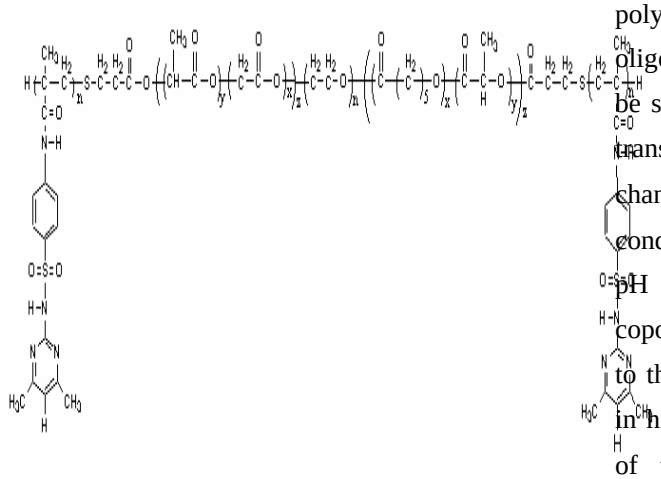
However, these hydrogels have several unresolved drawbacks, which make them difficult to use in injectable drug delivery systems. When temperature reversible hydrogels are injected into the body by using a syringe, they tend to change into the gel in the wormed needle by the body temperature. These appearances make it difficult to inject them into the body.

In this presentation, we would like to review our recent works on the novel pH & temperature sensitive block copolymer hydrogels and micelles to overcome these above unresolved problems.

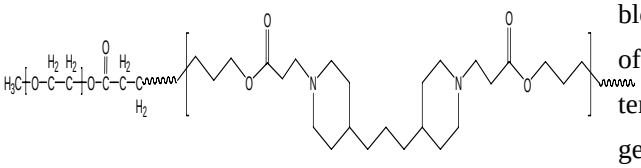
2. RESULTS AND DISCUSSION

In our system, the hydrophobic part of temperature sensitive block copolymer was composed of poly(ε-caprolactone-co-lactide)(PCLA) which is less biodegradable than PLGA. Also, in order to impart the pH-sensitivity on the temperature sensitive block copolymer, temperature sensitive block copolymer was coupled with pH-sensitive moieties such as sulfonamide derivatives (OSM).

Figure 1 shows the schematic chemical structures of OSM-PCLA-PEG-PCLA-OSM block copolymer and MePEG-poly(β-amino ester) block copolymer.



(a) OSM-PCLA-PEG-PCLA-OSM block copolymer



(b) MePEG-poly(β-amino ester) block copolymer

Fig. 1: Schematic chemical structures of OSM-PCLA-PEG-PCLA-OSM block copolymer (a) and MePEG-poly(β-amino ester) block copolymer (b).

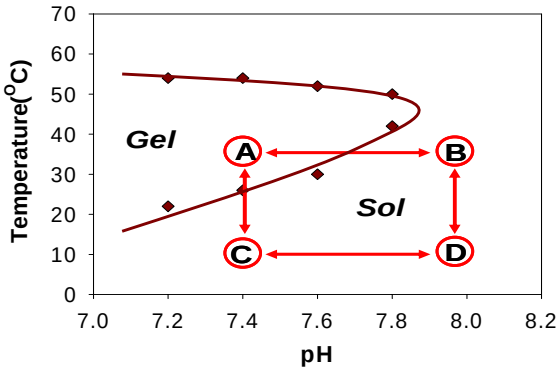


Fig. 2: The sol-gel phase diagram of OSM-PCLA-PEG-PCLA-OSM block copolymer hydrogels.

Figure 2 shows the sol-gel phase diagram of OSM-PCLA-PEG-PCLA-OSM(sulfamethazine oligomer-poly(ε-caprolactone-co-lactide)-poly(ethylene glycol)-poly(ε-caprolactone-co-lactide)sulfamethazine oligomer) block copolymers hydrogels. As can be seen in Figure, we can show the sol-to-gel transition behavior to not only temperature change but also pH change around the body condition(37°C, pH 7.4)(**A**). With increasing pH in the body condition, these block copolymer hydrogels was not formed(**B**) due to the ionization of OSM pH-sensitive moiety in high pH region. The sol-gel phase diagram of these hydrogels was modified by the controlling of PEG length, the ratio of hydrophobic block to hydrophilic block(PCLA/PEG ratio), and molecular weight of sulfamethazine oligomer. As the pH and temperature sensitive hydrogel cannot form the gel only by the temperature change, it can be employed as an injectable carrier using a long guide catheter into the body. Also, the pH of hydrogel was not changed by degradation of PCLA block for one month, and the gel was not collapsed by adding of buffer solution. These hydrogel properties ase possible to be used as an injectable carrier for some protein drug denatured by low pH environment.

On the other hand, we also investigated the possibility as an injectable carrier of the pH-sensitive polymeric micelle of MePEG-poly(β-amino ester) block copolymer. As we known, Micelle is formed in aqueous solution by the balance of hydrophilic and hydrophobic part. Therefore, here the MePEG block is acted as hydrophilic part and poly(β-amino ester) block had a role of hydrophobic as well as hydrophilic part with pH.

Figure 3 shows the pH variation of the

micelle formation of the MePEG-poly(β-amino ester) block copolymer measured by Fluorescence spectrometry.

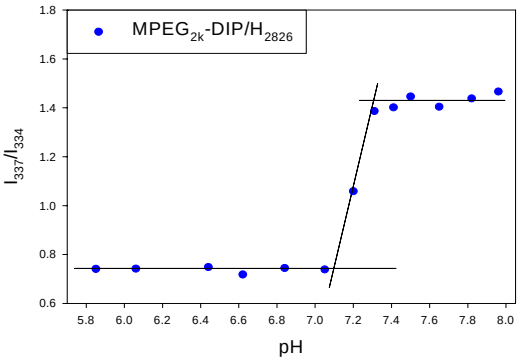


Fig. 3: pH variation of the micelle formation of the Me PEG-poly(β-amino ester) block copolymer measured by Fluorescence spectrometry.

As can be seen in Figure, the MePEG-poly(β-amino ester) block copolymer micelle is formed at high pH region(pH 7.4) and collapsed at low pH region(below pH7.0). That means the poly(β-amino ester) block becomes strong hydrophobic part at high pH region due to the deionization of poly(β-amino ester) block, while it is ionized at low pH region [3] and then the drugs can be released due to the demicellization. Therefore, these micelles may be applicable to target drug delivery and for diagnostic imaging as well as other potential applications.

REFERENCES

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