# Injectable Polyphosphazene gels for the Local Drug Delivery

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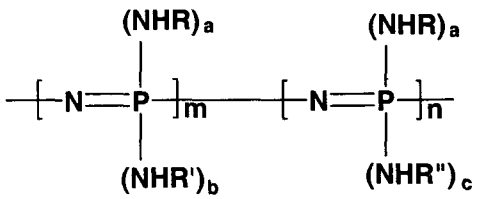
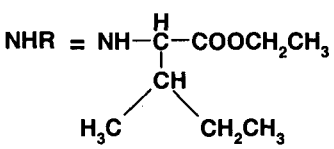
Thermosensitive polymers with a lower critical solution temperature (LCST) near or below body temperature are of great interest for biomedical applications such as local drug delivery and body temperature sensitive drug release. The advantages of thermosensitive polymers for drug delivery materials have been explained in terms of local delivery and controlled release of drugs. The phenomenon of LCST has been observed mainly in some water soluble homo- or copolymers of poly(ethylene glycol) and poly(propylene glycol), poly(vinyl alcohol) derivatives, and poly(N-substituted acrylamides). However, when these polymers are considered as materials for biomedical applications, they have shortcomings such as nondegradability and toxicity. Furthermore, molecular design to control the hydrophilic/hydrophobic balance for a desired LCST is difficult for these conventional polymers. In addition, the LCST of conventional thermosensitive polymers could not be designed precisely and reproducibly according to the desired purpose since they are polydisperse and not easy to control the composition of the hydrophilic and hydrophobic groups.

We have studied biodegradable thermosensitive poly(organophosphazenes) and cyclotriphosphazenes and have recently reported that some polyphosphazenes with α-amino-ω-methyl-PEG (AMPEG) and isoleucine ethyl ester (IleOEt) have thermo-thickening properties.

In this study, we discuss thermosensitive properties and application of these poly(organophosphazenes) as drug carriers.

Thermosensitive poly(organophosphazenes) bearing α-amino-ω-methyl-poly(ethylene glycol) (AMPEG), some hydrophobic amino acid esters, and a depsipeptide ethyl ester (ethyl-2-




(IleOEt)

NHR" = NH—CH2—COCHCH3COOCH2CH3

(GlyLacOEt)

NHR' = NHCH2CH2(OCH2CH2)10OCH3

(AMPEG550)

(*O*-glycyl)lactate) as a hydrolysis sensitive moiety have been synthesized. Most of the poly (organophosphazenes) synthesized showed sol-gel transition properties in an aqueous solution. In an aqueous solution, the poly(organophosphazenes) exhibited 4-phase transitions with temperature gradually increasing: a transparent sol, a transparent gel, an opaque gel and a turbid sol. The gelation properties of the polymers were affected by several factors such as the composition of substituents, the chain length of AMPEG, the concentration of the polymer solutions and types of amino acid esters. The more hydrophilic composition of the polymers offers higher gelation temperature. The gelation of the polymers is presumed to be attributed to the hydrophobic interaction between the side chain fragments of amino acid esters which act as the physical junction in the polymer aqueous solution.

The poly(organophosphazenes) obtained were hydrolytically degradable. Depsipeptide ethyl esters in the polymers accelerated the degradation of the polymers in an aqueous solution and change of their LCSTs. The degradation rate was also influenced by the pH of the polymer solutions and increased in the order of pH 10 < pH 7.4 < pH 5. Most polymers had half-lives of below 15 days in a neutral solution. The LCSTs of the polymers increased with the degradation of the polymers in an aqueous solution.

The aqueous solutions of the present polymers were injected subcutaneously into rats, which resulted in immediate gelation. The biocompatibility testing of the polymers has showed the minimum or mild tissue reaction in rats.

In vitro release behavior of albumin and doxorubicin from the polymer gels were examined. The anticancer agent, doxorubicin, loaded easily in the polymers at low temperature was released over a month from the polymer gels in a controlled rate. These gels will be expected to be useful for local delivery of protein and anticancer drugs.