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Thermo-sensitive Polymers for Controlled-release Drug Delivery Systems

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Abstract: In recent years, thermo-sensitive polymer as a novel carrier for controlled-release drug delivery systems has been widely concerned by researchers. With respect to thermo-sensitive polymer, Researchers study on its properties in controlled-release drug delivery systems, such as biodegradation, biocompatibility, Lower Critical Solution Temperature (LCST), biotoxicity, etc. In this study, we mainly review the characteristics of thermo-sensitive polymer, its present research state and further study tendency.

Key words: Thermo-sensitive polymer, drug delivery systems, biocompatibility, lower critical solution temperature

INTRODUCTION

Over the past several decades increasing attention has focused on designing new drug dosage forms in order to increase the effectiveness and decrease the side effect of existing medications. As the meaning of 'drug delivery' expands to the targeting drug at the proper time or the proper site, stimuli-sensitive drug delivery (Sahoo *et al*., 1998; Ganorkar *et al*., 1999; Sinha and Kumria, 2001; Qiu and Park, 2001; Miyata *et al*., 2002; Murdan, 2003; Kopecek, 2003) has been required depending on changes in physiological signals in the body.

Body temperature often deviates from normal temperature (37°C) owing to the presence of pathogens or pyrogens. This temperature change may be a useful stimulus that can modulate the delivery of therapeutic drugs for diseases with accompanying fever. In addition, temperature can also be easily controlled by manpower in the human body. Therefore, extensive research has been performed in the design of temperature-sensitive drug delivery systems (Bae *et al*., 1987; Hayashi *et al*., 1996; Chacona *et al*., 2000; Kim *et al*., 2000; Makino *et al*., 2001; Hsiue *et al*., 2002; Eeckman *et al*., 2003; Cohn *et al*., 2003; Fujimori *et al*., 2005; Zhang *et al*., 2005). Among them, the use of thermo-sensitive polymers has been successfully carried out. With these polymers, it is possible to administer the formulation as a solution, which undergo a temperature-induced reversible gel-sol transition upon heating or cooling of the aqueous solution.

Aqueous solutions of thermo-sensitive polymers show an inverse dissolution behavior, their phase diagrams presenting a Lower Critical Solution Temperature (LCST). The solutions are homogenous at low temperature and a phase separation appears when the temperature exceeds a critical value called the cloud point. The LCST is the lowest cloud point of the system; i.e. the minimum of the phase diagram. The polymers solutions are regular at temperatures below the LCST. However, when the temperature is raised above the LCST, polymer chains that swelled previously could contract and result in phase separation.

Thermo-sensitive polymers, also called intelligent polymers, have met with an increasing interest, particularly in the field of controlled-release drug delivery systems (Hayashi *et al*., 1996; Kim *et al*., 2000; Hsiue *et al*., 2002; Cohn *et al*., 2003; He *et al*., 2004; Eeckman *et al*., 2004; Fujimori *et al*., 2005; Lin *et al*., 2005; Na *et al*., 2006), based on their intelligent and reversible behavior in response to temperature variation. By utilizing thermo-sensitive polymers, a temperature-controlled on-off drug delivery system could be achieved. At present these thermo-sensitive polymers mainly include PNIPAAm, PEO-PPO-PEO, PEG-PLGA-PEG, PMPA, PNVCL, EPG and PLGA-PEG-PLGA.

UNDERLYING REQUIREMENTS OF THERMO-SENSITIVE POLYMERS IN CONTROLLED-RELEASE DRUG DELIVERY SYSTEMS

All thermo-sensitive polymers intended for controlled-release drug delivery systems in contact with

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living systems must meet certain criteria and regulatory requirements. The minimum requirements include the following: firstly, the mechanical and physical properties of these polymers, such as strength, elasticity, durability, etc., must be appropriate for the intended application; secondly, these polymers must be biodegradable, biocompatible and nontoxic and the significant one is that Lower Critical Solution Temperature (LCST) of these polymers should around the normal body temperature (37°C).

SOME DOMINANT THERMO-SENSITIVE POLYMERS

Poly (N-isopropylacrylamide) (PNIPAAm): Poly (N-isopropylacrylamide) (PNIPAAm), a typical thermo-sensitive polymer, has been widely studied, chiefly because of its phase transition, which occurs at about 32-37°C (Heskins *et al*., 1968; Boutris *et al*., 1997; Eeckman *et al*., 2003; Erbil *et al*., 2004; Kuckling *et al*., 2004; Gao *et al*., 2006), thus near the ambient temperature. Aqueous solutions of PNIPAAm exhibit a phase separation phenomenon, showing a very rapid and reversible hydration-dehydration process in response to small temperature changes. At temperatures below the LCST, PNIPAM chains are hydrated and expanded random-coil conformations in water. Above the LCST, PNIPAM chains become dehydrated and collapse into tightly packed globular conformation. That effect is due to the dual character of PNIPAAm whose structure contains both a hydrophobic isopropylic group and a hydrophilic amide group.

Moreover, the LCST of PNIPAAm aqueous solutions can be easily modified by copolymerization (Cheon *et al*., 1999; Masci *et al*., 2002; Zhu *et al*., 2002; Eeckman *et al*., 2004; Hirata *et al*., 2004; Guilherme *et al*., 2004; Gao *et al*., 2005; Zhao *et al*., 2005) or by addition of salts (Eeckman *et al*., 2002; Gao *et al*., 2006) or surfactants (Eeckman *et al*., 2003). That interesting feature makes almost every desired LCST value available.

Up to now, great interest has focused on the study of PNIPAAm, however, the toxicity of PNIPAAm in the body is unknown and one great limitation of it is the lack of compatibility with cells and blood, thus its application in drug delivery systems may be extremely restricted.

PEO-PPO-PEO: Poly (ethylene oxide-b-propylene oxide-b-ethylene oxide) (PEO-PPO-PEO), which consists of at least two blocks with different affinities, i.e., hydrophilic and hydrophobic has been widely studied for pharmaceutical and biomedical applications (Gaisford *et al*., 1998; Ivanova *et al*., 2001; Su *et al*., 2002; Liu *et al*., 2003; Sosnik and Cohn, 2004; Wang *et al*., 2005). Its aqueous solution undergoes phase transitions from sol to gel at 5-30°C and gel to sol at 35-50°C. Due to their amphiphilic character, the PEO-PPO-PEO block copolymers exhibit the unique property of amphiphiles in general to self-organize in supermolecular structure in solutions or at interfaces. These polymers, which are often referred to by the trade name Plutonic, are water-soluble and exhibit low toxicity. Because of low toxicity, they also have specialized applications in drug- controlled release (Liaw and Lin, 2000; He *et al*., 2004).

Pluronic® F127 is an important member of the family of triblock copolymers of PEO-PPO-PEO. It exhibits thermo-reversible gelation and has therefore generated considerable interest as a novel method for controlled-release drug delivery (Bohorquez *et al*., 1999; Scherlund *et al*., 2000; Desai *et al*., 2001; Matthew *et al*., 2002; Sharma and Bhatia, 2004). Pluronic® drug delivery applications often rely on a transition from liquid to gel occurring at a specific temperature. Aqueous F127 solutions display a liquid-to-gel transition at physiological temperatures; this is referred to as the gelation transition or the lower gel phase boundary. At higher temperatures the systems liquefy again and refer to as the gel-to-liquid transition, degelation, or the upper gel phase boundary. Both transitions can be influenced by the presence of hydrophobic drug solutes in the formulation. It is worthwhile to indicate that Pluronic has been approved by FDA as biomaterials used in human body.

However, because of the dissolution of micelle in aqueous solution, the integrity of PEO-PPO-PEO can only maintain a short time. thus, PEO-PPO-PEO is not applicable for sustained drug delivery.

PEG-PLGA-PEG: A thermo-sensitive triblock copolymer poly (ethylene glycol-b-(DL-lactic acid-co-glycolic acid)-b-ethylene glycol) (PEG-PLGA-PEG) has been widely researched over the past few years (Anderson and Shive, 1997; Jeong *et al*., 1999a, 2000b; Lee *et al*., 2006). With monotonically increasing temperature, its aqueous solutions undergoes sol to gel transition (lower transition) in the range of 30-35°C and gel to sol transition (upper transition) in the range of 40-70°C. The transition temperatures depend on the concentration of polymers. Between the two transitions, a gel phase exists. In particular, the sol to gel transition temperature and their degradability could make this system ideal for an injectable drug delivery system that can be formulated at room temperature which forms a gel at body temperature.

In addition to biodegradability of the polymers, the *in situ* formed gel maintains its integrity for more than 1 month in rats (Jeong *et al*., 2000a), while the known gelling polymer, Poloxamer, is not biodegradable and the

formed gel is dissolved in a few zhidays at most. Therefore, the PEG-PLGA-PEG system is applicable for injectable long-term drug delivery (Jeong *et al*., 1999b; Jeong *et al*., 2000b; Kan *et al*., 2005).

Poly (methyl 2-propionamidoacrylate) (PMPA): A thermo-sensitive polymer, poly (methyl 2-propionamidoacrylate) (PMPA) was reported, (Okamura *et al*., 2002), which has two substituted group at |α-carbon of each monomer unit. Each of the two groups consists of hydrophilic (ester and amide bonds) and hydrophobic moieties (methyl and ethyl groups) in a suitable balance.

It was found that PMPA shows the Lower Critical Solution Temperature (LCST) at 50.6°C sharply. The LCST of PMPA was almost independent of the polymer concentration above 40 g L^{-1}, while, below 40 g L^{-1}, it decreased with the increasing polymer concentration.

The effect of salt addition (NaCl, NaBr and Na_2O_4) on the LCST was also studied. The LCST of PMPA linearly decreased with the increasing concentration of each salt. In addition, it was found that the dependence of LCST on the salt concentration is related to the hydrophilicity of polymers; therefore, we can get almost every desired LCST value available around body temperature.

However, few have been reported about the toxicity, biodegradation and biocompatibility of the thermo-sensitive polymer.

Poly (N-vinylcaprolactam) (PNVCL): Recently, there has been much interest in the thermo-sensitive polymer Poly (N-vinylcaprolactam)(PNVCL) (Mamytbekov *et al*., 1999; Lozinsky *et al*., 2000; Makhaeva *et al*., 2000; Chen *et al*., 2002; Boyko *et al*., 2003; Vihola *et al*., 2005), which stands out based on the fact that it is not only nonionic, water-soluble, nontoxic and thermo-sensitive but also biocompatible. If the amide bond in the side group is hydrolysed in harsh strongly acidic conditions, a polymeric carboxylic acid builds up. Moreover, the LCST of PNVCL is in the range of physiological temperature (32-34°C). These properties make PNVCL suitable for use in some biotechnology, especially in drug delivery system (Vihola *et al*., 2002).

Considering the high biocompatible of PNVCL, it might be a novel thermo-sensitive polymer as a carrier for controlled-release drug delivery system.

Eudragit RS and PEG 400 blend polymers (EPG): The Eudragit RS and polyethylene glycol 400 (PEG 400) blend polymer (EPG), a novel thermo-sensitive polymer, was researched (Fujimorie *et al*., 2005) by the solvent casting method. The EPG membranes containing 2.5-10% PEG 400 (2.5-10%EPG) show the lower critical solution temperature (LCST) around the body temperature (32-42°C). In the water uptake study for the 10% EPG membrane, the degree of the swelling for the membrane tended to increase with increasing temperature above the LCST of the membrane and the thermo-sensitive permeation mechanism for the EPG membranes may be based on the structure change of the membranes caused by the phase transition.

Because of the high biological safety of Eudragit RS and PEG 400 and the LCST of its aqueous solutions can be easily modified by modulating the proportion of Eudragit RS and PEG 400 (Fig. 1), so we can make almost every desired LCST value available, the EPG membranes might be used to develop a novel thermo-sensitive drug delivery system.

PLGA-PEG-PLGA: Chen *et al*. (2005) synthesized a novel thermo-sensitive triblock polymer (PLGA-PEG-PLGA) by ring-opening polymerization of D,L-lactide and glycolide with polyethylene glycol (PEG) in the presence of stannous octoate. Different phase diagrams can be achieved depending on the block length and the copolymer concentration (Zentner *et al*., 2001). By adjusting the PLGA-PEG-PLGA triblock copolymer compositions and concentrations, thermo-sensitive polymer delivery systems may be used for controlled-release drug delivery systems for an extended period of time.

Due to high biodegradation and biocompatibility (Anderson and Shive, 1997) of PLGA-PEG-PLGA and the LCST of its aqueous solutions is around the body normal temperature (37°C) (Fig. 2). Thus, the biodegradable thermal thermo-sensitive polymer holds high potential as injectable, long-term drug delivery systems.

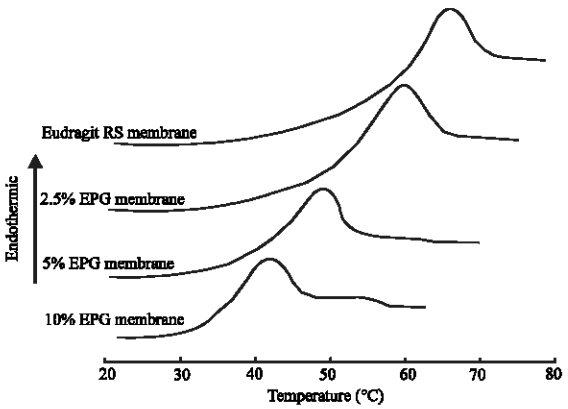
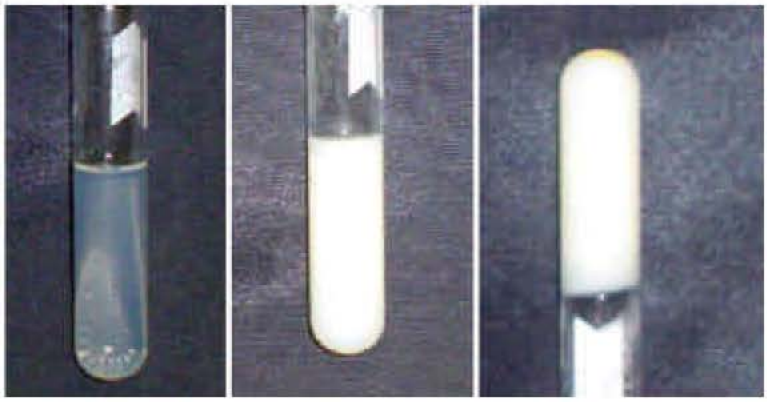


Fig. 1: DSC curves of Eudragit RS membrane and various membranes prepared by Eudragit RS-PEG 400 blend polymer (EPG). Heating rate, 20°C/min (Fujimorie *et al*., 2005)



(a) (b)

Fig. 2: Sol-gel transition of PLGA-PEG-PLGA triblock copolymers at different temperatures. (a) At room temperature or below (≤25 °C) and (b) at body temperature (37 °C) (Chen *et al*., 2005)

Table 1: Characteristics of these seven thermo-sensitive polymers

	Biocompatibility	Biodegradation	Biotoxicity	LCST(°C)
PNIPAAm	Lack	High	Unknown	32-37
PEO-PPO-PEO	Unknown	High	Low	5-30
PEG-PLGA-PEG	High	High	Unknown	30-35
PMPA	Unknown	Unknown	Unknown	50.6
PNVCL	High	High	Low	32-34
EPG	High	Unknown	Low	32-42
PLGA-PEG-PLGA	High	High	Unknown	37

CONCLUSION AND FUTURE PERSPECTIVES

In contrast to the conventional thermo-sensitive polymers, they have to overcome some limitations (Table 1), such as lack of biocompatibility and biodegradation, biotoxicity, lower critical solution temperature (LCST) besides the body temperature and a broad thermo-sensitive range. In addition, thermo-sensitive polymers offer a new attractive carrier for drug delivery systems: a temperature-controlled on-off drug delivery system. Indeed, their performance has still to be improved. Also, their behaviors in the body and their toxicity have to be clarified. However, rational design of thermo-sensitive polymer may lead to a new technology, which achieves accurate controlled-release drug delivery.

Although many researchers have done much about the biological effect of these thermo-sensitive polymers, the knowledge about them is superficial. Because we should develop a new drug delivery concept making thermo-sensitive polymers suitable for an effective application *in vivo*, which seems quite difficult to be achieved by classical means. Moreover, the object aimed at requires that the LCST of the thermo-sensitive polymer should be around the body normal temperature (37 °C), which is also difficult to be achieved. It is a procedure with mutually linked and relatively independent phases. It needs co-research of more disciplines, such as polymer science, engineering, pharmaceutics, biochemistry and molecular biology.

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