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*Review Article*

# The Application of Thermosensitive Nanocarriers in Controlled Drug Delivery

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Thermosensitive nanocarriers as the "smart" drug delivery systems have shown tremendous promise in the field of controlled drug delivery due to their special property. Thermosensitive nanocarriers with long circulation properties can accumulate in the pathological sites by enhanced permeability and retention (EPR) effect or attach targeting ligands to the surface of the nanocarriers, and the drug release rates of these pharmaceutical nanocarriers can be adjusted in response to thermal variability of the environment. In this paper, we first discuss the classification of thermosensitive polymer according to their functional properties in thermosensitive nanocarriers. On the basis of this, our main purposes are focused on reviewing the characteristics of various thermosensitive nanocarriers including the strategies for their functionalization, thermosensitive behavior, or site-specific targeting. Furthermore, the paper discusses the current and future trends of the thermosensitive nanocarriers in controlled drug delivery.

## 1. Introduction

Due to the obvious properties of enhancing the efficiency of drugs in vivo, pharmaceutical nanocarriers including micelles, hydrogels, liposomes, and dendrimers (Figure 1) have been paid much attention in drug delivery system (DDS) [1–5]. Their obvious properties can be classified into two aspects: the nature properties of pharmaceutical nanocarriers, such as solubility, stability in vivo, and biodistribution [6]; the additional properties of pharmaceutical nanocarriers, such as longevity in the blood, passive or active targeting to the pathological sites, and responsiveness to local change in environmental conditions.

Differing from the nature properties of pharmaceutical nanocarriers, the additional properties of pharmaceutical nanocarriers can improve the efficiency of carried drugs not only by the nanometer region of the carriers but also by the artificiality of nanocarriers. The pharmaceutical nanocarriers as foreign particles are always opsonized and easily eliminated by mononuclear phagocytic system (MPS) before they accumulate in pathological sites through the circulatory. So long circulation is the primitive property of pharmaceutical nanocarriers, and the essential property for passive or active targeting and environmental responsibility of pharmaceutical nanocarriers [11]. Modifying certain polymers to the surface of pharmaceutical nanocarriers through physical adsorption or chemical grafting is the most effective way to increase the circulation time of pharmaceutical nanocarriers in vivo. The modified polymers should possess a well-solvated and flexible, immunogenic, and antigenic polymer chain, such as poly(ethylene glycol) (PEG) or poly(ethylene oxide) (PEO). The pharmaceutical nanocarriers with the property of long circulation can accumulate in the required pathological sites by passive or active targeting nanocarrier-based delivery systems. Passively-targeted nanocarriers are based on the properties of nanocarriers (such as size distribution and surface charge) and the disease pathology in order to spontaneously accumulate the nanocarriers in the pathological sites. Because of the high permeability of the vasculature and lack of lymphatic drainage in tumors and infarcted areas, the long-circulating pharmaceutical nanocarriers, whose size ranges from 10 to 500 nm, can spontaneously accumulate in there by the EPR effect [12]. The actively targeted ability of long-circulating

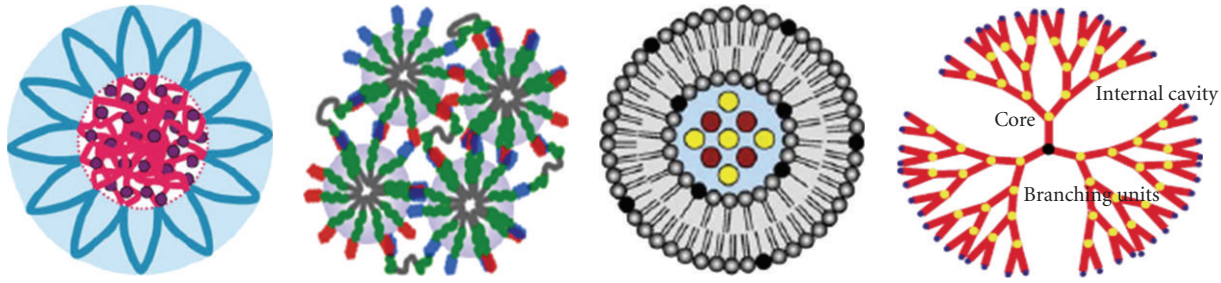


Figure 1: Examples of thermosensitive nanocarriers (adapted from [7–10]).

pharmaceutical nanocarriers relies on attaching specific ligands (such as antibodies and peptides) to the nanocarriers surface that will be recognized by the cells presenting at the required pathological sites [13, 14]. Figure 2 shows the potential application of the pharmaceutical nanocarriers for site-targeted drug delivery.

Environmental drug delivery system responding to different conditions, such as temperature, pH, magnetic field, electric field, ultrasound, and so forth, has gained a great attention for controlled drug delivery [15–19]. Temperature is a typical example of "triggers" at the diseased site that could be exploited with nanocarriers. In fact, it would be most desirable if the drugs could be efficiently administered in a manner that precisely matches physiological needs at the proper sites and at proper times [20]. Nanocarriers with long circulation and thermosensitive properties offer a promising way to achieve these [7, 9, 21]. Firstly, because the thermosensitive nanocarriers specially accumulate in the required sites through passive or active targeting, the distribution of the carried drugs is efficiently controlled, and the side effects and waste of drugs are remarkablly limited. Moreover, when the nanocarriers reach the maximum acculturation in the required sites, the carried drugs are sustained released in response to changes in environmental temperature. With greater understanding of the difference between normal and pathological tissues and parallel advances of material design, there is a highly promising role of thermosensitive nanocarriers for controlled drug delivery in the future.

In this paper, we first discuss the functional properties of thermosensitive polymers in nanocarriers and classify thermosensitive polymers with a new perspective. Moreover, we describe the specific forms of thermosensitive nanocarriers in detail and discuss their characteristics of thermosensitive behavior and site-specific targeting.

## 2. Functional Properties of Thermosensitive Polymers in Thermosensitive Nanocarriers

In modern drug delivery technology, the status of thermosensitive nanocarriers is not only as traditional nanocarriers to increase stability and solubility or reduce immunogenicity and toxicity of carried drugs but also as functional nanocarriers to improve circulation time, passive target-specific delivery, and sustained release of drugs [22–24]. By introducing thermosensitive polymers to prepare thermosensitive nanocarrier systems, these thermosensitive nanocarriers possess the ability of active response to the thermal changes of external environment [25].

The thermosensitive polymers can response to changes in temperature of the external environment, which results in the large change of its interesting features such as conformation, solubility,and hydrophilic/hydrophobic balance. These features are generally quantitatively described by the lower critical solution temperature (LCST). Thermosensitive polymer aqueous solution exhibits LCST phenomenon, below which polymer solution has one phase and above which they are phase-separated as a result of collapse and aggregation of polymer chains and expelled water [26]. It has to be noted that LCST is affected by the ratio of hydrophilic and hydrophobic monomers in thermosensitive polymers.

Dozens of reviews have classified thermosensitive polymers from the aspect of thermosensitive mechanism of polymers (polymers based on LCST and polymers based on amphiphilic balance) or composition of polymers (biopolymers with nature temperature responsive behavior and synthetic thermosensitive polymers) [27]. In order to discuss the functional properties of thermosensitive polymers in thermosensitive nanocarriers, we classified the thermosensitive polymers into two subclasses (Table 1). (a) Thermosensitive polymers as modified compounds endue nanocarriers with temperature responsive behavior [28–30]. The representative thermosensitive polymer of this type is Poly(N-isopropyl acrylamide) (PIPAAm) [31–33]. The LCST of PIPAAm is 31–32.8°C, above which it undergoes a reversible phase transition as a result of the coil-to-globule transition. Designed at the molecular level, the LCST of PIPAAm can be adjusted to around the physiological temperature of 37°C by introducing a hydrophilic comonomer, such as dimethylacrylamide (DMAAm) or acrylic acid (AAc). PIPAAm as modified compounds generally endue nanocarriers with temperature responsive behavior, such as micelles, liposomes, and solid nanocarriers. (b) Thermosensitive polymers as the main components of the nanocarrieres. In general, the structures of these thermosensitive polymers have two subcategories

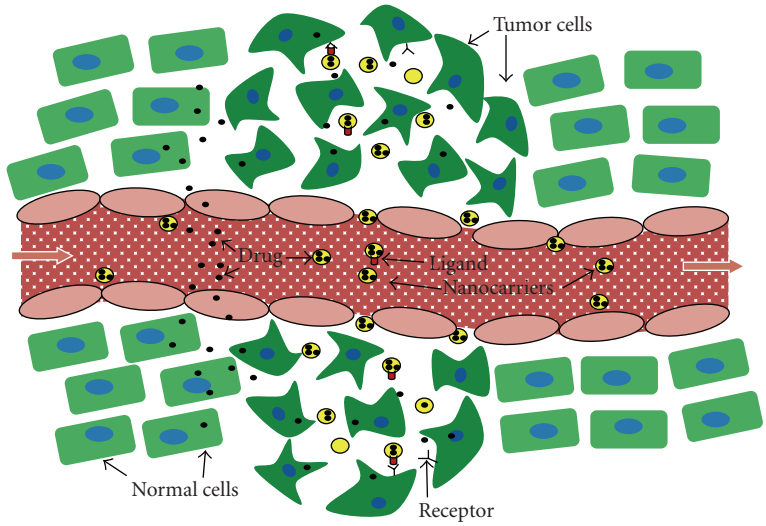


Figure 2: Schematic of nanocarriers for site-targeted drug delivery.

including linear structure and dendritic or heteroarm star structure [34, 35]. Amphiphilic block copolymers with AB type or ABA type are the well-known linear thermosensitive polymers, whose thermosensitive behavior is adjusted by shifting the hydrophilic/hydrophobic balance in its backbone [36–39]. Representatively, the poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) triblock copolymer, known as Pluronic or Poloxamer, has been applied in controlled drug delivery due to its properties of temperature responsive micellization and gelation [40]. Differing from linear structure, the thermosensitive dendronized polymers undergo a sharper transition than linear thermosensitive polymers because their highly branched structure yields a small transition enthalpy in the phase transition process [41].

Though PIPAAm has been extensively studied for controlled drug delivery, its biomedical applications have been limited by some drawbacks such as possible presence of monomeric acrylamide-based residues (neurotoxin) and low biodegradability [42]. The similar drawbacks have also puzzled Poloxamers. Pluronics have poor biodegradability and have been found to induce hyperlipidemia and increase the plasma level of cholesterol in rabbits and rats [43]. In order to solve the above problems, a series of amphiphilic biodegradable block copolymers were synthesized by introducing a variety of biodegradable components such as poly(L-lactic acid) (PLLA) [44], poly(3-carprolactone) (PCL) [45, 46], and PHB [47, 48] into the Pluronics copolymer backbone for enhancing the biodegradability of the thermosensitive polymers.

## 3. Different Thermosensitive Nanocarrier Systems

*3.1. Thermosensitive Micelles.* As known, amphiphilic block copolymers consisting of hydrophobic and hydrophilic blocks tend to form micelles in aqueous solution to reduce free energy mainly depending on hydrophobic interactions [49]. Due to the hydrophobic interactions among the hydrophilic segments of amphiphilic block copolymers, polymeric micelles which possess typical shell-core structure are self-assembled with the size ranging from 10 to 60 nm in aqueous solution (Figure 1(a)). The willowy hydrophilic shell cannot only provide a stabile structure of micelle but also escape from renal exclusion and the reticuloendothelial system. The hydrophobic core, meanwhile, can be used to solubilize hydrophobic drugs and protect the drug in the core from external interference. The critical micelles concentration (CMC) of polymeric micelles is much lower than that of surface acting agent. It means that micelles can spontaneously assemble very easily in the water at a low concentration of polymer. The nanograde size also enhances vascular permeability of micelles [50], especially at the solid tumor site. Therefore, the micelles were researched widely as nanocarriers for genes [51, 52], imaging agents [53, 54], and kinds of anticancer drugs [55–58].

Due to the different triggered parts of amphiphilic block copolymers, thermosensitive polymeric micelles can be categorized into two types (Table 2): polymeric micelles with thermosensitive outer shell and polymeric micelles with thermosensitive inner core. For the former type (Figure 3(a)), as their name implies, the thermosensitive character is possessed by the thermosensitive outer shells of the polymeric micelles. When the external environment temperature is above the phase transition temperature, the structure of polymeric micelles becomes instable and the carried drugs releases from the core, which result from the shrink and hydrophobicity of thermosensitive outer shell [64, 65]. Teruo Okano and other groups prepared the former type of thermosensitive polymeric micelles, which were composed of thermosensitive PIPAAm blocks or P(IPAAm-co-DMAAm) blocks as the outer hydrophilic shell and hydrophobic PLA blocks or PBMA blocks as the drug-incorporated inner core [66, 67]. PIPAAm is the most widely used thermosensitive

Table 1: Classification of thermosensitive polymers from the aspect of their function in thermosensitive nanocarriers.

| The type of thermosensitive polymer | Representative thermosensitive polymer | LCST (°C) | Application | References |
|---|---|---|---|---|
| As the modified compounds of thermosensitive nanocarriers | PIPAAm | 31–32.8 | Modifying polymeric micelles | [31] |
| | | | Modifying dendrimers | [32] |
| | | | Modifying liposomes | [33] |
| | poly(EOEOVE) | 40–45 | Modifying liposomes | [28] |
| | PDMA | 31–35 | Modifying dendrimers | [29] |
| | P(IPAAm-co-DMAAm) | 37–42.5 | Modifying polymeric micelles | [30] |
| As the main component part of the thermosensitive nanocarriers | PIPAAm-co-PCIPAAm | 32–37 | Thermosensitive hydrogels | [34] |
| | PEO-PPO-PEO | 5–30 | Thermosensitive hydrogels | [40] |
| | (DM-b-CD)-PEG-PPG | 37 | Thermosensitive hydrogels | [36] |
| | PIPAAm-PBMA | 32.5 | Thermosensitive micelles | [37] |
| | PIPAAm-PHB-PIPAAm | 28–29 | Thermosensitive micelles | [38] |
| | PLGA-PEG-PLGA | 37 | Thermosensitive micelles | [39] |
| | Biaryl-based G3 dendrons with pentaethylene glycol and decyl chain | 32–42 | Thermosensitive dendrimers | [35] |

Poly(EVEOVE): poly(2-ethoxy) ethoxyethyl vinyl ether (EOEOVE); PDMA: poly(N,N-dimethylaminoethyl methacrylate); P(IPAAm-co-DMAAm): poly(N-isopropylacrylamide-co-N,N-dimethylacrylamide); PCIPAAm: poly(2-carboxyisopropylacrylamide); PEO: poly(ethylene oxide); PPO: poly(propylene oxide); DM-b-CD: heptakis (2,6-di-Omethyl)-b-cyclodextrin; PHB: Poly[(R)-3-hydroxybutyrate]; PLGA: poly(DL-lactic acid-co-glycolic acid).

polymer because of its phase transition temperature near the physiological temperature, and its phase transition temperature can be adjusted by introducing hydrophilic segments [68, 69]. In order to sharpen thermoresponsiveness and obtain biodegradable properties of copolymers, they used PLA block instead of PBMA block [31]. In contrast with the former one, the latter type (Figure 3(b)) consists of hydrophobic blocks as the core played thermosensitive properties, such as acryloxy succinimide, pHPMAmDL, and HPMAm-Lacn. Once the environment temperature is above the LCST, the thermosensitive polymeric micelles are gradually destabilized due to hydrolysis of hydrophobic blocks [70]. Hennink and colleagues [61] prepared thermosensitive polymeric micelles consisting of pHPMAmDL-b-PEG block copolymers and investigated its drug release behaviors and cytotoxicity of the polymeric micellar formulation of loaded PTX in vitro. Through the polymerization of methacrylate groups and UV illumination, Rijcken and colleagues [62] prepared core cross-linked thermosensitive polymeric micelles with excellent physical stability and increased their accumulation at tumor sites.

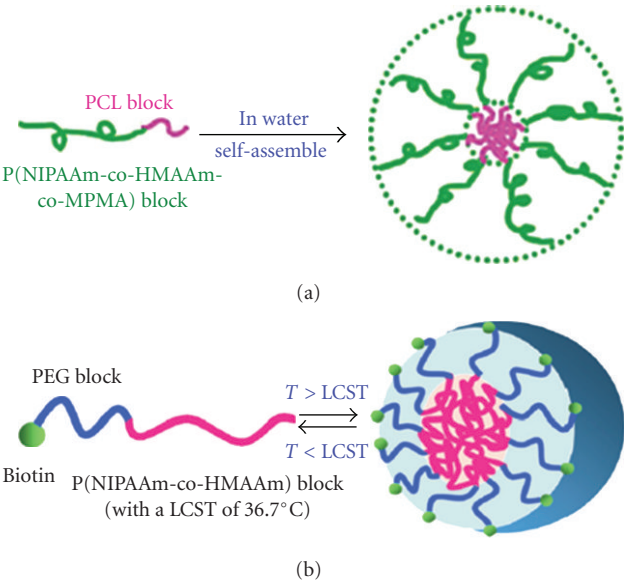


Figure 3: Schematic of the two types of thermosensitive micelles (adapted from [56, 71]).

To date, there are mainly two routes to achieve targeting drug delivery for the thermosensitive micelles. Firstly, micelles can accumulate passively in tumor site better than normal tissues, due to the EPR effect of vascular endothelia at the tumor tissues. Once circulating to tumor tissues where environmental temperature is above the LCST, the outer shells of these micelles will become hydrophobic and the apparent size of micelles increases through their aggregation. Thus, micelles may be selectively retained at these sites, resulting in the enhancement of drug efficiency by increasing its release at the target area [71]. In addition, the research [37, 68] demonstrated that dehydrated shell of micelles above the LCST can be uptaken by cells more easily than micelles below the LCST (Figure 4). A novel thermosensitive copolymer poly(N-isopropylacrylamide-co-acrylamide)-b-poly(DL-lactide) was synthesized for docetaxel carrier [72]. A significantly higher antitumor efficacy was observed in mice treated with docetaxel-loaded micelles

Table 2: Thermosensitive micelles for the drug delivery.

| Type of thermosensitive micelles | Composition of thermosensitive micelles | Encapsulated drug | LCST (°C) | Therapeutic outcome | References |
|---|---|---|---|---|---|
| Thermo-responsive shell | PBMA -PIPAAm | ADR | 32.5 | Thermoresponsive release by the changes of the LCST | [37] |
| | PDLLA a-P(IPAAm-co-DMAAm) | ADR | 37–42.5 | Control of ADR cytotoxic activity by temperature and effective target therapy | [30] |
| | PCL-PIPAAm | CNZ | 29.5–35.2 | Showed enhanced sustained drug release | [59] |
| | PCL-PIPAAm-PCL | PA | 35.8–36.2 | Showed enhanced thermosensitive controlled release behaviors | [7] |
| | PLGA-P (IPAAm-co-DMAAm) | DOX | 37–39.5 | Effective nuclei therapy and greater cytotoxicity above the LCST | [60] |
| Thermo-responsive core | P(IPAAm-co-HMAAm)-biotin-PEG | MTX | 41 | About 90% of the drug is released from the micelles in 96 h at 37°C | [56] |
| | pHPMAmDL-b-PEG | PTX | 10–65 | 70% of PTX is released in 20 h at 37°C | [61] |
| | p(HEMAm-Lacn)-b-mPEG | — | 0–37.5 | A superior circulation profile and enhanced thermosensitive controlled release behaviors | [62, 63] |

PBMA: poly(butylmethacrylate); PDLLA: poly(D,L-lactide); PCL: poly($\varepsilon$-caprolactone); P(NIPAAm-co-HMAAm): poly(N-isopropylacrylamide-co-N-hydroxymethylacrylamide); ADR: adriamycin; pHPMAmDL: poly(N-(2-hydroxypropyl) methacrylamide lactate); PA: prednisone acetate; p(HEMAm-Lacn): poly(N-(2-hydroxyethyl)methacrylamide)-oligolactates); CNZ: clonazepam; DOX: doxorubicin; MTX: methotrexate; PTX: paclitaxel.

accompanied by hyperthermia compared with the conventional docetaxel formulation. When a drug is partitioned into dense micelles, the systemic concentration of free drug is decreased, which diminishes intracellular drug uptake by normal cells and reduces unwanted side effects caused by drug interactions with healthy tissues. However, when drug is encapsulated in micelles, its uptake by cancerous cells is also decreased [73]. Therefore, another effective method cancer therapy is triggering the drug release from the micelles at the tumor site [74].

*3.2. Thermosensitive Hydrogels.* Thermosensitive hydrogels are three-dimensional hydrophilic polymer networks capable of imbibing large amounts of water or biological fluids (Figure 1(b)), which can either be synthesized to degrade at a certain rate or to respond to temperature stimuli in the body [75]. These systems undergo a reversible volume phase transition with a change in the temperature of the environmental conditions. This type of behavior is related to polymer phase separation as the temperature rises to a critical value known as the LCST [24]. Networks exhibiting LCST tend to shrink or collapse as the temperature increases above the LCST. Changes of the local temperature could lead to gel swelling or collapse. In these situations, the release rates would be altered significantly. The swelling of these hydrogel beads in response to small changes in temperature can be successfully used to control drug release.

Thermosensitive hydrogels have been widely studied for biomedical and pharmaceutical applications, especially for drug delivery system [76–78]. These thermosensitive hydrogels as drug carriers not only provide a sustained release formulation but also enhance the stability of drugs. However, a great many of researches focused on improving controlled-release properties of this thermosensitive hydrogel carriers based on the sol-gel transition [20], whereas the research for site-targeted drug delivery has been rarely reported until now. Indeed, these polymers have potential applications in site-targeted drug delivery, especially in delivering drug to tumor sites [79, 80].

Our group recently proposed a "novel thermosensitive hydrogel" for site-targeted drug delivery (Figure 5) [81, 82]. We used the PLGA-PEG-PLGA hydrogel to fabricate the novel thermosensitive nanocarriers. The sol-gel transition

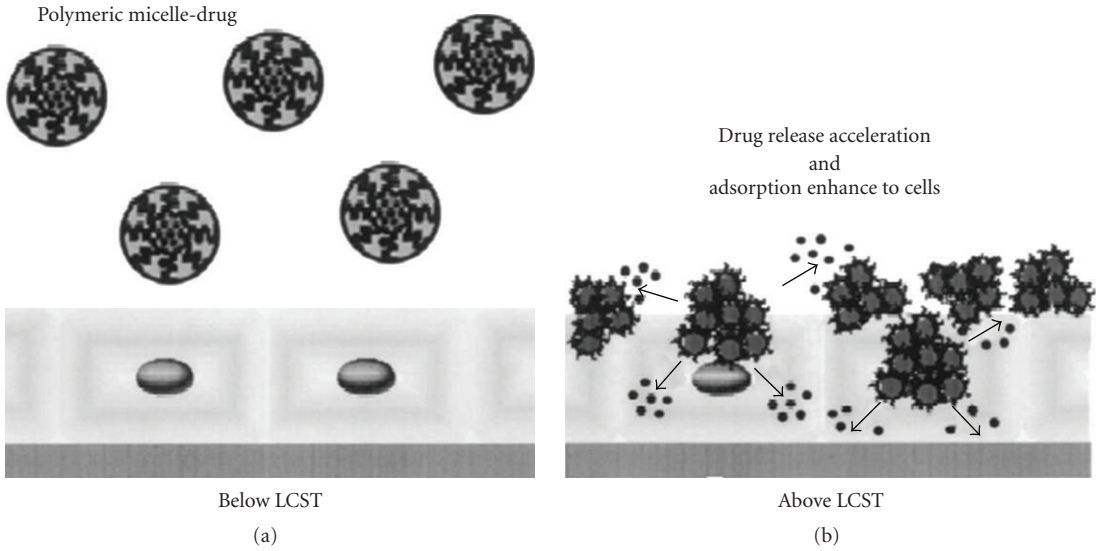


Figure 4: Schematic of thermosensitive micelles for site-targeted drug delivery (cited from [37]).

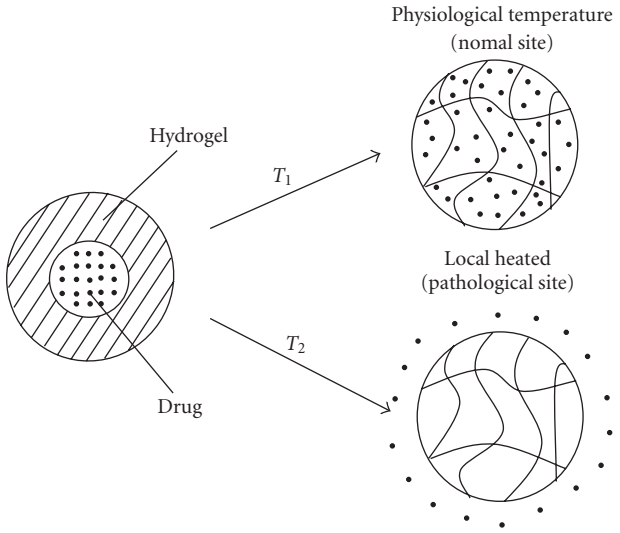


Figure 5: Thermosensitive nanocarriers for site-targeted delivery.

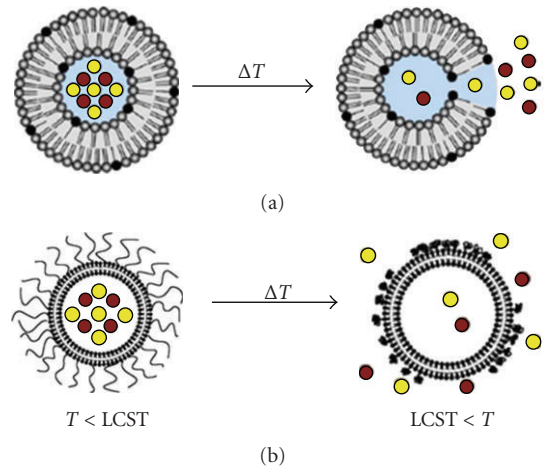


Figure 6: Schematic of the two types of thermosensitive liposomes (adapted from [9, 85]).

temperature ($T_1$) of the hydrogel was below the body temperature, and the gel-sol transition temperature ($T_2$) was greater than the physiological temperature but less than the temperature that the body can bear, about 40–44°C. Our studies also suggested that the drug release of the nanocarriers had none or a little at the physiological temperature, while at the high temperature, about 42°C, it had large. In this way, thermosensitive drug delivery system can undergo reversible structural transitions from a closed state to an open state with the help of external temperature stimuli, giving on-off switches for modulated drug delivery (Figure 6).

*3.3. Thermosensitive Liposomes.* Liposomes are spherical, self-enclosed structures formed by a phospholipid bilayer surrounding an aqueous inner compartment (Figure 1(c)). Liposomes, about 100 nm in diameter, can accumulate only in perivascular regions in tumor tissues after i.v. injection. Conventional liposomes have been clinically evaluated and approved in a variety of diseases [83]. Undoubtedly, drug leaking out of liposomes accumulates in tumor tissues, where slow release provides therapeutic benefit and may be efficacious. However, antitumor efficacy has often been limited by slow release of bioavailable drug within the tumor [84]. Thus, the ability to control and produce a burst release would be extremely advantageous.

The effective combination of functional head groups, lipid chains, and linker groups in membrane components can achieve controlled stability of the liposomal membrane and selective release of encapsulated material under specific environmental conditions. Several release mechanisms, most being thermosensitive, have been described [86–88].

Generally, thermosensitive liposomes make use of lipids with transition temperatures between 40 and 45°C [89–91]. The application of this type of liposome in combination with local hyperthermia can be used for specific drug release in solid tumors. Thus, thermosensitive liposomes have been studied for chemotherapeutic purposes to enhance the release of anticancer drugs at tumor sites.

The traditional strategy for the production of thermosensitive liposomes is based on the theory that once the ambient temperature is near the gel-to-liquid crystalline phase transition temperature of liposome, the liposome becomes destabilized and leaks carried drug (Figure 6(a)). However, in order to obtain excellent drug release kinetics and various thermosensitive functionalities, another strategy for preparing thermosensitive liposomes is conjugating thermosensitive polymers, as triggered parts of thermosensitive liposomes, in liposomal membranes (Figure 6(b)) [33]. The liposome is stabilized by highly hydrated polymer chains, when the environmental temperature is below the LCST of thermosensitive polymers. Once the environmental temperature is above their LCST, the liposome becomes destabilized due to the dehydration and contraction of the polymer chains.

Thermosensitive polymers are fixed on liposomal membranes by anchors, which have hydrophobic side groups or amino groups at the end of chain. The method of fixed thermosensitive polymers can be categorized into two types: anchors connected randomly to the polymer backbone and anchors connected specifically to the end of the polymer chain [85]. Kono and colleagues reported that the liposomes modified with a terminal anchor-type polymer possess a significant improvement of the drugs release in a narrow temperature region. By living cationic polymerization, they also [28] prepared thermosensitive polymer modifed liposomes, in which poly(EOEOVE) block acts as a thermosensitive moiety and the poly(octadecyl vinyl ether) (ODVE) block plays as an anchor between the liposome membrane and octadecyl chains of thermosensitive moiety, and found that a longer polymer chain can enhance drug release within a narrow temperature region.

The temperature-dependent effect can be strongly increased by the use of thermosensitive liposomes in combination with local hyperthermia which specifically release the entrapped drug in the heated tumor tissue [92–94]. Needham and colleagues [93] focused on developing a new thermal-sensitive drug delivery system containing DOX that has been optimized for both mild hyperthermic temperatures that are readily achievable in the clinic and rapid release times of drug. Their studies showed the advantages of the new lipid composition compared with existing liposome formulations. The studies also exhibited that novel thermosensitive liposome, in combination with mild hyperthermia, was found to be significantly more effective than free drug or current liposome formulations for reducing tumor growth in a human squamous cell carcinoma xenograft line. The studies by Han and colleagues [94] have shown that the antitumor activity of thermosensitive liposomes was enhanced significantly when they were administered in combination with hyperthermia. And the liposomes were also found to be highly efficacious carriers for in vivo delivery of anticancer drugs.

*3.4. Thermosensitive Dendrimers.* Dendrimers (Figure 1(d)) serve as nanoscopic drug carriers due to their unique architecture and properties, such as high controllability of structure, surface properties, and size. By the physically entrapped or chemically conjugated, many commercial drugs can be efficaciously incorporated into dendrimers [95, 96]. Due to increasing therapeutic effects of the drug-loaded dendrimers, the dendrimers with thermosensitive properties have been extensively investigated for controlled drug delivery system [97–99].

The initial strategy for providing thermosensitive properties to dendrimers is preparing the thermosensitive dendrimers with core-shell nanostructure by modifying the outer dendrimer surface with thermosensitive polymers (Table 3). Much attention has been paid to graft PIPAAm to chain ends of dendrimers [32, 100]. However, these PIPAAm-modified dendrimers lose their significant characteristic of molecular uniformity due to the fundamentally polydisperse morphology of PIPAAm chains. To improve this situation, Haba and colleagues [99] introduced IBAM group, a common structural unit with thermosensitive poly(N-vinylisobutyramide), to the chain end of PAMAM dendrimers. It is another method for modifying dendrimers. In order to achieve double thermosensitive dendrimers, Xu and colleagues [102] prepared core-shell-corona nanostructures with hydrophobic H40 as the core, swollen PNIPAM as the inner shell, and swollen PDMA as the corona (Figure 7).

The later strategy for functionalization of thermosensitive dendrimers is building branched macromolecules constructed with hydrophilic and hydrophobic units. Various LCSTs of thermosensitive dendrimers are ensured by the different rates of hydrophilic and hydrophobic units in their backbone. It is noteworthy that the thermosensitive properties of these dendrimers are based on their amphiphilic dendronized polymers, rather than grafting thermosensitive polymers to the dendrimers surface. Aathimanikandan and colleagues [35] synthesized amphiphilic dendrimers with pentaethylene glycol as the hydrophilic part and a decyl chain as the hydrophobic part, which exhibits thermosensitive behavior and possesses possibility of utilizing for nanocarriers.

## 4. Conclusions and Future Perspective

Thermosensitive nanocarriers have been regarded as a safe and effective drug delivery vehicle, due to their unique capability of loading a large amount of various drugs, long circulation in the bloodstream, accumulation in tumor tissues by EPR effect, biological compatibility, and remote controlled drug release in response to mild heating. Though thermosensitive nanocarriers possess the above advantages in drug delivery, this system still needs to be continuously improved to meet the needs of clinical applications.

To improve content release efficiency, the phase transition temperature (Tp) of thermosensitive nanocarriers

Table 3: Classification of thermosensitive dendrimers.

| Strategy | Architecture | | LCST (°C) | References |
|---|---|---|---|---|
| | Dendritic core | Temoerature-sensitive shell | | |
| Thermosensitive polymers modified dendrimers | DAB-dendr-$SCOCH_3$/-SH | PIPAAm | 34–36 | [32] |
| | Dithiobenzoate-terminated dendrimer | PIPAAm | 25–35 | [100] |
| | PAMAM/ PPI | IBAM-$G_{1–5}$ | 20–60 | [99, 101] |
| | PAMAM | PDMA | 31–35 | [29] |
| | Bolton H40 | IPAAm<br>DMA | 32<br>40–50 | [102] |
| | PAMAM | Phe residues or<br>Ile residues | 20–30<br>— | [97] |
| | Dex-AI | PIPAAm | 25.7 | [103] |
| | PAMAM | PIPAAm | 33 | [104] |
| Amphiphilic dendrimers | Biaryl-based G3 dendrons with pentaethylene glycol and decyl chain | | 32–42 | [35] |
| | Branched 3-fold polymethacrylate derivatives, gallic acid as branching point, TEG units as linker | | 62–65 | [105] |

PPI: poly(propylenimine); IBAM: isobutyramide; PAMAM: polyamidoamine; Dex-AI, dextran-allyl isocyanate.

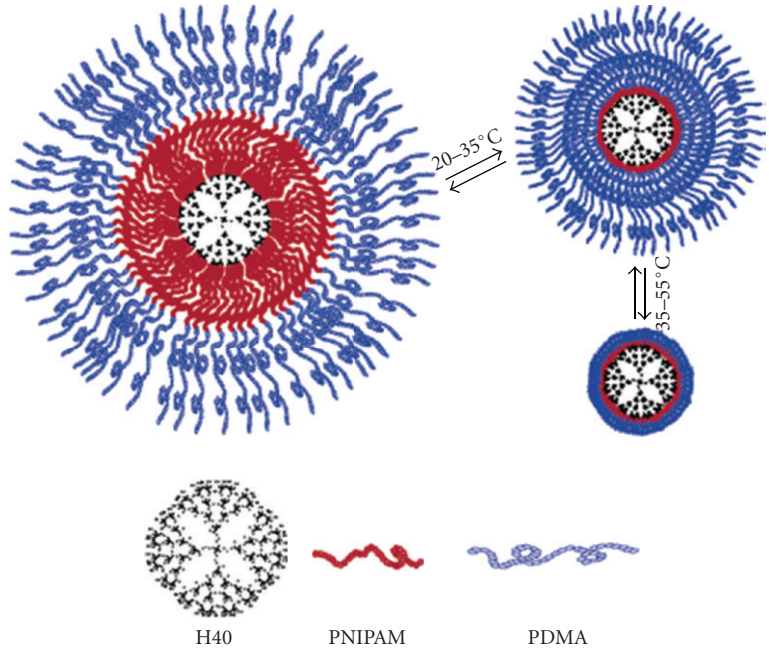


Figure 7: Schematic illustration of the double thermosensitive dendrimers (cited from [102]).

should be in the following specifying points: (a) the Tp should be near the physiological temperature (about 37°C) but not below this temperature resulting in none or a little drug release before being under local hyperthermia [106]; (b) the Tp should be less than the temperature that the body can bear and within a very narrow temperature range (about 4-5 °C) [107]; (c) the structures of thermosensitive nanocarriers should be significantly changed once near the Tp in order to shorten the time of the release reaching the maximum [108]. So it is necessary to synthesize the thermosensitive polymers with better-controlled structures to precisely adjust the LCST. The development of thermosensitive polymers synthesis from free-radical and anionic polymerization to controlled radical and cationic polymerization offers a way to realize it [109]. Recently, establishing the thermosensitive macromolecules with the supramolecular organization such as star-shaped [110] or highly branched architectures [111] was another successful chance to achieve it.

The subsequent accumulation of the thermosensitive nanocarriers in the target sites still remains a challenge due to the limitations of passive targeting drug delivery. The multifunctional thermosensitive nanocarriers which conjugated with different ligands such as avidin [56] or folate [112] are the current trend to optimize these site-specific therapeutic systems. It is noteworthy that thermosensitive nanocarriers change not only their behaviors of

drug release but also their behaviors of intracellular uptake in response to the change of environmental temperature. Thermosensitive nanocarriers which possess PIPAAm-based outer coronas can enhance interactions between the micelles and cell membranes through the dehydration of corona-forming thermosensitive polymer chains, and the micelles localize at the Golgi apparatus and endoplasmic reticulum [113]. It indicates that thermosensitive nanocarriers are greatly promising as intracellular delivery vehicles to intracellular targeted drug delivery in conjunction with applied heating. Due to the different accumulation processes of thermosensitive nanocarriers among individual patients, it is critical to determine the maximum acculturation of the nanocarriers in the target sites before triggered drug release from the nanocarriers. In order to overcome this problem, it is necessary to provide imaging functions to the carrier by incorporating various imaging probes, for example, magnetic resonance imaging (MRI) probes [114]. Under the high detectability with MRI, the accumulation and drug release of the thermosensitive nanocarriers are remotely controlled [115]. It provides a way to engender the efficient patient-optimized therapy.

Thermosensitive nanocarriers have already been used for a wide range of applications in controlled drug delivery. The large number of available approaches to generate these smart nanocarriers illustrates the versatility of the system and the great potential to be explored for future applications.

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