Materials Express

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Printed in the United States of America

2158-5849/2018/8/021/014
doi:10.1166/mex.2018.1406
www.aspbs.com/mex

Review

Poly(N-vinyl caprolactam) thermoresponsive polymer in novel drug delivery systems: A review

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ABSTRACT

Thermoresponsive polymers have been attractively and scientifically significant in the recent years due to the utilization of various pharmaceutical and biomedical formulations. Poly(N-vinylcaprolactam) (PNVCL) is a temperature-responsive polymer, only second to poly(N-isopropylacrylamide) (PNIPAM), the most popular temperature-responsive polymer. PNVCL should be considered an important focus due to the phase transition temperature of such polymer that is close to the physiological temperature. PNVCL is a polymer which offers unrivaled qualities for different potential medical device applications. Specifically, it offers one kind of thermoresponsive abilities, which satisfies the material innovation imperatives required in focused drug delivery applications. PNVCL and PNIPAM polymers are well-studied thermoresponsive abilities since its lower critical solution temperature (LCST) is near the physiological temperature and has mostly been used in biomedical applications. Therefore, it can be investigated as a potential candidate for pharmaceutical utilization. This review highlights a comparison of PNVCL with PNIPAM regarding comparable characteristics which also delve into selected examples and the most recent published of applications based on PNVCL with a specific focus on drug delivery system. The consequence exhibits that the PNVCL will play a pivotal role in nanotechnology and the environment.

Keywords: PNVCL, PNIPAM, Thermoresponsive Polymers, Drug Delivery.

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1. INTRODUCTION

In massive research, polymer nanocomposites with small dimensions of the reinforcement phase <100 nm, have been producing practical materials by integrating the properties of constitutive materials.[1–6] The composite generation requires an incorporation of the fillers like layered silicates into the polymer materials, which has already been known for half a century. In the elastomers field, the organically modified layered silicates used strengthening by Ref. [7] also in the aqueous solution[8] indicate the blending of clays into polyvinyl alcohol. However, in the early nineties, a study on polyamide nanocomposites by a group of Toyota researchers filled the polymer matrix with (1 nm) thick layers of the layered aluminosilicates at a nanometer level. This step led to sight on

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the nanocomposites based on layered silicate, which is an exponential growth in the research.

Toyota researchers[2, 9, 10] adopted the *in situ* polymerization of polymer nanocomposites by polymerizing the monomers in the silicates. Thence[11, 12] improved the synthesis of polymer nanocomposites via using melt intercalation process, which became the most preferred route for the polymerization of nanocomposites. Subsequently, many researchers reported fundamental improvements in the nanocomposites properties such as flame retardancy, strength, modulus, reduction in gas permeability and thermal stability with lower contents of filler compared to the composites.[13–16]

While the electrical conductivity and extended thermal have started to be necessary, integration of the clay as a filler in the polymer matrices acquires important attention.[17–19] The researchers labored to design novel strategies to provide therapeutically effective and safe drug delivery systems by selection clay minerals as active agents. Since the last century, the significant improvement in polymer science and nanotechnology based on discovering a different type of clays and their use in a variety of applications marked the end of the last century. Kotal and Bhowmick described clay as a type of synthetic layered silicates, also in other words, a mineral characterized by the content of organic matter and metal oxides.[20] Each layer of clay is characterized by robust interlayer covalent bonds.[21] This advantage became a solution for the polymer matrix dispersion during the preparation of polymer nanocomposites.

Most of the studies related to medical applications chiefly in drug delivery discussed polymers, especially on thermoresponsive polymers. Poly(N-isopropyl acrylamide) (PNIPAM) is the most prevalent one with lower critical solution temperature (LCST) around 32 °C. This temperature is very valuable for biomedical applications since it is close to the body temperature 37 °C.[22–25] In the second place, Poly(N-vinylcaprolactam) (PNVCL) is a perfectly thoughtful thermoresponsive polymer regarding its significance after poly(N-isopropylacrylamide) (PNIPAM).

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PNVCL exhibits similar LCST behavior in water between 30 °C and 32 °C.[26]

The most important similarity point between the two polymers is the temperature of the swelling to collapsing transition in water is the same as its lower critical solution temperature (LCST).[27]

Years ago, the difficulty of polymerizing NVCL to produce PNVCL compared to PNIPAM lacked popularity among researchers. Subsequently, they developed the polymerization method by controlling free-radical polymerization techniques thus resulted in an increasing number of studies mostly in biomedical and environmental fields. From another standpoint, the biocompatibility of PNVCL is an important trait, making it very attractive for biomedical and environmental applications, while it has not been demonstrated for PNIPAM.[28] In the subsequent sections, authors will review the limitations and required process improvements of PNVCL as a nanocomposite by discussing the work of previous researchers focusing on biomedical applications. Also, the review gives some insights of PNVCL nanocomposites properties that would influence the market of drug delivery and pharmacy system.

2. THERMORESPONSIVE POLYMERS

Among various environmental stimuli, the temperature is most commonly studied due to its physiological significance. Therefore, for biomedical applications, the thermoresponsive feature is one of the most concentrated stimuli responsivities.[29] The polymer in the solution can be described for two-phase diagrams namely, temperature and concentration as a function as shown in Figure 1.[30–32] The upper critical solution temperature (UCST) and the lower critical solution temperature (LCST) are the two types of the phase diagrams. This means that when the temperature is increasing, the transition between the two-phase and single-phase regions occurs, and the (UCST) can be recognized at that point. At the same time, the decreasing temperature between the single- and two-phase LCST at this transition also appear.

The UCST of the polymers dissolved in an organic solvent is more prevalent compared to the LCST dissolved in aqueous solvents that are observed recently. For polymeric drug delivery systems which are being focused in this article, the lower critical solution temperature (LCST) of aqueous polymer solutions is applicable. A general rule was introduced by Ref. [33]: at all temperatures, the polymer which is soluble in water is synthetically increasingly hydrophobic, prior complemented water insolubility is achieved. Meanwhile, a range of compositions will get it, which will have temperature converse solubility, and the higher hydrophobic, the lower the LCST.

In this review, most of the studies have discussed polymers that present an LCST. A classical thermoresponsive material known as Poly(N-isopropylacrylamide) (PNIPAM) is a volume phase transition temperature. On the other hand, an intense phase transition close to body temperature at 37 °C is utilized to control drug delivery systems.[22–25] However, the potential advantage of PNIPAM was limited because of the unwanted neurotoxin.[34] To handle this issue, an authoritative strategy is used to manufacture more biocompatible and environment responsive polymers. Poly(N-vinylcaprolactam) (PNVCL) has been proven to become incipient drug carrier due to identical change of the temperature and mesh sizes dependent volume phase transition of the gel network.

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3. THERMORESPONSIVE POLY(N-VINYL CAPROLACTAM)

The generality reported the most commonly studied thermoresponsive polymer in aqueous solution is Poly(N-vinyl caprolactam), PNVCL due to being close to the temperature after of PNIPAM. PNVCL fits the group of poly-N-vinylamide polymers as it is water-soluble, a non-ionic, and when at almost 32 °C has the LCST value in an aqueous solution.[35] Therefore, PNVCL breaks down the temperature near to the physiological temperature, which is

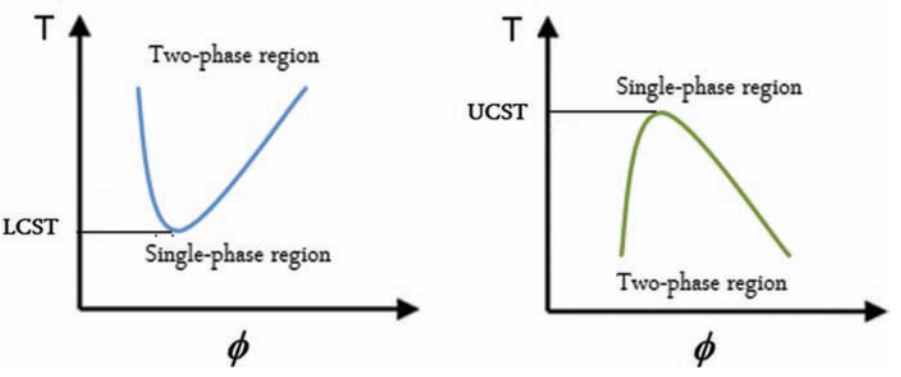

Fig. 1. UCST and LCST referring the two graphical performances of phase diagrams (T is temperature, ϕ is the weight fraction of polymer in solution).[32]

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considered to be appropriate for biomedical applications. The known toxicity, water solubility, and identical LCST resemble the properties of PNVCL and PNIPAM. However, they are different in several aspects.[36] These differences can be found in the thermodynamics of the phase transition and the mechanisms. Also, the LCST of PNVCL dropped with the increasing concentration of both of the polymer and chain length, which means by controlling the molecular weight of the polymer, its lower critical solution temperature (LCST) could be modified.[37] Moreover, under intensive acidic conditions, the PNIPAM hydrolysis would produce a toxic organic amine compound, which is unfavorable for the biomedical purpose.[38] In contrast, PNVCL in the same condition will solely produce a polymeric carboxylic acid rather than toxic organic amine compound, as in the case of PNIPAM. PNVCL has hydrophilic cyclic amide side groups that are immediately attached to the hydrophobic carbon–carbon main chain.

The LCST of the PNVCL ranged from 32 °C to 50 °C as shown in Table I. LCST dropped with the increasing polymer molecular weight in the range of 18000–150000 $g \cdot mol^{-1}$. Thus, this exclusive feature modifies the LCST of a PNVCL-based thermoresponsive system by controlling the molecular weight on the other side of the PNIPAM independent on the molecular weight.[39]

Although PNIPAM is less familiar, several characteristics and applications of PNVCL in the field of biotechnology and biomedicine were studied.[42–45] Through the assistance of PNVCL, the stability of enzymes was increased and enzyme immobilization was achieved by protecting the enzymes from denaturation by entrapment.[42, 43, 46] In the 1960's, PNVCL was utilized in multi-layered glass materials as a separation material in specific membranes and as an ingredient in the wound-healing film.[47] For controlled delivery applications, researchers have studied the self-assembling thermoresponsive containers which are contagious of slim films of PNVCL that are settled onto porous support membranes. Recently, with the aid of PNVCL's selective determination, some of the opiate drugs in aqueous media has been achieved.[48] Consequently, PNVCL is particularly interesting due to the reality that it is biocompatible and very stable versus hydrolysis and is a better choice when used to prepare for a potential carrier for the biomedical application.[34, 49]

Table I. Comparison between PNIPAM and PNVCL.

	PNIPAM	PNVCL
Thermoresponsiveness		
LCST	30–34 °C[40]	32–50 °C[40]
Dependence on molecular weight	Independent	Dependent (18000–150000 $gmol^{-1}$)
Flory–Huggins phase-change	Type I	Type II
Polymerization and polymers		
CRP techniques	Well-established	Few
Well-defined copolymers	Lots	Few
Biocompatibility		
In vitro cytotoxicity	None (before hydrolysis) Toxic (after hydrolysis)	None (before hydrolysis) None (after hydrolysis)
In vivo toxicity	Systemic toxicity Detected[41]	Not yet reported

4. SYNTHESIS OF PNVCL POLYMERS

4.1. Free Radical (FR) Polymerization

Radical polymerization is the only polymerized technique to synthesize the NVCL monomer.[50] A mutual approach of polymerization is free radical polymerization (FRP), which polymer forms was achieved via the consecutive extension of free radical structure blocks. This technique can be described as applicable under temperate conditions and unpretentious performance. Moreover, the advantage of FRP is that it does not demand advanced equipment and can be performed in a broad temperature range in dispersion, bulk, and solution. Initiation, propagation, and termination are the major steps for FRP process of PNVCL.[50, 51] Azoisobutylnitrile (AIBN) is one of the most commonly utilized initiators used to polymerize PNVCL and produces nitrogen gas and two radicals across heating. The production of the initial propagating type involves the radicals that are added to NVCL monomers. The alternate addition of a major quantity of NVCL monomer to the primary active radical center refers to the propagation procedure, which is usually considered as a very fast step. Every addition yields a neoteric active radical which is more than one monomer unit. Later the termination step starts with irreversible termination on the growth of the polymer chain.

Having a filtered NVCL monomer blended with AIBN and melted subsequently in an organic solvent, which is almost e benzene or dioxane at high temperatures, the synthesis of PNVCL will be a typical Free radical polymerization (FRP). Different molecular weights of PNVCL can be prepared by using a variety of solvent, a different value of initiator and temperature range. The molecular weights of PNVCL can be accessible from 20 k to 1300 k and the range molecular weight distribution PNVCL from 1.4 to 2.0.[52] The polymers synthesized via FRP display a comparatively wide molecular weight distribution because of the continuous initiation and termination steps. The difficulty in prediction and minimal control of molecular weights has indicated several limitations of the FRP approach. The synthesis of block copolymers is impossible when the alternate addition of a second monomer onto the first polymer cannot find the effective radicals of the polymer ends. It also improves the controlled polymerization approaches as it is a prerequisite to composing

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PNVCL polymers with the ability to control architecture and molecular weights.[49, 53, 54]

4.2. Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization

The expression of monitoring free radical polymerization (MRP) or the so-called living radical polymerization is described as the free radical polymerization that creates effective end-series on the polymer bonds.[55–57] Novel mechanism of MRP requires reducing the ending reaction and supply observation to the molecular weight and its allocation of a polymer. Moreover, the MRP method combines many of the desired features of classical free radical polymerization such as surface reaction conditions, possibility of many operations, and approved with a variety of monomers.[58]

The synthesis of PNVCL by RAFT was firstly reported by Ref. [52], in which these polymers include weak molecular weight with approximate amount around 4 k to 11 k and high molecular weight distribution further than 1.3. Recently, the MADIX/RAFT process has obtained PNVCL with accurate molecular weight distributions by using ideal chain-transfer agents (CTAs) and reaction conditions. The polymerization of NVCL by AIBN as initiator and O-ethyl-S-(1-methoxycarbony) ethyl dithiocarbonate (CTA1) as the RAFT agent could successfully be achieved in 1,4-dioxane at 60 °C.[59]

The reaction equation and structure of CTA1 are shown in Figure 2. For the polymerization of NVCL, a rise of quantity rate of molecular weight with conversion has observed the ratio of monomer to CTA1 via using refractive index detector with gel permeation chromatography. The yield and the reaction time are relatively effective to the molecular weight of PNVCL. The molecular weight of production was raised when the conversion of the monomer was enhanced when compared to the yield. Hence, the product was influenced by the molecular weight, reaction duration, and mutation of the monomer which can be controlled via modifying the reaction time. When all the monomers were used and modified to the polymer, the molecular weight of the yiels ded promptly concerned to the molar ratio of the monomer to the RAFT agent. As a consequence, the molecular weight of PNVCL can control the polymerization by controlling the input amount of the monomer to the RAFT agent.

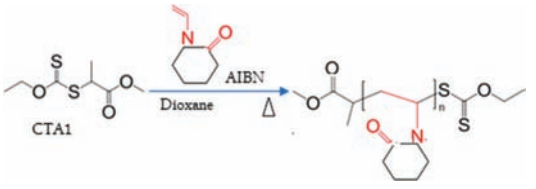

Fig. 2. RAFT polymerization of PNVCL.[59]

5. SIGNIFICANCE AND BASIC PROPERTIES OF PNVCL

Great attention had the water-soluble polymers with LCST owing to their possible application in biotechnology and biomedicine. Cheng et al.[60] utilized the radiation polymerization to the synthesis of N-vinyl caprolactam (NVCL) which was attained in a very high productivity and had perfect thermo-sensibility. Controlling the phase behavior of PNVCL in the adsorption from solution and aqueous solutions can manipulate the colloid stability of silica reversibly. Qiu et al. conducted survey experiments on the phase behavior and absorption of the aqueous solutions of poly(vinyl caprolactam) (PNVCL), and it concerned with the stability of silica dispersions.[61] At low pH, an associated rapid flocculation of the dispersion and a large increase in adsorption were observed during the elevation of the temperature above the LCST of PNVCL.

At the same area,[62] searched for solid–liquid separation through coagulation and flocculation which indicated a significant stage of many technological processes. The authors used PNVCL instead of PNIPAM in their investigation as it is a biocompatible polymer and compared to the flocculation efficiency of chitosan and combinations of chitosan-PNVCL, it also used Aerosil OX50 dispersions as flocculants and temperature, followed by the concentration of the polymers as a function. The temperature of the sensitive bio-compatible PNVCL in a combination with the biodegradable polyelectrolyte chitosan granted a compact residue at temperatures higher than the LCST temperature of 45 °C and the density of the sediment is 33% higher compared to the use of CH2500 only. Through employing this strategy, the sediment was more compact, contains had less water, and a slight amount of biodegradable CH2500 and biocompatible PNVCL.

The coil-globule transition is one of the motivating phenomena occurring in polymer systems, which has been extensively studied for the last three decades.[63] Makhaeva et al. studied a modern triple system containing poly(vinylcaprolactam) and used the dynamic light scattering technique to look at the behavior of PNVCL in the water.[64] The comparison of notorious experiments performed on PNIPAM was investigated, offering a clearer view of the global features for the ternary systems through a neutral thermoresponsive polymer.

6. APPLICATIONS

Poly(N-vinylcaprolactam) has attracted the attention over the past couple of decades because of its biocompatible and biodegradable features. Table II outlines the recent significant utilization of PNVCL in biomedical, bioanalytical, catalytic, and environmental applications. In the biomedical applications, PNVCL has been successfully applied for entrapment of various enzymes as well

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Table II. Summary of thermoresponsive poly(N-vinylcaprolactam) application.

Poly(N-vinylcaprolactam) application	Fields	Example	Reference
Biomedical applications	Entrapment of enzymes	Gel-immobilized enzymes as promising biocatalysts: Results from Indo-Russian collaborative studies	[66]
	Entrapment of cells	Studies on the suitability of alginate-entrapped chlamydomonas reinhardtii cells for sustaining nitrate consumption processes	[67]
	Tissue engineering	Initiated chemical vapor deposition of thermoresponsive poly(N-vinylcaprolactam) thin films for cell sheet engineering	[68]
	Affinity chromatography	Polymer versus monomer as displacer in immobilized metal affinity chromatography	[69]
Bioanalytical applications	Displacement chromatography	Effect of synthetic polymers, poly(N-vinyl pyrrolidone) and poly(N-vinyl caprolactam), on elution of lactate dehydrogenase bound to Blue Sepharose	[70]
	Membrane chromatography	Track etched membranes with thermoadjustable porosity and separation properties by surface immobilization of poly(N-vinylcaprolactam)	[47]
	Bioseparation	Protein-like copolymers: Effect of polymer architecture on the performance in bioseparation process	[71]
	Sensors	Poly(N-vinylcaprolactam) gel/organic dye complexes as sensors for metal ions in aqueous salt solutions	[72]
	Fluorescent thermometer	Fluorescent thermometer based on poly(N-vinylcaprolactam) with 2D-π-A type pyran-based fluorescent dye	[73]
	Magnetic resonance (MR) imaging clinical technology	Gadolinium-loaded poly(N-vinylcaprolactam) nanogels: Synthesis, characterization, and application for enhanced tumor MR imaging	[74]
	Nanotechnology/catalytic applications	Stimuli-responsive and biocompatible poly(N-vinylcaprolactam-co-acrylic acid)-coated iron oxide nanoparticles by nanoprecipitation technique	[75]
Catalytic and environmental applications	Flocculation	Flocculation of a synthetic rubber latex with homopolymers and copolymers of N-vinylcaprolactam and N-vinylimidazoles	[76]
	Waste water treatment	Effective systems based on hydrophilic polymers for extraction of phenols from aqueous solutions	[77]
	Dental applications	Synthesis and characterization of a novel N-vinylcaprolactam-containing acrylic acid terpolymer for applications in glass-ionomer dental cements	[78]
Other applications	Cosmetics	The role of polymers in cosmetics: Recent trends	[79]
	Fiber formation	Tunable thermo-responsive poly(N-vinylcaprolactam) cellulose nanofibers: Synthesis, characterization, and fabrication	[80]

as for animal cell immobilization.[65] Also, the technology of environment-responsive membrane is becoming an attraction in bioanalytical applications. Wouter et al.,[47] prepared a thermo-responsive (PNVCL-PET) membrane composite from poly(ethylene-terephtalate) to a separation of a macromolecular mixture.

Hydrogels can be recognized as a class of materials that exhibit a three-dimensional and elastic network, which is formed from hydrophilic copolymers or homopolymers crosslinked chemically or physically to form insoluble polymer matrices.[81] Since Wichterle and Lim firstly investigated a hydrogel for a contact lens in the biological application in 1960, a significant attention on the polymers has been achieved which is used for synthesis and fabrication of hydrogels in various applications.[82] In aqueous solutions, the hydrogel mechanism has the ability for swelling or deswelling, therefore, it is used vastly in the pharmaceutical industry. A specific stimulus like temperature is utilized to form the physical hydrogels alternative of the covalent crosslinking of a precursor solution.[83] Particularly, thermoresponsive hydrogels are suitable in biomedical applications due to their gelation and changes in swelling by temperature change.[84]

However, a major number of organic crosslinker polymer hydrogels show poor mechanical properties which lead to random nature of the cross-linking reactions, which robustly reduce their utility in structural applications. Various nanofillers such as metals,[85] ceramics,[86] silicates,[87]

Table III. Compendium of the novel substantial studies on the poly(N-vinyl caprolactam) PNVCL for pharmaceutical and biomedical applications.

Polymer composition		Drug loaded	Application	Reference
PNVCL-sodium itaconate	Hydrogels	Farmazin (tylosine tartrate)	Drug controlled release	[98]
PVCL-graft-$C_{11}EO_{42}$	Hydrogel particles	Nadolol, propranolol, and ketoprofen	controlled drug delivery	[99]
Chitosan-g-PNVCL	Hydrogels	–	Drug-delivery carrier	[100]
Block copolymer PNVCL-b-PEG-FA	Hydrogels	5-fluorouraci (5-FU)	The anti-cancer drug carrier	[101]
PVCL-NH_2/PMAA	Hydrogel films capsules	–	Controlled drug delivery	[102]
Poly(PVCL)	Microgels	Doxorubicin (DOX)	Anticancer drug-controlled release	[103]
P(VCL-co-NaAlg)	Microgels	5-fluorouraci (5-FU)	Colon cancer drug controlled release	[104]
Graft copolymer PAA-g-PNVCL	Hydrogels	Ornidazole (ONZ)	Controlled drug release	[105]
GO-PVCL	Hydrogels	Camptothecin (CPT)	Controlled drug delivery	[106]
Poly(VCL-co-UA)	Microgels	Doxorubicin	Anticancer drug-controlled release	[107]
SA/poly(Am-co-NVC-co-AGA)	Hydrogel nanocomposites	5-fluorouraci (5-FU)	Controlled release/Antibacterial	[108]
Gold@PVOH-b-PNVCL	Hydrogel nanocomposites	Nadolol	Controlled drug release	[109]
HPCL-click-PNVCL	Hydrogel films	–	Controlled drug delivery	[110]
Glycopolymer (P(OVNG-co-NVCL))	Hydrogel nanocomposites	Ferulic acid (FA)	Targeted drug delivery	[111]
5-FU/Meg-fib-graft-PNVCL	Nanogels	5-fluorouraci (5-FU) Megestrol acetate (Meg)	Breast Cancer drug-controlled release	[112]
P(VCL-ketal-HPMA)	Nanogels	Doxorubicin (DOX)	Anticancer drug-controlled release	[113]
Poly(NVCcoDMAEMA)	Nanogels	5-fluorouraci (5-FU)	Targeted drug delivery	[114]
Poly(NVCL-co-HEMA)	Nanogels	Curcumin	Targeted drug delivery	[115]
PNVCL-PEGMA	Nanohydrogels	5-fluorouraci (5-FU)	Controlled drug release	[116]
-Copolymer [p(VCL-co-MMANa)] and [p(VCL-co-IANa)]	Microgels	-Rhodamine B (RhB)	Drug release	[117]
-Terpolymer [p(VCL-co-MMANa-coIANa)]		-Nadalol (beta-blocker drug)		

graphene,[88, 89] and, magnetic particles[26] were integrated into the hydrogel matrices for gaining the identical nanocomposites. Nowadays, the use of natural fibers as fillers in polymer nanocomposites has obtained much solicitude due to an incremental motivation toward environmental issues.[90] Among natural fibers,[91] represents nanocrystalline cellulose as appropriate filler for hydrogels due to its perfect renewability and mechanical properties. They used frontal polymerization technique characterization (FP) to the green synthesis of PNVCL with biocompatible materials nanocrystalline cellulose. After the characterization of phase transition behavior of PNVCL nanocomposites showing an LCST ranged at 33–34 °C, this value is nearer to the physiological look like PNIPAM itself. By using nanocrystalline cellulose, the nanocomposites becomes safer and cheaper and should be preferred particularly in biomedical applications.

New materials producing polymeric biomaterials with enhanced mechanical properties, biocompatibility, and responsiveness were what the recent research focused on this novel. Polymeric biomaterials are used in the medical field, which involves tissue engineering, dental implants, polymer-coated stents, controlled drug delivery systems, artificial organs, coatings of tablets, and sutures.[92, 93] Through synthesizing newly polymeric materials with coveted properties, this will be the pioneer toward the development of polymeric therapeutic devices. Table III summarizes the significant studies on PNVCL for biomedical applications.

The microgels based on temperature-sensitive polymers have been in the global attention due to their potential use for the biomedical application.[94–97] The preparation of hydrogels containing Farmazin (tylosine tartrate) as an immobilized antimicrobial agent and vinyl caprolactam sodium itaconate as copolymer was studied by Ref. [98] to provide the release of the drug controlled by the ambient temperature. The phase transition temperature behavior shifted 2.5 °C to lower temperatures,

due to hydrogen bonding of the lactam oxygen atom of the polymer to amino groups of tylosine tartrate contrast to the gel without the drug. In 2007, the thermoresponsive Poly(N-vinylcaprolactam) was studied for pharmaceutical applications. The phase of the transition temperature of PNVCL was near the physiological temperature, thus Vihola et al., research it was considered as a potential nominee for pharmaceutical use; experimental studies included preparation and characterization of drug loaded.

For cancer treatment, PNVCL has been widely used due to its cytocompatibility and facility of modification with other functional molecules.[94, 100, 104, 118–121] Stimuli-responsive graft copolymer based on chitosan and PNVCL was successfully synthesized by Ref. [100], through utilizing grafting agents to graft carboxyl-terminated PNVCL (PNVCL–COOH) chains on to chitosan backbone as controlled drug delivery carriers. The chitosan-g-PNVCL showed dependent swelling behavior, which makes them appropriate for stimuli-responsive delivery of drugs. However, a novel type of thermoresponsive PNVCL-b-PEG block copolymer coupled with folic acid was prepared as an anti-cancer drug carrier synthesized by Ref. [101]. In the anticancer field, the preparation of the PNVCL-based microgels using convenient and environmentally friendly precipitation polymerization was studied by Ref. [103]. To obtain a smart, robust, biocompatible, and degradable drug carrier, the incorporation of the disulfide-bonded crosslinker *N*,*N*′-bis(acryloyl)cystamine (BAC) was done, which can release anticancer drugs in response to redox potential, pH and temperature.

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In addition, a study on breast cancer was carried out by Ref. [112], in which the feasibility of 5-fluorouracil (5-FU) and Megestrol acetate (Meg) which loaded fibrinogen-graft Poly(N-Vinyl caprolactam) nanogels (5-FU/Meg-fib-graft-PNVCL NGs) was studied. The changes in hydrogen bonding interaction between polymer carrier and drug molecules in solution are the interpretation of this distinguished drug released above LCST due to the hydrophobic hydration followed by high entropy changes. As depicted in Figure 3, the hydrogen bonding of polymer carrier with drug molecules would be weaker than their interaction with water molecules.

Nowadays, the nanocomposites containing clay is demanded in different utilizations. The main properties of natural clay are hydrophilic, specific surface area, rise adsorption capacity, swelling capacity, solubility, and nonpoisonous for human, which have increased its significance.[122, 123] As the polymer nanocomposite field specialists have started to be very interested in using clay minerals, they revised the hydrophilic character on organophilic to have a perfect dispersion of clay layers into the polymer matrix. This is to obtain a successful intercalation of clay in the polymer matrix and improve its mechanical and thermal properties. The revision should modify the clay minerals with organic compounds while being used as a filler for different polymer nanocomposites.[103, 124] The researchers were interested and aimed to prepare clay minerals intercalated by organic compounds and use it as a filler for polymer composites. Pazourkova et al. (2014) modified the montmorillonite and vermiculite by adding the amount of monomer or polymer of N-vinylcaprolactam and poly(N-vinylcaprolactam) based on the cation exchange capacity (CEC) of each clay with ethanol as a solvent.[125] The intercalation was mainly characterized by Fourier transform infrared spectroscopy (FTIR), X-ray powder diffraction (XRD), and scanning electron microscopy (SEM). As a result, good intercalation was observed. Also, the modified montmorillonites were found smoother than the pure clay which is rough.

In the controlling drug delivery area,[111] studied the fabrication of the Poly(6-O-vinyl-nonanedioyl-dgalactose-co-N-vinylcaprolactam) (P(OVNG-co-NVCL)) thermoresponsive double-hydrophilic glycopolymer using a free radical copolymerization and chemo enzymatic procedure to obtain nanofibers via an electro spinning process. During the polymerization process of the DHG polymers, the molar fraction of galactose (OVNG) monomer (NVCL) in the copolymers was set to achieve the desired lower critical solution temperature (LCST) between 32 °C and 40 °C. Aside to this, ferulic acid (FA) loaded double-hydrophilic glycopolymer (DHG) nanofibers were prepared successfully. Therefore, P(OVNG-co-NVCL) nanofibers may have a potential application in the design of temperature controlled drug release formulations.

Özkahraman et al. focused on the release behaviors and drug loading of the microgels via precipitation polymerization process.[117] The procedure based on copolymeric and terpolymeric microgels used N-vinylcaprolactam PNVCL, metacrylic acid sodium salt, and its conic acid sodium salt. Rhodamine B (RhB) and Nadolol were used as a model drug. After that, these microgels were described by colloidal properties determination, SEM technique and cloud points determination. Hence, the volume phase transitions temperature obtained by cloud point experiments was 32–37 °C close to human temperature. SEM analysis successfully obtained and characterized the particle size of microgel formation. As a result, the researchers observed PNVCL based microgels appropriate for drug delivery applications.

Based on poly(N-vinyl caprolactam-co-2dimethyl aminoethylmethacrylate), Sudhakar et al.[114] used the same emulsion polymerization for the incorporation of nanogels. In this study, a hydrophobic curcumin model drug was encapsulated successfully during the polymerization process. The nanogels showed more bioavailable, thermoresponsive, high aqueous stability, and was useful

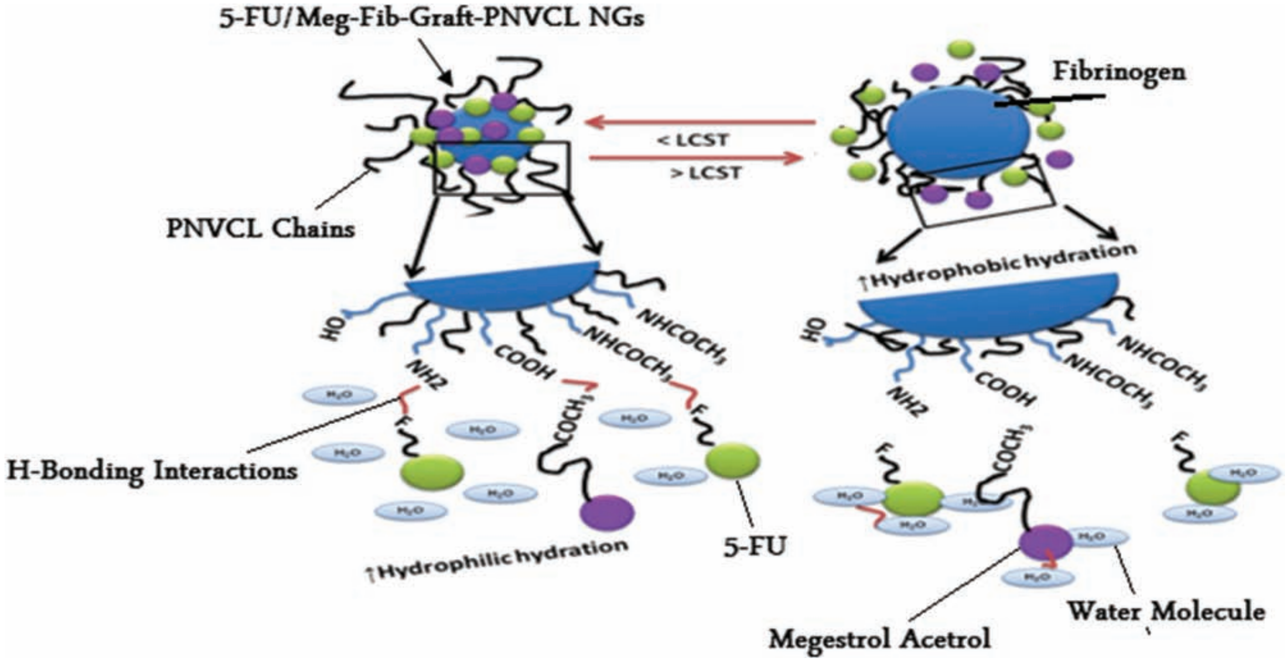

Fig. 3. The plausible thermoresponsive released mechanism above LCST for the multi drugs from fib-graft-PNVCL NGs.[112]

to be targeted as a drug delivery application. Owing to the biocompatibility, responsiveness, and stability of nanogels, the nanogel platforms are better for the release and loading of bioactive agents than other carriers[126,127] *in vivo* destiny. This shows that the particle size of the nanogels plays a decisive role in colloidal drug delivery systems.[128] Therefore, it indicates a major importance for being effective and able to provide easy control over the particle size. Other than that,[129] fabricated poly(vinylcaprolactam) PNCVL, thermoresponsive nanogels while being developed for drug delivery by sedimentation polymerization in water. Meanwhile, synthetic N-(2-hydroxypropyl) methacrylamide (HPMA) is available as a co-monomer and ketal-based 2,2-dimethacroyloxy-1-ethoxypropane (DMAEP) acts as a cross-linker. Furthermore, it also depends on a miniature in the size of nanogels to increasing the temperature evidence for volume phase transition temperature (VPTT) with a maximum concentration of HPMA. The nanogels present accelerated declination profiles together with the combination of ketal linkages by decreasing the pH and increasing temperature. Therefore, the temperature and pH of the environment observed substantial position in the interpretation of the nanogels.

Furthermore, the gold nanoparticles were investigated extensively as a filler in the biomedical field due to its low toxicity, multilateral surface functionality, and chemical stability.[130,131] These gold nanoparticles also utilized metals as a filler, which was studied by Detrembleur et al.[26] to fabricate a novel type of thermoresponsive gold/poly(vinyl alcohol)-b-poly(N-vinylcaprolactam) nanocomposite. They used *in situ* polymerization method and decreased the gold salt inside the aqueous solution as an active factor. The drug loading capacity, responsiveness to temperature, released behaviors, and colloidal stabilization were studied. As the ultimatum, the authors assured that there was a utility and effectiveness of the gold in thermoresponsive copolymers in nanoparticles for controlled delivery and release of drugs.

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7. CONCLUSION

The significance of synthetic of thermoresponsive polymers networks was aimed to extend the application scope in biomedical applications. Although the number of the articles on the developments in the investigation of PNVCL is currently small compared to those research about PNIPAM, PNVCL demonstrated an attractive feature and utility of good biocompatibility. Thermoresponsive polymers realizing the drug delivery prerequisite system which is the provision of a sufficient concentration of drug at the accurate time and site of action. In this perspective, several drugs, nucleic acids, and proteins have been encapsulated in specific conditions and various release mechanisms have been described. To design novel polymeric structures of PNVCL with the possibility to determine and control the factors that release biologically active molecules, this study offers numerous opportunities to the scientific community for influencing therapeutic systems and flexible development. This is a future trend of which massive advancement in drug delivery and material chemistry has been directed towards designing smart thermoresponsive polymers in utilizing well-engineered nanofillers to obtain smart nanocomposite.

Review

LIST OF ABBREVIATIONS

PNVCL	Poly(N-vinylcaprolactam)
PNIPAM	Poly(N-isopropylacrylamide)
LCST	Lower critical solution temperature
NVCL	N-vinylcaprolactam
UCST	Upper critical solution temperature
FP	Frontal polymerization
$C_{11}EO_{42}$	poly(ethylene oxide)
5-FU	5-Fluorouraci
PEG	Poly(ethylene glycol)
FA	Folic acid
PMAA	Poly methacrylamide
DOX	Doxorubicin
AGA	Acrylamidoglycolic acid
NH_2	Aminopropyl
ONZ	Ornidazole
PAA	Polyacrylamide
CPT	Camptothecin
GO	Graphene oxide
UA	Undecenoic acid
SA	Sodium alginate
Am	Acrylamide
AGA	Acrylamidoglycolic acid
PVOH	Poly(vinyl alcohol)
HPCL	Poly(ε-caprolactone)
Meg	Megestrol acetate
fib	Fibrinogen
P(OVNG)	6-O-vinyl-nonanedioyl-D-galactose
HPMA	N-(2-hydroxypropyl)methacrylamide
DMAEM	2-Dimethyl aminoethylmethacrylate
HEMA	2-Hydoxyethyl methacrylate
PEGMA	Poly(ethylene glycol)methacrylate
MMANa	Metacrylic acid sodium
IANa	Itaconic acid sodium
RhB	Rhodamine B
PNVCL–COOH	Carboxyl-terminated poly(N-vinylcaprolactam)
BAC	*N*,*N*′-bis(acryloyl)cystamine
NGs	Nanogels
CEC	Cation exchange capacity
FTIR	Fourier transform infrared spectroscopy
XRD	X-ray powder diffraction
SEM	Scanning electron microscopy
DHG	Double-hydrophilic glycopolymer
VPTT	Volume phase transition temperature
FRP	Free radical polymerization
AIBN	Azoisobutylnitrile
RAFT	Reversible Addition Fragmentation Chain Transfer
MRP	Monitoring free radical polymerization
MADIX	Macromolecular design via the interchange of xanthenes
CTAs	Chain-transfer agents.

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Acknowledgments: The authors would like to thank the Universiti Malaysia Pahang for providing laboratory facilities and financial support.

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Received: 6 August 2017. Revised/Accepted: 5 December 2017.

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