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Siirilä, Joonas

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Feature article

Soft Poly(*N*-vinylcaprolactam) Based Aqueous Particles

Joonas Siirilä and Heikki Tenhu

Department of Chemistry, University of Helsinki, Finland

** Corresponding author: E-mail: joonas.jukonen@helsinki.fi heikki.tenhu@helsinki.fi*

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Abstract

Soft nanoparticles are an important class of material with potential to be used as carriers of active compounds. Swollen, penetrable particles can act as a host for the active ingredients and provide stability, stimuli-responsiveness and recyclability for the guest. Thermoresponsive colloidal gel particles are especially attractive for such applications due to the extremely soft structure, size and responsiveness. Poly(*N*-vinylcaprolactam) (PNVCL) is a much studied, popular thermoresponsive polymer. The polymer has low toxicity and the phase transition temperature is close to body temperature. During the phase transition, the polymer becomes less soluble, the particle expels a large part of water and the particle collapses to a more compact form. The diffusion of material in and from the particles is largely affected by this transition. As the solubility of the polymer changes, so do the interactions with the loaded compound. This feature article focuses on the synthetic methods, properties and applications of soft PNVCL particles.

Keywords: Microgel; nanogel; synthesis; responsive; poly(N-vinyl caprolactam)

1. Introduction

There is a need for aqueous carriers of active compounds as a large portion of drugs is insoluble in water, a solvent which is the basis of biological fluids.[1] Especially for cancer drugs, there is a need to deliver the drug to target site in a way that supresses the toxicity on healthy cells and also supresses side-effects.[2–4] In these applications the particles are used to mask the toxicity of the drug during the transport and to release it at a target site. Water is also an important environmentally benign solvent for chemical transformations, but many catalysts and reagents need to be stabilized in water either to increase their availability and reactivity or to protect them from degradation. Soft (deformable) nanoparticles may help in compatibilization of the reagents and catalysts and act as nanoreactors. The particles may also help in separation of the catalyst from the product. Typical catalysts include both enzymes[5] and metal nanoparticles.[6,7]

From the different options available; self-assemblies of amphiphilic polymers, mesoporous silica particles, latex particles and such, micro- and nanogel particles are unique due to their dualistic nature between a branched soluble polymer and a crosslinked dispersed insoluble polymer particle [8–12] These, 1 nm to few μm sized polymer particles are robust, swollen with water and extremely soft / deformable. The deformability has been recognized as an important factor in determining the fate of carriers in human body as softer particles exhibit longer circulation times due to smaller response to the body immune system and due to being able to deform and pass through membranes.[13–15]

Especially interesting soft nanoparticles are the stimuli responsive microgel particles as the responsiveness can be utilized to control the diffusion of material in and out from the particles[16] and in separation of the particles from a dispersion. Stimuli can also be used to change the conformation of the polymers in the particle to reveal active binding sites.[17] Responsiveness is typically caused by the changed solubility of the sub-chains of the particle in response to a stimulus. Typical stimuli include pH, light and temperature.

There are for example applications where the catalytic activity of a loaded catalyst is controlled by the swelling degree of the polymer particle.[18] On the other hand, many microgel particles have also been reported to possess surface active properties and been used to stabilize emulsions.[5,19–22] There is then a possibility to use these microgel particles as emulsifiers, which gives interesting possibilities when accompanied with a loaded catalyst for the catalysis at interphases.[23–25]

Poly(N-vinyl caprolactam), PNVCL, is a popular polymer in general and also as a basis of responsive micro-

gel particles. The main reasons are the low toxicity, thermoresponsiveness at moderate temperatures and the compatibility with a great variety of polar and non-polar compounds. PNVCL has been used in cosmetic products,[26] protein affinity columns,[27] and as a kinetic hydrate growth inhibitor in oil industry[28]. The polymer is made via radical polymerization of *N*-vinylcaprolactam (NVCL; Figure 1). The monomer is synthesized from acetylene and caprolactam, which is a monomer mainly used for the synthesis of Nylon-6.[29] Recently, a company named Genomatica announced it had synthesized a precursor for caprolactam in a 1 metric ton scale by fermentation from renewable resource.[30] An excellent and comprehensive review exists about PNVCL.[31] Biomedical applications of the polymer are becoming increasingly important and have been the subject of two recent review articles.[32,33]

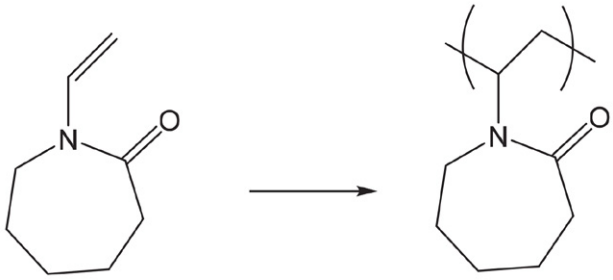

Figure 1. Synthesis of poly(N-vinyl caprolactam)

1. 1. Thermoresponsivenes

The phase transition temperature of PNVCL depends on both the concentration and the molar mass of the polymer. [34] Increasing either of these will result in lowering the transition temperature. Similarly, added electrolytes or cosolvents will shift the transition temperature to a degree determined by the choice of the additive. [27, 35–38] Commonly, the phase transition temperature is given as a cloud point, which is the temperature where a solution turns turbid as the polymer becomes less soluble and aggregates. Depending on the concentration the aggregation may result in monodisperse spherical aggregates referred to as mesoglobules or in a macroscopic phase separation.[38] Even though a single temperature value, i.e. the cloud point, is often used to describe the phase transition, high sensitivity DSC measurements and IR measurements have revealed that the phase transition process is gradual and happens within a relatively broad temperature range. [39,40] According to the DSC measurements, the released heat per NVCL unit is in the range of 4–5 kJ/mol.[39] The transition has been studied using several methods. In a work by Spevácek et al. NMR, IR and SAXS data combined with quantum chemical calculation elucidated the molecular basis of the transition.[41] Below the transition temperature the polymer is well solvated due to extensive hydrogen bonding. Every PNVCL carbonyl binds on average two water hydrogens. During the phase transition the extent of this hydrogen bonding decreases, non-directly bound water is expelled and after the transition PNVCL oxygen binds only one hydrogen. It is important to notice that the polymer is still hydrated, but to a lesser degree.

For a microgel particle, the phase transition temperature is often referred to as a volume phase transition temperature. The covalently crosslinked particles exhibit similar partial dehydration as the linear counterparts during heating, but instead of forming aggregates the particles shrink as water diffuses out from the gel network. Dynamic light scattering is the most utilized tool for analysing the transition. The degree of crosslinking is very important in determining the stability of the particles during heating. When the crosslinking degree is low, the microgels tend to aggregate similarly as the linear polymer.[42] It is fascinating, how the prepacking to particles results in stability. Other tools used for analysing the transition are NMR, SANS, and DSC that directly monitor the transition. Various release tests analyse the effect of the transition on the loaded compounds; fluorescence probes and model drugs have been used in release analysis. There are also examples of responsive microgels with interacting moieties which allow temperature-switchable binding and release of proteins and bacteria.[17]

Copolymerization can be used to tailor the transition temperature of the PNVCL containing copolymer.[43] Statistical copolymers of PNVCL with a more hydrophobic comonomer, such as vinyl acetate exhibit lower phase transition temperature compared to the PNVCL homopolymer with similar molecular weight. Vice versa, copolymers with a more hydrophilic comonomer, such as *N*-methyl-*N*-vinylacetamide, exhibit higher phase transition temperature compared to PNVCL homopolymer. Distribution of repeating units in the copolymer has also a decisive role in determining the degree to which the incorporated comonomer affects the thermal behaviour. Therefore, it is possible to synthesize block copolymers with PNVCL block and another thermoresponsive block, which exhibit two distinct phase transition temperatures, whereas a copolymer with more randomly distributed repeating units along the chain would exhibit only one transition.

In nano/microgels, the responsiveness is also often altered with comonomers, and comonomers are used to alter the stability of the dispersions. [42–52]Acidic and basic comonomers affect the swelling degree depending on the pH.[44,47,51,52] Crosslinking degree was already mentioned to have a huge impact on the gels. However, there are also several examples of gel particles with different sensitive cleavable crosslinkers, including pH, oxidation/reduction, enzymatically degradable and mechanoresponsive ones.[42,48,55–57] The transformations induced by cleaving the crosslinks are generally not recoverable unlike the thermosensitivity derived from the responsive polymer.

1. 2. Utilization of the Thermoresponsiveness

During the thermal transition, interactions between the dispersing medium and the polymer PNVCL change. This affects also the interactions between the polymer particle and the loaded content.[45,49,58,59] The diffusion into and out of the particle is reduced above the phase transition temperature as the polymer collapses and forms a barrier.

Thermoresponsive nanoparticles, including PNVCL particles, have been widely studied as drug delivery systems.[45,48,49,51,58] The release from the particles is often diffusion controlled.[16] The thermoresponsiveness is utilized to obtain a fast and efficient loading at lower temperatures and a sustained release at higher temperatures. The sustained release is important for the particle to reach its target prior to release. Specific interactions may be created by incorporating comonomers, often charged ones, to the particles. Acidic or basic units can provide a means for pH specific release.[53] Since the diffusion into and out of the particle depends on the swelling degree, accessibility and thus the activity of a loaded catalyst may be controlled with the swelling degree.[18,60] Yang *et al.* have reported silver nanoparticle loaded poly(*N*-acryloylglycinamide) microgels with temperature on/off switchable catalytic activity. The reagents were able to reach the catalytic site only in the swollen state of the microgels. Similarly, functional groups in the gel structure may be available only in the collapsed state.[17] Paul *et al.* have synthesized poly(*N*-isopropyl acrylamide) based microgels with a carbohydrate based comonomer. A protein *i.e.* lectin, and E.coli bacteria were shown to bind to the microgel particles at elevated temperatures, when the microgel was at the collapsed state and carbohydrate moieties were enriched on the particle outer layers.

Soft microgel particles have also been studied as stabilizers of emulsions, and in these cases the thermal collapse of the polymer changes the colloidal stability of the microgel and results in destabilization of the emulsion.[5,19–21,23] There is potential in thermoresponsive soft nanoparticles in the above listed applications. However, so far the thermorepsonsiveness of poly(N-vinylcaprolactam) has been utilized only in the loading and release of active ingredients, as far as authors are aware.

1. 3. Synthesis of Soft PNVCL-Based Particles

Soft PNVCL polymer particles can be synthesized from a preformed polymer using self-assembly or from the monomer by means of polymerization, either emulsion or precipitation polymerizations. Also, "from top to bottom" approach has been reported, where microgel particles where prepared by grinding a macro hydrogel down to microgels.

1. 4. Synthesis by Self-Assembly

PNVCL homopolymer may form stable self-assembled aggregates in aqueous solutions upon heating above the thermal transition temperature under dilute conditions. The particle size and size distribution depends on the molecular weight and concentration of the polymer and on the heating program.[39,61,62] The self-assembled structures are stable for days, even months, and the self-assembly process can be used to capture material inside the particles. The particles are dynamic in their nature, stable against dilution, but disassemble by lowering the temperature. However, hydrogen bonding with phenols may be used to make the particles to withstand cooling.[61,63] Similarly, PNVCL-block copolymers can form assemblies upon heating and can be stabilized against heat induced disassembly.[64,65]

In addition to thermoprecipitation, PNVCL block copolymers form assemblies as any amphiphilic block copolymer. In these assemblies PNVCL can be either one, the solvophobic or solvophilic block depending on the other block and on the conditions. PNVCL-PEG copolymer particles have been formed for example both with thermoprecipitation[61]and with solvent-exchange from DMF to H_2O (37 °C).[66] Additionally, PNVCL block copolymers have been self-assembled using nanoprecipitation and by film-dehydration followed by membrane extrusion.[67]

PNVCL has also been assembled with silk fibroin using the layer-by-layer method to form multilayers on silica particles. Hydrophobic interactions and hydrogen bonding are responsible for the interactions between silk fibroin and PNVCL.[68] The use of the self-assemblies of PNVCL copolymers in biomedical applications has recently been reviewed.[69]

2. Synthesis by the Means of Polymerization

2. 1. Precipitation Polymerization

Precipitation polymerization is a type of free radical polymerization that is used to make particles, especially colloidal gels. In the polymerization the monomer is soluble in the solvent, but the formed polymer is not and as a result, the polymer will precipitate during the polymerization. When synthesising a thermoresponsive polymer, the synthesis temperature is selected such that the formed polymer is insoluble. Surfactants are often used in the synthesis to guide the polymer to precipitate into well-defined, similar sized aggregates, which keep dispersed in the reaction mixture. When synthesizing colloidal gel particles, multiple polymerizable bonds containing comonomers *i.e.* crosslinkers, are used. Then the polymer particles/aggregates formed during the synthesis become permanent polymer networks that do not break even upon improving the solvent quality. Synthesis of colloidal PNVCL hydrogels has been well studied and various comonomers have been incorporated to the particles during the polymerizations.[44–52,70–77]

Typically, precipitation polymerizations have been performed as batch polymerizations, meaning that all

monomers are present from the start. In batch polymerizations, the reactivity difference between monomers can lead to a composition gradient in the particle structure as the more reactive monomer is incorporated first.[52,71,72,75] For this reason, PNVCL colloidal gels usually have a more crosslinked core and dangling chains on the surface, as the crosslinker, which is the more reactive monomer, has polymerized first.[72,75] Continuous and semi-continuous addition of monomers can be used to control the spatial arrangement of the monomers in the gel particles. Imaz *et al.* and Willems *et al.* have reported synthesis of homogeneously crosslinked hydrogel particles with continued feed of the crosslinking monomer during the polymerization.[52,72] Temperature ramp and continuous feed have also been used to synthesize large 1 to 5 μm sized particles.[78] Precipitation polymerization has also been performed without surfactants in a inject printer, where high shear forces and pressures have resulted in small stable particles (50 nm).[79] Precipitation polymerization in a continuous flow reactor has been reported as well.[80]

Precipitation polymerization can also be used to polymerize a PNVCL shell on a pre-existing particle or on a sacrificial template such as a dimethyldiethoxysilane droplet.[81] Removal of the sacrificial template will produce particles with inner lumen, *i.e.* capsules.

2. 2. Emulsion Polymerization

Emulsion polymerization is "polymerization whereby monomer(s), initiator, dispersion medium, and possibly colloid stabilizer constitute initially an inhomogeneous system resulting in particles of colloidal dimensions containing the formed polymer", according to the IUPAC definition.[82]

The typical precipitation polymerization of NVCL in water is sometimes referred to as an emulsion polymerization. However, in this text the term precipitation polymerization is used for the aqueous polymerizations of NVCL, which are performed above the phase transition temperature of PNVCL, and where the starting NVCL concentration (0.5–3 wt% monomer with respect to H_2O) is close to the solubility limit of NVCL. Most of the PNVCL particle synthesis are precipitation polymerizations. The use of larger concentrations of NVCL has been reported to lead to colloidal instability and to the formation of coagulum during the polymerization.[72]

In addition to precipitation polymerizations in water, PNVCL particles have also been synthesized with miniemulsion[83,84] and inverse miniemulsion polymerizations.[85,86] In miniemulsion and in inverse miniemulsion polymerizations, the initial polymerization mixture consists of evenly sized droplets dispersed in a continuous phase, and these droplets act as the loci of the polymerization and in the end turn in to polymer particles (Figure 2).[87,88] In contrast, in (macro)emulsion polymerization the picture is more complex. The starting mixture typically contains small surfactant micelles and large monomers droplets. There is a need for mass transportation from the monomer droplet to the growing particles during the polymerization. This can cause problems, including macro phase separation and formation of coagulum, when the formulation contains very solvophobic components with limited ability to migrate in the continuous phase. With these formulations, to avoid phase separation and instability, it is beneficial to choose the miniemulsion polymerization method, where transportation form monomer droplets to growing particles does not happen. Suitable conditions for miniemulsion are achieved by choosing correct surfactant and by using an intensive premixing process to create evenly sized small droplets before the polymerization. Additionally, the dispersed droplets often need to be stabilized against Ostwald ripening with a costabilizer, which is a compound that is very insoluble in the continuous phase, but soluble in the monomer phase.

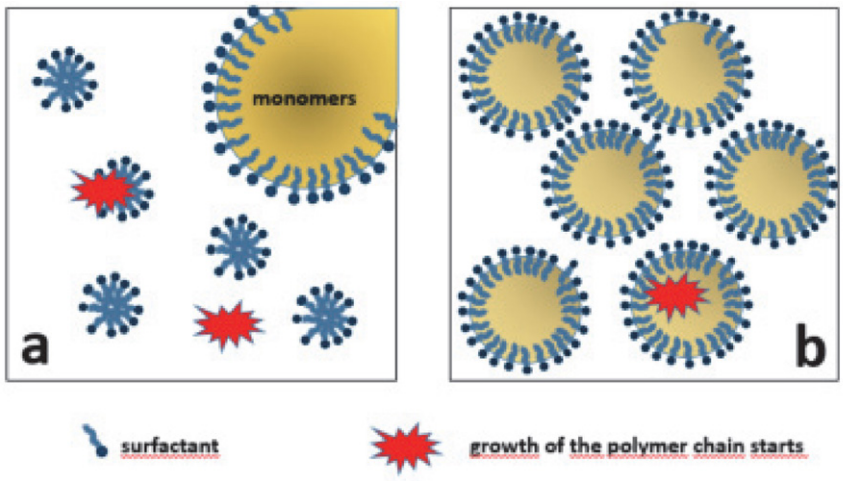

Figure 2. In emulsion polymerization (a) the polymer chains start to grow either in the surfactant micelles or in the continuous phase, whereas in miniemulsions (b) the chains grow in surfactant stabilized monomer droplets.

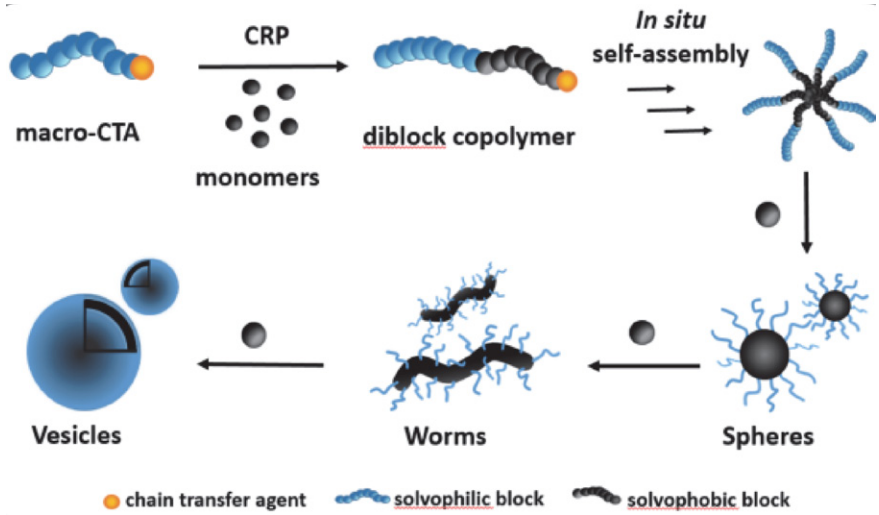

Figure 3. Polymerization induced self-assembly in water (drawn by Vikram Baddam)

In inverse miniemulsion polymerizations, the dispersed droplets consist of a polar solvent (usually water) and the monomer, and the continuous phase is non-polar. This method is suitable for the synthesis of water-soluble polymers. When the polymerization takes place in the droplet phase instead of the continuous water phase, polymer particles are formed instead of a macrogel. Effective incorporation of water-soluble compounds to the formed PNVCL colloidal gel particles could be a reason to use this syntheses method.

In miniemulsion polymerization, the dispersed phase is organic and contains the monomer, and the continuous phase is aqueous. The method has been used for the synthesis of PNVCL particles with high monomer concentrations (up to 16 $wt_{\%}$ with respect to H_2O)[83,84] and to synthesize PNVCL particles with a water insoluble comonomer,[89] which can be difficult with precipitation polymerization. The miniemulsion polymerization often demands the use of an additional hydrophobe (costabilizer) such as hexadecane and possibly the use of a cosolvent for the formation of the dispersed phase. The additives can result in a need of extensive purification steps. There are however, reports of miniemulsion-like polymerization of NVCL without any cosolvent or costabilizers,[89,90] with CTAB as the stabilizer and with starting NVLC concentration <1.4 $wt_{\%}$ performed after homonogenization with a microfluidizer (at least 1100 bars and 8 cycles). The polymerization conditions are almost identical to those used in the precipitation polymerizations, except for the homogenization process. NVCL is soluble in water at the used concentration, however relatively stable (at least for 250 min) monomer/surfactant droplets were observed with dynamic light scattering prior to addition of the initiator. This was because of the slowness of the dissolution of NVCL in water. This raises a question about the homogeneity of the starting situation in the precipitation polymerizations and on the correctness of the use of the term. In studies on the precipitation polymerization of NVCL, the starting mixture has seldom been investigated to verify the homogeneity.

2. 3. Polymerization Induced Self-Assembly

Polymerization induced self-assembly (PISA) is a type of controlled polymerization, where a solvophilic polymer is chain extended with a solvophobic block (Figure 3).[91,92] During the polymerization the growth of the solvophobic block causes the polymer to self-assemble. The polymerizations are most often reversible addition-fragmentation chain transfer (RAFT) polymerizations, where a solvophilic macromolecule with a chain transfer agent (CTA) as an end group, *i.e.* macromolecular CTA (macroCTA), is used to control the polymerization and as the soluble block in the forming copolymer. This is also a synthetic route to obtain polymer particles. These particles are not polymer networks but amphiphilic self-assemblies consisting of block copolymers with narrow molecular weight distributions. Usually, no surfactant is needed in addition to the soluble polymer whose chain is to be extended. Another appealing aspect of the polymerization is the possibility to obtain different well-defined morphologies by changing the block length ratio and concentration of the polymerization. Typically, high monomer concentrations (10 to 30 $wt_{\%}$) can and are used in the PISA polymerizations.

Recently, the first example of PISA of NVCL as the sole monomer was reported.[65] Prior work has shown how a partial utilization of the PISA concept can also be beneficial compared to the precipitation/emulsion free radical polymerizations. Etchenausia et al. have synthesized cationic hydrogel particles by polymerizing NVCL in water above the phase transition temperature of PNVCL with crosslinker and a cationic macroCTA.[93] Using a crosslinker in a batch polymerization makes it unlikely to obtain a controlled po-

lymerization and hence the polymerization induced self-assembly. However, the synthetic approach proved to be suitable for the production of colloidal hydrogel particles at high monomer concentrations (up to 10 $wt_{\%}$ in respect to mass of H_2O) compared to a free radical precipitation polymerization counterpart (no CTA, just surfactants). The macroCTA group reacted during polymerization and conferred unanticipated stability to the system against coagulation. The same group also performed aqueous PISA copolymerization of NVCL and vinylacetate with a PEG based macroCTA.[94] Control over molecular mass was limited and only few polymerizations were made, but the resultant material was interesting as the formed polymers resembled by composition Soluplus[95] (a commercial PNVCL containing polymer in clinical trials). No crosslinker was used as the hydrophobic comonomer prevented the dissolution of the formed assembly upon cooling if used in sufficiently high amounts (47 $mol_{\%}$ of monomers in feed).

3. Comparison of the Synthesis Methods

Tabela 1. Various selected aspects of synthesis methods of PNVCL particles

Method	Concentration[a]	Suitable for	*Surfactant*[b]	REF.
Self-assembly	≤ 0.2 wt%	homo- and copolymers	*not used*	37,59,60,62,65,66
Precipitation polymerization	0.5–3 $wt_{\%}$	homo- and copolymers	*0–8 $wt_{\%}$, or surfactant-type comonomer (2 – 50 $wt_{\%}$)*	42–44, 46–50, 57,68–78,94
Miniemulsion polymerization	≤ 16 $wt_{\%}$	homo- and copolymers	*0.4-2 wt% + possibly an additional costabilizer*	81,82,87,88
Inverse miniemulsion polymerization	≤ 5 $wt_{\%}$	homo- and copolymers	*100 $wt_{\%}$*	84
PISA	1–30 $wt_{\%}$	copolymers	macroCTA	63,91,92

a) monomers with respect to the weight of solvents plus continuous phase
b) wt% given in respect to monomer weight

Various aspects of the different synthesis methods to obtain soft PNVCL nanoparticles are presented in Table 1, to allow convenient comparison between them.

4. Conclusions and Future

The PNVCL particles are widely utilized as active ingredient carriers and emulsion stabilizers. PNVCL provides a thermoresponsive matrix for hosting the guest. The polymer is ideal for this purpose due to its non-toxicity and compatibility with a broad variety of compounds. Solventphobicity is an efficient driving force in loading of the particles. The particles themselves can act as nanoreactors and the temperature-dependent conformation controls the accessibility of reagents inside the particles and diffusion of material into and from the particle. Together with the surface active properties, this offers opportunities for interfacial reactions.

Current trend is to add functionality to the microgels for more specific tasks, and for more accurate delivery and release of the active ingredient. Similarly, more sophisticated architectures such as vesicular particles with drug loaded to the inner lumen surrounded by a membrane with temperature dependent permeability,[67] degradable crosslinks for triggered release,[64,81] and core-shell particles with pH dependent accelerated release of proteins[53] are promising.

There is also a report of PNVCL gel particles showing antiviral activity against HIV-virus.[77] Additionally, soft particles may be found in future in various scavenging applications including temperature dependent interactions with bacteria[17] or removing small amounts of oil from water [22]. New innovative applications keep appearing. As the synthesis methods develop and are getting industrially applicable, we see a great potential for soft PNVCL particles.

Acknowledgement

We thank Vikram Baddam for Figure 3.

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Povzetek

Mehki nanodelci so pomembna vrsta materiala in se lahko uporabljajo kot nosilci aktivnih spojin. Nabrekli in prehodni delci lahko delujejo kot gostitelj za aktivne sestavine in zagotavljajo stabilnost, odzivnost na dražljaje in reciklabilnost za gosta. Termoodzivni koloidni gelski delci so še posebej privlačni za takšne aplikacije zaradi njihove izjemno mehke strukture, velikosti in odzivnosti. Poli(N-vinilkaprolaktam) (PNVCL) je veliko raziskan in priljubljen termoodzivni polimer. Ni (oz. je zelo malo) strupen, temperatura faznega prehoda pa je blizu telesne temperature. Med faznim prehodom postane polimer manj topen, PNVCL nanodelec izloči velik del vode in se skrči v bolj kompaktno obliko. Ta prehod v veliki meri vpliva na difuzijo materiala v delce in iz njih. Hkrati s topnostjo polimera se spreminjajo tudi interakcije z vgrajeno spojino. Ta članek se osredotoča na sintetične metode, lastnosti in aplikacije mehkih PNVCL delcev.