Thesis book

TUNING THE INTERNAL STRUCTURE OF pNIPAm BASED MICROGEL PARTICLES AND MULTILAYERS

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Introduction

Soft materials have gained much attention as candidates in many industrial and medical applications. Among them stimuli-responsive hydrogels have attracted a widespread interest in the past decades. These materials can give reversible non-linear response in their swelling and shrinking to environmental stimuli. The stimuli that have been investigated to induce changes in polymer gels are diverse, and they include temperature, pH, solvent and ionic composition, electric field, light intensity, and introduction of specific molecules.

Disadvantage of macroscopic hydrogels is their slow response to the changes in the external conditions. However, this problem can be overcome by preparation of microgels. Microgel particles are cross-linked macromolecules that swell in the solvent. They have several orders of magnitudes smaller characteristic dimensions than that of the macrogels resulting in a considerably accelerated kinetic behavior. Besides their technical applications (e.g. surface coatings, rheological control and stabilizing agents) microgels are promising candidates for the development of biochemical and biomedical applications, controlled drug delivery systems, heavy metal scavengers, etc.

Of great possibility is the potential use of stimuli responsive microgels as biomaterials. Many investigations demonstrated that they can be suitable to fabricate drug-releasing systems or they can be employed as tissue engineering matrices. Biocompatibility is a crucial factor for the mentioned applications and it is known that microgels have better biocompatibility when they have high water content in swollen state. The degree of swelling is closely related to the internal structure of the microgel particles, which is well known to be highly inhomogeneous due to the non uniform cross-link density distribution within the particles. The necessity to prepare and use microgel particles with a homogeneous internal structure has been discussed and emphasized by many research groups but it has not been solved yet.

Responsive microgels also gave a great contribution in developing material science. Many studies dedicated special attention in using them for tuning materials at

interfaces and careful design the topmost surface layers. In this way a given material, depending on the condition under which is utilized, has a variable surface response, e.g. it can be hydrophobic or hydrophilic, adhesive or repellent, able to release or adsorb some species. The method par excellence used in the preparation of responsive surfaces is the Layer by Layer deposition. The degree of swelling again plays a very important role, which is largely influenced by the materials used for the surface modification and the interactions they establish with the microgel particles.

The swelling ability of responsive microgels makes them particularly interesting for the preparation of drug targeting systems known as polyelectrolyte complexes. They are divided into two classes: complexes of anionic and cationic polyelectrolytes and complexes of polyelectrolytes and oppositely charged surfactants. These complexes may efficiently modify the release; improve the stability and character of the drug substances due to their capacity to entrap the drug at molecular level. Hence, the polyelectrolyte complexes have great potential in the design of novel drug delivery systems.

Aims of achievements and methods

My work was intended to investigate the application of the pNIPAm particles as responsive nanocontainers applied either attached to a solid support or as free individual particles in bulk.

In the first case the traditional layer by layer deposition technique was used to form the multilayers. The negatively charged thermoresponsive poly(N-isopropylacrylamide-co-acrylic acid), p-(NIPAm-co-AAc) microgel particles have been alternated to the positively charged microfibrillated cellulose fibers (MFC) on polyethilenimine coated quartz and silica substrates. Previous investigations have indicated that negatively charged p(NIPAm-co-AAc) particles can form self-assembled multilayers with oppositely charged polyelectrolytes and the multilayers can be loaded and they can release drug molecules. However, these investigations also showed that the released amount levels off after a few layer of microgel particles due to the interpenetration of the oppositely charged polyelectrolytes. To overcome this difficulty positively charged microfibrillated cellulose fibers (MFC) was used to build a microgel multilayer. Quartz Crystal Microbalance (QCM-D) and Ellipsometry measurements were used to monitor the multilayer build-up. AFM images were also prepared to visualize the formed surface structures. The multilayers were then loaded with fluorescein isothiocyanate isomer I and the release characteristics were examined at room temperature and by temperature cycling to induce the particle collapse.

The incorporation of hydrophobic domains into the p-(NIPAm-co-AAc) particles by means of surfactant addition was also studied to design a drug releasing system. The interaction between the Cetyl Trimethyl Ammonium Bromide and the p-(NIPAm-co-AAc) was investigated by the surfactant binding isotherm measurements. Binding isotherm and dynamic light scattering measurements were performed to follow the surfactant binding and monitor its effect on particle size and stability in the function of the surfactant concentration. In the range of charge neutralization phase separation occurred.

To avoid phase separation in the range of stoichiometric surfactant binding the possibility of preparing sterically stabilized temperature and pH responsive p(NIPAm-co-AAc) microgel particles we also investigated. To achieve this goal first the kinetics of the microgel formation were investigated using ultrafiltration to separate the unreacted incorporation monomers and HPLC to measure their concentration in the reaction mixture. The measured kinetic data allowed the determination of the optimal feeding time of a poly(ethylene oxide) PEO macromonomer to the reaction mixture to form PEO shell on the microgel particles. We prepared two types of p(NIPAm-co-AAc)-PEO shell particle (5 and 10 mol% PEO) and investigated their swelling (by DLS measurements) and their electrophoretic mobility in the function of temperature and pH. The interaction of the prepared microgel particles by an oppositely charged surfactant (dodecyl trimethyl ammoniumbromide) was also investigated.

In the literature several investigations demonstrated that microgel particles prepared by precipitation polymerisation can be described as having core-shell morphology. Kinetic studies demonstrate that cross-linker monomers are faster incorporated than NIPAm monomers, which results in the formation of particles with a highly cross-linked core and a looser shell. Since the properties of the swollen microgel particles are closely related to their internal structure an other important aim of this thesis was to develop a method that allows the preparation of microgel particles with uniform crosslink distribution.. To achieve this goal we have investigated the kinetics of the cross-linker incorporation into the microgel particles by HPLC and then by controlling the composition of the reaction mixture we were able to synthesize homogenously cross-linked pNIPAm particles. The particles have been characterized by DLS and their properties are compared to the properties of microgel particles prepared by the conventional preparation method using the same average crosslink density.

New scientific results

1. Stable multilayer thin films of cationic cellulose I nanofibrils and anionic poly(N-isopropylacrylamide-co-acrylic acid) can be constructed by LbL deposition. The rigid structure and relatively big size of the nanofibrils (5-10 nm thickness and up to 1 μm length) prevent the interpenetration of the oppositely charged components. It gives rise to the formation of an open composite structure that is highly penetrable for other molecules.

2. In opposition to polyelectrolyte based multilayers, the multilayer thin films of cationic cellulose I nanofibrils and anionic poly(N-isopropylacrylamide-co-acrylic acid) microgel can load and release the probe molecule at room temperature (~25 °C). By collapsing the deposited microgel particles over the Volume Phase Inversion Temperature close to quantitative release of the entrapped probe molecules can be achieved in a single step.

3. The interaction of the cationic Cetyl Trimethyl Ammonium Bromid surfactant with the negatively charged poly (NIPAm-co-AAc) microgel particles takes place in two steps binding process. The surfactant binds to the polyelectrolyte gel particles in the form of monomers, i.e. the interaction is non-cooperative. The interaction results in the colloid instability of the microgel-surfactant complex when the microgel charge is neutralized, which leads to the phase separation of the system. In the excess of surfactant the dispersion becomes stable due to the charge reversion of the microgel/surfactant complex.

4. One step synthesis was successfully developed for the preparation of PEO shell containing poly(N-isopropylacrylamide-co-acrylic acid) microgel particles. The presence of the PEO shell sterically stabilizes the electrically neutral p(NIPAm-co-AAc)-surfactant complexes in a wide range of temperature, pH and ionic strength.

5. A novel method, first in the literature, was developed for the preparation of homogeneously cross-linked pNIPAm microgel particles. The method is based on keeping constant concentration of the NIPAm monomer and the BA crosslinker in the reaction mixture by means of regulated feeding of the monomer and cross-linker during the polymerization.

6. The optical properties and the swelling of the homogeneously cross-linked pNIPAm microgel particles significantly differ from the characteristics of the traditional inhomogeneously cross-linked microgel.

List of publications

1. Attila Borsos, **Roberta Acciaro**, Róbert Mészáros, Tibor Gilányi
   „*Interaction of Cetyl Trimethylammonium Bromide With Poly-(N- Isopropylacrylamide-Co-Acrylic Acid) Copolymer Nanogel Particles"*,
   Progr. Colloid Polym. Sci., **2008**, *135*, 188–193.

2. **Roberta Acciaro**, Christian Aulin, Per M. Claesson, Lars Wågberg., Imre Varga
   "*Investigation of the formation, structure and release characteristics of self-assembled composite films of cellulose nanofibrils and temperature responsive microgels*"
   Soft Matter, **2011**, *7*, 1369 – 1377.

3. **Roberta Acciaro**, Tibor Gilanyi, Imre Varga
   "*Preparation of monodisperse p(N-isopropyl acrylamide)Microgel particles with homogeneous segment density distribution*"
   Langmuir, **2011**, *Accepted*

List of presentations

1. R. Acciaro, A. Borsos, T. Gilányi, *Characterization of poly(N-Isopropylacrylamide-co-Acrylicacid) nanogels and interaction with cationic surfactants,* Chemical Research Center, Budapest, Hungary, 19th January 2009.

2. R. Acciaro, I. Varga, *Fluorescein release from thermoresponsive microgel - cellulose fiber thin films,* ESC 2009*,* European Student Colloid Conference, Almeria, Spain, 15th -18th July 2009.

3. R. Acciaro, I. Varga, T. Gilányi, *Controlling the internal structure and the release characteristics of pNIPAm microgel particles,* MTA Kolloidkémiai és Anyagtudományi Munkabizottság, Balatonvilágos, Hungary, 27th-28th May 2010.