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Conventional and Radiation Synthesis of Polymeric Nano- and Microgels and Their Possible Applications

J.M. Rosiak*, P. Ulanski and S. Kadlubowski

Institute of Applied Radiation Chemistry, Technical University of Lodz,
Wroblewskiego St. 15, 93-590 Lodz, Poland

Abstract

Soft nanomaterials – polymeric nanogels and microgels – have made a fast and brilliant career, from an unwanted by-product of polymerization processes to an important and fashionable topic of interdisciplinary research in the fields of polymer chemistry and physics, materials science, pharmacy and medicine. Together with their larger analogues – macroscopic gels, most known in the form of water-swellable hydrogels – they have a broad field of actual and potential applications ranging from filler materials in coating industry to modern biomaterials.

A multitude of techniques has been described for the synthesis of polymeric nano- and microgels. Most of them can be classified in two groups. The first one are techniques based on concomitant polymerization and crosslinking (where the substrates are monomers or their mixtures), called by some authors "crosslinking polymerization". The second group are methods based on intramolecular crosslinking of macromolecules (where the starting material is not a monomer, but a polymer).

The possibilities of employing macroscopic polymer gels as biomaterials, mostly in the form of hydrogels based on synthetic polymers, have been explored since 1960's, when these materials were first synthesized [1]. Since then, a number of products reached the stage of commercial application, soft contact lenses, drug delivery systems and wound dressings being the most widely known examples. Given the number of research groups involved and progress being made in this field, one may anticipate that in the future the number of hydrogel-based biomedical products on the market will be constantly increasing.

Introduction

Soft nanomaterials – polymeric nanogels and microgels – have made a fast and brilliant career, from an unwanted by-product of polymerization processes to an important and fashionable topic of interdisciplinary research in the fields of polymer chemistry and physics, materials science, pharmacy and medicine. Together with their larger analogues – macroscopic gels, most known in the form of water-swellable hydrogels – they have a broad field of actual and potential applications ranging from filler materials in coating industry to modern biomaterials.

There are at least two ways of defining polymeric *nanogels* and *microgels*. One of them originates from the definition of polymer gels. A *polymer gel* is a two-component system consisting of a permanent three-dimensional network of linked polymer chains, and molecules of a solvent filing the pores of this network. *Nanogels* and *microgels* are particles of polymer gels having the dimensions in the order of nano- and micrometers, respectively. The other definition says that a *nanogel* or a *microgel* is an internally crosslinked macromolecule. This approach is based on the fact that, in principle, all the chain segments of a nanogel or microgel are linked together, thus being a part of one macromolecule. It also reflects the fact that such entities can be synthesized either by intramolecular crosslinking of single linear macromolecules or in a single polymerization event (*e.g.* initiated by one radical) that in the absence of crosslinking would lead to the formation of a single linear polymer chain.

The latter definition allows us to consider nano- and microgels as a specific form of macromolecules, along with linear, branched, comb-like, circular, star-

*corresponding author. E-mail: rosiakjm@mitr.p.lodz.pl

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shaped, dendrimer, and others. Since usually the shape of a nano- or microgel resembles a linear macromolecule in a coiled conformation, these structures are often seen as permanently "frozen" polymer coils.

In fact, molecular weights and dimensions of swollen nanogels are often similar to these of typical single macromolecules in solution, but the presence of internal bonds results in different physicochemical properties, including fixed shape, different rheological behavior, higher resistance to degradation and the ability to trap other molecules within their structure.

Microgels belong to the large family of crosslinked polymeric *microparticles*. Their distinct property is the ability to swell in a suitable solvent. Certainly, the choice of such a solvent is a function of the chemical structure of the polymer network. Therefore a crosslinked microparticle that remains impermeable and does not swell in contact with a group of solvents, may become a microgel in another group of solvents.

Very important and perhaps most studied so far are microgels composed of hydrophilic polymers, thus being capable of swelling in water. Such gels, irrespective of their dimensions, form a large group of compounds named *hydrogels*. Typical hydrogel-forming polymers are those containing hydrophilic groups as –OH, –COOH, $–NH_2$, $–CONH_2$, –CONH–, $–SO_3H$ or ether linkages. In principle, nearly all water-soluble polymers, including those of natural origin, can be transformed into hydrogels. Macroscopic hydrogels have been extensively studied since 1960's [1] and till now a number of large-scale applications emerged from this field (contact lenses, drug-delivery systems, wound dressings *etc.*) [2-6]. Hydrogels, due their good biocompatibility and ability to mimic the properties of some tissues like cartilage and muscles, are especially suitable for use as biomaterials.

All polymer gels, macro- and microscopic, can be divided in two classes with respect to the character of the bonds linking the chains. In a *physical gel* or *pseudogel*, the links may be relatively weak van der Waals forces, hydrophobic or electrostatic interactions or hydrogen bonds. These phenomena will not be discussed here. *Chemical gels* or *permanent gels* are polymer networks where the links between the chains are covalent bonds. Therefore, such gels cannot be easily destroyed or dissolved, since their destruction would require the covalent bonds to be broken.

A distinct class of nano- and microgels are stimuli-sensitive ("smart", "intelligent") structures. They are able to react, usually by a pronounced change in dimensions and swelling ability, to external stimuli such as temperature, pH, ionic strength, concentration of a given substance, electric field, light *etc.* Such structures may find applications in controlled or self-regulating drug delivery, signal transmission or micromachinery.

First reports regarding microgels date from 1930's, when Staudinger described the formation of a styrene-divinylbenzene microgel [7,8]. Since then, hundreds of reports have been published on this topic. For a full insight, the reader is directed to the excellent review papers by Funke *et al.* [9] and Saunders and Vincent [10], covering most of the relevant aspects, as well as to a number of reviews dedicated to more specific issues [11-13].

In this report we will first discuss the methods used to synthesize microgels, than briefly review their actual and potential applications.

Synthesis

A multitude of techniques has been described for the synthesis of polymeric nano- and microgels. Most of them can be classified in two groups. The first one are techniques based on concomitant polymerization and crosslinking (where the substrates are monomers or their mixtures), called by some authors "crosslinking polymerization". The second group are methods based on intramolecular crosslinking of macromolecules (where the starting material is not a monomer, but a polymer).

Formation of microgels by crosslinking polymerization

Crosslinking polymerization is the most common process used to synthesize polymeric network. The substrate is usually a mixture of monomers, where at least one of the components contains two or more polymerizable functions. For example, in the case of free-radical crosslinking polymerization of vinyl compounds this would require that at least one of the monomers contains two or more vinyl groups. When radicals are generated in such system, in the process of propagation monomer molecules add one after another to the free radical at the end of the growing chain. Since some monomer molecules bear two or more active groups, upon incorporation in the (initially) linear chain, some of their functionalities are not yet used and form pendant active groups along the macromolecule. Therefore, the propagating chain may react not only with monomer molecules, but also

with these pendant groups. If the pendant group belongs to another chain, the two chains become linked together (intermolecular crosslinking). If the propagating radical reacts with a pendant group localized on its own chain, a closed loop is formed (intramolecular crosslinking). Intermolecular crosslinking leads to the formation of branched structures and finally to macroscopic gel filling the whole volume of the reaction vessel ("wall-to-wall" gel). In an ideal case, after all the functionalities reacted, the final product would be a single molecule occupying the whole reaction vessel, with all chain segments linked together. On the other hand, pure intramolecular crosslinking leads to separate, highly internally crosslinked single macromolecules, *i.e.* nanometer-size microgels. In practice we can speak about prevailing inter- or intramolecular crosslinking. Most microgels synthesized by crosslinking polymerization are formed by combination of these two processes.

Crosslinking polymerization in solution

Most of the work on the microgel synthesis by crosslinking polymerization is solution has been done on the systems reacting according to the free-radical mechanism. An alternative is the synthesis by anionic crosslinking polymerization in solution.

Free-radical polymerization

Free-radical crosslinking polymerization in solution, although less commonly used than emulsion-based techniques, is a subject of considerable interest, both in the area of gelation theories and experimental studies. This seems to result from the fact it is probably the simplest available method for the preparation of microgels, it has a broad range of applications, is highly versatile and does not require the use of surfactants. The latter, employed in most versions of emulsion polymerization techniques, may be present in the final product and may need to be removed in a separate purification step, thus making the synthetic procedure more complex. On the other hand, microgel formation by crosslinking polymerization in solution requires a very careful choice of reaction parameters. In general, it provides less precise control of the size of the products and yields microgels of broader size distribution than emulsion polymerization.

In order to obtain microgels by crosslinking copolymerization in solution, it is necessary to control the competition between propagation of linear chains, intermolecular crosslinking and intramolecular crosslinking in such a way that microgels of desired average molecular weight and/or dimensions are formed, but no macrogelation occurs. One of the decisive factors is the concentration of the monomer mixture. In a dilute solution where the growing chains are separated, the local concentration of the pendant reactive groups within the macromolecule is much higher than their average concentration in the whole reaction volume. Therefore, reaction of the growing chain end with a pendant group belonging to its own chain is much more probable than a reaction with a pendant group of another chain. Thus, intramolecular crosslinking is promoted and, at a certain stage, the system contains mainly microgels. On the contrary, in a concentrated solution where the coils of both growing and dead chains overlap, the probability of the chain end reacting with a "foreign" pendant group may be higher that with its own one. This promotes intermolecular crosslinking and, in consequence, macrogelation, often not being preceded by a distinct microgelation stage. For a detailed description of the phenomena related to microgel formation in free-radical crosslinking polymerization, consult the review paper of Funke *et al.* [9] and a recent theoretical study of Okay [14].

In the course of a crosslinking polymerization reaction proceeding through a microgelation stage, two factors tend to shift the competition between intra- and intermolecular crosslinking towards the latter process. The first factor is that the number (and concentration) of microgels increases, making the interparticle contact and reaction more probable. The second is that within a microgel particle the number of pendant groups available for further intramolecular crosslinking events decreases (probably not only due to their actual decay in the crosslinking reaction, but also due to the increasing sterical constraints within the internally crosslinked structure). Therefore, even in the relatively dilute systems where intramolecular crosslinking initially prevails, one can finally expect macrogel formation.

An interesting example illustrating how versatile this method may be is the first report on the synthesis of fullerene-containing microgel structures [43]. Fullerenes, acting as multi-functional monomers, were co-polymerized, in a free-radical process in *o*-dichlorobenzene solutions, with 4-vinylbenzoic acid, as well as with 2- and 4-vinylpyridine to form submicron- and micron size microgels of interesting rheological and electroactive properties.

Another new and elegant way to control the kinetics and yields of free-radical crosslinking polymerization reactions is the idea of radical living polymerization [16-22]. In this technique, a spin-trapping agent (iniferter) is present in the polymerizing system that can reversibly combine with the propagating radical at the end of a growing polymer chain. The free chains, spin trap and their product – blocked, inactive ("dormant") radical – are in equilibrium. As a result of that, at given polymerization conditions the momentary concentration of active propagating (or crosslinking) radicals can be kept at a much lower level than in the absence of the iniferter. This concentration may be controlled by varying the concentration of the spin trap. The use of living polymerization is rapidly expanding in polymer synthesis due to its many advantages (*e.g.* precisely controlled average molecular weight and molecular weight distribution), and has also found its way to the field of synthesis of microgels.

A specific case of crosslinking polymerization in solution is precipitation polymerization, when the microgels being formed in solution have the tendency of de-swelling and precipitation. Since the further growth and cyclization reactions are limited mostly to the surface and the inner sphere of such a phase-separated particle (that can be considered as a de-swollen, collapsed microgel), the resulting products are often nearly monodisperse.

It seems that precipitation polymerization is especially suitable for preparing thermo-sensitive microgels, since one can control the precipitation/deswelling tendency by changing temperature. For example, for a polymer that undergoes a phase transition leading to precipitation above a given temperature (lower critical solution temperature, LCST), it is possible to carry out precipitation polymerization above LCST, and subsequently re-solubilize the product by lowering the temperature.

Recent studies indicate that precipitation polymerization can be also used to fabricate a sort of imprinted microgel structures [23], per analogy to the molecularly imprinted non-swellable microspheres of broad biomedical use, synthesized by a similar technique [24].

Anionic polymerization

In ionic polymerization [25-28], the active centers participating in chain growth are not radicals, but ions. In principle, three groups of monomers can be used: hydrocarbon (including vinyl), polar (acrylates, methacrylates) and cyclic (oxiranes, lactones *etc.*). Although the ring-opening polymerization of the latter group of compounds is a promising technique used to obtain microspheres [83], so far only the first two groups have gained some attention in the field of microgel synthesis. The carbanions being the active centers in anionic polymerization usually do not undergo any spontaneous deactivation, thus such a process may be considered as a living polymerization. However, since carbanions react rapidly with any substances bearing reactive H-atoms (water, carboxylic acids, alcohols), a pre-requisite of performing a living polymerization is high purity of the reactant mixture. Since even traces of water from air can prevent the polymerization and in general the concentration of impurities should be kept at a sub-micromolar level, this requirement is one of the main difficulties encountered when using this technique. In the case of polar monomers, polymerization is often carried out at a low temperature (*e.g.* below -75°C) in order to eliminate side reactions.

The technique of anionic polymerization, due to the formation of (theoretically) infinitely long-lasting active centers, is particularly useful in the synthesis of structured microgels, mostly based on block copolymers. A typical approach is a two-step procedure. In the first step, only one monomer (A) is polymerized until the monomer is used up but the active centers at the chain ends still present. Upon addition of a second monomer (B), the polymerization continues. In a simplest case, a block copolymer of the structure $(A)_n$-$(B)_m$ is formed. If A is a bifunctional monomer and B is a monofunctional one, this approach leads to the formation of core-shell star-shaped structures, with a microgel as a core and linear chains bound as branches. This technique (called by some authors "core-first") has been applied to the systems where the microgel core is built of 1,4-divinylbenzene [29-33]. A reverse technique ("arm-first"), where the bifunctional monomer is added to the living linear chains, was used *e.g.* to synthesize products having EGDMA microgel core and poly(*t*-butyl acrylate) arms [34]. Much work has been done on the microgel formation in another block copolymer system, *t*-butylstyrene-divinylbenzene (TBS-DVB) [35-39].

Emulsion polymerization

Macroemulsion

In the synthesis of microgels by polymerization in solution, the most important difficulty is how to

avoid macrogelation, *i.e.* how to confine the crosslinking reactions into small, separated spaces. This problem can be overcome by using emulsion polymerization, where each micelle may serve as a separate microreactor, protected from the contact with other micelles by the stabilizing action of a surfactant. Thus, in such a confined space the polymerization and crosslinking reactions can be carried out to a high degree of monomer conversion, resulting in a single microgel particle, with no or very limited macrogel formation. Because of this advantage, emulsion polymerization is a very popular way of microgel fabrication.

In a classical free-radical emulsion polymerization [40,41], the system initially consists of monomer molecules that are dispersed in the liquid phase (usually water) in the form of micelles (of a size in the order of a few nm) and monomer droplets, typically of the size of 0.1÷1 mm. Such microheterogeneous system is stabilized by the presence of surfactants. The radicals are generated in the liquid phase. In some systems, initiation and first propagation steps also take place in the solution. As the growing chain has the tendency to become phase-separated, surfactant-protected polymer-monomer particles are being formed, where the further polymerization and crosslinking steps take place. In other systems (especially when monomers are poorly soluble in water), initiation may occur within a monomer-filled micelle by an initiator radical that diffuses into the micelle from solution. During the chain growth, monomer molecules diffuse from the droplets and any inactive micelles to the active particles containing growing chain(s). After these outer monomer sources are used up and only the rests of monomer inside the active particles react, these particles do not grow any longer (or may even contract due to internal crosslinking when multifunctional monomers are present) and, upon nearly complete consumption of the monomer, the process is finally terminated.

Emulsion polymerization of monofunctional monomers leads to the formation of coagulated polymer particles (latexes), while in the presence of multifunctional monomers internally crosslinked particles – microgels – are formed, having the ability to swell in a good solvent.

Microemulsion

Some of the disadvantages of the classical emulsion polymerization can be avoided by using miniemulsion or microemulsion polymerization [9,13,42,43].

In a monomer-containing emulsion, with increasing surfactant concentration the amount of monomer stored in the droplets decreases while more monomer molecules form micelles. When a critical value of emulsifier concentration is reached, no monomer droplets are left, with all the monomer being present in micelles (and to some extent in the solution). Such a transparent micellar solution is a starting point for the polymerization in microemulsion. In such a system the polymerization in monomer droplets is avoided. In the absence of this side effect known from the macroemulsion technique, nearly monodisperse microgels can be easily synthesized.

Inverse emulsion

Most of the emulsion polymerization syntheses are performed in systems where the continuous liquid phase is water or aqueous solution, and the monomers and polymers are of relatively hydrophobic character. Certainly, it is possible to reverse this situation and polymerize hydrophilic monomers in organic, hydrophobic liquid phase.

The mechanism and kinetics of microgel formation in inverse emulsion polymerization have been extensively studied in the case of acrylamide [44]. The influence of the kind of solvent, kind and concentration of emulsifier, monomer content, agitation speed *etc.* on the rate of process and product properties were described.

Beside of synthesizing neutral hydrophilic microgels [44,45], this technique is especially well suited for producing polyelectrolyte microgels of uniform size. For example, spherical gel microparticles of acrylic acid co-polymerized with diethylene glycol diacrylate have been fabricated by inverse miniemulsion polymerization [13]. The products were having various diameters, depending on the surfactant concentration, and a polydispersity lower than 10%.

Surfactant-free emulsion polymerization

Emulsion polymerization, besides its numerous advantages, has also some shortcomings, the most important being the presence of surfactants that usually have to be removed from the products in a separate step after the synthesis. A complete removal of a surfactant is not always possible, since its molecules may be in some cases incorporated (bound or trapped) into the products. This problem is especially pronounced in the case of microemulsion polymeriza-

tion, where, relatively large quantities of emulsifiers must be used in order to force all monomer to be present in micelles.

A way out of this problem, although limited to some particular systems, is the use of a technique called by some authors "surfactant-free emulsion polymerization" (SFEP), where the stabilization of emulsions is provided by the monomer and/or polymer itself. This can be realized in at least two ways: either the initiator of free-radical polymerization is an ion, that, when incorporated into a growing oligomeric chain, causes this molecule to be surface active, or the substrates for polymerization are unsaturated (*i.e.* polymerizable) oligomers bearing ionized groups at one or two ends.

Crosslinking polymerization in the bulk

Bulk polymerization is a possible but, in general, not particularly suitable way of synthesizing microgels, primarily since the polymerizing and crosslinking system tends to form a macroscopic "wall-to-wall" gel in the whole reaction volume. According to classical gelation theory [46] involving homogeneous growth of linear chain and their subsequent linking together, formation of distinct microgels as intermediate stages should not take place. However, in reality most polymerizing and crosslinking systems are not strictly homogeneous (see a brief general discussion in ref. [9] and references cited therein). If, before macrogelation is reached, the polymerization and crosslinking processes proceed trough stages characterized by inhomogeneous density of crosslinks, *i.e.* when microgels are formed that are not (yet) linked together, there is some chance that they could be potentially separated.

Polymerization with non-classical initiation

Most of the work on the synthesis of microgels by combined polymerization and crosslinking has been done using classical initiation methods, *i.e.* with chemical initiators, which, when activated (mostly thermally decomposed) give rise to reactive intermediates capable of initiating the chain reactions of polymerization and crosslinking. This approach, although most commonly used, has some disadvantages. First of all, the initiator or its fragments usually remain in the products, either chemically bound or entrapped within the polymer structure. This may pose serious problems in these applications where purity of the material is of high importance (biomaterials, optics, electronics). Secondly, in some cases the heating of the reaction mixture in order to activate the initiator may be undesirable. Therefore there is a need for alternative techniques where initiation is provided by other means. One may envisage that the techniques already used in polymerization processes, like photopolymerization, radiation polymerization, initiation by the action of ultrasound or microwaves will find an application in the microgel synthesis as well.

Photopolymerization and photocuring are very intensely studied synthetic techniques, widely used in industry [47,48].

Radiation-induced polymerization is a well-established, versatile synthetic technique used in the polymer science and, to a limited extent, also in technology (for reviews see [49-56]). Polymerization initiated by ionizing radiation (typically gamma rays from isotope sources or fast electrons generated by accelerators) is quite similar to the classical one and can be performed in the bulk, in solution, in emulsion *etc.*, the main difference being only the initiation step. Ionizing radiation can interact with monomers and polymers by direct or indirect effect. In the former, the energy is absorbed by a monomer molecule, which may result in a radical formation, in the latter the energy is absorbed by the solvent, and reactive products (mostly radicals) resulting from this event may in turn attack monomer to initiate polymerization. In the case of aqueous systems, the species initiating the polymerization is most often the hydroxyl radical.

Ionizing radiation can be used in the synthesis of polymer gels (both macro- and microscopic) in two general ways: either by inducing crosslinking polymerization of monomers, or by inducing crosslinking of polymer chains in the absence of monomers. The latter technique has some important advantages and will be discussed separately. It is important to know that at late stages of radiation-induced polymerization, when only low quantities of free monomer molecules are left in the system and the radicals are still generated randomly along the chains, intermolecular recombination (crosslinking) reactions may occur with a considerable yield even in the total absence of any bifunctional monomer. Therefore, by using ionizing radiation it is possible to obtain a polymer gel starting from monofunctional monomers. More often than not, multifunctional monomers are used anyway, usually in order to increase the yield of crosslinking and thus reduce the radiation dose necessary to produce a gel of a given crosslink density. Applica-

tions of this technique range from the formation of gels based on relatively simple compounds (*e.g.* acrylamide [57] or *N*-vinylpyrrolidone [4]) to complex stimuli-sensitive "smart" gels targeted for advanced biomedical purposes [58-62]).

Examples of radiation-induced polymerization employed to synthesize internally crosslinked polymer microparticles are the works of Yoshida *et al.* [63-67] and Naka *et al.* [68-70]. Various monomer mixtures, mainly containing diethylene glycol dimethacrylate, were irradiated without any auxiliary substances in organic solution to yield products that were suitable for derivatization or immobilization of biomolecules, and intended for biomedical applications. Microgels can be also synthesized by radiation-induced crosslinking polymerization in emulsion, as shown on the example of styrene-based gels co-polymerized with cationic polymerizable surfactants [71].

Ultrasound is often used in microgel or microparticle synthesis, albeit not for initiating chemical reactions, but rather as a tool for solubilization, agitation, homogenization, formation of miniemulsions *etc.* It seems that the well known fact that the same ultrasound can induce polymerization (for reviews see [72-74]) has so far largely escaped the attention of the researchers working on microgel synthesis.

Although no extensive studies on the possibility of microgel synthesis by ultrasound have been made so far, there are first reports on the possibility of ultrasound-induced polymerization of bifunctional monomers [75] and fabrication of microspheres [76].

It has been shown that concomitant action of ionizing radiation and ultrasound may lead to interesting results in the synthesis of internally crosslinked microspheres (that would become microgels in a suitable solvent). In a radiation-induced crosslinking polymerization of diethyleneglycol dimethacrylate in ethyl acetate, the action of ultrasound affects the size and shape of formed particles, probably by promoting interparticle interactions [77].

Intramolecular crosslinking of polymer chains: monomer-free techniques

In most research work and applications, microgels are synthesized using procedures based on polymerization processes starting from monomers as the basic substrates. This is, however, not the only possible way. An alternative approach to the synthesis of microgels, in particular the *nanogels* of small size (typically < 0.1 μm), is intramolecular crosslinking of individual macromolecules. An obvious and important advantage of this method is the absence of monomer. This is of great value when the product is intended for biomedical use, where even small quantities of residual monomer may be potentially harmful and thus unacceptable. Furthermore, intramolecular crosslinking may provide means to obtain crosslinked structures of various molecular weight and size, including very small structures, depending on the molecular weight of the parent polymer. Such nanogels obtained from single macromolecules are interesting physical forms of polymers as they are a sort of "frozen" polymer coils of limited segmental mobility. One can also expect that a combination of intra- and intermolecular crosslinking [78-80] will provide a tool for synthesizing nanogels and microgels of independently chosen molecular weight and dimensions (various internal densities). Last but not least, intramolecular crosslinking of individual macromolecules is an interesting reaction. A number of questions regarding this process, particularly its kinetics, have not been answered yet [81-83].

Chemical intramolecular crosslinking

Intramolecular crosslinking, similarly as polymerization, can be performed either as a thermally initiated chemical reaction or as a photo- or radiation-induced process. Chemical intramolecular crosslinking of individual polymer chains can be achieved in at least two ways. One is to prepare linear or branched polymer with pendant reactive (*e.g.* vinyl) groups and initialize the crosslinking by a suitable initiator. Another way does not require any special substrate preparation (no polymerizable pendant groups needed). It has been shown that intramolecular crosslinking of single chains of water-soluble polymers can be carried out by reacting them with a suitable crosslinking agent in dilute solutions. The crosslinker must be capable of reacting with the functional groups (–OH, –COOH *etc.*) of the polymer, and should be at least bi-functional. Synthesis is carried out in solution. Polymer concentration must be chosen sufficiently low to avoid intermolecular crosslinking, *i.e.* it must be significantly lower than the coil overlap concentration. By varying the concentration of the crosslinker one can influence the internal crosslink density. Burchard *et al.* used this approach to synthesize internally crosslinked single macromolecules (nanogels) of poly(vinyl alcohol) with glutaraldehyde as the crosslinker [84] and of poly(allylamine) cross-

linked with 1,4-dimethoxybutane-1,4-diimine dihydrochloride [85] (also [86,87]). Similar approach is used to obtain microgels of polysaccharides.

Radiation-induced crosslinking

Synthesis of nano/microgels by intramolecular crosslinking of individual polymer chains can be also initiated by ionizing radiation. The main advantage of this method is that it can be carried out in a pure polymer/solvent system, free of any monomers, initiators, crosslinkers or any other additives, therefore it seems to be especially well suited for the synthesis of high-purity products for biomedical use. In this approach, discussed in more detail below, pure aqueous solution of a polymer is subjected to a short (a few microseconds), intense pulse of ionizing radiation. In this way, many radicals are generated simultaneously along each polymer chain, and their intramolecular recombination leads to the formation of nanogels. This approach has been first tested on neutral water-soluble polymers: poly(vinyl alcohol) [82], polyvinylpyrrolidone [88] and poly(vinyl methyl ether) [89,90], and later expanded to poly(acrylic acid) as an exemplary polyelectrolyte [83,91].

The main parameter influencing the competition between inter- and intramolecular recombination of polymer radicals in dilute solutions is the average number of radicals present at each macromolecule at the same time [81]. If this number, under the given synthesis conditions, is much lower than 1, there is only a meager chance that a radical will find a reaction partner within the same chain. In such cases, recombination is only possible between radicals localized on two separate macromolecules. On the other hand, when there are tens of radicals present along each chain, the probability of intramolecular encounters and reactions is higher than that of intermolecular ones. The latter processes are relatively slow, since they require that two large entities – polymer coils – diffuse towards each other.

In the case of the radiation-induced radical formation, these two opposite conditions, *i.e.* a very low or very high number of radicals per chain, can be fulfilled by means of a proper choice of irradiation conditions. Continuous irradiation at a relatively low dose rate, such as typical irradiation with gamma rays from isotope sources, leads to a steady-state concentration of polymer radicals in the order of 10^{-7} M. When the concentration of polymer coils is significantly higher than this value (this condition is usually easily fulfilled), the average number of radicals per chain is much lower than unity and intermolecular crosslinking is observed. In order to promote intramolecular crosslinking, short, intense pulses of radiation can be employed, such as pulses of fast electrons from an accelerator, generating radical concentrations in the order of $10^{-4}\div10^{-3}$ M. If the concentration of polymer coils is low (that is to say, $10^{-6}\div10^{-4}$ M), many radicals are generated on each macromolecule (typically many tens or even over a hundred), and the conditions for intramolecular recombination are fulfilled. Certainly, this does not mean that intermolecular reactions are totally eliminated in such a case. Some coils may come into contact before all the radicals decay, and if there is an uneven number of radicals on a chain, at least one of them must finally find a reaction partner at a neighboring macromolecule.

The data on changes in molecular weight, viscosity and radius of gyration following the pulse-irradiation of dilute polymer solutions clearly indicate that strongly internally crosslinked nanogels are formed, which, in comparison with the starting macromolecules, have somewhat higher molecular weight but at the same time significantly lower dimensions [82,83,88, 91]. While the main reason for the increase in molecular weight is the intermolecular crosslinking occurring in the system with very low yields in parallel to intramolecular recombination, the latter process is the dominant reason for the reduction in coil dimensions.

A balance between inter- and intramolecular recombination of polymer radicals may be also maintained when continuous irradiation is used. Therefore it is possible to synthesize microgels by crosslinking in a solution using isotope sources, as has been experimentally demonstrated and supported by simulations for poly(vinyl alcohol) by Wang *et al*. [78-80,92].

Disruption of macroscopic networks

The idea of obtaining microscopic gel particles by disrupting continuous "wall-to-wall" gels seems to be conceptually the simplest of all synthetic approaches, since the procedures used to obtain macroscopic networks are usually simple, with less parameters to be controlled than in the above described typical microgel synthesis methods – there is no need to control the micelle size or to observe the precautions necessary to avoid macrogelation. Disadvantages of this "non-elegant" method are that the size distribution is very broad (however for microgels in the scale of many micrometers it can be reduced *e.g.* by using

mechanical sieves), one cannot usually expect producing extremely small gel particles in this way nor obtaining products of a regular, spherical shape. On the other hand, the disruption method may be of some advantage for synthesizing microgel fractions of various diameters, but precisely the same crosslink density (since they are derived from one specimen of a macroscopic gel) [93]. In the authors' laboratory this method is used routinely to fabricate large amounts of coarse polyvinylpyrrolidone microgel of dimensions below 50 μm, following radiation-induced synthesis of macroscopic gel in the bulk [94]. A gel disruption process has been reported to yield crosslinked polysaccharide microgels (of dimensions in the 100 nm range), as one of the steps to construct polysaccharide/phospholipide biovectors for drug delivery [95].

It should be noted that important final steps of almost all synthetic procedures used to obtain microgels are purification and drying. It has been clearly demonstrated that drying methods and conditions may have significant influence on the final structure and properties of microgels [45,96].

Applications

Biomaterials

The possibilities of employing macroscopic polymer gels as biomaterials, mostly in the form of hydrogels based on synthetic polymers, have been explored since 1960's, when these materials were first synthesized [1]. Since then, a number of products reached the stage of commercial application, soft contact lenses, drug delivery systems and wound dressings being the most widely known examples. Given the number of research groups involved and progress being made in this field, one may anticipate that in the future the number of hydrogel-based biomedical products on the market will be constantly increasing.

Broad, although not very recent publications on the medical use of hydrogels are the collective works edited by Peppas [2] and DeRossi *et al.* [97]. Park *et al.* reviewed the narrower field of biodegradable hydrogels [98]. Out of more recent books and book chapters on this subject [99] provides more general outlook, while the scope of ref. [100] is limited to silicone-based hydrogels. For exemplary review papers on the medical applications of hydrogels, see [3,101-108].

Although certainly the characteristics of hydrogels differ from one to other formulation, a few common properties can be listed that make these materials suitable for biomedical applications. In their high water content and hydrophilicity hydrogels are similar to tissues. They also mimic some properties of soft tissues as reversible swelling and elasticity. Due to their network structure they may be loaded with a drug, which can be subsequently released at a controlled rate. This rate can be adjusted, one of the main factors being the mesh size. The latter parameter allows also constructing semi-permeable membranes or containers, for example an outer shell of a hybrid artificial organ (an implant containing living cells) allowing the transport of water, oxygen, nutrients and enzymes, but being impermeable to larger entities as immunoglobulins and other components of the immune system [109-111]. Due to their fair to excellent biocompatibility, hydrogels are usually well tolerated as implants.

An example of a mature biomaterial technology based on classical, homogeneous hydrogels is the large-scale production of wound dressings, by a technique combining radiation-induced crosslinking of polyvinylpyrrolidone and concomitant sterilization of the final product [4,112]. A number of other products based on similar technology, *e.g.* systems for local delivery of anticancer drugs and for induction of childbirth, have successfully passed clinical tests [103,111,113,114].

While "regular" hydrogels are already common components of biomaterials, current efforts of the researchers are now concentrated on the stimuli-sensitive ("intelligent", "smart") gels [5,11,97,115-119]. These materials are able to respond to external stimuli, such as temperature, pH, ionic strength, light, electric field or even to (selective) changes in the concentration of a given chemical species. The latter property can be used *e.g.* in glucose-responsive insulin-releasing devices [120] or antigen-responsive systems [121]. The response to the stimulus, being induced by conformational changes of the polymer chain segments, usually manifests itself as a pronounced change in the gel volume (strong contraction or expansion) and in the amount of bound liquid (decrease or increase in the degree of swelling). Due to these properties, stimuli-sensitive gels are tested for applications as sensors, actuators, chemical valves, controllable or self-regulating drug-delivery systems or even artificial muscles. Certainly, there is still some gap between the artificial hydrogel fish that moves by swinging its tail in a laboratory bath [122] or electrically driven gel finger working in the air [123] and

a future implementation of a hydrogel-based muscle, but fast developments in the field of stimuli-sensitive hydrogels allow to expect that biomaterials based on these materials will be implemented very soon.

Microgels are also intensely studied with respect to their biomedical applications (reviews: [9,11,117, 118,124-127], exemplary patents [128-132]. Of course, the product range is different than that of macroscopic gels, although there is a significant overlap in the field of controlled drug delivery. The most important microgel applications in the biomedical field are: carriers for enzymes, antibodies *etc.* used in diagnostics (*e.g.* immunoassays), drug carriers for therapeutic purposes (local, controlled drug delivery), and, potentially, microdevices, artificial biological fluids and synthetic vectors for drug delivery.

Coupling microgels with selective biochemicals leads to materials applicable in biological testing [9, 11,133]. This technique is used since some time with solid nanospheres [125,133,134]. In some cases, in comparative tests microgels performed better than polystyrene-based microsphere supports, providing testing material of higher sensitivity [135]. A typical way of action of the microgel-based immunoassay is based on an aggregation of antibody-bearing microgels with the specific antigens. The large particles formed in this way can be detected by microscopic techniques. In a modified immunoassay, magnetic microgels can be applied, containing encapsulated polymer core with adsorbed magnetic nanoparticles [128,136]. Magnetically labeled cells can be separated from a cell mixture by applying magnetic field, for example in a section of tubing in which the cell mixture is flowing.

Albeit there is a broad field of potential biomedical applications of conventional microgels, a strong tendency is observed to focus the research on complex microgels and on stimuli-sensitive systems. The preference for using stimuli-sensitive gels is even more pronounced for microgels than for the "wall-to-wall" gels. One of the important reasons is much shorter response time. While the reaction of macroscopic responsive gels to a stimulus is sometimes unacceptably slow (for example, when the molecules of a chemical stimulus have to diffuse into the whole volume of a gel slab), microgels, due to their small dimensions and high surface-to-volume ratio respond much faster.

Temperature-sensitive microgels are tested for controlled binding of biomolecules. It has been shown that poly(*N*-isopropylacrylamide) – pNIPAM – microgels can bind various proteins by physical sorption above the phase transition temperature (*i.e.* at *ca.* 40°C), and release them upon lowering the temperature to 25°C [137,138]. Proteins can be also covalently bound to such gels, and their activity can be controlled by temperature changes [139]. In complex systems such as described by Yasui *et al.* [140], one can achieve high enzyme activity within a defined, relatively narrow (a few degrees) temperature range. Pichot and co-workers demonstrated the possibility of using thermo- and pH-responsive microgels for binding nucleic acids [118,141]. It has been shown that the interaction of temperature-sensitive microgels with elements of the immune system like granulocytes (foreign-body attacking cells) can be moderated by changes in temperature [142]. It is worth noting that the interaction of pNIPAM gel particles was much weaker than that of polystyrene microspheres, which may indicate that, in the context of attack by immune system cells, these microgels have higher biocompatibility than solid microspheres.

Thermosensitive microgels have been also tested as drug carriers. The structure and hydrophilic/hydrophobic properties of the drug have been identified as important factors influencing the phase transitions and uptake/release characteristics of poly(N-vinyl caprolactam) gel particles [143]. In order to achieve the desired release profile, composite microgels may be used, for example combined nonporous silica/pNIPAM gels [144]. The rate of the thermally triggered drug release may be then controlled by changing the composition of this hybrid product. Another interesting example of a composite structure based on drug-loaded thermosensitive microgels is a wound dressing, where drug-bearing pNIPAM gel particles are incorporated into a self-adhesive film [145]. The product combines adhesive and temperature-controlled absorptive functions, and is easy to peel off after use.

Compositions containing poly(*N*-vinylcaprolactam-*co*-sodium acrylate) microgels and gelatin undergo a reversible macrogelation upon temperature increase above *ca.* 32°C [146]. Such materials, liquid (injectable) at R.T., but forming a gel at the temperature of human body, are considered for applications in surgery and drug delivery.

Another group of responsive materials tested for use as biomaterials are pH-sensitive and/or ionic-strength-sensitive microgels. For these products, there are at least two mechanisms allowing for controlled drug delivery. One can load the gel particles with a drug at a pH where the particles are fully swollen

(expanded), trap it inside by a pH change leading to the collapse of the microgel, and subsequently allow the drug to diffuse out at a pH-controlled rate. Similar mechanism applies as well to the systems where ionic strength is the stimulus for expansion and collapse, or where both pH and ionic strength effects are operating. Another mechanism is pH-dependent reversible ionic binding of drugs. Drug- and protein binding and release from anionic microgels have been studied *e.g.* by Eichenbaum *et al.* [147,148] and Soppimath *et al*. [149], while Vinogradov *et al.* [132, 150,151] described the synthesis and properties of some cationic systems.

Sophisticated drug-delivery system, mimicking the action of secretory granules, has been constructed by Kiser *et al.* [152-154]. The core is an anionic microgel particle based on methacrylic acid, loaded with a drug. Subsequently, by lowering pH, a collapse of the microgel is induced. In this form, the particle is coated with a lipid bilayer, to simulate the natural secretory granule and to protect the particle from premature swelling. Poration of the lipid bilayer (*e.g.* by applying electric field) causes the gel to swell, allowing release of the drug. A different synthetic procedure leading to similar systems is based on encapsulation of hydrogel-forming components into liposomes and subsequent polymerization [155]. Further example of this kind is a group of products intended for drug delivery of vaccine formulations, consisting of crosslinked polysaccharide microgel core surrounded by a lipid bilayer [95].

A pH-sensitive microgel preparation based on poly(methacrylic acid-*co*-ethyl acrylate) has been devised for oral delivery of a novel drug being a HIV-1 protease inhibitor [156]. It has been demonstrated that the absorption of this poorly water soluble drug from the tested system was much better than from the suspension of a free drug.

Solid sustained release devices for oral delivery of drugs can be obtained by compressing microgels. Such a system based on polyurethane microgels has been shown to retain its integral structure but become microporous on swelling with water [131].

Microgels can be functionalized not only by coupling them with biomolecules, but also by molecular imprinting. This process leads to microgels bearing structural binding sites specific to target molecules. A general procedure of molecular imprinting of a polymer is as follows. Monomers being in contact with a template molecule are polymerized and crosslinked, the template is removed and the polymer network contains a complementary binding site able to rebind the same template or analogous molecules. Ye *et al.* and Biffis *et al.* demonstrated the applicability of this procedure for synthesizing molecularly imprinted microgels and proved their binding performance [23, 24,157].

Stability of shape and dimensions of microgels when compared with linear polymer chains may be helpful in their potential use for blocking dental microchannels in cases when there is a need to use a synthetic substitute for the natural gel-like substance performing this function [158].

An interesting and potentially valuable property of microgels is their enhanced resistance against degradation when compared to linear macromolecules [107,159]. As a result of any intense or long-lasting stimulus inducing chain breakage (a mechanochemical action, ultrasound, the formation of peroxyl radicals along the chain *etc.*), a linear macromolecule is easily degraded to short fragments. The same number of chain breaks formed in a microgel may cause no or very little fragmentation, since the chain segments are linked together in many points and will not fall apart as a result of a single chain break.

The above described effect has been demonstrated on microgels of poly(acrylic acid) – PAA [91,160]. Aqueous solutions of linear chains and microgels of PAA were subjected to the action of ionizing radiation in the presence of oxygen. Under such conditions, no crosslinking takes place in the system. Initially formed carbon-centered radicals are rapidly converted into the corresponding peroxyl radicals, which in turn initiate processes leading to chain scission. As the concentrations of linear and crosslinked chains of similar average molecular weight were identical, the yield of scission events should be equal for both samples. However, the changes in molecular weight and in the radius of gyration in the case of linear and microgel PAA revealed striking differences. While linear PAA is easily degraded even at relatively low doses, which is evidenced by parallel decrease in weight-average molecular weight and radius of gyration, microgels, within the same dose range, seem to remain intact, their molecular weight and radius of gyration being constant.

This degradation-resistance combined with suitable rheological properties may be used in fabricating materials for medical applications. A commercialized example of such a product is a polymer drug based on microgels of a natural polysaccharide used to enhance the viscoelasctic performance of malignant

synovial fluid [161]. These macromolecules are subjected to mechanochemical stress and to the attack of reactive oxygen species, mainly free radicals. It has been shown that under such conditions internally crosslinked macromolecules perform better than the corresponding linear ones [162]. Preliminary tests on a substitute synovial fluid containing microgels made of a synthetic polymer proved the high degradation resistance and proper viscoelastic properties of this product [163].

First tests have been performed on the application of microgels as synthetic, non-virial vectors in gene delivery. The latter is regarded as a powerful tool for curing some hereditary diseases and treating genetically based disorders. Certainly, the issue is a very complex one, since such vectors must be capable of performing many processes as binding DNA fragments, attachment to cells, internalization, and intracellular plasmid release. First attempts of using microgel-like structures for gene delivery were based mainly on chitosan, but synthetic structures based on 2-(dimethylamino)ethyl methacrylate, *N*-vinylpyrrolidone and *N*-isoporpylacrylamide have been tested as well, with promising results [126].

There are also projects to design microgel-based intravenous drug carriers that could remain in blood for a suitable period of time, facilitate the cellular uptake and possibly also selectively deliver the drug to a target site. Animal tests have shown that by varying properties of such structures (chemical composition, hydrophilicity) one can change the biodistribution patterns of the microgels and that drug-loaded microgels were more efficient than equivalent concentrations of free drug in curing melanoma in mice [126].

Some further perspectives in the application of nano- and micro-sized particles and devices in drug delivery are discussed in ref. [127].

Coatings

When actual, large-scale applications of microgels are concerned, the surface coatings industry seems to be the most prominent field. Hundreds of research papers published and patents issued (for a few representative examples see [164-180]) dealing with microgel-containing coatings emphasize the significance of this application. The interest in the use of microgels as components of coatings originated mainly from environment protection needs and regulations. In order to reduce the amount of volatile organic compounds in the coating formulations, the manufacturers tend to increase the total solid content. This is, however, problematic if polymer components of a given molecular weight range are used in binders, since the viscosity of formulations becomes too high. When microgels are used, viscosity can be maintained at a desired level. Another approach besides the high-solid products is to use water-borne coating systems. Microgels can be used both in solvent-borne and water-borne coating products. Besides their advantageous rheological properties, they often exert reinforcing effect on the cured coating. The use of microgels in coating technologies has been the subject of concise but informative reviews [9,181] (see also book chapters in [182,183]).

Microgel-containing solutions and dispersions are usually characterized by pseudoplastic, strongly non-Newtonian rheological properties. They are highly viscous at low shear rate (they don't flow at a zero shear rate), but their viscosity decreases remarkably with increasing shear rate. This is in a perfect accordance with the needs for a typical paint application process. In the storage tank (no or low shear rate) the viscosity should be high to prevent pigment settling, during the gun-spraying (high shear rate) low viscosity is desired, and at the object surface (no or low shear rate again) viscosity should increase rapidly so that no sagging effect occurs, even for films of high thickness. Another useful property of microgels is their positive influence on the orientation of flake pigments in metal effect coatings.

Microgels have also positive influence on the mechanical properties of cured paint films as stone chip resistance, impact flexibility and elasticity. This is attributed to the crosslinked polymer structure, high molecular weight of gel particles and the microheterogeneous structure of the microgel-containing polymer film that probably allow the impact energy to be more efficiently dissipated [181].

In the automotive industry, the primer coating layer is often applied by electrodeposition. It has been shown that compositions containing amine-based cationic microgels, mostly in the form of aqueous dispersions, can be used for electrocoating [184,185].

Problems that have been recently investigated with respect to the use of microgels in coatings include deeper understanding of the relationship between microgel structure and rheological properties (and ways to adjust the latter) [186], the influence of substrate composition and synthetic procedures on the shelf stability of the product and affinity between microgels and pigments [187], influence of microgels

on the drying time [44] and ability to form films suitable for drying at ambient temperatures [188].

Microgels can be used not only as constituents of regular coatings, but also as self-adsorbing and self-organizing film-forming layers for protecting metal surfaces against corrosion. It has been shown that core-shell microgels based on styrene, butyl acrylate and phosphate-substituted acrylates form a layer of a structured molecular order on a surface of technical aluminum and provide efficient protection against corrosion in standard tests [189,190].

Albeit the use of synthetic microgels in coatings started in the late 1960's [191] or, depending on what we consider as true microgel, perhaps rather in the 1970's [192,193], one should mention that physical and chemical studies on a highly durable ancient oriental lacquer used in Asia since millennia revealed a structure containing self-formed, natural core-shell-like microgel particles [194].

Miscellaneous

Besides their applications in coatings (biggest market) and in biomaterials (perhaps the most promising direction for the future), microgels are used or tested for use in a number of other fields.

Besides large-scale use of microgels in coating industry, similar properties make them interesting for the manufacturers of *cosmetics*, namely nail varnishes [195,196]. In varnishes based on organic solvents, organophilic clays are used to prevent pigment sedimentation. These compounds, however, exert some unwanted side effects and usually require toluene as a component of the formulation. The presence of microgels allows reducing or eliminating the use of clays, while maintaining the proper rheological properties of the varnish and preventing the precipitation of the pigments.

Historically one of the first applications of microgels was in the *papermaking* [197-199]. In manufacturing quality products starch and other polysaccharides used as paper and paperboard sizes may be replaced with poly(vinyl alcohol) (PVAL) for better performance. It has been demonstrated that microgels of PVAL show clear advantages over the same polymer in a linear form, *e.g.* they have lower tendency to penetrate into paper, which is an undesirable effect.

Microgels can be a valuable component of *fibers*. An exemplary application is the admixture of vinylidene chloride gels to an acrylic fiber, significantly improving the flame retardancy [200]. Similar gels have been shown to improve load-bearing properties and flame retardancy of polyurethane *foams* [201].

Microgels can be also applied as supports in *catalysis*. Organo-aluminum compounds coupled to organopolysiloxane microgel particles serve as co-catalysts in the polymerization of olefins [202,203]. By using microgel-supported catalyst, a homogeneous catalysis in a flow reactor may be carried out. If the inlet and outlet of the reactor are equipped with membranes that the gel particles cannot pass, the reactants are in a constant flow but the catalyst remains in the reactor, despite it is present in a nearly molecular dispersion.

Particular rheological properties as well as higher mechanochemical resistance of microgel solutions when compared to the solutions of linear chains are the basis of their applications in the fields of liquid thickening, *oil recovery* and *hydraulics*. Solutions of relatively inexpensive polyacrylamide-based microgels are used as thickening agents and agents for restricting the flow of liquids through subterranean formations [204]. Microgel solutions can be applied as a non-Newtonian, shear-resistant, non-leaking hydraulic fluid for hydraulic energy transmission systems and devices absorbing mechanical energy (liquid springs, shock absorbers) [205].

Due to their swelling and water-retaining properties, hydrophilic microgels have been postulated and tested, with good results, for use as *soil conditioners* [206-208].

An extensively tested and potentially broad field of microgel application is in *printing* and *photographic technology*. Since the rheological properties of microgel can be tailored to meet specific needs (a sophisticated method of viscosity adjustment may be varying the hair length of a core-hair type microgels), they may be useful in liquid photopolymer formulations used to cover the screen in the screen printing technique [209]. Incorporation of microgels in the photosensitive layer of a kind of modern lithographic plates leads to a product that can be developed directly on a printing press, without a post-exposure wet development step [210]. This technology allows saving time and labor as well as reduced the use of volatile organic compounds. Another technology has been elaborated to obtain printing plates for flexographic printing [211,212]. Microgel-based photosensitive resin allows the plates to be water-developable, thus eliminating the use of harmful halogen-containing solvents used to develop the plates in a conventional technique. A variety of photosensitive composi-

tions for use in printing and manufacture of printed circuit boards employ microgels to enhance physical properties, eliminate cold flow, improve storage stability, enhance photospeed and to render these materials the suitability for water-processing [213-216].

Some inks and electrographic liquid developers contain finely dispersed microparticles of magnetic substances. Several problem have to be overcome in producing these "magnetic fluids", one the most important being the poor dispersion stability. This can be significantly improved when incorporating these solid microparticles, during synthesis, into polymeric microgels [217].

Macroscopic polymer gels can be made photosensitive, not only by introducing chromophores that undergo permanent changes (*e.g.* crosslinking) upon irradiation, but also by incorporating structures that enable reversible photochemical switching of properties (reversible crosslinking) [218]. This indicates that also microgels themselves can be turned into photosensitive materials, either by using suitable monomers or by post-synthesis modification. In fact, coumarin-containing organosilicon microgels have been demonstrated to undergo photoinduced cluster formation [219]. So far, most often microgels are used in photography and imaging as auxiliary substances, either as binding agents improving the physical properties of the film layers, or as additives that help to incorporate the photographically active or other (*e.g.* antistatic) substances into the photographic layers [220,221].

Debord *et al.* have demonstrated that relatively simple microgels made of poly(N-isopropylacrylamide) can be manipulated to form colloidal crystals of specific colors depending on the fabrication parameters [222]. In another approach, polymeric nanospheres are incorporated into a stimuli-sensitive hydrogel [223]. Under the action of a chemical stimulus, the distances between the nanospheres can be varied, thus causing shifts the wavelength of the Bragg peak of the diffracted light. This leads to the changes in color of the specimen. It is expected that such colloidal crystals can find a wide range of applications in *photonics* and *chemical sensing*.

One may expect that in the near future interesting applications will be found for the recently described *electrically conducting microgels* based on pyrrole and aniline polymers bound to a gel core [224]. The products have promising properties in the aspects of electrical conduction, electromagnetic frequency interference shielding and electrostatic prevention.

Sorption and *binding* of a variety of compounds is an intensely studied application field of polymer gels. Most of research in this area concerns the use of hydrogels. Exemplary applications of macroscopic hydrogels being investigated, besides drug-delivery systems described in "Biomaterials" section, include *e.g.* binding of metal ions [225], selective removing of pollutants (arsenate and selenite [226], textile dyes [227], organic substances [228]) or collecting uranyl ions from seawater [229]. Reversible sorption of water by hydrogels is tested for an application in sludge dewatering [230].

A number of studies revealed the potential application of microgels in *metal ion binding* and *ion exchange*. An advantage of using micro- instead of macrogels is primarily the binding kinetics – in microgels the binding groups are easily accessible, in contrast to most macroscopic gel structures, where considerable time is needed for the substrates to diffuse into the gel volume. Gel particles bearing carboxylate groups bind divalent alkali earth cations (Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}) more effectively than monovalent cations (as Na^{+}) [231]. Binding of calcium ions has been studied in more detail [146,232]. Other studies have shown that there may be a pronounced selectivity in binding divalent metal ions. For example, binding of Hg^{2+} cations by poly(*N*-vinylcaprolactam-*co*-sodium acrylate) microgels is much stronger than binging of Cu^{2+} and divalent alkali metal ions [233]. Strong, albeit reversible, binding of Pb^{2+} by microgels of poly(*N*-isopropylacrylamide-*co*-sodium acrylate) has been reported as well [234,235]. These observations indicate that microgel-based systems may be used for selective ion binding.

One of the most fascinating prospective uses of stimuli-microgels is in *microdevices* and *micromachinery*. Due to their fast response time, they may be for example used as self-regulated, pH- or temperature-controlled microvalves. Contrary to conventional microactuators (electromagnetic, electrostatic, thermopneumatic *etc.*), microgel-based valves are simple and do not require external power for operation. Fully operational exemplary devices of this kind, having short response times, have been recently presented by Beebe *et al.* [236].

Microgels can be used as building bricks for constructing complex polymer structures and materials. A simple example may be a fabrication of a polymer material (foil, coating, *etc.*) of well-developed, rough (in the microscale) surface. This may be carried out just by casting a foil from a microgel solution. Such

a surface, even after drying and collapse of microgels due to a loss of solvent remains structured, when compared to analogous sample obtained from solution of linear chains of the same polymer [91].

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