POLYMERIC NANOGELS OBTAINED BY RADIATION TECHNIQUE

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1. 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 by 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-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.

A multitude of techniques has been described for the synthesis of polymeric nano/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).

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 (…this situation corresponds to a random coil which is essentially *frozen* in one conformation, like a piece of twisted wire. A molecule of this type in dilute solution could be called a "single chain glass" (Pierre deGennes). One can also expect that a combination of intra- and intermolecular crosslinking 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.

Given the commercial availability of a multitude of polymers, including food- and medical grade products, starting from a polymer rather than from a monomer can be a reasonable synthetic option. Moreover, in some cases, where monomers do not exist (like poly(vinyl alcohol)) or polymerization either impossible or very difficult (carbohydrates), intramolecular crosslinking of polymers may be the best way to produce nanogels.

2. 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. Batzilla and Funke synthesized linear poly(4-vinyl styrene) and subsequently carried out a crosslinking of this polymer in dilute solution using 2,2`azobis(isobutyronitrile) (AIBN) as an initiator.[1] Reaction conditions and time could be chosen where intramolecular crosslinking prevailed. In a similar way, microgels can be made of pre-formed polymers by photocrosslinking.[2]

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[3] and of poly(allylamine) crosslinked with 1,4-dimethoxybutane-1,4-diimine dihydrochloride[4] (*cf.* also [5,6]). Similar approach is used to obtain microgels of polysaccharides. For example, hydroxypropylcellulose microgels can be produced by (presumably mostly intramolecular) crosslinking of linear chains with divinylsulfone.[7] Analogous processes are utilized for the synthesis of commercially produced preparations of internally crosslinked hyaluronic acid.[8-11]

3. 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)[12], polyvinylpyrrolidone[13] and poly(vinyl methyl ether)[14,15], and later expanded to poly(acrylic acid) as an exemplary polyelectrolyte[16,17].

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.[18] 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 $10^{-4} \div 10^{-3}$ M. If the concentration of polymer coils is low (that is to say, $10^{-6} \div 10^{-4}$ 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.[12,13,16,17] 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.* [19–22]

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