RADIATION PROCESSING OF POLYMERS IN AQUEOUS MEDIA

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1. INTRODUCTION

The focus here is on radiation-initiated processes that synthetize or modify polymers using water as a reaction medium. The motives for using water as the medium for polymerization reactions are reviewed. An historical perspective gives an outlook on the opportunities that radiation processing of polymers in water offers, especially in the emerging fields of bio- and nanotechnology. Some basic concepts of radiation-initiated polymerization and water radiolysis are noted. A distinction is made between homogeneous and heterogeneous polymerization processes in aqueous media. The radiation-initiated crosslinking of polymers is covered. This is an approach to the synthesis of hydrogels and their nanoscale analogues, nanogels (NGs), which represent two of the most successful uses of radiation-initiated synthesis of functional materials for biomedical applications. Finally, there is a brief discussion of the possible use of water radiolysis products to control the molecular weight of biopolymers and to produce nanoparticles.

1.1. WATER AS REACTION MEDIUM

The reasons for using water as a reaction medium are numerous. Generally, water-based processes are more environmentally friendly than those that make use of organic solvents. Using water as the reaction medium, whenever is possible, is one of the paradigms of "green chemistry". More specifically, the advantage of using water as the reaction medium in radiation processing is that the radiation chemistry of water is a well-established field. The nature and yields of radiolytic species are known and can be tuned by changing the irradiation conditions and/or by adding co-solutes to suit the purpose of initiating

chemical reactions. Water radiolysis products can be exploited to initiate polymerization reactions, the grafting of monomers onto polymers or substrates, and to initiate crosslinking, without requiring the addition of initiators and catalysts. As a result, purer products are obtained, containing no residues of the components that are inevitably present when polymerization is carried out by conventional processes, such as thermally initiated or photoactivated processes. This aspect is of particular importance for uses in medicine or electronics where high purity product yield is a requirement.

Polymerization, grafting or crosslinking can be regarded as additive processes, where the level of organization and complexity increases, along with the functionality; the system evolves from monomers to polymers, from monomers/polymers to graft-copolymers, from polymers to crosslinked networks. Subtractive processes can also be of interest. The oxidizing radicals, generated by the radiolytic decomposition of water, can be effective in promoting polymer degradation and in controlling polymer molecular weight.

Water can be present at the surface of materials exposed to ionizing radiation in various environments. Water can also be saturated with oxygen from the air or by other gases. Varnishes and encapsulation compounds, matrices of reinforced structural composites, adhesive and sealant compounds for nuclear reactors, polymers used in aerospace vehicles, satellites and resins used for the encapsulation of radioactive wastes are some examples of where water radiolysis products can promote the modification of the chemical structure of some polymers and consequent degradation of their properties. Even when polymerization or crosslinking is the desired process, molecular degradation of the formed chains or networks can occur. An understanding of the reaction mechanisms by which polymers exposed to water are produced and/or modified is important to the selection of the process conditions that can minimize adverse secondary processes and unwanted by-products.

1.2. HISTORICAL OUTLINE OF RADIATION PROCESSING OF POLYMERS IN AQUEOUS MEDIA AND OUTLOOK

The radiation processing of polymers in aqueous media has an almost century-long history, but with a somewhat discontinuous development. The pioneering studies of Hopwood and Phillips in 1939 [1] and, a few years later, of Joliot [2] provided the scientific community with the evidence that monomers, such as methyl methacrylate (MMA) or styrene, could be polymerized in solution (or in bulk) by either gamma rays or fast neutrons. The optical clarity and mechanical properties of radiation-polymerized poly(methyl methacrylate) (PMMA) was superior to its thermally polymerized analogue because of a lack of internal stresses.

After the Second World War, when the nuclear fission reactors provided relatively inexpensive, powerful gamma radiation sources, large-scale development of radiation-initiated polymerizations took place. In particular, waterborne polymers and latexes were produced from methyl methacrylate (MMA), styrene (St), and vinyl acetate (VAc) monomers, amongst others. Fundamental studies were carried out by eminent scientists in the United Kingdom, France, the United States, the former Soviet Union, the Czech Republic, Italy, Japan, and Poland in the 1960s and 1970s. In the following years, material scientists working in industry were renowned for their ability to engineer materials into products, processes and devices, and dominated the field. Radiation-initiated processes and products thereof, as well as the technology behind the electron beam accelerators then and now in use, were developed almost exclusively by private companies. The result was that some processes became commercially relevant. The radiation vulcanization of natural rubber latex, the degradation of polysaccharides dissolved in water and the radiation crosslinking of water--soluble polymers to produce hydrogels are some examples. These programmes were not always supported by studies on reaction kinetics and mechanisms. The lack of a systematic organization of the knowledge base has somehow limited the possibility of new developments in the field. At the turn of the twenty-first century, the emergence of nanoscience and nanotechnology and the rising expectations for better performing and multifunctional materials are forcing scientists and technologists to cross the boundaries between disciplines and to invent new ways of manufacturing materials. Designing polymeric materials at the nanoscale joins the world of chemistry and macromolecules with the world of nanomaterials and nanotechologies, since "manipulation" of materials at the nanoscale, *i.e.* at the molecular level, is often required to achieve nano-enhanced performance. This is facilitated by using focused energy sources, such as energetic photons or electron beams. Radiation chemistry and radiation processing have a role in this field. To this aim, any research and development activities must progress along two parallel tracks: (i) the synthesis of new nanomaterials which clearly demonstrate the benefits, either in the manufacturing process or in their properties, stemming from the use of ionizing radiation and radiation chemistry; and (ii) the study of the mechanisms of reactions that are at the basis of the formation of nanostructures.

A clear understanding of the reasons behind the success or failure of past endeavours is a necessary tool for any future developments.

2. POLYMERIZATION IN AQUEOUS MEDIA

2.1. GENERAL CONSIDERATIONS

Before examining more in detail the different possible strategies to either synthetize or modify polymers in aqueous media by high energy irradiation, some basic concepts will be briefly recalled.

Radiation-initiated polymerizations can occur *via* either neutral free-radical or ionic-radical mechanisms. In aqueous systems, the neutral free-radical mechanism is ubiquitous since water is a universal ionic inhibitor. Ionizing radiation can initiate the polymerization by producing primary radicals in the solvent and in the monomer.

At a given time, the concentration of propagating radicals is the net result of the reactions that form them, such as the non-thermal initiation and radical transfer toward the monomer or polymer, and the reactions that consume them, such as termination by combination or disproportionation. Since termination depends on the probability that two radicals meet, it is governed by the concentration of radicals and then on the instantaneous concentration of primary radicals formed, hence on the dose rate. Moreover since there is a competition between primary radical propagation and mutual recombination, termination markedly depends on the concentration of the organic substrate.

The availability of different type of irradiation sources (gamma cells, electron accelerators) and irradiation conditions can give rise to a wide range of accessible dose rates. This, together with the possibility of choosing either diluted or concentrated solutions of monomer and/or polymers, leads to a great variety of polymerization rates and final products.

A distinction between reactions occurring in dilute systems and in concentrated systems is made. Relatively low dose rates processes, such as those carried out with gamma sources, and high dose rate processes from electron beam accelerators will also be looked at for their impact on the reaction mechanisms and product properties.

2.2. THE ROLE OF WATER RADIOLYSIS IN INITIATING POLYMERIZATION

In dilute aqueous solutions, water absorbs ionizing radiation. In concentrated solutions or mixtures, the radiation energy is absorbed by both the solvent and the solutes, leading to both "direct" and "indirect" effects. Direct effects are related to the energy directly absorbed by the solute, while indirect effects, mainly when dealing with dilute solutions, are the consequences of reactions between aqueous radiolysis products and solutes.

Understanding water radiolysis and knowing the G-values for the radiolysis products of water are of importance for a proper process design. Even small changes in the composition of water, such as those responsible for changes in pH, or the presence of dissolved molecular oxygen, can significantly affect the G-values. For instance, solvated electrons, e^-_{aq}, are protonated at low pH, thus increasing the yield of hydrogen atoms, while at very high pH, the hydroxyl radical ($^\bullet$OH) can undergo deprotonation to produce the less reactive $O^{\bullet-}$. Different oxidizing species are produced in aerated or O_2-saturated solutions, such as hydroperoxyl radicals ($HO_2^\bullet$) from hydrogen and a superoxide radical anion ($O_2^{\bullet-}$) from the solvated electron, the latter being the deprotonated form of the hydroperoxyl radical [3]. These two formed species are considerably weaker oxidants than hydroxyl radicals. Hence, depending on the material, the final yield of oxidized products may not be significantly altered by the presence of O_2.

Oxygen can also react with propagating radicals leading to a reaction pathway, which involves the formation of peroxides and their possible evolution towards the formation of aldehydes, ketones and carboxyl groups. To avoid the influence of O_2, solutions can be purged with inert gas such as N_2 or Ar.

Elevated solute concentrations can also induce a change in G-values if a competition takes place between the reactions involving solutes and the primary radiation chemical reactions [4-6].

Hydroxyl radicals under deaerated conditions and hydroperoxyl radicals, in the presence of oxygen from air, are the main species generating polymer radicals. The reactions between unsaturated and saturated carbons, as in vinyl and acrylic monomers or polymers and $^\bullet$OH or $HO_2^\bullet$ radicals are much faster than those with solvated electrons so that their effects in free radical polymerization can often be ignored [7]. Hydroxyl and hydroperoxyl radicals are neutral, so their initiation can be efficient without the need of electrolytes and buffers which are often required for most chemical systems.

When a higher concentration of initiating radicals is needed, solutions are saturated with nitrous oxide. Under these conditions solvated electrons give rise to hydroxyl radicals, thus doubling their yield. However, since a hydroxyl radical is not very selective in its reactions, it can react with many organic materials and functional groups *via* addition, hydrogen abstraction and/or electron transfer, resulting in a multitude of products and reducing the process selectivity.

In order to improve selectivity, the hydroxyl radical can be converted to a more selective one-electron oxidant by the addition of N_3^- or HCO_3^-, which will react with the hydroxyl radical according to reactions (1) and (2) [8, 9]:

$$^\bullet OH + N_3^- \rightarrow HO^- + N_3^\bullet \tag{1}$$
$$^\bullet OH + HCO_3^- \rightarrow H_2O + CO_3^{\bullet-} \tag{2}$$
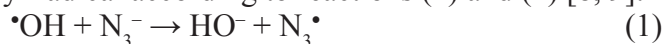
Strong oxidizing conditions can be produced by adding $S_2O_8^{2-}$ to convert the solvated electron to $SO_4^{\bullet-}$ according to reaction (3):

$$e^-_{aq} + S_2O_8^{2-} \rightarrow SO_4^{2-} + SO_4^{\bullet-} \tag{3}$$

2.3. THE REACTION OF INITIATING RADICALS WITH ORGANIC SOLUTES

Organic solutes react with the radiolysis products of water predominantly *via* abstraction or addition reactions. Table 1 gives an overview of the reactivity of primary radicals toward low molecular weight molecules which have some specific functional groups. A very concise description of the reactivity of hydroxyl radicals with a variety of materials is given.

Hydroxyl radicals are strongly electrophilic; as a consequence, the rates of hydrogen abstraction reactions from aliphatic and aromatic carbons are generally very high. They become lower when electron-withdrawing groups, such as carboxyls, carbonyls, nitriles, nitro, esters, amides, are present in aliphatic compounds. The aromatic analogues have comparatively higher reaction rates. Electron repelling groups, such as the amino group in organic amines, increase the reactivity.

Electrophilicity is also responsible for the addition of hydroxyl radicals to unsaturated bonds, both in alkenes and arenes, which often takes place in competition with hydrogen abstraction. As an example, with propylene as the material, the formation of the OH adduct (the addition of hydroxyl radicals to double bonds) is prevalent rather than the formation of the allyl radicals through hydrogen abstraction [11]. With alkenes containing more labile, secondary and tertiary allylic C–H bonds, having higher free radical stability, hydrogen abstraction can become the dominating reaction [12]. With aromatic compounds, the dominant reaction is the addition to the aromatic ring leading to intermediate cyclohexadienyl type radicals. For example, with toluene the cyclohexadienyl intermediates, cresol or the benzyl radicals are formed, depending on the pH of the solution [13]. Polarity is not the only factor affecting the reactivity of $^{\bullet}$OH radicals. The resonance stabilization energy of the radical products and their bond enthalpy changes contribute to introducing further selectivity. For instance, the reactivity for the hydrogen abstraction from alkanes is reported to increase in the order: primary < secondary < tertiary 1:5.4:9.9 (for gas phase reactions) [14].

The organic radicals formed will further evolve toward stable products by addition or abstraction reactions (that change the properties of the radical) and by combination or disproportionation reactions, which give rise to molecular or ionic compounds which do not carry an unpaired electron. In the presence of molecular oxygen, oxygen readily adds to free carbon-centred radicals giving rise to relatively stable peroxyl radicals, depending on the structure of the original alkyl radical. This will further evolve towards the formation of oxidation products. Disproportionation is an alternative to or competitive with combination, giving rise to two stable molecules, one of which is unsaturated. These reactions are briefly presented in Table 2.

Table 1. Reactivity of primary radicals towards low molecular weight molecules bearing specific functional groups. The symbols used to represent rate constant ranges $(dm^3 \cdot mol^{-1} \cdot s^{-1})$ are: $+++ \; k > 10^9$, $++ \; k = 10^7\text{-}10^9$, $+ \; k = 10^5\text{-}10^7$, $- \; k < 10^5$ [3, 10].

Molecule bearing a specific functional group	Rate constant range		
	e^-_{aq}	$H^\bullet$	$^\bullet OH$
H_3O^+	+++	–	–
O_2	+++	+++	–
Saturated hydrocarbon	–	++	+++
Unsaturated hydrocarbon	–	+++	+++
Aromatic hydrocarbon	+	+++	+++
Pyrimidine	+++	++	+++
Nitrile	++[a]	++	++[b]
Carbonyl	+++	+	++[b]
Carboxyl	++[a]	++	++[b]
Ester	++	+	++[b]
Amide	++	++	++
Amine	+	++	+++
Nitro	+++	++	–
Alcohol	–	++	+++
Ether	–	++	++
Chloride	++[c]	++	–
Bromide	+++	++	–
Iodide	+++	+++	–
Thiol[d]	+++	++	+++
Disulfide	+++	++	+++

[a] Range valid for low molecular weight aliphatic compounds; rate constants may exceed 10^9 $dm^3 \cdot mol^{-1} \cdot s^{-1}$ for the aromatic analogues (7.1×10^9 for benzoic acid, 1.9×10^9 for benzonitrile).
[b] Range valid for low molecular weight aliphatic compounds; rate constants may exceed 10^9 $dm^3 \cdot mol^{-1} \cdot s^{-1}$ for the aromatic analogues (4.5×10^9 for benzoic acid; 4.4×10^9 for benzonitrile).
[c] The rate constant may exceed the range assigned with increasing the number of chlorine substituents.
[d] pH-dependent.

Table 2. Generic reactions describing the development of organic radicals in aqueous solutions. (Adapted from Ref. [3]).

Reaction	Description
$2RH^{\bullet} \rightarrow RH-RH$	Combination to give dimeric product
$2RH^{\bullet} \rightarrow RH_2 + R$	Disproportionation to give an insaturated product
$RH^{\bullet} + O_2 \rightarrow RHO_2^{\bullet}$	Reaction with molecular oxygen
$2RHO_2^{\bullet} \rightarrow RO + RHOH + O_2$	Formation of stable oxygenated products, *e.g.* carbonyl compounds, alcohols
$2RHO_2^{\bullet} \rightarrow RH-O-O-RH + O_2$	Formation of organic peroxide

2.4. POLYMERIZATIONS IN HOMOGENEOUS AND HETEROGENEOUS AQUEOUS SYSTEMS

Polymerizations can rely on a solvent and be carried out in solution, when both monomers and polymers are soluble in the reaction medium, or, in heterogeneous systems, such as emulsions or dispersions. The advantages of making use of a solvent are several: (i) the heat of reaction is efficiently absorbed by the solvent, therefore the reaction rate and polymer molecular weight can be better controlled as opposed to broadening of the molecular weight distribution, and thermally labile substances (as monomers or additives) can be incorporated directly into the solution; and (ii) the viscosity of the reaction mixture is reduced, which may prevent autocatalytic polymerization and gel effects at high conversion rates (the Trommsdorf effect). There are limits to water-soluble monomers and the possible contamination of the products from surfactants or other solutes which can be the drawbacks with respect to bulk polymerization.

Water is a very good solvent: it is inexpensive and non-toxic, it dissolves more substances than any other solvent and it has a very important role in radiation-initiated reactions. On the other hand, its relatively high heat of vaporization and high normal boiling point are responsible for significant costs for its removal by evaporation and/or by degradation of the product properties. Furthermore, water purification for recycling or before disposal can be expensive. Polymerizations in aqueous media are definitely preferred in applications where the water can be considered part of the product (*e.g.* hydrogels, water--based paints, polymeric nanoparticles for biomedical applications, *etc*.). High conversion rates, in order to avoid undesired lengthy purification processes, are also highly desirable.

The physicochemical properties of the monomer and its polymer as well as the target physical form and use of the product dictate whether the reaction system should be homogeneous or heterogeneous.

Solution polymerization is possible for water-soluble monomers and polymers, such as vinyl pyrrolidone, acrylonitrile, vinyl acetate, acrylic acid and esters of acrylic acids.

Partially soluble or insoluble monomers can be polymerized in the emulsion state. In the conventional approach, direct emulsion polymerization is a free radical polymerization process which involves emulsification of a relatively hydrophobic monomer in water by an oil-in-water emulsifier, followed by thermal initiation with either a water insoluble initiator (*e.g.* sodium persulphate (NaPS)) or an oil soluble initiator (*e.g.* azobisisobutyronitrile (AIBN)). The surfactant used for stabilizing the monomer droplets (one type of molecule or, more often, a mixture) is generally also effective in stabilizing the final polymer particles. This has been the predominant emulsion polymerization process for vinyl acetate, chloroprene, butadiene/styrene/acrylonitrile copolymers and several acrylates. It has also been used for producing methyl methacrylate, vinyl chloride, vinylidene chloride and styrene emulsion polymers [15].

The finely divided, stable latexes and dispersions find a wide range of uses such as for synthetic rubbers and thermoplastics, coatings, adhesives, rheological modifiers, plastic pigments, standards for the calibration of instruments, immunodiagnosis tests, polymeric supports for the purification of proteins and drug delivery systems, *etc*. Conventional thermal activation cannot be used for polymers whose glass transition temperature is lower than the polymerization temperature, otherwise aggregation will occur. It requires separation and purification of the polymer from the surfactant, or a contaminated product must be acceptable for the end-use.

Dispersion polymerization is carried out by suspending relatively large droplets (10-1000 μm) of insoluble monomers along with the catalyst in water. The water to monomer weight ratio varies from 1:1 to 4:1 in most polymerizations. The monomer droplets are prevented from coalescing by stirring in the presence of stabilizers. Suspension stabilizers are typically used in less than 0.1 wt% of the aqueous phase. Two types of stabilizers are used: (i) water soluble polymers such as poly(vinyl alcohol), sodium polystyrene sulphonate, hydroxypropyl cellulose, *etc*., or (ii) water insoluble inorganic compounds such as talc, barium sulphate, kaolin, calcium phosphate, *etc*.

3. POLYMERIZATIONS IN HOMOGENEOUS AQUEOUS SYSTEMS

3.1. RADIATION POLYMERIZATION OF DILUTE AQUEOUS SOLUTIONS OF VINYL MONOMERS
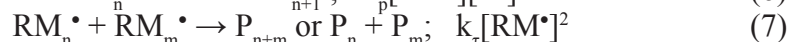
The polymerization of dilute monomer solutions are of little practical importance in the production of many vinyl polymers. Most of these polymers are commodity plastics with high volume production of different grades to suit various end-use applications. The use of dilute monomer solutions is not a viable option for mass production. Yet, such solutions have been of fundamental importance in understanding the radiolysis of water and in demonstrating that free radicals were produced from water (the monomers then act as free radical scavengers) [16]. Indeed, the presence of hydroxyl groups in the polymer, and of deuterium or tritium when using heavy water or radioactive water, was used to support the formation of $^\bullet$OH radicals and H from water radiolysis.

Experiments with monomers have been used to determine the G-values of radical products from water radiolysis. If all the initiating radicals derive from water radiolysis (at a low monomer concentration) and the mechanism of chain termination is known (in terms of the ratio between combination and disproportionation and relative importance of termination by primary radicals), the average number of polymer chains formed for a given dose can be used to determine the number of primary radicals and thereby their G-values.

Another reason for doing radiation-initiated polymerization of dilute aqueous solutions of vinyl monomers has been to study the kinetics of their polymerization reactions. The most instructive studies have been carried out using monomer/polymer systems that are water soluble, *e.g.* acrylamide, where the system is homogeneous throughout the polymerization process. The dependence of the polymerization reaction rate on monomer concentration and dose rate have been investigated. Radiation-initiated polymerization of polyacrylamide presented some expected and some anomalous results. The most common observations were:

- The polymerization rate as function of the time showed an induction (or inhibition) period followed by an acceleration period, up to a maximum value that remained constant until all of the monomer was depleted.
- Post-irradiation effects were observed: after irradiation, the reaction continued, yet at slow rate.
- The reaction order with respect to the monomer was equal to one or slightly higher than one (depending on the experimental conditions).
- The square-root law for the dependence on dose rate was generally observed but exponents higher than 0.5 were found for low dose rates.

The reaction mechanism that was proposed is the following:

$$H_2O + \gamma\text{-rays} \rightarrow R^\bullet; \quad R_i \tag{4}$$

$$R^\bullet + M \rightarrow RM^\bullet; \quad k[R^\bullet][M] \tag{5}$$

$$RM_n^\bullet + M \rightarrow RM_{n+1}^\bullet; \quad k_p[RM^\bullet][M] \tag{6}$$

$$RM_n^\bullet + RM_m^\bullet \rightarrow P_{n+m} \text{ or } P_n + P_m; \quad k_\tau[RM^\bullet]^2 \tag{7}$$

The following assumptions have been made: (i) the initiation is caused only by the free radicals generated by water radiolysis and (ii) the primary radicals do not compete with the monomer in the propagation reaction or in growing the polymer chains to termination.

The general rate equation that can be derived, assuming steady-state conditions (chains are initiated at the same rate as they are terminated) and that the combination of primary radicals is negligible, is

$$R = k_p k_\tau^{-1/2} R_i^{1/2}[M] \tag{8}$$

Deviation from the above equation has been observed on several occasions. In some circumstances, polymer-water interactions were taken into account. If water is not a good solvent for propagating polymer chains, the polymer chains may take a coiled conformation, especially at low dose rates when higher molecular weights can be achieved. Therefore, radicals may not be available for chain termination. Other researchers have proposed that the formation of more stable radicals than the acetamide one, which will not easily react with either the double bond of the monomer or with another free radical (buried amongst the polymer radicals), was at the basis of the deviations [16]. None of the two hypotheses were supported by experimental data.

Ferric salts (*e.g.* ferric perchlorate) can be added to aqueous solutions to facilitate chain propagation and to efficiently terminate polymerization, according to the equation:

$$RM_n^\bullet + Fe^{3+} + H_2O \rightarrow P_n + Fe^{2+} + H_2O^+; \quad k_\tau'[RM_n^\bullet][Fe^{3+}] \tag{9}$$
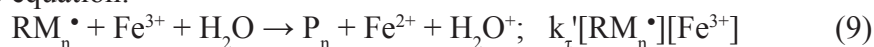
Assuming stationary state conditions, the overall polymerization rate and average number molecular weight become:

$$R = \frac{k_p R_i[M]}{k_\tau'[Fe^{3+}]}; \quad \overline{P}_n = \frac{k_p[M]}{k_\tau'[Fe^{3+}]} \tag{10}$$

The overall rate of polymerization and the average molecular weight decrease with an increasing concentration of ferric salts.

3.2. RADIATION-INDUCED POLYMERIZATION OF CONCENTRATED MONOMER SOLUTIONS

With concentrated monomer solutions, initiation is more complex and generally a less understood process. Hydroxyl radicals and hydrogen can be still involved in the initiation, but a direct effect of radiation on the monomer cannot be ruled out. Furthermore, "energy transfer" effects are also important.

Therefore, it cannot be assumed that free radicals are being formed independently from monomer and water. The relation

$$G(R^{\bullet}) = G(OH^{\bullet}) + G(H^{\bullet}) + G(M^{\bullet}) \qquad (11)$$

may or may not be true.

Figure 1 illustrates a typical experimental curve for reaction rate as function of monomer concentration for the gamma-induced polymerization of aqueous acrylamide solutions from dilute to concentrated. This reaction shows an increase in reaction rate with monomer for concentrations below around 2 M and a drop in reaction rate as the concentration further increased. Acceleration and post-irradiation effects were also observed. At high concentrations, the solutions were very viscous and a "gel effect" could happen, reducing the efficiency of the termination reactions. White spots were also reported for conversions above 10%, which further grew to fill the entire volume for higher conversion values. Under these conditions, the polymerization resulted in a white, opaque polymer that looked like "popcorn". Above 6 M, the monomer is no longer soluble, so the curve is truncated.
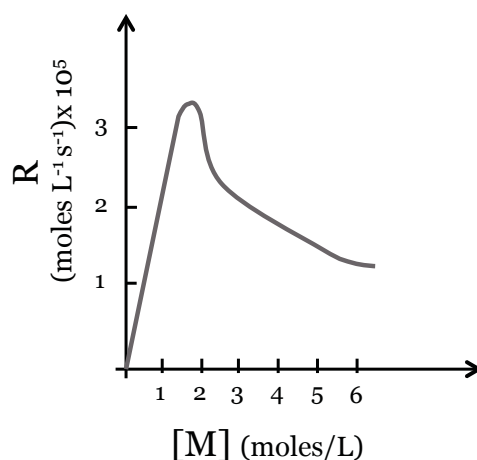

Fig.1. Influence of monomer concentration on the rate of gamma polymerization of acrylamide in aqueous solutions at a dose rate of 0.036 rad/s (= 0.36 mGy/s). (Adapted from Ref. [17]).

As for the dependence of polymerization rate on dose rate, at low dose rates, the rate of polymerization is proportional to the square root of the dose rate if the polymer remains in solution. When the dose rate is high and the monomer concentration low, the concentration of initiating radicals rises and termination starts to occur by a reaction between the growing polymer chains and the initiating radicals. The greater this effect, the lower the exponent that expresses the dependence on dose rate. If the polymer precipitates out from solution, there is a marked increase in the reaction rate (autoacceleration). The rate of polymerization increases above that expected from the (dose rate)$^{0.5}$ law. There are also significant post-irradiation effects, due to the formation of

"buried" radicals. If the dose rates are very high (*e.g.* 10 000 rad/s), termination proceeds very rapidly and much of the product consists of a water-soluble material containing only one or two monomer units.

Although these different situations can be qualitatively understood, a detailed mechanism of these processes has not yet been developed [18].

4. POLYMERIZATIONS IN HETEROGENEOUS AQUEOUS SYSTEMS

4.1. RADIATION-INDUCED FREE RADICAL POLYMERIZATION IN OIL IN WATER EMULSIONS

Water-born polymer colloids have long been the focus of academic and industrial research [19-23]. In particular, ^{60}Co gamma ray-initiated emulsion polymerization has been discussed in the literature since the 1960s [24]. Radiation-induced free radical polymerization in microemulsions has been reported in the more recent years [25-29]. Focus will be on only oil in water (o/w) emulsions and on microemulsions. Inverse emulsions (water in oil, w/o), where the continuous phase is an organic solvent, are not an option for radiation-induced polymerizations, because of the interference of the organic solvent radiolysis products with the polymerization reaction.

Emulsion polymerization is a rather complex process where the steps of particle nucleation, growth and stabilization are affected by both the polymerization kinetics and by the various colloidal phenomena that occur simultaneously. Chemical reactions and colloidal phenomena are interlaced and mutually interfering.

The starting condition for emulsion polymerization is an oil-in-water emulsion, which consists of the monomer or a mixture of monomers, representing the dispersed oil phase, an aqueous solution as continuous water phase, and surfactant molecules in the form micellar aggregates or located at the oil/water interface (surface of the monomer droplets). The role of the surfactant is to reduce the surface tension of the oil phase and to prevent coalescence of the polymer particles being formed during their nucleation and growth, as well as to provide stability to the resulting latex.

The monomer can be completely water insoluble or partially soluble. In this latter case, it is partitioned in the continuous and dispersed phase. In general, monomer-swollen micelles are the principal loci for the initiation (micellar or "heterogeneous nucleation"). Polymerization does not likely take place inside the monomer droplets because of their relatively smaller surface area with respect to the micelles and the low capturing ability of the initiating free

radicals. Homogeneous nucleation becomes significant only for systems with low surfactant concentration and/or for the polymerization of partially hydrophilic monomers. The radical-visited micelles grow over time being refurbished by monomer and surfactant from the other micelles. The particle nucleation stage generally ends with the disappearance of the micelles. The number of growing particles is then fixed and polymerization proceeds in the polymer particles at a constant rate (and homogeneously). The monomer concentration in the particles is maintained at a constant concentration by diffusion of the monomer from the monomer droplets through the solvent. When the monomer droplets disappear in the system, the particle growth stage ends, the reaction rate decreases and the conversion reaches a plateau.

During polymerization, processing conditions must be carefully controlled, since an external input in the form of mechanical energy (stirring, sonication, *etc*.) is required to disperse the oil phase in the water. The generation of particle nuclei during the early stage of the polymerization plays a crucial role in determining the final latex particle size, particle size distribution and the overall quality of the latex product.

The control of the particle nucleation process is a very challenging task. It requires an efficient transport of the initiating radicals, monomers and surfactant molecules to the growing polymer chains through the continuous medium and across the surfactant layer. Prolonged nucleation may result in products with a very broad particle size distribution and broad molecular weight distribution. The supply of monomer and of surfactant by the emulsified monomer droplets (acting as a reservoir) to the monomer-swollen polymer particles (primary reaction loci) is a key factor that governs particle growth stage. The distribution of growing chains among the discrete monomer-swollen polymer particles can greatly reduce the probability of their bimolecular termination and results in faster polymerization rates (with respect to solution polymerization) and in polymers with higher molecular weight. This last feature is often sought in emulsion polymerization.

One main advantage of using irradiation to initiate polymerization is that initiation is temperature independent and can be carried out at relatively low temperatures, below the T_g of the polymer particles (thus reducing the risk of their aggregation), and with limited or no risk of runaway reactions caused by the exothermic heat released by the polymerization reaction. Propagation, that is addition of monomer to the growing chain, is less affected by temperature than termination. Therefore polymers with higher molecular weight can be produced by keeping the reaction temperature relatively low.

Radiation can generate a virtually unlimited range of radical fluxes, which can be easily monitored during the course of the polymerization reaction. The ability to control the initiating radical concentration enables a better control of the increase in molecular weight and particle size distribution.

There are also some drawbacks. Irradiation can induce chemical changes in the formed polymer and in the surfactant. The polymer can undergo branching, crosslinking or changes in chemical functionality. The surfactant can be partially grafted onto the polymer, thus changing its structure and properties.

Water soluble initiators generate radicals only in the aqueous phase, whereas irradiation can generate radicals in both phases. So, it is important to know and compare the G-values of the radicals in the two phases: for monomers like styrene, G(radicals) in the monomer phase are almost one order of magnitude lower than in the aqueous phase, whereas for vinyl acetate these values are comparable. This last situation complicates the modelling of these reaction systems.

Finally, difficulties can be encountered in ensuring a homogeneous dose rate within a stirred tank on an industrial scale. For this reason, microemulsions are easier to handle, since stirring is not crucial to controlling latex particle size.

4.2. RADIATION-INDUCED FREE RADICAL POLYMERIZATION IN OIL IN WATER MICROEMULSIONS

Microemulsions are thermodynamically stable and optically transparent systems, which consist of monomer droplets (varying from 10 to 100 nm) dispersed in water or alcohol/water solutions or mixtures with the aid of an emulsifier at a concentration that exceeds its critical micelle concentration. Their classification as a heterogeneous system may not be correct. Nonetheless, polymerization of a microemulsion leads to a phase separated, solid polymer with submicron-sized particles and is more analogous with emulsion polymerization than with solution polymerization. Also for their end-use applications, emulsion polymerizates are similar to those of their micron-scale analogues [30].

Monomers become distributed between the continuous aqueous phase and the micelles, depending on their solubility. Hydrophobic monomers, such as styrene or butyl acrylate, mostly distribute inside the micelles. More hydrophilic monomers, such as methyl methacrylate, can be present in both phases.

For monomers with low radical yield, water radiolysis products initiate the polymerization. When the nucleation of polymer particles inside the micelles predominates, the monomer-swollen micelles interacting with the initiating radicals act as nano-reactors and polymer chains propagate over time. The other micelles act as reservoirs of monomer and surfactant.

The polymerization rate *vs.* irradiation time (dose) has a typical bell-shape, as shown in Fig.2A. After an induction time, the rate increases, then reaches a maximum and finally decreases when the monomer is depleted. The induction period depends on the O_2 content and other impurities (*e.g.* polymerization
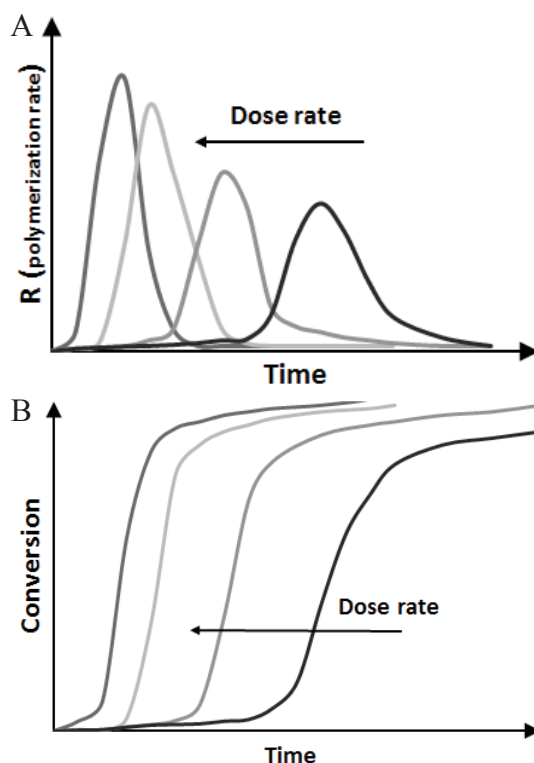
Fig.2. A – Polymerization rate as function of time at various dose rates, B – conversion as function of time at various dose rates.

retardants) present in the emulsion. Higher dose rate results in higher initiating radical concentrations, which results in faster particle nucleation (shorter incubation period) and an increased initial polymerization rate. The typical monomer conversion *vs*. irradiation time (dose) curve is S-shaped, as shown in Fig.2B. Monomer conversion reaches higher values at higher dose rates and generally higher than those attained by the use of chemical radical initiators.
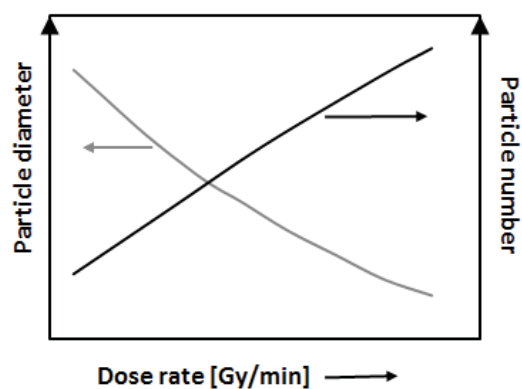

Fig.3. Effect of dose rate on the diameter and number of particles formed per unit of volume.

This is mainly due to a more homogeneous production of initiating radicals in the system [31].

Five to ten times higher molecular weight latexes are obtained by radiation--induced polymerization than for common microemulsion polymerization, since reactions are generally carried out at lower temperatures which favour propagation over termination [19].

The dose rate governs the rate of nucleation, *i.e.* the instantaneous concentration of "active" micelles. Therefore, an increase in dose rate generally leads to a decrease in the latex particle size and a relative increase in the number of particles, since dose rate increases the number of "active" polymer nuclei, as shown in Fig.3.

Only a few studies describe the variation of particle size and size distribution with absorbed dose or, in other terms, with monomer conversion [26-27]. At the very early stage of polymerization (low monomer conversion, < 10%), polymer nuclei are rapidly swollen by the monomer and they have their largest size (around 100 nm). When the polymerization further progresses, the size of the particles decrease as more growing particles are formed and the monomer is redistributed in the system. The larger swollen particles, that act as monomer reservoirs, decrease in size and the newly formed particles progressively develop. Newly nucleated particles can also form, especially when homogeneous nucleation is possible. When the system becomes depleted of monomer, there is no longer any further nucleation. This condition often leads to a reduced polydispersity. At very high conversions, there may be a slight increase in dimensions due to particle aggregation and bridging. Nanoparticles with size in the range of a few tens to a few hundred of nanometers can be produced.

4.3. RADIATION-INDUCED DISPERSION POLYMERIZATION

In dispersion polymerization, the starting system is a clear homogeneous phase that becomes turbid and heterogeneous at the early stage of polymerization, due to the reduced solubility of the growing polymer chains in the aqueous medium, where the monomer is still soluble. Stabilizers, monomer initiators, solvents and their concentrations, all play important roles in determining the ultimate particle size and the molecular weight of the product [32-34]. The solvent must be a good solvent for both the stabilizer and the monomer used, but a poor solvent for the formed polymer. Alcohols (ethanol or isopropanol) are often added to increase the solubility of the monomer and are involved in chain transfer reactions that can reduce the polymerization rate and help to control the growth of polymer molecular weight.

The typical monomer conversion *vs.* irradiation time curve in dispersion polymerization is also S-shaped. After a short initial period, the polymerization rate generally increases, almost linearly, up to a maximum, and then it de-

creases [35-38]. At an early polymerization stage, the system is homogeneous since polymerization occurs mainly in the continuous phase. When chains have grown to a length that makes them insoluble, then particle nucleation takes place. This situation is attained at relatively low monomer conversions, generally lower than 10%, for radiation-induced polymerization, which is higher than for thermal processes, which are generally only 2-5%. Indeed, the induction period and the nucleation phase are both quite short, since high energy irradiation can produce free radicals homogeneously in the system and at a very high rate, producing a metastable "supersaturated" solution and "delaying" the onset of phase separation. A rapid initiation and short nucleation phase are beneficial in order to obtain monodispersed systems: the particle number is soon fixed, and the particles grow independently and simultaneously [39]. As the monomer conversion increases, the locus of the reaction becomes the particle through the capture of oligomeric radicals from the continuous phase. Because of the higher viscosity within the particle, the rate of propagation becomes higher than the rate of termination, with termination being a diffusion controlled process, and the polymer molecular weight increases. This phenomenon is known as the "gel effect", similar to what happens in "bulk" polymerization.

For radiation-induced dispersion polymerization differs from conventional chemical polymerization in that stirring during irradiation is often not beneficial. The contact between two particles containing active propagating sites may lead to irreversible agglomeration. Therefore, it is essential to keep the solution stationary during irradiation, to ensure the maximum average distance between the particles. Some graft-copolymerization of the stabilizer may occur due to the low selectivity of primary radicals. The highest yields for grafting are expected on those polymer-monomer combinations in which the free radical yield of the polymer ($G(P°)$) is much larger than that of the monomer M ($G(M°)$) [23]. Therefore, by choosing a proper stabilized polymer-monomer combination, chemical grafting can be favoured over physical adsorption. Furthermore, since initiation is a continuous process during irradiation, by prolonging the irradiation, polymeric surfactant grafting, that was not initially favoured over monomer homopolymerization, may compete as a reaction product. This approach is particularly appealing if the polymeric dispersant can have a role in generating nanoparticles.

5. POLYMER CROSSLINKING IN AQUEOUS MEDIA

5.1. RADIATION PROCESSING FOR THE PRODUCTION OF HYDROGELS FOR BIOMEDICAL APPLICATIONS

Hydrogels are polymeric materials that can absorb significant amounts of water, because of their hydrophilic functional groups, without dissolving in water, since there are intermolecular bonds that link the different chains together. When in contact with aqueous solutions, hydrogels can swell up to a characteristic "equilibrium swelling" value, that corresponds to a balance between the osmotic pressure that drives water inside the network and the retroactive elastic forces that arise from the stretched polymeric segments between the crosslinks on swelling. Crosslinking is "chemical" when there are covalent bonds formed. Thus, the intermolecular bonds in hydrogels are called "chemical" or "permanent". The bonds between hydrogel molecules can also be "physical" or "non-permanent". These are due to electrostatic forces, hydrogen bonds, hydrophobic interactions or chain entanglements and the corresponding systems are called "physical" hydrogels or simply "gels". These interactions can be weakened by a modification of the physical and/or chemical properties of the environment (temperature, pH, salts, solvents), or by application of an external field (mechanical, electric, *etc.*), thus leading to partial or complete dissolution of the gel. Depending on their specific structure chemical (covalent) crosslinks can also be broken, *e.g.* through hydrolytic or enzymatic reactions. That is the case, for example, of ester bonds and amide bonds, the former being both hydrolytically and enzymatically labile, the latter degradable by the action of proteases.

Because of their general biocompatibility, and their soft consistency resembling many natural constituents of the human body, hydrogels, when in contact with body fluids and tissues, have been successfully used in several biomedical applications, as soft contact lenses, wound dressings, drug-delivery systems, super-absorbents, *etc.* More recent developments in the field deal with the design and synthesis of "smart" or "responsive" hydrogels capable of reacting to various environmental stimuli, such as temperature, pH, ionic strength, solute concentration, electric field, light, sound, *etc.* These materials can change their shape or volume as a response of a stimulus (by swelling or contracting), or undergo a specific, measurable change of a physical property (optical, electrical, *etc.*). For this ability, these "smart" hydrogels have been proposed as the actuators in drug delivery devices, in artificial muscles, in valves, *etc.* or as active materials used in sensing devices.

The interest in the use of radiation processing to produce hydrogels for biomedical applications began in the late 1960s as noted in the papers and patents published by Japanese and American scientists, among others Sakura-

da and Ikada, Kaetsu, and Hoffman [40-43]. Professor Janusz M. Rosiak and co-workers in Poland in the 1980s made a substantial contribution to this field by strengthening the underlying radiation chemistry and supporting the development of a commercial product in 1992 [44-46]. The simplicity of the process, the possibility of combining sterilization and crosslinking in a simultaneous operation, and the support of the International Atomic Energy Agency (IAEA) in promoting the technology transfer of the radiation production of hydrogel dressings and other hydrogels from the laboratory of Prof. Rosiak to many other laboratories around the world boosted the use of this technology in other countries.

Hydrogels can be synthetized by irradiating the solid polymer, the monomers (in bulk or in solution) or starting from aqueous solutions of a polymer. The irradiation of hydrophilic polymers in the dry form requires a pre-moulding step and much higher doses of ionizing radiation compared to irradiation in solution. Similar to other fields where radiation-inducing crosslinking is performed (coatings, adhesives and matrices of fiber-reinforced composites), difficulties may be encountered in obtaining homogeneous macroscopic networks when irradiation is performed in the solid state. It may be difficult to fully remove the oxygen that can promote unwanted side reactions.

Irradiation of some monomers in aqueous solutions can lead to polymerization and simultaneous crosslinking. Multifunctional monomers are often used to increase the degree of crosslinking. Particular attention must be given to purify the product of unreacted monomers, should the monomers be harmful or toxic. During irradiation many consecutive and parallel reactions occur, making the system rather complicated and difficult to describe even qualitatively.

There are clear advantages to initiating crosslinking in already formed polymers in the form of aqueous solutions. Indirect effects can help reducing the gel dose. Hydrogels can be produced starting from non-toxic and chemically stable polymers which lead to very pure products.

5.2. RADIATION-INDUCED POLYMER CROSSLINKING IN CONCENTRATED AQUEOUS SOLUTIONS

Since the demonstration by Charlesby and Alexander in the late 1950s [47, 48], it has been known that aqueous solutions of several crosslinking type polymers transform into macroscopic gels under high energy irradiation, especially if irradiated under deaerated conditions. It was also known that no gel was observed if the polymer concentration was lower than a certain value, which depends on factors such as the type of polymer, its degree of polymerization and the composition of the solvent. When the concentration is above this threshold value, gelation occurs suddenly and the irradiation dose required for incipient gelation (gel dose, D_g) decreases rapidly with increasing concentra-

tion. After reaching a minimum, Dg increases again, yet slowly. The gelation dose is generally determined from the sudden changes in viscosity, the degree of swelling (weight of a swollen sample compared to the weight of a dry sample) or the amount of sol fraction (the weight of the dry soluble fraction compared to the weight of the initial dry polymer), which occur at gel point. This critical concentration corresponds to the concentration at which polymer chains in solution start to intertwine.

Free radicals (hydroxyl radicals and hydrogen atoms) can be formed by water radiolysis. They can be transferred to the polymer by hydrogen abstraction, if the polymer is a fully saturated and/or by addition to double bonds present as the unsaturation in the polymer. Because of the high reactivity of primary radicals, hydrogen abstraction is a non-selective process; therefore, different kinds of macroradicals may form. The position of radicals in the polymer may also change due to intramolecular hydrogen abstraction and/or addition reactions [49, 50]. Direct effects such as the radiolysis of polymer, have to be taken into account at high polymer concentrations.
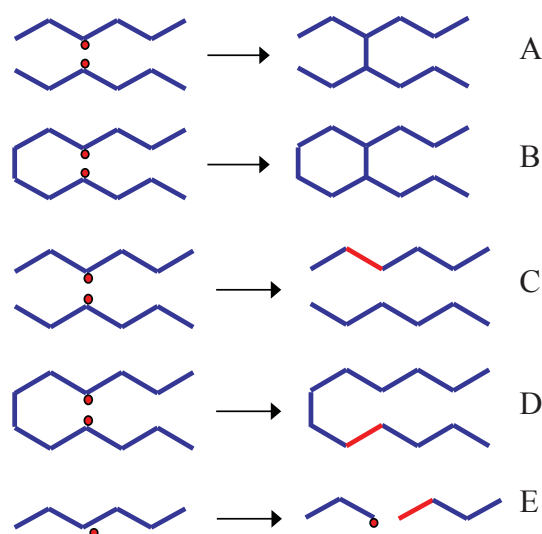

Fig.4. Schematic representation of all possible reactions producing macroradicals: A – intermolecular combination; B – intramolecular combination; C – intermolecular disproportionation; D – intramolecular disproportionation; E – chain scission. The segments in blue represent saturated bonds, the segments in red represent unsaturation.

Macroradicals are mainly involved in termination reactions (inter and/or intramolecular crosslinking and disproportionation), or propagation reactions (hydrogen transfer and chain scission). Hydrogen transfer reactions will only change the position of the radical centre and its reactivity, but will not affect the molecular weight of the polymer. Figure 4 is a schematic of all of the possible reactions that can produce macroradicals (excluding hydrogen transfer reactions).

Intermolecular termination reactions are diffusion controlled reactions that are without an activation barrier and involve two separated entities. They are bimolecular processes following second order kinetics with a reaction rate that can be expressed as:

$$-d[P\bullet]/dt = 2k_2[P\bullet]^2 \qquad (12)$$

where $P\bullet$ is the instantaneous macroradical concentration and k_2 is the second order rate constant.

Compared to the starting linear polymer, intermolecular crosslinking gives rise to a three-dimensional molecular structure, with an increase of molecular weight to infinity. Intramolecular crosslinking causes changes in the polymer conformation and reduces segmental mobility. Disproportionation reactions do not affect the polymer molecular weight, but change the polymer chemical structure by introducing unsaturation that can further react with radicals generated upon irradiation. Chain scission results in a reduction of molecular weight of the polymer, leading to degradation. Scission reaction rates generally follow first order kinetics [50].

The progression of macroradical towards crosslinking or chain scissioning essentially depends on the chemical structure of the polymer even if these two processes compete. Polyvinylpyrrolidone (PVP) and poly(ethylene oxide) (PEO) mainly undergo crosslinking, while polysaccharides mainly undergo chain scissioning. The relatively long lifetime of the formed radicals in polysaccharides and the limited flexibility of the polymer chains in solution make termination *via* chain scissioning favoured over crosslinking [51, 52]. Nevertheless, also for the crosslinking-type polymers the relative contribution of degradation with respect to crosslinking can significantly change during irradiation, due to structural modifications of the irradiated material, such as an increase in rigidity, functionalization due to oxidation, *etc*.

When the starting polymer is a polyelectrolyte (*e.g.* poly(acrylic acid) (PAA)), electrostatic repulsions establish between the ionized groups on the polymer chain, belonging to the same chain or to different chains. These repulsions can affect crosslinking in two opposite ways, by preventing the combination of polymer radicals and by favouring a chain extended conformation of the polymer chains, thus increasing the probability that the polymer segments of different chains can be in contact with each other.

The extent of repulsive forces can be controlled by pH (changes of ionization level) and by the presence of salts (charge screening effects). In Fig.5A, the gel dose as function of polymer concentration is plotted for an aqueous poly(acrylic acid) solution irradiated to varying degrees of ionization, α, achieved by adding different amounts of sodium hydroxide. When the degree of ionization increases, the repulsions increase as does the critical polymer concentration for incipient gelation, as shown in Fig.5B. Figures 5C and D show the influence of NaCl in the solution. Salt is beneficial to gelation up to a maximum value then it becomes detrimental. There is a minimum in curve
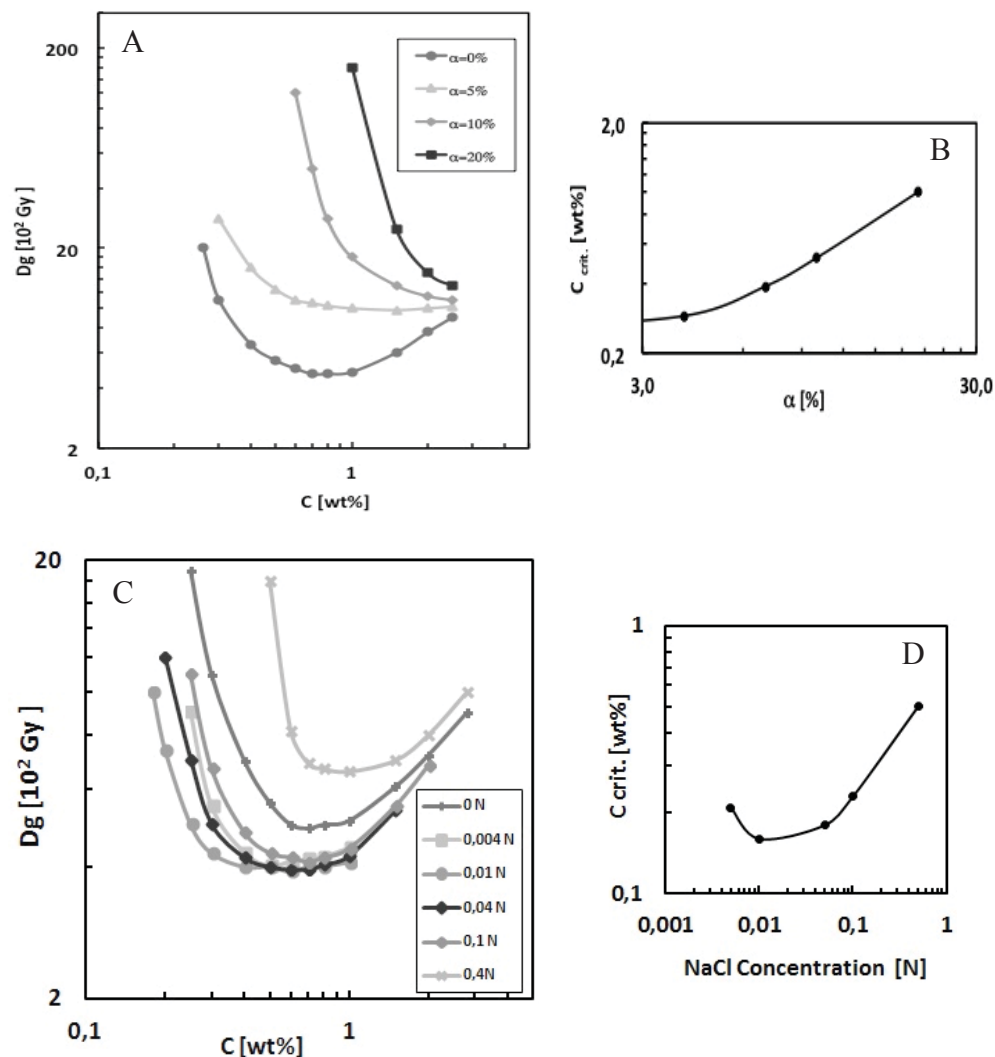
Fig.5. Irradiation of deaerated polyacrylic acid solutions with a ^{60}Co irradiator at 1.5 kGy/h: A – gelation dose, Dg, as function of polymer concentration for polyacrylic acid with various degrees of neutralization, α, and PAA irradiated in salt-free conditions; B – critical concentration for gel formation as function of the ionization degree and PAA irradiated in salt-free conditions; C – relation between gelation dose and polymer concentration for PAA in acid form with various amounts of NaCl; D – critical concentration for gel formation of PAA in acid form with various amounts of NaCl. (Adapted from Ref. [40]).

of critical concentration as function of salt concentration, as shown in Fig.5D. This is the result of the above described competing effects coming from repulsions between the ionized groups. At low salt concentration, the repulsion of fixed charges in the polymer prevents radical combination that then decreases so that gelation can occur more readily. If the NaCl concentration becomes too

high, the polymer coils shrink and repulsion from groups on the same chain is screened so that macroscopic gelation by intermolecular crosslinking is no longer favoured.

If the radical recombination is prevented, the over-all extent of degradation will become larger. So, polyelectrolytes may undergo degradation more effectively when their charge density increases.

The relations between absorbed dose, sol fraction and gel fraction, gelation dose, the radiation dose at which the first "insoluble" fraction is formed, and the radiation yields for scissioning (Gs) and crosslinking (Gx) can be quantitatively described by the Charlesby-Pinner equation. This model relies on "sol-gel analysis" data and requires a number of simplifying assumptions for the description of the polymer system (random molecular weight distribution) and the reactions that occur (radiation crosslinking and scissioning occur at random and they are independent and only dependent on dose). The agreement between model and data is not always satisfactory for flexible polymers of the crosslinking type and several modifications of this equation have been proposed.

The Charlesby-Pinner equation and its consequences can be used only for the early stages of crosslinking. There is a point in the crosslinking process of a polymer when further crosslinking does not manifest itself in an increase of the degree of crosslinking (gel fraction) but in modifications of crosslinked density (reduction of the mesh size of the network, increase or decrease of the homogeneity in crosslinking points distribution). Other techniques than sol-gel analysis can be used for the calculation of Gx, *e.g.* by estimating the mesh size of the gel network through equilibrium swelling studies and/or by rheological measurements, or by assessing the homogeneity of the network by NMR techniques based on the measurements of the spin-spin relaxation time [44].

Typical examples of synthetic polymers used for macroscopic hydrogel formation by this method are poly(vinyl alcohol) (PVA), polyvinylpyrrolidone (PVP), poly(ethylene oxide) (PEO), poly(N-isopropylacrylamide) (PNIPAM), poly(acrylic acid) (PAA) and poly(vinyl methyl ether) (PVME), and their blends for producing interpenetrated networks. Gels obtained from PAA are responsive to pH and ionic strength, while gels from PNIPAM and PVME are temperature responsive. Variants of polyhydroxyethyl aspartamide (PHEA), a biodegradable synthetic polyamino acid, with side chains bearing both double bonds and carboxyl groups, have been transformed by irradiation into pH/electric field responsive hydrogels suitable for use with the stimuli triggered release of proteins [53, 54].

5.3. NANOPARTICLE FORMATION *VIA* INTRAMOLECULAR CROSSLINKING IN DILUTE AQUEOUS SOLUTIONS

Some of the possible approaches to the synthesis of hydrogel nanoparticles or nanogels (NGs), using radiation processing are covered. Indeed, the lack of inexpensive and well-established preparation techniques for such nanoparticles *via* conventional methods has been a main limitation to their development and use, despite of the great potential nanogels have as delivery devices for therapy and diagnosis.

The processes for the preparation of nanogels are either "top down", micro-fabrication techniques, such as photolithography, microfluidic, micro-molding, or "bottom up" self-assembly approaches, which rely on ionic or hydrophobic interactions [55, 56]. The former techniques require expensive equipment; the latter generally make recourse to nanocolloids as templates. Polymerization and crosslinking occur in the aqueous phase of an inverse nano/microemulsion. Surfactants and organic solvents are used to make a soft template, initiators and catalysts are required to drive the chemical reactions. These components can have a detrimental effect on the toxicological profile of the nanogels if they are not completely removed after synthesis. Product purification can, indeed, be time consuming, expensive and not particularly environmentally friendly.

Nanogels can be made by irradiating semi-diluted polymer aqueous solutions with pulsed electron beams without the use of surfactants as templates [57-59]. Polymers that mainly undergo crosslinking upon irradiation should be selected for this purpose [60-62]. The formation of nanogels with tailored particle size at the nanoscale is favoured by the prevalence of intramolecular crosslinking reactions over all the possible termination reactions that may occur during irradiation. This condition can be achieved at low polymer concentration
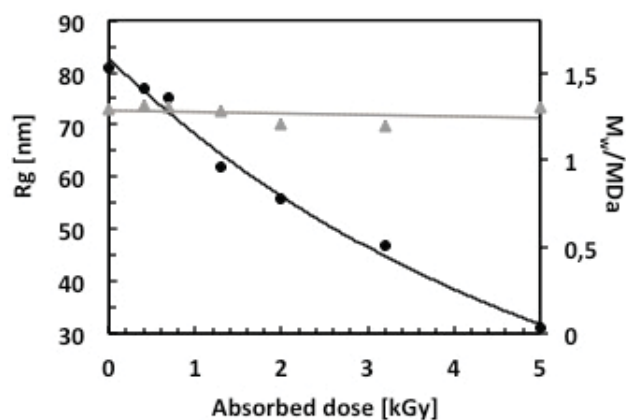

Fig.6. Molecular properties of electron beam irradiated PVP in aqueous solution as a function of an average absorbed dose; M_w of PVP = 1.3×10^6 g·mol^{-1}, dose/pulse = 320 Gy, pulse frequency = 0.5 Hz, pulse duration (width) = 2 µs. (Adapted from Ref. [60]).

(intermolecular termination is not favoured) and by the simultaneously formation of more than one radical on the same chain. For this reason, traditional nanogels are produced by carrying out irradiation under N_2O-saturated conditions, at high dose per pulse (high dose rates). These conditions ensure the simultaneous formation of many radicals per chain. The assumption is made that all the radicals formed in water (by water radiolysis) are efficiently scavenged by the polymer. For example, the irradiation of PVP at high dose per pulse (320 Gy/pulse) and low integrated doses (< 5 kGy) leads to nanogels with smaller radius of gyration (R_{gyr}) but the same weight average molecular weight (M_w) as the non-irradiated polymer. Intramolecular crosslinking explains the observed progressive contraction of the polymer coils at an increase of dose, as shown in Fig.6.

Interestingly, macroradical decay due to intramolecular crosslinking does not follow the homogeneous second order kinetics that is characteristic of intermolecular termination reactions. Since the reactive entities belong to the same polymer chain, the kinetics are governed by the mobility of the segments on which radicals are located, with a timescale and energy barrier depending on both their mutual distance and relative positions on the chain [63]. Since the formation of bonds within the polymer segments reduces their mobility and affects the kinetics of further reactions, the process cannot be described by a single activation energy or rate constant, but by their distributions. For this reason intramolecular crosslinking has been described as using a dispersive kinetics model, *i.e.* by recourse of "time-dependent" kinetic constants (non--homogeneous kinetic model) [64-66]. Intramolecular crosslinking is expected to become less effective with an increase of dose.

Recent studies [67-69] indicate that the final structure and properties of radiation-initiated crosslinked polymer nanogels are affected by several experimental parameters. They can be either related to the material system properties, such as polymer concentration, dynamics and diffusion kinetics of polymeric segments (affected, in turn, by temperature, nature of the solvent, polymer molecular weight distribution, *etc*.), type and half-life of formed macroradicals, or to irradiation process parameters, such as duration of each single pulse (*i.e.* pulse width), pulse repetition rate (or frequency), total dose delivered. In particular, polymer concentration has to be significantly lower than the critical chain overlap concentration, C* for dilute or semi-dilute systems. Dilute polymer conditions should ensure there is a sufficient distance between polymer chains so that a radical formed on a chain terminates by reaction with another radical formed on the same chain, before any encounter with radicals on different chains can occur during their random Brownian motion [66]. Concentration regimes depend on polymer molecular weight and chain conformation in solution. They can be experimentally determined, *e.g.* by measurements of zero-shear viscosity *vs.* polymer concentration. A log-log plot of zero-shear viscosity, $\eta°$, *vs.* polymer concentration is shown in Fig.7. For
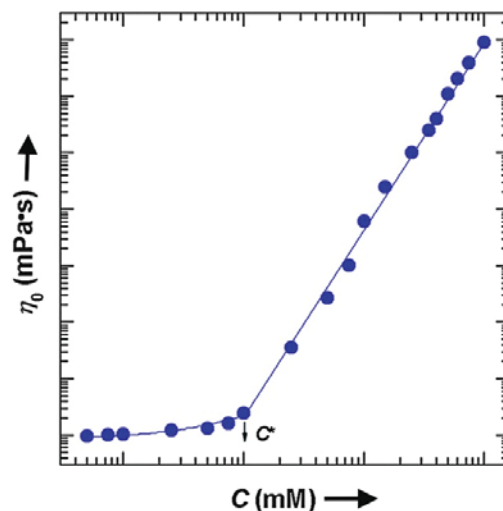
Fig.7. A typical concentration dependence of zero-shear viscosity for a polymer solution in a double logarithmic plot.

C << C*, the zero-shear viscosity is almost a constant ("dilute regime") and the chains are isolated. For C >> C* ("concentrated regime"), the zero-shear viscosity generally follows a power law and coils are overlapping and strongly entangled. In the vicinity of C* (C < C*), in the "semi-dilute regime", the viscosity rises more or less steeply with the concentration. Semi-dilute conditions are a characteristic feature of polymers and do not have analogies in solutions for low molecular weight materials where such regime does not exist.

All of the conditions that lead to a coiled conformation of polymer chains also favour intramolecular crosslinking. For example, in the case of PVP, the increase of the reaction temperature above 60°C gives rise to nanogels with lower molecular weight [69]. This effect is due to the break of the PVP–water hydrogen bonds, which are responsible for a chain extension conformation at lower temperatures. "Pure" intramolecular crosslinking leads to nanogel particles whose size and molecular weight are mainly controlled by the size and molecular weight of the starting polymer.

The effect of pulse frequency on the physicochemical properties of nanogels is such that if the time between two successive pulses is longer than the average lifetime of the macroradicals, radicals disappear in intra-pulse reactions and each pulse can be considered independent from the others. If polymer radicals have longer lives (they are more stable or too few), they can survive to the successive pulse. In the case of dilute PVP aqueous solutions, a pulse frequency effect has been observed on both the molar mass and on the hydrodynamic diameters of the nanogels even when the time between two successive pulses was considerably longer than the measured half-life of the carbon--centred macroradicals based on pulse radiolysis experiments. In particular, nanogels with higher molar mass and higher hydrodynamic size have been

made at the lowest pulse frequency. It has been postulated that slower decaying radicals, which are not detected by the UV analysis of pulse radiolysis experiments, may form and become involved in interparticle reactions occurring in the "dark time" between pulses [69].

5.4. NANOPARTICLE ENGINEERING *VIA* MIXED INTRA/INTERMOLECULAR RADIATION CROSSLINKING IN SEMI-DILUTE AQUEOUS SOLUTIONS

A greater variety of nanogels, different in particle size, molecular weight and functionality, can be produced by the use of irradiation doses within the sterilization dose range 20-80 kGy with semi-dilute polymer solutions [68, 70-72].

When the polymer concentration is approaching C*, the two modes of crosslinking, intra- and intermolecular, concur in the initial phase of the process, at lower doses. The combined effect of these two reactions is that intramolecular combination progressively increases the crosslinked density of the nanogel, which reduces the macroradical segmental mobility; intermolecular combination reduces the number of independent polymer chains in the system and the probability of further reacting as well as the ability of the polymer to scavenge the primary radicals formed in water. Therefore, with an increase of dose both intra- and intermolecular crosslinking become less and less favoured, and the initiating radicals continuously produced by water radiolysis can mutually react, producing H_2 and H_2O_2. The radiolytic decomposition of hydrogen peroxide will become a source of molecular oxygen in the system which, after the gel nanoparticles are formed, starts to compete with intra/intermolecular termination to react with the newly forming macroradicals, thus leading to functionalized nanogels. Research activities carried out by Dispenza and collaborators have shown that carboxyl groups and amino groups can form on PVP nanogels, made by the irradiation of pure aqueous solutions of PVP at doses in the 20-80 kGy range [68, 73].

The presence of carboxyl groups and primary amino groups transforms the otherwise "chemically inert" PVP nanogels into multifunctional nanocolloids, amenable to modification with (bio)molecules and cell receptor-specific ligands of therapeutic and/or diagnostic relevance.

For the same purpose, the same and other research groups have pursued crosslinking and simultaneous grafting of functional acrylic monomers or polymers [71, 72, 74-77].

These strategies were successful in demonstrating the possibility of making nanogels with controlled particle size and functional groups that could be used for the incorporation and triggered release of molecular drugs [78], or in conjugation with oligonucleotides and proteins to be protected by enzymatic degradation and carried then to their targets [79, 80].

6. POLYMER NANOPARTICLE FORMATION FROM RADIATION-DEGRADABLE POLYMERS

Ionizing radiation is a well-known method that reduces the molecular weight of radiation-degradable polymers by controlled degradation. This approach is often used to improve the solubility of polysaccharides for a large variety of applications, including health care and personal care products, plant growth adjuvants, viscosity modifiers in the food industry, and in the textile industry. The mechanism of nanoparticle formation of polysaccharides consists in the irradiation leading to the breakdown of the ordered system of intermolecular as well as intramolecular hydrogen bonds. As a consequence, chain mobility increases, as well as the permeability by oxygen or water radiolysis products, and acetal linkages may also break [49, 81].

In 2010, Pasanphan *et al.* [82] have studied the possibility of making nanoscale-particle chitosan by exposing chitosan to γ-rays at room temperature in different physical forms (as solid flakes or in aqueous colloidal form) to achieve a fairly good control over particle size distribution. Both particle size and particle polydispersity decrease progressively with an increase in dose. Although the reaction pathway of radiation-initiated degradation of polysaccharides is well described in the literature [82-85], the mechanism that leads to the narrowing of particle size distribution has not yet been fully clarified.

7. CONCLUSIONS

Polymerization initiated by ionizing radiation in water is a process that leads to a large variety of functional polymeric materials for the many diverse applications.

A proper choice of the irradiation conditions, in particular the dose rate (continuous irradiation from radioisotopes) or the dose per pulse and pulse frequency (pulsed electron beam sources), produces initiating radicals from water radiolysis products at controlled rates and independent of reaction temperature. These radicals can react with the material or with themselves, triggering or sustaining chemical reactions that follow and that will then involve other solutes present in the system, such as monomers and polymers.

Because of the high penetration of ionizing irradiation, the primary reactive species are formed homogeneously within the system and throughout the process, both in the solvent and in the solutes or dispersed phases, including formed polymers. These reactants can be used not only to initiate polymerization but also to resize micro/nanoparticles, to induce a progressive change of

their composition and surface functionality (*e.g.* by crosslinking, grafting of functional monomers onto already formed polymers, by oxidation, *etc*.).

The non-thermal activation of the main process permits an independent control of the rate of the eventual concurrent or competitive reactions (primarily by controlling dose rate, material concentration, pH and temperature). This can be used to increase the yield, or to fine-tune the composition, the topology, the morphology and, in turn, the properties of the desired product.

Material optimization, both in terms of properties and production process, relies on the fundamental knowledge about the mechanisms of the reactions from their precursors and the kinetics of the elementary steps involved. This knowledge is quite developed for some material systems while considerable research is called for in other cases.

Acknowledgements

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