THE APPLICATION OF HYDROGELS BASED ON *N*-ISOPROPYLACRYLAMIDE AND ANIONIC COMONOMERS

Aleksandar S. Zdravković^{1*}, Ljubiša B. Nikolić², Snežana S. Ilić-Stojanović², Vesna D. Nikolić²

¹Vocational High School for Technology and Art, Leskovac, Serbia

²University of Niš, Faculty of Technology, Leskovac, Serbia

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Hydrogels represent three-dimensional networks of polymer chains that have the ability of absorption of a significant amount of water or biological fluid. A special group of hydrogels are copolymers which respond to changes of pH values and temperature. Desirable characteristics of temperature- and pH-sensitive hydrogels based on *N*-isopropylacrylamide and anionic comonomers for different applications, from pharmaceutical to the environmental one, can be designed by composition of copolymers. The presence of the amide and carboxyl group in the structure of these hydrogels enables their application as adsorbents in the processes of removing the pollutants from aqueous solutions. Hydrogels based on *N*-isopropylacrylamide and anionic comonomers represent desirable three-dimensional matrices for controlled and sustained release of agrochemicals and drugs in relation to temperature and pH of the surrounding medium. Hydrogels, as separation devices, perform the concentrating of compounds or microorganisms solutions by absorption of greater amounts of water. One more application of these copolymers is for immobilization of enzymes.

Keywords: hydrogel, adsorption, pollutants, agrochemicals, separation, controlled delivery

Introduction

Hydrogels are hydrophilic functional polymer materials with a specific three-dimensional cross-linked structure composed from polymer chains joined in crosslinking points. They are composed from chemically or physically crosslinked polymers in the way that they can absorb and retain a great amount of water within their three-dimensional network without dissolving [1-3]. In 1960, the investigations of hydrogels began with a landmark paper on poly(hydroxyethylmethacrylate) [4]. Polymer chains of hydrogels are connected to each other, and the nature of their crosslinking can be physical or chemical. Polymer chains of physically crosslinked hydrogels are connected by electrostatic forces, hydrogen bonds or hydrophobic interactions. Polymer chains of chemically crosslinked hydrogels are connected by covalent bonds. According to the origin of monomers, they can be natural, synthetic and the combination of both natural and synthetic types. Hydrogels can be obtained from natural polymers or they can be synthesized from hydrophilic monomers. Hydrogels obtained from natural polymers are biocompatible and biodegradable, but they do not possess good mechanical properties and they can contain pathogens. Synthetic hydrogels have a defined structure which can be designed in order to reach desirable properties [5,6].

In recent years, the researchers' attention has been drawn to temperature- and pH-sensitive synthetic hydrogels based on *N*-isopropylacrylamide (NIPAM) and anionic comonomers (acrylic acid (AA), methacrylic acid

(MAA), itaconic acid (IA), maleic acid (MA) and crotonic acid (CA)) for various applications: environmental [7-9], biological [10], pharmaceutical [11], biomedical [12] and the concentration of solutions [13]. The presence of ionizing groups in their structure enables better absorption of the solution and their application as adsorbents for the removal of heavy metals, dyes and radioactive elements [8,9]. The most important advantages of their application are the ability to regenerate, which is accomplished by adding acids, the possibility of adsorption in a wide range of pH values and time of contact with an adsorbate until the equilibrium has been reached [14]. The environmental application of copolymer hydrogels based on NIPAM and anionic comonomers, in addition to the removal of the pollutants, is reflected in controlling the release of agrochemicals: pesticides and fertilizers. Copolymers represent the delivery systems which protect agrochemicals from degradation, prevent contamination of the soil and surface water due to runoff from the arable land [15-17]. The characteristics of absorption and superabsorption of hydrogels can be used for concentrating the solutions of different compounds and microorganisms, i.e. their separation from aqueous solutions [18,19]. Superabsorbent materials are hydrogels with the possibility of water absorption from 10 to a few thousands greater than their weight in a dry state (10-1000 g/g_{xerogels}) [20,21]. According to some authors, a hydrogel which absorbs the amount of water or biological fluid 100 times greater than the xerogels weight has superabsorbent character-

* **Author address:** Aleksandar Zdravković, Vocational High School for Technology and Art, Vilema Pušmana 17, 16000 Leskovac, Serbia
E-mail: zdravkovic.aleksandar87@gmail.com
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istics [22]. Dual responsive hydrogels represent desirable matrices for drug delivery [11,12,23]. However, in physiological conditions (36 °C; pH=7.4), copolymers based on NIPAM and anionic comonomers can lose their sensitivity to temperature changes. This problem can be overcome by adding a triggering agent (a compound with hydrophobic nature) or decreasing the pH values (if the drug delivery takes place in the environment with lower pH) [11,12]. Copolymer hydrogels are used for immobilization of the enzymes by the copolymerization method with the solution of this biological catalyst [10].

The aim of this paper is the review of potential applications of hydrogels based on NIPAM and anionic comonomers as adsorbent materials for the removal of pollutants, as systems for delivery drugs or agrochemicals, and devices for compound separation as well. In addition to these, the methods of synthesis of copolymer hydrogels and characteristics of the obtained products will be discussed.

Temperature- and pH-sensitive hydrogels based on NIPAM and anionic comonomers

Hydrogels are very often divided according to the type of external stimuli to which they respond, such as: pH, temperature, pressure, ionic strength, electrical impulses, ultrasound, magnetic field, light, the presence of biomolecules and their combination. They can be divided into neutral and ionic hydrogels based on the polarity of side groups. Reversible hydrogels sensitive to external stimuli are the ones for which changes are reversible in relation to the changes of the external stimulus [1,24,25].

Thermo-sensitive hydrogels can swell or contract due to changes in the temperature of the surrounding fluid because of the presence of hydrophilic monomers such as NIPAM, pluronic, methylcellulose, *N*-vinylcaprolactam and tetronic [2]. Poly(*N*-isopropylacrylamide), p(NIPAM), is known as a typical thermo-sensitive polymer which shows a lower critical solution temperature (LCST) at about 32 °C in water [26]. One of the examples of negatively thermo-sensitive hydrogels represents its copolymer poly(*N*-isopropylacrylamide-*co*-2-hydroxypropyl methacrylate), p(NIPAM/HPMet) [5,6,27].

pH-sensitive hydrogels possess ionizing side groups, and small changes in pH values of the medium can lead to significant changes in the swelling degree. In the aqueous medium, side groups ionize and electrostatic repulsive forces appear between polymer chains. Their appearance causes the increase of the distance between nodes of network and the increase of absorption and the swelling degree. According to the nature of side groups, hydrogels can be anionic, cationic and amphiphilic [25,28,29].

Hydrogels based on NIPAM and anionic comonomers (AA, MAA, IA, MA and CA) can be synthesized by emulsion polymerisation [9], dispersion polymerisation [30], free radical polymerization in the solution [12,31] with cross-linker *N,N'*-methylene-bis(acrylamide) (BIS) and γ -rays polymerization [32,33]. Chemical structures of NIPAM and anionic comonomers are shown in Figure 1.

Figure 1. Chemical structure of NIPAM monomer and anionic comonomers AA, MAA, IA, MA and CA

The influence of the temperature change (18-49 °C) on hydrogels based on NIPAM and MAA, synthesized with a different content of monomers using cross-linker tetraethylene glycol dimethyl acrylate (TEGDMA), has been investigated. Temperature sensitivity of poly(*N*-isopropylacrylamide-*co*-methacrylic acid) copolymer, p(NIPAM/MAA), with the molar content of NIPAM up to 70% is very mild. Greater sensitivity is noticed with a higher molar content of NIPAM monomer in the structure of p(NIPAM/MAA) copolymer [34].

In the research of Zdravković et al., superabsorbent hydrogels of poly(*N*-isopropylacrylamide-*co*-acrylic acid), p(NIPAM/AA), have been synthesized by radical polymerization with ethylene glycol dimethacrylate (EGDM) as a cross-linker. Hydrogels have showed pH sensitivity. The increase of pH value of the solution from 2.2 to 6.8 at 25 °C led to the increase of the equilibrium swelling degree of hydrogel with 10 mol% AA and 1.5 mol% EGDM from 8.3 to 259.8 [35]. The swelling of ionic hydrogel depends primarily on the ionic groups content (the acidic and/or basic), their degree of ionization, pH value, the ionic strength of the surrounding media, valence and nature of the counterion and of the swelling medium composition. Hydrophilicity of the polymer network increases with the increase of the ionic groups content in the hydrogel structure, which causes a higher swelling degree. This group of hydrogels (polyampholyte) is characterized by a high swelling degree just because of the ion group ionization, which depends on the pK values and ions hydration. Amphiphilic hydrogels swell significantly in the solutions with low or high pH values [36,37]. In hydrogels based on NIPAM and anionic comonomer, the increases of pH values above pK_a of ionic monomer lead to a higher degree of ionization of carboxyl groups (COO⁻). Electrostatic repulsive forces that appeared between carboxyl anions have caused the expanding of the polymer network and greater absorption of water or biological fluid. In the highly acidic environment, carboxyl groups are protonated which decreases the capacity of hydrogels absorption [11,12,38,39]. Superabsorbent hydrogels can be used for the disposable diapers production and as soil conditioners [39,40].

Improving the sensitivity of poly(*N*-isopropylacrylamide-*co*-itaconic acid) hydrogel, p(NIPAM/IA), pH and

temperature changes can be reached by adding NaCl during the copolymerization reaction in the solution but up to a certain limit (up to 0.2 g of NaCl on 0.5 g of NIPAM and 0.015 g of IA in 8 mL of water). Besides the mentioned salt, characteristics of swelling are also influenced by temperature and pH value of the surrounding fluid. The maximum swelling degree in distilled water (161.3) is reached for the hydrogel sample where 0.2 g of NaCl is added into the starting reaction mixture [31].

UV photopolymerization method in the solution was used for obtaining p(NIPAM/MAA) hydrogel with the biodegradable cross-linker, poly(ethylene glycol)-co-poly(ϵ -caprolactone) (PEG-co-PCL) macromer. Hydrolytic degradation of p(NIPAM/MAA) copolymer at pH 7.4 occurred by breaking up the labile ester bonds. With the increase of the MAA content in hydrogel, hydrolytic degradation of the polymer was increased. This effect was the result of degradation of ester bonds of the PCL segment due to the exposure to a higher amount of water in the swollen gel. Higher absorption and expanding of the polymer network were the results of a higher number of ionizing carboxyl groups (COO^-) at pH 7.4 between which the electrostatic interactions appeared. After 6 weeks of simulated physiological conditions, a significant loss of weight of hydrogel appeared [38].

Removal of pollutants by adsorption

By discharging the effluents from textile industries and nuclear power plants, the production of electrical cables, batteries, ores, steel and electrical TVs, the wastewater is contaminated by heavy metals, dyes and radioactive elements [41-43]. Heavy metals are toxic for living organisms and they show the properties of bioaccumulation and non-biodegradability [44-46]. Also, dyes express toxic effects on humans and aquatic organisms. The consequence of dyed water is restriction of photosynthesis in plants [47,48]. The exposure to radiation of radioactive elements can cause cancer in living organisms [49]. Adsorption by hydrogels is a selective and efficient process for the removal of heavy metals, dyes and radioactive elements [8,32,50]. The adsorption process of pollutants from aqueous solutions by hydrogels can be schematically shown in Figure 2.

Figure 2. Schematic review of pollutant adsorption from aqueous solutions

Removal of heavy metals and radioactive elements

High adsorption capacities, simplicity of application, as well as the ability for regeneration make hydrogels suitable adsorbent materials for the heavy metals removal [51]. Regeneration, *i.e.* desorption of metals in temperature- and pH-sensitive copolymer hydrogels is performed by temperature or pH changes (by using nitric or hydrochloric acid) [50,52,53]. Hydrogels which contain one or more electron donor atoms (N, S, O and P) can form coordinate bonds with metal ions (chelates) [54].

In Table 1, the review of hydrogels based on NIPAM and anionic comonomers used for the removal of heavy metals and radioactive or rare earth elements from solutions by adsorption is shown.

Table 1. Hydrogels based on NIPAM and anionic comonomers which are used as adsorbents for the removal of heavy metals, radioactive and rare earth elements.

Hydrogel	Adsorbate	Adsorption capacity (mg/g)	References
p(NIPAM/AA)	Cu^{2+}	58.95	[9]
p(NIPAM/MAA)	Cu^{2+}	0.765*	[56]
p(NIPAM)	Pb^{2+}	≈ 120	[52]
p(NIPAM)	Cu^{2+}	$\approx 0.015^*$	[58]
p(NIPAM/MA)	UO_2^{2+}	94.8	[32]
p(NIPAM/IA)	Cs^+	≈ 120	[60]
p(NIPAM)	In^{3+}	0.854*	[59]

*mmol/g

In p(NIPAM) hydrogels, the process of heavy metals adsorption depends on temperature changes, the so-called temperature-swing (TS) technique [55]. In the work of Ju et al., p(NIPAM) was used as an adsorbent material which can easily adsorb Pb^{2+} ions in temperatures below LCST of homopolymers. The adsorption capacity of homopolymer hydrogel for Pb^{2+} ions was investigated in the temperature range of 23-50 °C, where the maximum capacity was reached at 23 °C, at about 120 mg/g (Table 1). By increasing the temperature above LCST, desorption of Pb^{2+} ions with p(NIPAM) hydrogel appeared [52]. Amino and amide groups of acrylamide in hydrogels represent adsorption places for heavy metals [55].

Cu^{2+} ion was removed from the solution as well, by p(NIPAM/AA) hydrogel and micro/nano particles of p(NIPAM/MAA) copolymer. The mechanism of Cu^{2+} ion adsorption occurred by chelation with the carboxyl group of AA, *i.e.* MAA, and one copper cation complexed with two functional groups [9,56]. The synthesized p(NIPAM/AA) hydrogel in the work of Chen et al. was applied in polymer-enhanced ultrafiltration (PEUF) for the removal of Cu^{2+} ion. Retaining the Cu^{2+} ion and hydrogel complex on the cellulose acetate membrane was more favourable at the temperature lower than 40 °C and pH=5. It was concluded that environmental factors, temperature and pH, have influence on the adsorption process of Cu^{2+} ion on p(NIPAM/AA) hydrogel [57].

Besides a classical technique of adsorption, there is the so-called solid-phase extraction (SPE) which occurs in many phases. Metal ion is complexed with an extract-

ant in the aqueous solution, and then the complex of metal and extractant is adsorbed on temperature-sensitive hydrogels at the temperature above LCST. Between the metal-extractant complex and hydrogels, such as p(NIPAM), hydrophobic interactions were reached. Sodium *N*-dodecylbenzenesulfonate (SDBS), *N*-dodecylbenzenesulfonic acid (DBS) and *N*-octyl phosphate (OP) were used as extractants. By temperature change, the process of adsorption could be controlled, *i.e.* desorption of the metal and surfactant complex [58,59], which at the same time represents the TS adsorption technique. The advantage of the SPE technique in comparison to the conventional extraction by solvent is cost-effectiveness and use of the lower volume of a solvent [58]. TS and SPE techniques for adsorption of heavy metals or radioactive elements are schematically shown in Figure 3.

Figure 3. Schematic review of TS and SPE techniques for adsorption of heavy metals or radioactive and rare earth elements

By SPE and TS technique, Cu^{2+} ions were adsorbed on homopolymer p(NIPAM) in the presence of SDBS and DBS surfactants. On p(NIPAM) hydrogel, a higher amount of Cu^{2+} ions was adsorbed in the form of the complex with SDBS by hydrophobic interactions, about 0.015 mmol/g (Table 1), at the concentrations ratio $\text{CuCl}_2/\text{SDBS}$, 0.2/1 mol/dm³ [58]. The same researchers tested the possibility of application of the SPE technique for the adsorption of rare earth element indium (In) on p(NIPAM) hydrogel in the presence of extractant OP. The adsorption efficiency of In^{3+} ions from aqueous solution was almost 90% [59]. Poly(*N*-isopropylacrylamide-co-maleic acid), p(NIPAM/MA), and p(NIPAM/IA) hydrogels were good adsorbent materials for the removal of UO_2^{2+} and Cs^+ ions [32,60]. Increasing the content of MA in p(NIPAM/MA) hydrogel leads to the adsorption of a higher amount of UO_2^{2+} ions, which can indicate that carboxyl group of MA is an interacting group for a heavy metal [32].

Adsorption of dyes

Dyes can be classified on the basis of the chemical structure and application. In regards to the application, dyes can be classified into acid, reactive, direct, dis-

persive, base (cationic), vat, mordant (fixative), sulphur, metal complex and azoic dyes [61]. Cationic dyes were investigated mostly as a model substance for the adsorption process on temperature- and pH-sensitive hydrogels based on NIPAM and anionic comonomers [8,62].

Conventional methods proved to be unsuitable for purification of wastewater contaminated by dyes due to cost-effectiveness of the process and production of secondary effluents [62,63]. The advantage of the adsorption of dyes as a method reflects in high efficiency and easiness of using [63]. The adsorption of cationic dyes on active carbon and other sorbent materials is not optimal therefore, the investigators' attention has been directed towards hydrogels [61,62]. Hydrogels are more suitable adsorbents because of their regeneration feature, designing of desired physico-chemical properties in the synthesis, the introduction of appropriate ligands in the structure, as well as the preparation of the composite with natural materials [64-71]. One of the example of obtaining hydrogels with adequate physical-chemical properties, sensitivity to external stimuli or selectivity, for the adsorption process of dyes, is the synthesis of p(NIPAM/MA) copolymer by γ radiation [72].

The comparison of adsorption characteristics of hydrogels based on NIPAM and anionic comonomers for the removal of dyes is shown in Table 2.

Table 2. The comparison of adsorption characteristics hydrogels based on NIPAM and anionic comonomers for the removal of dyes from aqueous solutions

Hydrogel	Adsorbate	Adsorption capacity (mg/g)	References
p(NIPAM/IA)	Brilliant Green	228	[8]
p(NIPAM/IA)	Safranine T	207	[8]
p(NIPAM/IA)	Brilliant Cresyl Blue	204	[8]
p(NIPAM/IA)	Methylene blue	17.67	[68]
p(NIPAM/MA)	Methylene blue	322.6	[72]
p(AM/AA)	Remazol Red 3BS	44.19	[73]
p(MAA) (0%)*	Basic yellow 28	65.8	[76]
p(MAA) (80%)*	Basic yellow 28	77.2	[76]
p(NIPAM)	Methylene blue	8.95	[68]

*neutralization degree of monomer

Temperature- and pH-sensitive p(NIPAM/IA) hydrogel was used for the removal of dyes Brilliant Green, Safranine T and Brilliant Cresyl Blue. Adsorption capacities of p(NIPAM/IA) hydrogel for dyes were higher than 200 mg/g (Table 2). With increasing the number of carboxyl groups, *i.e.* the content of IA sodium salt in the structure of p(NIPAM/IA) copolymer led to the increase of adsorption capacities for dyes Brilliant Green, Safranine T and Brilliant Cresyl Blue. It has been thought that the adsorption of cationic dyes on temperature- and pH-sensitive hydrogels is the result of electrostatic interactions and exchange of electrons between dyes and adsorbent [8]. A significantly lower adsorption capacity of p(NIPAM/IA) hydrogel for cationic dye (Methylene blue) was obtained in the work of Taşdelen et al. (Table 2). The investigators tested the adsorption capacities of p(NIPAM) homopolymer and composite of p(NIPAM/IA) copolymer with pumice. The highest capacity for the removal was shown by the composite, 22.62 mg/g. By introducing pumice into the structure of hydrogel, the number of negative adsorption

places increased and the possibility of the ion exchange and interaction between adsorbent and adsorbate as well [68].

Copolymer based on NIPAM and MA showed a high removal capacity of the dye Methylene blue, 322.6 mg/g. The content of MA in the structure of copolymer had influence on the adsorption capacity of p(NIPAM/MA) hydrogel for Methylene blue [72]. So, in the case of poly(acrylamide-co-acrylic acid) copolymer, p(AM/AA), the increase of anionic comonomer content showed the rise in the adsorption capacity of hydrogels for cationic dyes, Safranin-O and Magenta [62]. In the research of Corona-Rivera et al., p(AM/AA) hydrogel was used for the dye Remazol Red 3BS, and a maximum adsorption capacity was obtained for hydrogel with 1% BIS as a cross-linker, 44.19 mg/g (Table 2) [73].

In the research of Fradj et al., interactive mechanisms of polyelectrolytes poly(acrylic acid), p(AA), and dyes Methylene blue and Toluidine blue were investigated and the influence of salts and surfactants on formed complexes of dyes and hydrogels as well [74]. Two kinds of interactions have appeared between polyelectrolytes and dyes: hydrophobic and electrostatic [75]. Anionic adsorption places of p(AA) hydrogel were responsible for complexation of positive cationic dyes, and interactions were mostly electrostatic. The influence of surfactant cetylpyridinium chloride and NaCl was negative, *i.e.* the addition of these compounds caused destabilization of the dye and hydrogel complex [74].

Besides homopolymer based on AA, poly(methacrylic acid) homopolymer, p(MAA), was applied for the removal of the dye Basic yellow 28. P(MAA) homopolymer with the 80% neutralization degree of monomers showed better adsorption characteristics for the dye, 77.2 mg/g, in comparison to hydrogel with the 0% neutralization degree of monomers, 65.8 mg/g (Table 2). The sorption mechanism of hydrogels with the 0% neutralization degree of monomers is physisorption, whereas in hydrogels with the neutralization degree of 80%, both physisorption and chemisorption occur [76].

Aggregates of p(NIPAM/AA) microgels obtained by polymerization in the presence of BIS as a cross-linker, can efficiently remove the dye Orange II from water, even 73.1%. The capacity of dyes removal by microgels aggregate depends on temperature, the concentration of cross-linker and a number of cycles of heating and cooling [77]. Parasuraman et al. investigated adsorption capacities of the same p(NIPAM/AA) microgels in the unaggregated state for the same dye, where the capacity for the removal of Orange II was 56.6% at the higher temperature [78]. Figure 4 schematically shows the removal of Orange II by microgels and aggregated p(NIPAM/AA) microgels. The reuse of p(NIPAM/AA) microgels and their aggregates was reached by the methanol extraction, where a slight decrease of extraction efficiency appeared with the increased number of recycling cycles [71].

Figure 4. Schematic review of dyes removal by unaggregated and aggregated p(NIPAM/AA) microgels

Composites of hydrogels with natural materials such as kaolin clay [67], montmorillonite clay [70] and zeolite [69] were used for the removal of dyes from aqueous solutions, *i.e.* wastewater. The composite of p(AA) and kaolin clay, p(AA)-K, was synthesized by conventional polymerization and ultrasound induced polymerization. The composite p(AA)-K obtained by ultrasound had a greater adsorption efficiency of the dye Brilliant Green, because during polymerization the kaolin clay was uniformly dispersed into the matrix of p(AA) hydrogel, the consequence of which was the increase of adsorption capacities of the composite [67]. In the work of Aref et al., nanocomposite of poly(acrylamide-co-maleic acid) hydrogel, p(AM/MA), and montmorillonite clay synthesized *in situ* polymerization was used for the removal of Crystal violet from aqueous solutions [70]. Hydrophobic ZSM-5 and hydrophilic A zeolite were used for the synthesis of p(MAA) based composite by free radical polymerization at higher temperature (80 °C). Composite with 30 wt% of hydrophilic A zeolite reached higher adsorption capacity for the dye Basic yellow 28, 180 mg/g. The process of the dye removal depends significantly on swelling of the composite based on p(MAA) and zeolite [69].

By controlling the temperature and pH values, the degradation of the previously adsorbed dye on the composite of hydrogels with encapsulated titan dioxide by UV radiation could be reached. P(NIPAM/AA) hydrogel with encapsulated 2.5 µm titan dioxide at pH=4, 20 or 30 °C and UV radiation time of 25 min, the degradation degree of Methyl orange of 55.6% could be reached. The photocatalytic activity of the composite after the fifth reusing was still good, and a degree of dye degradation was above 75% [79].

Adsorption characteristics of hydrogels sensitive to pH and temperature changes were used for the removal of antibiotic ciprofloxacin from aqueous solution [80].

Hydrogels have found their application in the removal of nutrient from water [81-83] which, in higher concentrations, can lead to eutrophication of aqueous bodies,

the excessive growth of algae. Compounds of nitrogen and phosphor, *i.e.* nitrites (NO_2^-), nitrates (NO_3^-) and orthophosphates (PO_4^{3-}) are considered under the term nutrient. The consequence of eutrophication is a decrease of dissolved oxygen, which has a negative effect on ecosystem and can cause the death of fish species [14,84].

Controlled release of agrochemicals

Hydrogels are widely used as the agrochemical delivery system for a controlled and sustained release of pesticides and fertilizers [85]. By conventional application of pesticides and fertilizers, the surface water is contaminated due to runoff from an arable land. By using the systems based on hydrogels for a controlled release of active components, the dose is decreased and the time for the application of agrochemicals is increased. These systems disable the degradation of agrochemicals by light, air, humidity, microorganisms and evaporation [15-17]. Besides the application for the controlled release of agrochemicals, hydrogels can be used for retaining water in the soil (soil conditioners) with the aim of providing water for the plants growth [86].

The systems for the controlled release of pesticides or fertilizers based on hydrogels can be produced in two ways. The first method includes the synthesis of hydrogel and then, afterwards, loading the hydrogel with an active component by absorption from aqueous solutions [15,16]. In the second method, hydrogel is synthesized in the solution of an active component [86-88]. Different factors can affect the loading of hydrogels with pesticides and fertilizers as active components: the initial concentration of agrochemicals, porosity of hydrogel and absorption time [15].

Figure 5. Schematic review of agrochemical release from polymer by water penetration

In investigations of Saraydin et al., hydrogels based on AM and CA, *i.e.* IA, were used as carriers for the controlled release of a pesticide sodium 2,2 dichloropropionate (dalapon) and fertilizers ammonium nitrate (NH_4NO_3), potassium nitrate (KNO_3) and ammonium sulphate ($(\text{NH}_4)_2\text{SO}_4$). Hydrogels are synthesized by the method of radiation copolymerization (source ^{60}Co) along with the aqueous solution of agrochemicals. Hydrogels poly(acrylamide-co-itaconic acid), p(AM/IA), and poly(acrylamide-co-crotonic acid), p(AM/CA), with loaded agrochemicals represent the systems for release which is controlled by swelling. Pesticides or fertilizers

are uniformly dispersed within a glassy polymer matrix. Immersion of polymers into water leads to water penetration into the matrix and swelling of the copolymer which enables diffusion of the active component to the outside [87-89]. Figure 5 schematically shows the process of releasing the agrochemical by swelling.

Hydrogels based on AM and IA, *i.e.* CA, obtained by radiation induced polymerization are suitable as carriers for the release of dalapon, ammonium nitrate, potassium nitrate and ammonium sulphate. The controlled release of pesticides and fertilizers can be reached by varying the content of IA and CA comonomers and dose of radiation as well [87,88]. The release rate of agrochemicals from the matrix of hydrogel depends on the percentage of loading of an active component [15].

Another type of system for slow release of agrochemicals was synthesized by free radical polymerization of AA monomer with BIS as a cross-linker in the presence of liquid fertilizers. The release of two liquid formulations of fertilizers was investigated: (1) LFA mixture of mono- and dipotassium phosphates, urea and demineralized water (LF-A) (2) mixture of mono- and dibasic potassium and ammonium phosphates, urea and demineralized water (LF-B). The release rate of liquid formulation LF-B from hydrogel matrix at room temperature was lower due to a higher content of ionic groups which interacted with phosphates salts. The crosslinking degree had the influence on the release of fertilizers formulation, and with the increase of the crosslinking degree, the swelling degree of p(AA) hydrogel decreased and therefore the release rate of agrochemicals [86].

The system for agrochemicals delivery can be based on natural and synthetic polymers. Thus, for the controlled and sustained release of a fungicide thiram, the system based on p(MAA) and starch was used. At the beginning, the release of fungicide increased and then, after a certain time, the agrochemical was released in a controlled way. The synthesized hydrogel with a higher concentration of BIS as a cross-linker enabled the sustained release of thiram [16].

Composites with p(AA) hydrogel and wheat straw, *i.e.* lignin, were applied for the release of urea and pesticides [90,91]. In the work of Sun et al., p(AA) hydrogel and its composite with lignin was synthesized for its application for the cumulative release of pesticides paraquat, cyfluthrin and cyhalofop-butyl. Grafting of lignin on p(AA) network enabled the higher capacity of water absorption for different pH values. p(AA) hydrogel reached lower capacity of loading of pesticides and a cumulative release rate (50.06-68.42%) in comparison to the composite (84.27-91.23%) for 10 days [90].

Separation of compounds

Temperature- and pH-sensitive hydrogels have application as devices for separation, *i.e.* concentrating of aqueous solutions of different compounds [13,18,92,93]. The advantage of hydrogels for compounds separation is the possibility for its own regeneration [93].

In the work of Cai et al., concentrating of lignin was performed by p(NIPAM) and p(NIPAM/AA) hydrogels. A significantly higher separation degree of hydrolytic lignin was obtained for ionic hydrogel, p(NIPAM/AA), which can be explained by the fact that it came to ionic repulsion between lignin and hydrophilic AA groups in the structure of hydrogel. In the case of p(NIPAM) application as a device for lignin separation, the adsorption of lignin appeared on the hydrogel itself. The efficiency of the lignin separation depended on the time of the process. Concentrating of lignin by p(NIPAM/AA) hydrogels was increased in the first few hours and maximal separation could be reached for 5 h. With every next cycle of using, p(NIPAM/AA) copolymer showed higher separation efficiency (η) of lignin (Indulin AT), the values for separation in percentages for the first and third cycle were 40.9 and 85.2%, respectively [18].

Copolymer based on NIPAM and AA was used for the separation of poly(ethylene oxide) (PEO) and dextran blue (DB) compounds in aqueous solutions. The separation efficiency of DB and PEO can be controlled by the degree of hydrogel crosslinking, the initial concentration of the compound and molecular mass (for PEO). Maximal concentrating of DB was obtained for the lowest concentration of DB (0.25 g/dm³) and the highest concentration of a cross-linker (1 mol% BIS), $\eta=0.98$. Concentrating of PEO was the highest at the higher initial concentration of PEO (1 g/dm³) and cross-linker (1 mol% BIS), and a higher molecular mass of the compound for the separation as well (1700 kg/mol), $\eta=0.99$ [13].

Figure 6 schematically shows the application of hydrogels for the process of concentrating of different compounds.

Figure 6. Schematic review of concentrating different compounds by hydrogels

Temperature- and pH-sensitive hydrogels have advantages for separating bio-products due to mild conditions during concentrating and preventing their denaturation in comparison to conventional methods. One more advantage is the cost-effectiveness of the process since hydrogels, i.e. polymers, are cheaper than ion exchangers. During the process of separation, a hydrogel absorbs water and compounds of a small molecular mass, whereas proteins are not absorbed but concentrated in the solution [92,93]. Non-ionic p(NIPAM) hydrogel had good separation characteristics during a greater cycle of using for the concentration of cellulase enzymes, pro-

duced by the fermentation of the fungus *Trichoderma reesei* RUT C-30 [93]. A hydrogel sensitive to pH changes synthesized from polyacrylamide, p(AM), and carboxymethyl cellulose by the grafting method in the work of Mohy Eldin et al. was applied with the aim of concentrating bovine serum albumin (BSA) [92].

Microorganisms can be also concentrated by the application of hydrogels based on AM and anionic comonomers. Millimetre sized beads of superabsorbent p(AM/IA) copolymer represent the material which can be used for concentrating of microorganisms: *Escherichia coli* and bacteriophage MS2 [19].

Other application

The application of hydrogels for the development of modern drugs is significant because of the possibility for designing the desirable properties. Potential use of hydrogels based on NIPAM was investigated for the modified release of drugs, e.g. paracetamol, phenacetine, ibuprofen, naproxen and piroxicam [94-96]. The synthesis of hydrogels with the minimal content of residual reactants is a necessary condition for human application [94].

Hydrogels based on NIPAM and anionic comonomers are applied as carriers for drugs delivery [97], materials for immobilization of enzymes [10,98] and sorbents for protein isolation [30].

The percentage of loading a drug and the mechanism of its release from the temperature- and pH-sensitive hydrogel can be regulated by the hydrogel content itself, i.e. the content of the pH sensitive component (IA, AA, MA) and cross-linker. The system for delivery of paracetamol was obtained by copolymerization of AM and IA monomers with the use of BIS as a cross-linker. A lower degree of crosslinking and a higher content of IA provided the fastest release of the paracetamol drug [23]. The increase of the content of a pH-sensitive component in biodegradable p(NIPAM/MAA) hydrogel, synthesized by PEG-co-PC macromolecular cross-linker at pH 7.4, caused a higher rate of releasing the BSA [38].

Dual responsive p(NIPAM/MAA) and p(NIPAM/MA) hydrogels represent self-regulated drug delivery systems. At physiological temperature and pH, these hydrogels lose sensitivity to temperature and therefore the application for the drug delivery is harder. Electrostatic interactions of carboxyl anions of MAA or MA part of the structure of copolymers with hydrophobic compounds of positive charging (triggering agent), diphenhydramine, lidocaine, metoclopramide and propranolol, enabled the temperature sensitivity of copolymer and its collapse at physiological temperature. The pH-sensitive component is a 'biosensor' whereas the drug delivery is done by the temperature-sensitive hydrogel. As a triggering agent, protons (H⁺) can be used, i.e. the pH change of the environment from the physiological pH value (pH=7.4) to weak acidic conditions (pH=5.7). Microgels of p(NIPAM/MAA) and p(NIPAM/MA) copolymers, previously loaded with the drug have the possibility of application in tumour

therapy [11,12].

In the work of Milašinović et al., the immobilization of the lipase enzyme from *Candida rugosa* by p(NIPAM/IA) and p(NIPAM) hydrogels was investigated. Polymerization of hydrogels was performed in the presence of lipase enzyme. Copolymer hydrogel proved to be better for immobilization of the enzyme, which is ascribed to its polyelectrolyte structure. The increase of the IA content in the structure of hydrogels increased the activity of the immobilized enzyme; the optimal sample is with 10 mol% IA [10]. With the immobilization by hydrogel, the enzyme was protected from negative environmental factors. The sufficient size of the pores of hydrogel should be provided so that molecules of the substrate and products of the reaction can penetrate. Further in their research, the investigators came to the conclusion that the addition of surface active matters during the synthesis of p(NIPAM/IA) copolymer does not have any influences on the activity of lipase enzymes [10,98].

As an adsorbent, p(NIPAM/AA) hydrogel isolates hemoglobin from the human blood. The isolation of protein is mostly based on electrostatic, hydrophobic and hydrogen interactions with hydrogel. Electrostatic interactions appear between carboxylate anions (COO^-) of hydrogel and a positively charged protein. By p(NIPAM/AA) hydrogel at pH=6, the efficiency of hemoglobin sorption of 93% can be reached [30].

Synthesized macroporous crosslinked copolymers of poly(methyl methacrylate-co-acrylamide), p(MMA/AM), with free volume of open pores from 50 to 90%, are not dissolved and do not swell in organic solvents, in contrast to usual crosslinked copolymers which become porous after swelling. If the obtained copolymer has open pores, it can be used for immobilization of microorganisms or enzymes within pores and as the initial material for obtaining ion exchanger resin, or as an adsorbent [99,100].

Dual pH- and temperature-sensitive antibacterial nanocomposite Ag-poly(*N*-isopropylacrylamide-co-itaconic acid), Ag-p(NIPAM/IA) was investigated. By introducing a small amount of itaconic acid, IA, the capacity of swelling and phase transition temperature of p(NIPAM/IA) copolymer increased. Nanocomposite Ag-p(NIPAM/IA) hydrogels show good antibacterial potential [101].

Conclusion

Hydrogels based on NIPAM and anionic comonomer (AA, MAA, IA, MA and CA) can be synthesized by different methods of polymerization: emulsion polymerization, dispersion polymerization, precipitation polymerization, free radical polymerization in the solution and UV and γ -rays induced polymerization. The content of pH-sensitive component, an anionic comonomer, has a synergistic effect on the swelling degree of hydrogels and the adsorption of pollutants from aqueous solutions. Interacting groups of copolymer for the adsorption of pollutants are amide groups of NIPAM and carboxyl groups

of an anionic comonomer. Hydrogels show sensitivity to surrounding stimuli, pH and temperature, and therefore, their application as systems for the controlled release of drug or agrochemicals. There are two ways of the preparation of the NIPAM and anionic comonomer based systems for the controlled release of pesticides or fertilizers. The first way is absorption of the aqueous solution of agrochemical by the previously synthesised copolymer, and the second one is when the synthesis occurs in the presence of the aqueous solution of agrochemical. Immobilization of enzymes by hydrogels is possible and it is performed by copolymerization of monomers with the addition of enzymes (the same as for agrochemicals, the second way). Concentrating the aqueous solutions of different compounds and microorganisms by hydrogels is based on the absorption characteristics of temperature- and pH-sensitive copolymers. General conclusion is that hydrogels based on NIPAM and anionic comonomers, depending on the composition, represent matrix systems for a wide range of applications: biomedical, biological, pharmaceutical, the environmental one, and as devices for separation.

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Abbreviations and symbols

Lower critical solution temperature - LCST

N-isopropylacrylamide - NIPAM

Acrylic acid - AA

Methacrylic acid - MAA

Itaconic acid - IA

Maleic acid - MA

Crotonic acid - CA

Poly(*N*-isopropylacrylamide) - p(NIPAM)

Poly(*N*-isopropylacrylamide-co-2-hydroxypropyl methacrylate) - p(NIPAM/HPMet)

Poly(*N*-isopropylacrylamide-co-acrylic acid) - p(NIPAM/AA)

Poly(*N*-isopropylacrylamide-co-methacrylic acid) - p(NIPAM/MAA)

Poly(*N*-isopropylacrylamide-co-itaconic acid) - p(NIPAM/IA)

Poly(*N*-isopropylacrylamide-co-maleic acid) - p(NIPAM/MA)

Poly(acrylamide-co-acrylic acid) - p(AM/AA)

Poly(acrylamide-co-maleic acid) hydrogel - p(AM/MA)

Poly(acrylamide-co-itaconic acid) - p(AM/IA)

Poly(acrylamide-co-crotonic acid) - p(AM/CA)

Poly(methyl methacrylate-co-acrylamide) - p(MMA/AM)

Poly(acrylic acid) - p(AA)

Poly(methacrylic acid) - p(MAA)

Poly(acrylamide) - p(AM)

Composite of p(AA) and kaolin clay - p(AA)-K
 Ag-poly(*N*-isopropylacrylamide-co-itaconic acid) - Ag-p(NIPAM/IA)
 Poly(ethylene glycol)-co-poly(ϵ -caprolactone) - PEG-co-PCL
N,N'-methylene-bis(acrylamide) - BIS
 Tetraethylene glycol dimethyl acrylate - TEGDMA
 Ethylene glycol dimethacrylate - EGDM
 Temperature-swing - TS
 Polymer-enhanced ultrafiltration - PEUF
 Solid-phase extraction - SPE
 Sodium *N*-dodecylbenzenesulfonate - SDBS
N-dodecylbenzenesulfonic acid - DBS
N-octyl phosphate - OP
 Poly(ethylene oxide) - PEO
 Dextran blue - DB
 Bovine serum albumin - BSA

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Izvod

PRIMENA HIDROGELOVA NA BAZI N-IZOPROPILAKRILAMIDA I ANJONSKIH KOMONOMERA

Aleksandar S. Zdravković^{1*}, Ljubiša B. Nikolić², Snežana S. Ilić-Stojanović², Vesna D. Nikolić²

¹Visoka tehnološko umetnička strukovna škola, Leskovac, Srbija

²Univerzitet u Nišu, Tehnološki fakultet, Leskovac, Srbija

Hidrogelovi predstavljaju trodimenzionalne mreže polimernih lanaca koje imaju sposobnost apsorpcije znatne količine vode ili biološkog fluida. Posebnu grupu hidrogelova predstavljaju kopolimeri koji reaguju na promene pH vrednosti i temperature. Poželjne karakteristike temperaturno- i pH-osetljivih hidrogelova na bazi N-izopropilakrilamida i anjonskih komonomera za različite primene, od farmaceutske do primene u zaštiti životne sredine, mogu se dizajnirati sastavom kopolimera. Prisustvo amidne i karboksilne grupe u strukturi ovih hidrogelova omogućava njihovu primenu kao adsorbenata u postupcima uklanjanja polutanata iz vodenih rastvora. Hidrogelovi na bazi N-izopropilakrilamida i anjonskih komonomera predstavljaju poželjne trodimenzionalne matrice za kontrolisano i produženo oslobađanje agrohemikalija i lekovitih supstanci u funkciji temperature i pH okolnog medijuma. Hidrogelovi kao separacioni uređaji vrše koncentrisanje rastvora jedinjenja ili mikroorganizama apsorpcijom većih količina vode. Metod imobilizacije enzima je još jedna primena ovih kopolimera.

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Ključne reči: hidrogel, adsorpcija, polutanti, agrohemikalije, separacija, kontrolisana isporuka