



Semi-interpenetrating Networks Based on (Meth)acrylate, Itaconic Acid, and Poly(vinyl Pyrrolidone) Hydrogels for Biomedical Applications

10

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Abstract

In this study, three series of semi-interpenetrating networks were synthesized based on 2-hydroxyethyl methacrylate (HEMA), 2-hydroxyethyl acrylate (HEA), itaconic acid (IA), and poly(vinyl pyrrolidone) (PVP) as interpenetrating polymer. Syntheses were performed by free radical cross-linking/polymerization reaction. The first series represented hydrogels based on 2-hydroxyethyl methacrylate, poly(vinyl pyrrolidone), and itaconic acid, varying of poly(vinyl pyrrolidone) content. The second series of samples were hydrogels based on 2-hydroxyethyl acrylate, poly(vinyl pyrrolidone), and itaconic acid, varying of itaconic acid content. The third series of synthesized samples were based on 2-hydroxyethyl acrylate, poly(vinyl pyrrolidone), and itaconic acid, varying of poly(vinyl pyrrolidone) content. The content of component was varied in order to examine the influence on the structure, pH- and temperature-sensitive swelling-“intelligent” behavior, mechanical properties of hydrogels, as well as antimicrobial and biocompatible potential of hydrogels. Poly(vinyl pyrrolidone) is a linear polymer, which shows satisfactory biocompatibility and hydrophilicity. Itaconic acid gives pH-sensitive-“intelligent” behavior and better hydrophilicity. Hydrogels based on HEMA and HEA show excellent biocompatibility and satisfactory hydrophilicity.

All three series of samples showed satisfactory cytocompatibility, as well as the antimicrobial potential tested against most common microbes. The results obtained and presented in this research can contribute to the development of new efficient polymeric biomaterials for biomedical applications.

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S. Jana, S. Jana (eds.), *Interpenetrating Polymer Network: Biomedical Applications*, https://doi.org/10.1007/978-981-15-0283-5_10

263

Keywords

Hydrogels · 2-hydroxyethyl (meth)acrylate · Poly(N-vinylpyrrolidone) · Itaconic acid · Biomedical applications

10.1 Introduction

Hydrogels as polymeric biomaterials due to their properties and potential applications in medicine and pharmacy are examined for a period of 50 years (Peppas et al. 2000). Hydrogels are cross-linked polymeric materials that can swell in water and biological fluids, but do not dissolve in them. Because of the high content of water, they have soft consistency and a favorable degree of flexibility that is very similar to living tissues. The ability of hydrogels to absorb water derives from hydrophilic functional groups bound to the polymer chain, while their dissolution resistance arises from the cross-linking of the chain's network. Hydrogels can absorb a large amount of water, making them very similar to living tissues, which results in increased biocompatibility, resulting in ever more extensive use in biomedicine. In the swollen state, they can reach a mass of 10–20% to up to tens of thousands more compared to the mass of dry gel, xerogel. Water retention capacity and permeability are very important properties of hydrogels. Cross-linking between different polymer chains results in viscoelastic, sometimes purely elastic, behavior and contributes to the gel having the appropriate hardness and elasticity. The choice of the starting components and the fraction in the synthesis provide the possibility of adjusting the structure of hydrogels; mechanical, thermal, and morphological properties; as well as swelling and sensitivity to external stimuli (Gulrez et al. 2011; Himi and Maurya 2013; Hoffman 2012; Chai et al. 2017; Pal et al. 2009).

Hydrogels are three-dimensional, physically or chemically cross-linked polymers, which have the ability to absorb a large amount of water or physiological fluids while preserving their dimensional and structural stability. High content of water, soft and elastic consistency, and minimal tendency of adsorption of proteins to the surface of hydrogels are basic properties that make hydrogels very similar to living tissues. A special group of hydrogels as biomaterials is made up of so-called “intelligent” hydrogels that have the ability to recognize the effect of the dominant stimulus in the body, giving it a response in the form of changing their physical and/or chemical properties. In 1960, Wichterle and Lim synthesized the first hydrogel based on 2-hydroxyethyl methacrylate (HEMA), which was intended to produce contact lenses. Since then, interest in hydrogels has started to grow. Many studies have been carried out to modify the structure and properties using different monomers and polymers. For hydrogels based on HEMA and HEA, they have been shown to exhibit exceptional biocompatibility and high hydrophilicity and are used for the synthesis of hydrogels that can be found in biomedicine and pharmacy. Poly(vinyl pyrrolidone) (PVP) is a linear polymer widely used for the synthesis of interpenetrating grid (IPN) hydrogels, due to its impact on the properties of hydrogels such as morphology, swelling, and release of the drug. Poly(vinyl pyrrolidone)

has antimicrobial properties to some extent. It can be used to produce medical devices such as surgical threads, prostheses, coatings, and implants. Its application can prevent the appearance of an infection, which may be due to the application of these devices. It is one of the most used polymers for the synthesis of semi-IPN networks. Itaconic acid gives the pH a delicate, “intelligent” behavior and contributes to hydrophilicity.

A group of hydrogels showing changes in swelling, in response to the action of stimuli from the environment, such as pH, temperature, ionic strength of the solution, intensity of light, and magnetic and electric field strength, belong to “intelligent” materials. Due to its specific properties, the application of hydrogels in the field of medicine and pharmacy has an increasing importance and scope. For application it is important that hydrogels during the swelling remain mechanically strong enough, i.e., to retain their geometry and shape, to be flexible, and to be able to release the active agent molecules that are loaded by fluid absorption in the polymer network at controlled rate. For certain bioengineering applications, the properties of “mimicry” are important, i.e., imitating the properties of living tissues.

A significant area where hydrogels are applied are controlled-release systems for active substances, as matrices in which active substances that are controlled release into the body fluids after loading are released; synthetic skin coatings in the treatment of wounds and burns that are also a barrier to bacteria; and contact lenses for use in ophthalmology, which may include drug (Okay et al. 2009; Singh et al. 2014; Jiao et al. 2006).

In order for hydrogels to be used in medicine and pharmacy, they must be biocompatible. This implies the interaction between the material and the organism in which the material is applied. In order to be used for making medical implants, which are used in contact with the cells, tissues, or body fluids of a human organism, they must satisfy certain criteria. An important feature of the material that it must possess is harmlessness, which means that the material does not cause cytotoxicity. They should not cause unwanted reactions to the body, irritation or allergy. Also, they must not be mutagens or carcinogens. If the tissue cannot accept the “foreign body,” then it is unacceptable for making the implants.

Biocompatibility is one of the most significant characteristics of newly synthesized hydrogels. In a preliminary biocompatibility assessment, *in vitro* cytotoxicity tests are most often used. If the newly synthesized materials would not be biocompatible, i.e., if they were to show a cytotoxic effect on normal cells, they could induce necrosis (accidental cell death) or apoptosis (programmed cell death) of these cells and thus could not be used for human use. This is the first phase in the research and development of new potential pharmaceutical products. Most of the toxicity problems in hydrogels are related to unreacted components during synthesis. Therefore, the understanding of the toxicity of various monomers used as constituents of hydrogels is very important. The relationship between chemical structures and the cytotoxicity of acrylate and methacrylate monomers has been studied. Some of the measures taken to solve this problem include modifying the polymerization kinetics to achieve greater conversion and rinsing of the hydrogel obtained. The formation of hydrogels without the initiator supplements was

examined to eliminate the problem of a lagging initiator. The most commonly used technique is gamma radiation (Ristić et al. 2011).

Hydrogels have significant applications in medicine and pharmacy, such as contact lenses and artificial skin, in controlled drug release. Infections associated with the application of medical devices made of polymeric biomaterials represent a significant clinical problem in medical practice, and there are still serious complications in the application of these products. When there is already an infection, there are difficulties in the treatment of existing antibiotic agents. More recently, new biomaterials based on polymers develop, which have specific antimicrobial properties over a longer period of time. An additional advantage is that some antimicrobial agents can be incorporated into such biomaterials to ensure infection control at the target site where the application of the given biomaterials is carried out. Synthesis of polymeric biomaterials for use in medicine and pharmacy, showing specific antimicrobial properties, is one of the important goals.

Infection is the most common complication associated with the use of medical devices (catheters, prostheses, surgical sutures, implants). One of the most well-known polymers, which in itself possesses to some extent antimicrobial properties, is poly(vinyl pyrrolidone) (PVP). One of the more important testing of polymers for their application in medicine is testing their antimicrobial activity. The most common causes of infection are known, and these microorganisms are used to test the antimicrobial potential of new materials (Rodriguez-Hernandez 2016; Salome and Schneider 2013).

Poly (N-vinyl-2-pyrrolidone) (PVP) is a synthetic, linear polymer. Based on the chemical structure, PVP is a polymeric lactam with internal amide linkages. It contains a very polar amide group that gives hydrophilic properties and nonpolar methylene groups that provide hydrophobic properties. This polymer possesses good biocompatibility and can be used as the main component in the synthesis of materials used for temporary skin dressings and bandages (Erizal et al. 2013; Ajji et al. 2005). Its use as biomaterials in artificial blood plasma dominated the Second World War. Lately, polymers based on PVP have been tested quite a lot. There are other applications, such as controlled drug delivery systems, tissue regeneration, and implant replacement (Barros et al. 2011).

PVP is one of the most used polymers for the synthesis of semi-interpenetrating networks. Semi-interpenetrating polymer network (semi-IPN) hydrogel polyacrylamide grafted with poly(vinyl alcohol)/poly(vinyl pyrrolidone) (PAM-g-PVA/PVP) was synthesized by free radical polymerization initiated by PVA $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$. It has been shown on the basis of the results that the morphology and swelling degree of PAM-g-PVA/PVP hydrogels can be changed and controlled using a different content of PVP. Also, it has been shown that these hydrogels are temperature-sensitive; the highest swelling degree is observed at a temperature of about 42 °C. The vicinity of the physiological temperature opens the possibility of the use of these copolymers in controlled drug release systems (Wei et al. 2014).

The pectin-PVP hydrogel membranes based on pectin and poly(vinyl pyrrolidone) (PVP) (PEVP) were synthesized. The properties of these samples and the influence of increased PVP fraction were examined. The DSC study shows that T_g

rises after mixing with PVP. It has been found that mechanical strength increases with increasing PVP content in hydrogel membranes. It has also been found that the synthesized samples are biocompatible with the melanoma B16 cell line. It has been shown that these samples are pH-sensitive. As a model for controlled release of the drug, salicylic acid was incorporated into the hydrogel membrane by the diffusion method. Based on the results of this study, it can be concluded that these hydrogels may be candidates for various biomedical applications, such as in controlled drug release (Mishra et al. 2008).

Hydrogel based on poly(vinyl pyrrolidone) (PVP) and κ -carrageenan (CK) is synthesized using radiation. The aim of this research is the synthesis of biomaterials that can be used in medicine. The characterization of these samples has been performed. Properties such as gel fractions, water absorption, water evaporation, elongation at break, and strength were tested to assess for the usefulness of wound healing hydrogels (Erizal et al. 2013).

pH-sensitive hydrogels based on poly(vinyl pyrrolidone) and acrylic acid (PVP/AA) are synthesized by free radicals polymerization. The content of monomers, polymers, and a cross-linking agent varies, and their influence on the swelling and release properties is tested. *N,N*-methylenebisacrylamide (MBA) was used as a cross-linker and tramadol HCl as a drug model. Grafting of PVP with AA improves the mechanical properties of the hydrogels and also makes them pH-sensitive. pH sensitivity of PVP/AA hydrogels can be modified by changing the composition and degree of cross-linking to be used for optimal drug release to the colon (Sohail et al. 2014).

Interpenetrating nets (IPN) of hydrogels based on chitosan (Ch), poly(vinyl pyrrolidone) (PVP), and poly(acrylic acids) (PAAc), cross-linked with glutaraldehyde (GA) and *N,N*-methylenebisacrylamide (MBA), were synthesized and their properties tested. The possibility of potential application as a controlled drug release system to the gastrointestinal tract was investigated. Amoxicillin was used as a drug model. Based on the results, it can be concluded that these pH-sensitive hydrogels can serve as a potential material for the drug release to the stomach or small intestine (Ekici and Saraydin 2007).

Three different formulations of PVP hydrogels have been synthesized, characterized, and used as a carrier for various drugs. Theophylline is incorporated into a PVP hydrogel with different concentrations. The mechanism of the theophylline release from the tablet, as well as the time of its release, was tested. Based on these results, it can be concluded that PVP hydrogels can be used as controlled drug release system (Ahmad et al. 2013).

The research was carried out on hydrogels as decubitus dressings, which were synthesized on the basis of poly(vinyl pyrrolidone) (PVP), polyethylene glycol (PEG), and agar. The study examined the biocompatibility of these samples. An *in vitro* biocompatibility test included cytotoxicity, antifungal, and antibacterial tests, which are most important for the application of samples as decubitus dressings. Based on the results, it can be concluded that these hydrogels show good biocompatibility (Biazar et al. 2012).

Wound healing is a dynamic process. The condition of the wound may further affect the progress of the healing process. It is widely accepted that a warm, humid environment encourages rapid healing. The state-of-the-art wound care products are designed to provide these conditions. Hydrogels are used for skin dressings based on poly(vinyl pyrrolidone) (PVP), κ -carrageenan, and polyethylene glycol (PEG) using ^{60}Co gamma radiation. These materials are suitable for use in tropical conditions and have a relatively long lifetime. Based on the results, it can be noted that the properties of the synthesized hydrogel are similar to commercial hydrogels and that they can be applied as wound dressings. The results of the study confirm that hydrogels based on PVP/ κ -carrageenan/PEG can continue with clinical trials (De Silva et al. 2011).

Semi-interpenetrating polymer networks (semi-IPNs) and interpenetrating polymeric networks (IPNs) have emerged as innovative materials for biomedical and pharmaceutical applications. The interest in these structures is due to the possibility of combining the favorable properties of each polymeric component of the IPNs or semi-IPNs leading to a new system with properties that often differ from those of the two single components (Bhardwaj et al. 2012; Rana et al. 2015; Bajpai et al. 2008; Singh et al. 2012; Sperling 1981; Banerjee et al. 2010). All these overall properties allow tailoring new materials, thus designing desired properties and preparing new hydrogels useful in the biomedical field (Das 2013; Roland 2013; Wang et al. 2011).

Poly(2-hydroxyethyl (meth)acrylate) (PHE(M)A)s are commonly used polymers for the synthesis of hydrogels, due to its biocompatibility and high hydrophilicity. PHE(M)A hydrogels found a lot of applications in pharmaceutical and biomedical fields. It can be used for biomaterials as coatings, intraocular lenses, tissue scaffolds, and devices for controlled drug delivery. To improve mechanical stability or swelling properties of hydrogels based on PHE(M)A, they can be combined with hydrophilic polymers into blends or semi-IPNs (Prasitsilp et al. 2003; Barrett et al. 1986; Menapace et al. 1989; Tomić et al. 2006; Babić et al. 2015; Baino 2010; Sanna et al. 2012; Chen et al. 2007).

Poly(vinyl pyrrolidone) (PVP), a water-soluble synthetic polymer, is widely used in medical applications, such as a blood plasma extender and a carrier for drug delivery. PVP has low toxicity, and it is used in medicine, food, and cosmetics and as a film-forming agent. Because of its special molecular structure, PVP has many outstanding properties. PVP has satisfied biocompatibility and hydrophilic properties, which have been used for composite tissue engineering matrices. It is one of the most frequently used interpenetrating polymers because it can be expected to influence hydrogel's morphological, swelling, and drug release characteristics (Abdelrazek et al. 2013; Chadha et al. 2006; Domingues et al. 2013; Erizar et al. 2013; Giri et al. 2011; Marsano et al. 2005; Naghdeali and Adimi 2015; Tomar and Sharma 2013; Wang and Wang 2010; Wei et al. 2014; Yanpeng et al. 2006).

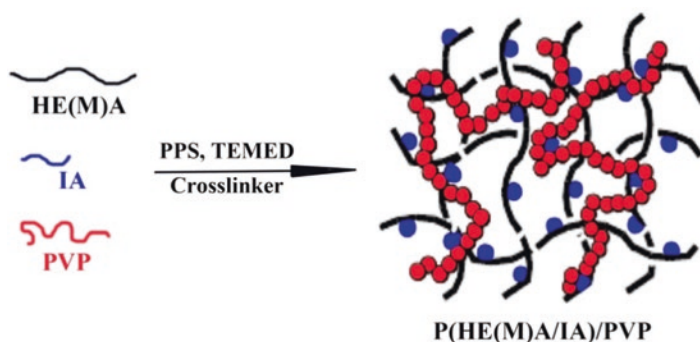
Itaconic acid (IA) can be produced from renewable sources by fermentation. IA is very hydrophilic and is expected to show good biocompatibility because of its

natural source. Small amounts of IA render good pH sensitivity and increased degree of hydrogel swelling (Bera et al. 2015; Gils et al. 2011; Okabe et al. 2009; Petruccioli et al. 1999; Rashid et al. 2016; Sakthivel et al. 2014; Sariri and Jafarian 2002; Sudarkodi et al. 2012).

2-Hydroxyethyl methacrylate (HEMA), 2-hydroxyethyl acrylate (HEA), itaconic acid (IA), and poly(vinyl pyrrolidone) (PVP) have specific properties and are therefore selected as components for samples syntheses to achieve biomedical applications. Three series of samples were synthesized. The fraction of components is varied to examine the effect on structure, pH- and temperature-sensitive swelling-“intelligent” behavior, and mechanical properties of gels. Their effect on the antimicrobial properties and cytotoxicity of the hydrogels was also examined.

10.2 Semi-interpenetrating Networks Based on (Meth)acrylate, Itaconic Acid, and Poly(vinyl Pyrrolidone) Hydrogels

Semi-IPNs were obtained by a simultaneous method where a single cross-linker which has no possibility of any interaction with the second polymer is used. HE(M)A and IA monomers were polymerized simultaneously in the presence of PVP polymer, in such a way that the HE(M)A/IA copolymer is cross-linked and intermingled with PVP linear polymer. TEMED is used as an activator in order to activate polymerization process, and EGDMA is used as cross-linker in order to create a three-dimensional polymeric network (Scheme 10.1).



Scheme 10.1 Schematic representation of the formation of semi-IPN hydrogels composed of HE(M)A, IA, and PVP

10.3 Hydrogels Based on 2-Hydroxyethyl Methacrylate, Itaconic Acid, and Poly(vinyl Pyrrolidone) with Varied Poly(vinyl Pyrrolidone) Fraction

10.3.1 Structural Properties of P(HEMA/IA)/PVP Gels

FTIR spectra were recorded to identify the most important functional groups containing the synthesized copolymer gels recorded. Structural analysis of gels with different PVP content shows the difference in all three spectra through the appearance of the shoulders at 1664 cm^{-1} . As the proportion of PVP increases (indicated by the peak shoulder size), so the smallest is for the P(HEMA/IA)/2PVP sample, and the largest for P(HEMA/IA)/10PVP. Characteristic OH peaks at 3450 cm^{-1} (C–O stretching), peak characteristic for esters at 1730 cm^{-1} (C=O stretching), and aliphatic peaks in the range of $2900\text{--}3000\text{ cm}^{-1}$ (C–H stretching) (Boran and Hitit 2015; Podkoscielna et al. 2012; Tu et al. 2008).

10.3.2 pH- and Temperature-Sensitive Swelling of P(HEMA/IA)/PVP Hydrogels

In order to test the pH sensitivity of P(HEMA/IA)/2PVP, P(HEMA/IA)/5PVP, and P(HEMA/IA)/10PVP hydrogels, the samples were immersed at $37\text{ }^{\circ}\text{C}$ solutions of different pH values (2.20, 3.85, 4.50, 5.45, 6.25, 6.80, 7.40, 8.00). It can be noticed that all samples exhibit a similar trend in the behavior of the equilibrium degree of swelling (q_e) with a change in the pH value. The lowest q_e values have samples at a low pH of 2.20. The lowest q_e values are below pK_a of the values of IA groups, when the carboxylic groups of itaconic acid are non-ionized. Then, intramolecular hydrogen bonds are formed, resulting in greater network compactness. The ionization occurs when the pH of the medium rises above the pK_a values of both carboxyl groups ($pK_{a1} = 3.85$ and $pK_{a2} = 5.45$). With an increase in ionization, the amount of permanent charge increases, causing an increased electrostatic repulsion between ionizing groups and therefore chains, the network's hydrophilicity, and the degree of swelling. With increasing IA content in hydrogels, q_e values increase. The maximum q_e values for all samples are at pH 6.25. The highest values were obtained for samples with 10 mol% IA as expected. Above this pH, the values of q_e slightly decrease, and above pH 7.40, there is a slight increase.

In order to investigate the behavior of hydrogels P(HEMA/IA)/PVP in buffer solutions, having pH values similar to biological fluids, the samples were swollen to an equilibrium state in buffer pH 7.40 at temperatures of 25, 37, 45, and $55\text{ }^{\circ}\text{C}$.

The dependence of the equilibrium degree of swelling on temperature in the buffer pH 7.40 P(HEMA/IA)/PVP hydrogels shows that all samples exhibit temperature sensitivity. The value of q_e drastically increases above $41\text{ }^{\circ}\text{C}$, which represents the temperature at which there is a change in volume (VPTT) of hydrogels P(HEMA/IA)/PVP. P(HEMA/IA)/PVP hydrogels have a VPTT at a physiologically important temperature of about $41\text{ }^{\circ}\text{C}$. When the temperature is below VPTT, the hydrogels

exhibit hydrophilic nature, because the interactions of polymer chains with water molecules dominate, and because of the hydration of the polymer chain groups, hydrogen bonds and hydrogel swells are established. However, when the temperature rises above the VPTT, there is a discontinuance of the established hydrogen bonds, the polymer chains are shrinking, and water is pushed out so that the gel is contracted into the hydrophobic state. This phase transformation is more pronounced for samples with a higher PVP content.

Based on these values, we see that the equilibrium swelling (q_e) decreases in the function of PVP and temperature. The equilibrium degree of swelling (q_e) for P(HEMA/IA)/PVP hydrogels is in the range of 2.56–3.78. If the influence of PVP content in gels on the equilibrium swelling degree (q_e) is observed, it can be concluded that as the PVP increases from 2 to 10 mol% at all temperatures, the equilibrium swelling degree decreases. This behavior of gels can be explained by the fact that with the increase in the PVP content, there are chains of the linear hydrophilic polymer of extremely high molecular weight (360000 g/mol) that affect the density of cross-linking within the polymer network and that, depending on the temperature, quantity of absorbed fluids decreases.

When considering the influence of temperature on the equilibrium degree of swelling, it can be observed that q_e decreases as the temperature rises in the range of 25–55 °C, for all gel samples, where this decrease is most pronounced for the sample with the highest PVP. This behavior of gels can be explained by the occurrence of long PVP chains difficult to move at higher temperatures and to increase q_e with increasing PVP content. It can be concluded that the loading of high-molecular-weight PVP within the gel polymer network reduces the degree of swelling of gels compared to gels of similar composition, but without PVP.

10.3.3 Morphology of (HEMA/IA)/PVP Hydrogels

The requirement for hydrogels to attach cells is to easily deliver oxygen, nutrients, water-soluble metabolites, and waste products between inside and outside of hydrogel. In order to fulfill these requirements, hydrogel must exhibit a large number of interconnected pores. In order to examine the morphology of synthesized gels, a scanning electron microscopy was performed. P(HEMA/IA)/10PVP xerogel showed porous structure, with texture of the honeycomb model. There is no significant difference in the pore size of the sample, which is consistent with the swelling of the samples. These hydrogels are suitable for biomedical applications.

10.3.4 Mechanical Properties of P(HEMA/IA)/PVP Hydrogels

Mechanical properties are expressed through the measurement of the shear modulus of the semi-IPN hydrogels. The value of the modulus ranges from 290 to 440 kPa. It can be seen that P(HEMA/IA)/PVP hydrogel possesses good mechanical properties, which are affected by long-chain PVPs within the gel network. A small amount

of PVP incorporated in semi-IPN hydrogels improves their mechanical properties (Shi et al. 2016). The value of G increases as the PVP fraction increases. The highest value is for the sample with 10 mol% PVP. P(HEMA/IA)/2PVP hydrogel shows the smallest G value. This behavior can be explained by the ability of PVP to improve mechanical properties due to the formation of hydrogen bonds. The addition of PVP to hydrogels significantly improves the mechanical properties of the gels, with the best properties being obtained for the sample with the highest content of PVP.

10.3.5 Biocompatibility of P(HEMA/IA)/PVP Hydrogels

Biocompatibility of semi-IPN P(HEMA/IA)/PVP hydrogels was examined in a cytotoxicity test on human cervix carcinoma (HeLa) epithelial cells. The results of this study for P(HEMA/IA)/PVP hydrogels with different PVP content are shown in Fig. 10.1. The obtained values show that there is no significant change in cell viability with the change of PVP content and confirm that P(HEMA/IA)/PVP hydrogels show a high level of cytocompatibility and therefore suitable for use as biomaterials. Cell viability is over 90% for all samples, for all concentrations of the extract.

10.3.6 Antimicrobial Properties of Hydrogels

Determination of antimicrobial activity is of great importance for biomedical application. Based on the results shown in Fig. 10.2, it can be noticed that the

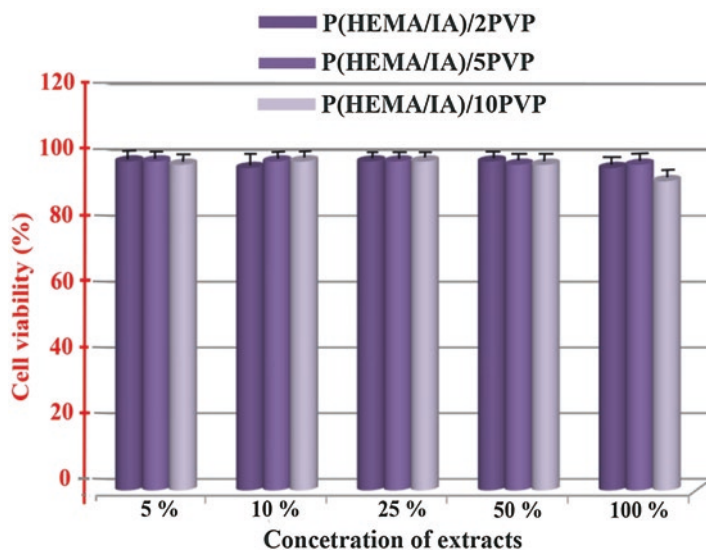


Fig. 10.1 Cell viability of P(HEMA/IA)/PVP hydrogels

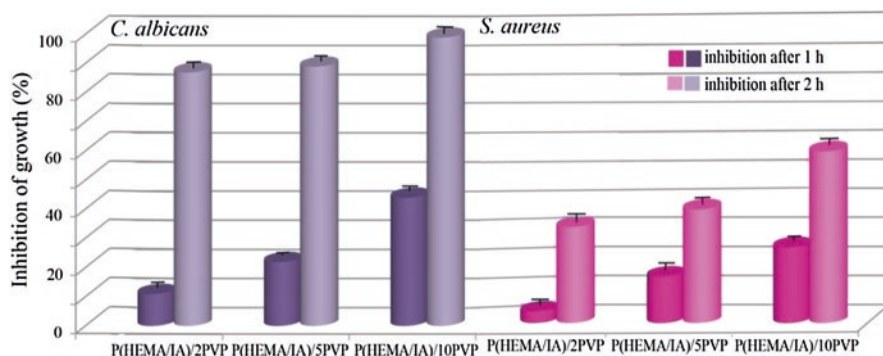


Fig. 10.2 Antimicrobial activity of P(HEMA/IA)/PVP hydrogels against *C. albicans* and *S. aureus*

antimicrobial effect depends on the fraction of PVP in the gels, and how the PVP fraction increases, thus increasing the efficiency. The highest sensitivity to the tested gels was obtained for *C. albicans* pathogenic yeast cells where the percentage reduction was achieved by about 85–95%. A slightly lower sensitivity to the antimicrobial activity of PVP hydrogels was shown by the Gram-positive *S. aureus* bacterium, with a percentage of the cell number reduction of about 60 % after the second hour of exposure for the sample with the highest proportion of PVP. Considering the influence of the exposure time of PVP hydrogels to the indicator strains, an increase in the percentage of cell number reduction with the duration of exposure is observed. This trend is present in all samples and refers to microbial cultures used.

10.4 Characterization of Hydrogels Based on 2-Hydroxyethyl Acrylate, Itaconic Acid, and Poly(vinyl Pyrrolidone) with Varied Fraction of Itaconic Acid

10.4.1 Structural Properties of P(HEA/IA)/PVP Gels

The FTIR spectra P(HEA/2IA)/PVP, P(HEA/5IA)/PVP, and P(HEA/10IA)/PVP hydrogels showed peak characteristic of PHEA, OH peaks at 3450 cm^{-1} (C–O Stretch), a peak characteristic of esters at 1730 cm^{-1} (C=O stretching), and aliphatic peaks in the range of $2900\text{--}3000\text{ cm}^{-1}$ (C–H stretching). The increase in the intensity of the peak C=O groups of about 1730 cm^{-1} in the spectrum indicates an increased number of C=O groups of IA for samples P(HEA/2IA)/PVP, P(HEA/5IA)/PVP, and P(HEA/10IA)/PVP. The absorption peaks about 1650 cm^{-1} , characteristic of the stretch vibration C=O, and those at 1290 cm^{-1} and 1020 cm^{-1} characteristic of C–N vibration, show that the PVP polymer is embedded in the HEA/IA network. The spectra of all the samples also show a wider peak of about 3400 cm^{-1} which originates from OH stretching vibration of the carboxyl groups IA overlapping with the O–H stretch vibration of PVP (Arndt et al. 1999).

10.4.2 Morphology of P(HEA /IA)/PVP Gels

Morphology of P(HEA/5IA)/PVP and P(HEA/10IA)/PVP hydrogels shows that hydrogels have a wavy surface, resembling a “coral” texture with microchannels. Hydrogels exhibit a large number of interconnected pores, which meets the requirements to be used in biomedicine.

10.4.3 Mechanical Properties of P(HEA/IA)/PVP Hydrogels

The evaluation of mechanical properties is important for the biomedical application of hydrogels. It is necessary to test the behavior under the influence of the appropriate stress. The shear modulus, G , was measured to examine whether P(HEA/IA)/PVP hydrogels are suitable biomaterials for biomedical applications. The values of the shear modulus are in the range from 7.86 to 13.04 kPa. It can be concluded that the modulus of P(HEA/IA)/PVP hydrogels increases with an increase in IA content of 2–5 mol%, but for a sample with 10 mol% IA, there is a reduction in the modulus due to the higher hydrophilicity of that sample, which leads to a higher-degree swelling (Quitana et al. 2002).

10.4.4 pH- and Temperature-Sensitive Swelling of P(HEA/IA)/PVP Hydrogels

“Intelligent” materials exhibit significant changes in the swelling degree, depending on the change in the external stimulus pH, ionic strength, temperature, and others. pH-sensitive hydrogels show a change in the properties due to a change in the pH of the surrounding medium. In order to examine the pH sensitivity of P(HEA/IA)/PVP hydrogels, the samples were characterized by measuring the equilibrium degree of swelling depending on the pH value (2.20–8.00) at a temperature of 37 °C. It may be noted that the lowest q_e values have samples at a low pH of 2.20. The lowest q_e values are below pK_a of the group IA values, when the carboxylic groups of itaconic acid are unionized and form intramolecular hydrogen bonds, resulting in greater network compactness. q_e values increase around pK_a values of IA carboxyl groups ($pK_{a1} = 3.85$ and $pK_{a2} = 5.45$). The ionization occurs when the pH of the medium rises above the pK_a value of both carboxyl groups. With an increase in ionization, the amount of permanent charge increases, causing an increased electrostatic repulsion between the ionizing group and therefore the chains. As a result, the network’s hydrophilicity, as well as the degree of swelling, is increasing. Hydrogels containing IA have a higher degree of swelling with a rise in pH. With increasing IA content in hydrogels, q_e values increase. The dependence of the pH of the surrounding medium shows a similar trend for all samples. The maximum q_e values for all samples are at pH 6.80. The highest values were obtained for samples with 10 mol% IA as expected. Above this pH, the values of q_e decrease slightly, and above pH 7.40, they increase again.

The temperature sensitivity of P(HEA/IA)/PVP hydrogels in the temperature ranges from 10 to 60 °C, in the buffer pH 7.40, which represents the pH of the physiological fluid, and was also tested. All samples show a similar trend. The swelling degree increases with an increase in the molar ratio of itaconic acid. The highest values of q_e are samples with 10 mol% of itaconic acid. The maximum q_e values for all samples are at 25 °C. All samples show a VPTT temperature of about 47 °C. Temperature-sensitive samples of hydrogels shrink due to the increase in temperature above VPTT and the swelling under VPTT. When the temperature is below the VPTT value, hydrogen bonds between hydrophilic groups and water molecules dominate, so q_e values are higher. When the temperature is above VPTT, hydrogen bonds are broken; hydrophobic interactions in hydrogels become dominant, which leads to the shrinking of hydrogels; and q_e values are reduced.

10.4.5 In Vitro Controlled Release of Vitamin B₃ from P(HEA/IA)/PVP Hydrogels

In this study, the controlled release of vitamin B₃, in the form of nicotinamide from P(HEA/IA)/PVP hydrogels, was studied to evaluate the influence of the structure and properties of the active substances on the release kinetics of the hydrogels, which contain a different fraction of IA. The kinetics of the release of active substance molecules from the hydrogels is shown in Fig. 10.3. It depends on several

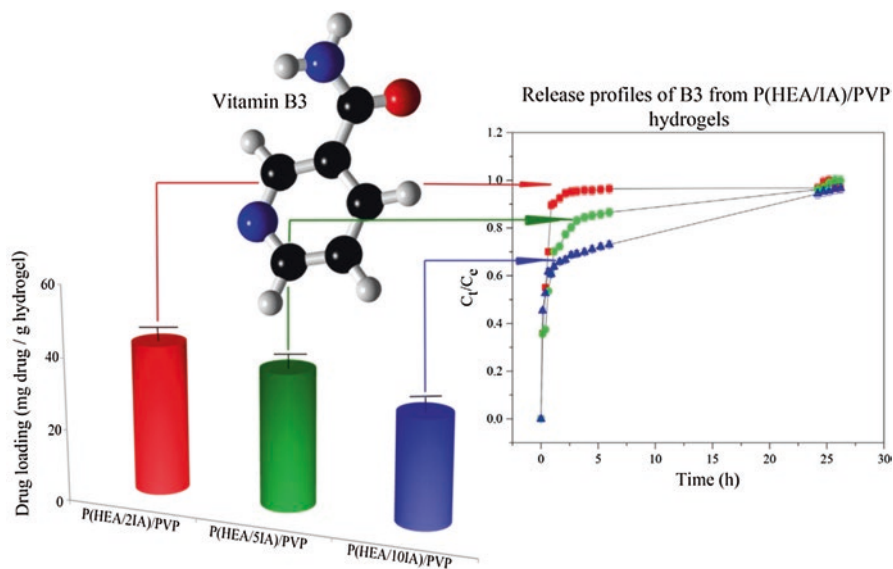


Fig. 10.3 The drug loading of vitamin B₃ into P(HEA/IA)/PVP hydrogels. Vitamin B₃ release profiles from P(HEA/IA)/PVP hydrogels

factors, such as the chemical structure of the polymer, the network structure, the release conditions, and other factors.

The values of drug loading (DL) of P(HEA/IA)/PVP hydrogels are shown in Fig. 10.3. Hydrogels with 2 mol% of IA are able to load highest amount of vitamin B₃ (DL 47.35 mg drug/g hydrogel). Increasing mole content of IA, DL is reduced, so that the smallest value was for sample with 10 mol% of IA (DL 40.00). At the same time, there are two parallel processes: diffusion of the drug into hydrogel and swelling of hydrogel. Degree of swelling increases with increasing of itaconic acid content, i.e., hydrophilicity increases. The highest water uptake is obtained for sample of 10 mol% IA. It is obvious that more water is absorbed within the hydrogel, which affects the reduction of DL.

Controlled drug release process from hydrogels shows initially a quick release of the drug, i.e. the initial burst effect (the so-called burst effect) appears, followed by the second phase-slower drug release. At the beginning of the release process, the release of the drug molecules that are attached to the surface and layers is closer to the surface of the hydrogel disk. The slow release phase takes place by the diffusion mechanism in the pores of the hydrogel. Sample with 2 mol% IA releases the highest amount of vitamin, and sample with 10 mol% at least. It was found that the release rate of the active substance from the samples P(HEA IA)/PVP depends on the content of IA in the gels.

Different release models were applied to the experimentally obtained release data of the active substance from synthesized hydrogels to calculate the characteristic parameters (Barakat et al. 2009; Canan et al. 2011; Peppas and Sahlin 1989; Serra et al. 2006). Akaike Information Criterion (AIC) is calculated for all samples, and it determines which equation best describes the polymer system in the controlled-release process. Based on the AIC criteria, it can be concluded that P(HEA 2IA)/PVP hydrogel best describes the release of the Peppas-Sahlin equation. The drug release from P(HEA/5IA)/PVP and P(HEA/10IA)/PVP hydrogels best describe by Ritger-Peppas equation. The exponent values, n , calculated using the Ritger-Peppas model are less than 0.5, indicating Fick's transport mechanism. On the basis of the obtained values for the coefficient R^2 , one can determine which model best describes the mechanism of release of vitamin B₃. It can be noted that the Ritger-Peppas model very well describes the release of vitamin B₃ from hydrogels P(HEA/IA)/PVP.

10.4.6 Biocompatibility of P(HEA/IA)/PVP Hydrogels

Biocompatibility of materials is a significant feature of the material for their further use in medicine and pharmacy. Biocompatibility of P(HEA/2IA)/PVP, P(HEA/5IA)/PVP, and P(HEA/10IA)/PVP hydrogels was tested using the MTT test, most commonly used as a fast method for determining the cytotoxicity of the test materials against different cells. Different concentrations of extracts (5, 10, 25, 50, and 100%) were used to examine the effect on cellular viability. Based on the results shown in Fig. 10.4, it can be noticed that all the tested hydrogels in all the investigated

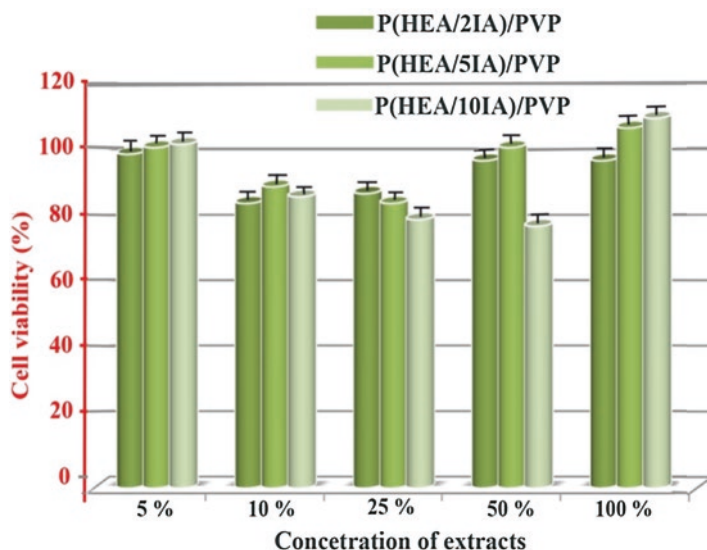


Fig. 10.4 The viability of L929 cells after cultivation with extracts of P(HEA/IA)/PVP hydrogels

concentrations of their extracts exhibited an acceptable level of cytotoxicity to normal mouse fibroblasts, as the percentage of viable cells in no case was less than 70% compared to control-treated cells. Cell viability depends on the molar fraction of itaconic acid. For values of 5 and 100% of the extract, with an increase of molar fraction of itaconic acid, cellular viability increases. So the best values are for the sample of IA 10 mol%. For 10 and 50%, extracts of the highest value are for the sample with 5 mol% of IA.

10.4.7 Antimicrobial Activity of P(HEA/IA)/PVP Hydrogels

The ability to inhibit the growth of microorganisms (antimicrobial activity) is important for the biomedical application of hydrogels. Antimicrobial activity of P(HEA/2IA)/PVP, P(HEA/5IA)/PVP, and P(HEA/10IA)/PVP hydrogels was examined according to Gram-positive bacterium *Staphylococcus aureus* and yeast *Candida albicans*, which are the most common causes of infection. The study was carried out after one- and two-hour treatment of the cultures of the aforementioned pathogens. The results are shown in Fig. 10.5. It turned out that 1-hour treatment has shown to have a better effect compared to a 2-hour treatment.

The type of pathogen and the proportion of itaconic acid also affect antimicrobial activity. The results of the study show that samples with 2 mol% IA according to the pathogens of *Staphylococcus aureus* and *Candida albicans* have the best antimicrobial activity, while the lowest value for the sample is 5 mol% of IA. The highest

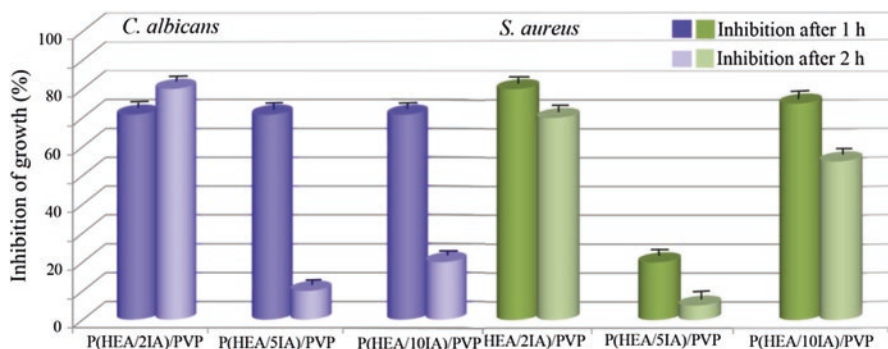


Fig. 10.5 Antimicrobial activity of P(HEA/IA)/PVP hydrogels according to *C. albicans* and *S. aureus*

percentage of inhibition of pathogen growth showed a sample with 2 mol% of IA, according to *Staphylococcus aureus*.

10.5 Characterization of Hydrogels Based on 2-Hydroxyethyl Acrylate, Itaconic Acid, and Poly(vinyl Pyrrolidone) with Varied Poly(vinyl Pyrrolidone) Fraction

10.5.1 pH- and Temperature-Sensitive Swelling of P(HEA/IA)/PVP Hydrogels

In order to test the pH sensitivity of P(HEA/IA)/PVP, P(HEA/IA)/PVP, and P(HEA/IA)/10PVP hydrogels, the dry samples were immersed until the equilibrium state in the buffers of different pH values at a temperature of 45 °C. Based on the results shown, it can be noticed that the samples show the smallest swelling at low pH values (pH 2.20). This was expected because the pH values below the pK_a of IA gels are in the non-ionized state, and the swelling is the smallest. With the rise in pH, the swelling degree is also increasing, which is expected due to the presence of IA. Itaconic acid has two carboxyl groups that ionize above the pK_a value ($pK_{a1} = 3.85$, $pK_{a2} = 5.45$). The degree of ionization of lateral acidic groups affects the swelling of the samples. With the rise in ionization, the amount of constant charge increases, which leads to increased electrostatic repulsion between negatively charged acid groups and chains. As a result, the network's hydrophilicity and also the degree of swelling increase. As the PVP content increases, the swelling degree is lower, as the long PVP chains represent additional cross-linking, prevent the mobility of polymeric chains, and lead to reduced swelling.

Temperature sensitivity of P(HEA/IA)/PVP hydrogels was carried out at temperatures from 10 to 60 °C, in buffer pH 7.40, which simulates the physiological fluid. Dry disk samples were immersed in buffer pH 7.40 at the selected temperatures. After certain time intervals, the samples were removed, filtered by a paper

filter, and weighed. After the measurement, they were returned to the buffer until an equilibrium state was established.

The temperature sensitivity of P(HEA/IA)/PVP hydrogels was performed in the temperature range from 10 to 60 °C, in a pH buffer of 7.40, which is the pH of the physiological fluid. All samples have a VPTT temperature of about 47 °C. Temperature sensitive samples shrink at the temperature above the VPTT value and swell below the VPTT. When the temperature is below the VPTT value, hydrogen bonds between hydrophilic groups and water molecules dominate; thus, q_e values are higher. When the temperature is above VPTT, hydrogen bonds are broken; hydrophobic interactions in hydrogels become dominant, leading to hydrogel shrinkage; and q_e values are reduced. Based on the dependence of q_e on the temperature, we see that the value of q_e depends on the fraction of PVP. For a sample with 10 mol% PVP, q_e value is lowest, at all temperatures, except at 10 °C. It can be assumed that PVP acts as an additional cross-linking, and therefore, as its content increases, swelling is reduced. The highest q_e value is at 25 °C and the lowest at 50 °C for all samples.

10.5.2 Mechanical Properties of P(HEA/IA)/PVP Hydrogels

Mechanical properties of hydrogels are one of the most important properties for biomedical applications. It is important that the samples during swelling retain shape and geometry and remain strength enough. G values are in the range of 5.36 KPa to 10.59 KPa. The values of the modulus depend on the degree of cross-linking of the samples; thus, the addition of PVP to hydrogels significantly improves the mechanical properties of the gels. With the increase of PVP content, the value of G increases. For the sample with 2 mol%, PVP is the lowest. The highest G value is for the sample with 10 mol% PVP. This behavior can be explained by the ability of PVP to improve mechanical properties due to the formation of hydrogen bonds. Hydrogen connections act as an additional, physical cross-linking.

10.5.3 Biocompatibility of P(HEA/IA)/PVP Hydrogels

Biocompatibility of P(HEA/IA)/2PVP, P(HEA/IA)/5PVP, and P(HEA/IA)/10PVP hydrogels was tested using the MTT test. Different concentrations of extracts (5, 10, 25, 50, and 100%) were used to examine the effect on cellular viability. The results are shown in Fig. 10.6. It can be seen that cell viability depends on the molar fraction of PVP. Cell viability increases with increase of PVP molar fraction (for 25, 50, and 100% of the extract). The highest cell viability is for the sample with 5% molar fraction of PVP (for 5 and 10% of the extract). For all samples, cell viability is over 60% for all concentrations of the extract. P(HEA/IA)/PVP hydrogels with varied PVP content showed satisfied cytocompatible properties for biomedical applications.

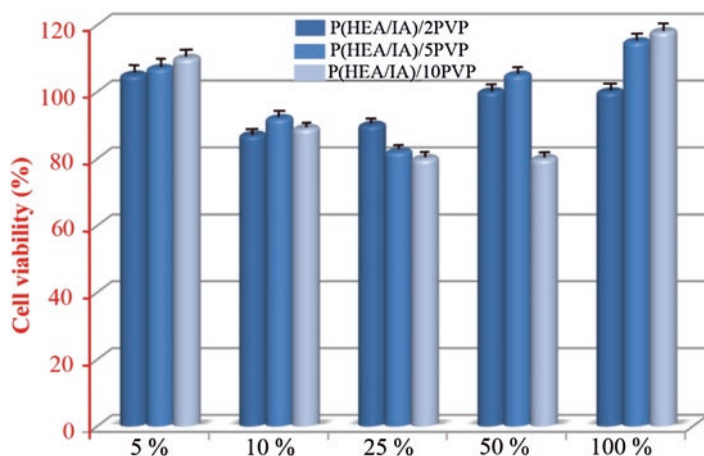


Fig. 10.6 The viability of L929 cells after cultivation with extracts of P(HEA/IA)/PVP hydrogels

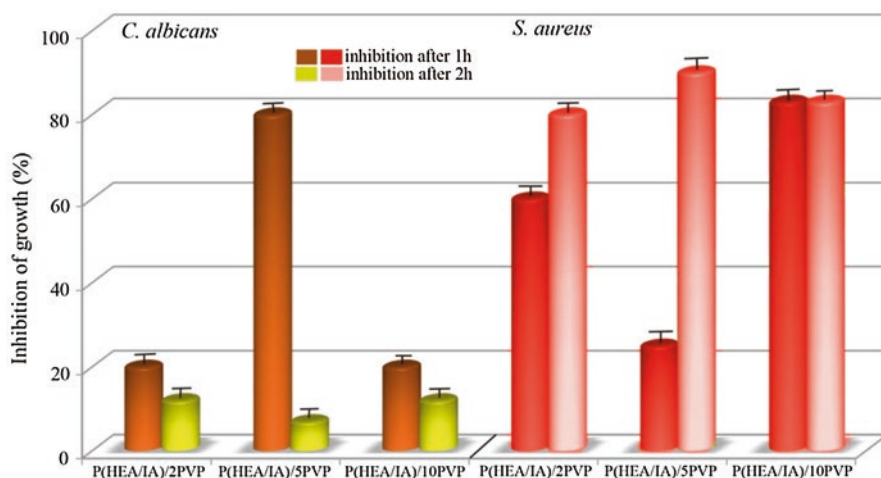


Fig. 10.7 Antimicrobial activity of P(HEA/IA)/PVP hydrogels for *C. albicans* and *S. aureus*

10.5.4 Antimicrobial Activity of P(HEA/IA)/PVP Hydrogels

The ability of the bacterial growth inhibitory of P(HEA/IA)/PVP samples is determined by performance of antimicrobial activity. The study of antimicrobial activity of P(HEA/IA)/2PVP, P(HEA/IA)/5PVP, and P(HEA/IA)/10PVP hydrogels was realized using bacterial strains *Staphylococcus aureus* and yeast *Candida albicans*. The results are shown in Fig. 10.7. The PVP content, type of pathogen, and exposure time have an effect on antimicrobial activity. For *C. albicans* after the first hour

of exposure, there is significantly better antimicrobial activity than after second hour. For the *S. aureus* strains, better results are obtained after the second hour of incubation for samples with 2 and 5 mol% PVP, while for a sample with 10 mol% of PVP, the values are the same after 2 h.

The best antimicrobial activity for *S. aureus* shows samples with 2 and 10 mol% PVP, after 2 h. These samples show the smallest percentage of cellular number reduction for *C. albicans* after 2 h of exposure. A sample of 5 mol% PVP shows the best antimicrobial activity after the first hour for the *C. albicans* strains and after the second for *S. aureus*.

10.6 Conclusions

In our work three series of semi-IPN polymeric networks, based on monomers of 2-hydroxyethyl methacrylate, 2-hydroxyethyl acrylate, and itaconic acid, with poly(N-vinylpyrrolidone) as interpenetrating agent, were synthesized by free radical copolymerization/cross-linking reaction. All samples showed “intelligent” behavior and properties that are extremely favorable for biomedical application—swelling, morphology, mechanical properties, controlled drug release, and cyto-compatible and antimicrobial potential.

10.6.1 Hydrogels Based on 2-Hydroxyethyl Methacrylate, Itaconic Acid, and Poly(vinyl Pyrrolidone) with Varied Poly(vinyl Pyrrolidone) Fraction

In this study, semi-IPN hydrogels based on 2-hydroxyethyl methacrylate, itaconic acid, and poly(vinyl pyrrolidone) with different PVP (2, 5, and 10 mol%) fractions were synthesized by free radical copolymerization/cross-linking in the aqueous environment.

The spectroscopic analysis of P(HEMA/IA)/PVP hydrogels showed the presence of bands indicating that PVP interpenetrate through the P(HEMA/IA) copolymer hydrogels and loaded at different content.

“Intelligent” behavior of P(HEMA/IA)/PVP hydrogels has been examined for potential application in medicine and pharmacy. Swelling of P(HEMA/IA)/PVP hydrogels depends on the PVP fraction and temperature. The equilibrium degrees of hydrogels in buffer pH 7.40 and at temperatures 25, 37, 45, and 55 °C are in the range from 2.56 to 3.78. The lowest equilibrium degree of swelling is shown for P(HEMA/IA)/10PVP at 55 °C, and the highest for P(HEMA/IA)/10PVP at 25 °C. When we consider the effect of temperature on the equilibrium degree of swelling, it can be noted that q_e decreases as the temperature rises in the range of 25–55 °C for all hydrogel samples, whereby the decrease is most pronounced for the sample with the highest PVP fraction. The sensitivity of these samples to pH values from 2.20 to 8.00 at 37 °C was also tested.

Mechanical properties of P(HEMA/IA)/PVP hydrogels, presented by the shear modulus, show the dependence on the composition of hydrogels. The largest value of modulus has a gel with the highest content of PVP, and the smallest with the smallest content of PVP. The value of the modulus ranges from 290 to 440 kPa.

Based on the results obtained by examining the cytotoxicity, it can be seen that P(HEMA/IA)/PVP hydrogels do not show significant changes in cell viability with the change in PVP content and are extremely cytocompatible and are therefore suitable for use as polymeric biomaterials for biomedical applications.

The antimicrobial activity of these samples depends on the proportion of PVP in the gels and how the PVP fraction increases, thus increasing the efficiency. The best antimicrobial properties were shown hydrogels for *C. albicans*, so almost 100% bacterial growth inhibition was almost complete. The lower gel activity is according to the *S. aureus* strain. The largest inhibition for the sample with a maximum of PVP content is 60%. In the investigated period of antimicrobial activity, inhibition of bacterial growth increases with time, for all samples and bacterial strains.

Analyzing the behavior of synthesized P(HEMA/IA)/PVP hydrogels, it can be concluded that all have shown satisfactory properties in in vitro conditions, which candidate them as optimal polymeric biomaterials for use in medicine and pharmacy, especially in topical and transdermal systems.

10.6.2 Hydrogels Based on 2-Hydroxyethyl Acrylate, Itaconic Acid, and Poly(vinyl Pyrrolidone) with Varied of Itaconic Acid Fraction

The synthesis of 2-hydroxyethyl acrylate, itaconic acid, and poly(vinyl pyrrolidone) was performed by free radical copolymerization/cross-linking. The PVP fraction was constant, while the IA (mol%, 2, 5, and 10) and HEA fraction were varied. FTIR spectra P(HEA/2IA)/PVP, P(HEA/5IA)/PVP, and P(HEA/10IA)/PVP hydrogels were recorded. The increase in the intensity of the C=O peaks of about 1730 cm^{-1} in the spectrum indicates an increase in the number of C=O groups of IA for the samples (IA content varied). Morphology of P(HEA/5IA)/PVP and P(HEA/10IA)/PVP hydrogels was recorded. Hydrogels have a wavy surface, resembling a “coral” texture with a large number of interconnected pores, which meets the requirements to be used in biomedicine.

The shear modulus, G , was measured to examine whether P(HEA/2IA)/PVP, P(HEA/5IA)/PVP, and P(HEA/10IA)/PVP hydrogels are suitable for biomedical applications. The shear modulus depends on the itaconic acid content. The values of the shear modules are in the range from 7.86 to 13.04 kPa.

In order to examine the pH sensitivity of P(HEA/IA)/PVP hydrogels, the samples were characterized by measuring the equilibrium rate of swelling depending on the pH value (2.20 to 8.00) at a temperature of $37\text{ }^{\circ}\text{C}$. The lowest q_e values have samples at a low pH of 2.20. The maximum q_e values for all samples are at pH 6.80. The highest values were obtained for the sample with 10 mol% of IA.

The temperature sensitivity of P(HEA/IA)/PVP hydrogels in the temperature range from 10 to 60 °C, in the buffer pH 7.40, was also tested. The swelling degree increases with an increase in the molar ratio of itaconic acid. The highest value of q_e has a sample of 10 mol% of itaconic acid. The maximum q_e values for all samples are at 25 °C. All samples show a VPTT temperature of about 47 °C.

The in vitro controlled release of the active substance, vitamin B₃ from P(HEA/2IA)/PVP, P(HEA/5IA)/PVP, and P(HEA/10IA)/PVP hydrogels, was performed. The highest amount of vitamin B₃ was released from sample of 2 mol% IA, and the smallest from sample of 10 mol%. It was found that the release rate of the active substance from the samples P(HEA/IA)/PVP depends on the content of IA in hydrogels. Different release models were applied to the experimentally obtained release data of the active substance from synthesized hydrogels to calculate the characteristic parameters. Based on AIC, the P(HEA/2IA)/PVP hydrogel best describes the release of the Peppas-Sahlin equation, while for P(HEA/5IA)/PVP and P(HEA/10IA)/PVP hydrogel the Ritger-Peppas equation. The exponent values, n , are calculated using the Ritger-Peppas model and are less than 0.5 indicating Fick's transport mechanism. Based on the obtained values for coefficient R^2 , the Ritger-Peppas model describes a very good release of vitamin B₃ from hydrogels P(HEA/IA)/PVP.

P(HEA/2IA)/PVP, P(HEA/5IA)/PVP, and P(HEA/10IA)/PVP hydrogels showed satisfied cytocompatible properties. Cytotoxicity depends on the molar fraction of itaconic acid. The antimicrobial activity of P(HEA/2IA)/PVP, P(HEA/5IA)/PVP, and P(HEA/10IA)/PVP hydrogels was tested according to *Staphylococcus aureus* and *Candida albicans*. The type of pathogen, the exposure time, and the content of itaconic acid affect antimicrobial activity.

Based on the results of this study, it can be concluded that all samples have shown satisfactory properties. It can be used as polymeric biomaterials in medicine and pharmacy.

10.6.3 Hydrogels Based on 2-Hydroxyethyl Acrylate, Itaconic Acid, and Poly(vinyl Pyrrolidone) with Varied of Poly(vinyl Pyrrolidone) Fraction

The synthesis of 2-hydroxyethyl acrylate, itaconic acid, and poly(vinyl pyrrolidone) was performed by free radical copolymerization/cross-linking. The IA fraction was constant, while the PVP (mol%, 2, 5, and 10) and HEA fraction were varied. pH and temperature sensitivity were tested. In order to test the pH sensitivity of P(HEA/IA)/2PVP, P(HEA/IA)/5PVP, and P(HEA/IA)/10PVP hydrogels, the dry samples were immersed until the equilibrium state in the buffers of various pH values, at a temperature of 37 °C. With an increase in pH, the swelling degree is increased due to the presence of IA. The temperature sensitivity of P(HEA/IA)/PVP hydrogels was tested in the temperature range from 10 to 60 °C, in a buffer pH of 7.40. All samples have a VPTT temperature of about 47 °C. Based on the dependence of q_e on the temperature, it showed that the q_e value depends on the PVP content.

The lowest q_e value is for sample with 10% PVP, at all temperatures, except at 10 °C. The highest q_e values are at 25 °C, and the lowest q_e values are at 50 °C, for all samples.

Mechanical properties of the samples were examined as shear modulus dependence on frequency. G values are in the range of 5.36 KPa to 10.59 KPa and depends on the PVP fraction.

P(HEA/IA)/2PVP, P(HEA/IA)/5PVP, and P(HEA/IA)/10PVP hydrogels showed satisfied cytocompatible properties. Cytotoxicity depends on the molar fraction of PVP. Antimicrobial activity of P(HEA/IA)/2PVP, P(HEA/IA)/5PVP, and P(HEA/IA)/10PVP hydrogels was studied for *Staphylococcus aureus* and *Candida albicans*. The PVP content, type of pathogen, and exposure time have an effect on antimicrobial activity. For pathogen *C. albicans* after the first hour of exposure, there is significantly better antimicrobial activity than after a second hour. For the *S. aureus* strains, better results are obtained after the second hour of incubation for samples with 2 and 5 mol% PVP, while for a sample with 10 mol% of PVP, the values after 2 h are the same. The best antimicrobial activity after 2 h shows samples with 2 and 10 mol% PVP for *S. aureus*. These samples show the smallest percentage of cell reduction for *C. albicans* for both hours of exposure. Based on the results of this study, it can be concluded that these samples have satisfactory properties; they could have potential application in medicine and pharmacy.

Three groups of semi-interpenetrating hydrogel networks were synthesized based on 2-hydroxyethyl methacrylate or 2-hydroxyethyl acrylate, itaconic acid, and poly(vinyl pyrrolidone) by free radical copolymerization/cross-linking. The fraction of each component were varied to examine the influence on the properties of the P(HE(M)A/IA)/PVP hydrogels. All samples exhibit satisfactory properties, which candidate them as optimal polymer biomaterials for use in medicine and pharmacy.

Acknowledgments This work has been supported by the Ministry for Education, Science and Technological Development of the Republic of Serbia (Grants No 172062 and 172026).

References

- Abdelrazek EM, Ragab HM, Abdelaziz M (2013) Physical Characterization of Poly(vinyl pyrrolidone) and gelatin blend films doped with magnesium chloride. *Plast Polym Technol (PAPT)* 2:1–8
- Ahmad B, Abbas S, Iqbal Z, Bashir S, Ali J (2013) Synthesis of cross linked PVP hydrogels and its use for the control release of anti-asthmatic drugs. *Middle East J Sci Res* 14:273–283
- Ajji Z, Othman I, Rosiak JM (2005) Production of hydrogel wound dressings using gamma radiation. *Nucl Inst Methods Phys Res B* 229:375–380
- Arndt KF, Richter A, Ludwig S, Zimmermann J, Kressler J, Kuckling D, Adler HJ (1999) Poly(vinyl alcohol)/poly(acrylic acid) hydrogels: FT-IR spectroscopic characterization of crosslinking reaction and work at transition point. *Acta Polym* 50:383–390
- Babić MM, Antić KM, Jovašević Vuković JS, Božić BD, Davidović S, Filipović JM, Tomić SLj (2015) Oxaprozin/poly(2-hydroxyethyl acrylate/itaconic acid) hydrogels: morphological, thermal, swelling, drug release and antibacterial properties. *J Mater Sci* 50:906–922

- Baino F (2010) The use of polymers in the treatment of retinal detachment: current trends and future perspectives. *Polymers* 2:286–322
- Bajpai AK, Shukla SK, Bhanu S, Kankane S (2008) Responsive polymers in controlled drug delivery. *Prog Polym Sci* 33:1088–1118
- Banerjee S, Ray S, Maiti S, Sen KK, Bhattacharyya UK, Kaity S, Ghosh A (2010) Interpenetrating polymer network (IPN): a novel biomaterial. *Int J App Pharm* 2:28–34
- Barakat NS, Elbagory IM, Almurshedi AS (2009) Controlled-release carbamazepine matrix granules and tablets comprising lipophilic and hydrophilic components. *Drug Deliv* 16:57–65
- Barrett GD, Constable IJ, Stewart AD (1986) Clinical results of hydrogel lens implantation. *J Cataract Refract Surg* 12:623–631
- Barros JAG, Brant AJC, Catalani LH (2011) Hydrogels from chitosan and a novel copolymer Poly(N-Vinyl-2-Pyrrolidone-Co-Acrolein). *Mater Sci Appl* 2:1058–1069
- Bera R, Dey A, Chakrabarty D (2015) Synthesis, characterization, and drug release study of acrylamide-co-itaconic acid based smart hydrogel. *Polym Eng Sci* 55:113–122
- Bhardwaj V, Harit G, Kumar S (2012) Interpenetrating Polymer Network (IPN): novel approach in drug delivery. *IJDDR* 4:41–54
- Biazar E, Roveimiab Z, Shahhosseini G, Khataminezhad M, Zafari M, Majidi A (2012) Biocompatibility evaluation of a new hydrogel dressing based on polyvinylpyrrolidone/polyethylene glycol. *J Biomed Biotechnol* 2012:1–5
- Boran F, Hitit FA (2015) Synthesis and characterization of Poly (HEMA-co-AAc)/Diatomite hydrogel composites: their application for heavy metal removal from the aqueous solution. *Hittite J Sci Eng* 2:173–179
- Canan H, Gunseli Y, Berna T, Nurten O (2011) Effect of formulation parameters on the drug release and floating properties of gastric floating two-layer tablets with acetylsalicylic acid. *Acta Pharm* 61:303–312
- Chadha R, Kapoor VK, Kumar A (2006) Analytical techniques used to characterize drug- polyvinylpyrrolidone systems in solid and liquid states – an overview. *J Sci Ind Res* 65:459–469
- Chai Q, Jiao Y, Yu X (2017) Hydrogels for biomedical applications: their characteristics and the mechanisms behind them. *Gels* 3:1–15
- Chen S, Hu T, Tian Y, Chen L, Pojman JA (2007) Facile synthesis of poly(hydroxyethyl acrylate) by frontal free-radical polymerization. *J Polym Sci Pol Chem* 45:873–881
- Das N (2013) Preparation methods and properties of hydrogel: A review. *Int J Pharm Sci* 5:112–117
- De Silva DA, Hettiarachchi BU, Nayanajith LDC, Yoga Milani MD, Motha JTS (2011) Development of a PVP/kappa-carrageenan/PEG hydrogel dressing for wound healing applications in Sri Lanka. *J Natl Sci Found Sri Lanka* 39:25–33
- Domingues JA, Bonelli N, Giorgi R, Fratini E, Gorel F, Baglioni P (2013) Innovative hydrogels based on semi-interpenetrating p(HEMA)/PVP networks for the cleaning of water-sensitive cultural heritage artifacts. *Langmuir* 29:2746–2755
- Ekici S, Saraydin D (2007) Interpenetrating polymeric network hydrogels for potential gastrointestinal drug release. *Polym Int* 56:1371–1377
- Erizal E, Tjahyono T, Dian PP, Darmawan D (2013) Synthesis of Polyvinyl Pyrrolidone (PVP)/κ-carrageenan hydrogel prepared by gamma radiation processing as a function of dose and PVP concentration. *Indo J Chem* 13:41–46
- Gils PS, Sahub NK, Rayc D, Sahoo PK (2011) Hydrolyzed collagen-based hydrogel system: design, characterization and application in drug delivery. *Int J Macromol Sci* 1:1–8
- Giri N, Natarajan RK, Gunasekaran S, Shreemathi S (2011) ¹³C NMR and FTIR spectroscopic study of blend behavior of PVP and nano silver particles. *Arch Appl Sci Res* 3:624–630
- Gulrez SKH, Al-Assaf S, Phillips GO (2011) Chapter 5: Progress in molecular and environmental bioengineering – from analysis and modeling to technology applications. In: Carpi A (ed) *Hydrogels: methods of preparation, characterisation and applications*. InTech, pp 117–150
- Himi M, Maurya SD (2013) Preparation and evaluation of stomach specific IPN hydrogels for oral drug delivery: a review. *JDDT* 3:131–140
- Hoffman AS (2012) Hydrogels for biomedical applications. *Adv Drug Deliv Rev* 64:18–23

- Jiao Y, Liu Z, Ding S, Li L, Zhou C (2006) Preparation of biodegradable crosslinking agents and application in PVP hydrogel. *J. Appl Polym. Sci* 101:1515–1521
- Marsano E, Bianchi E, Vicini S, Compagnino L, Sionkowska A, Skopińska J, Wiśniewski M (2005) Stimuli responsive gels based on interpenetrating network of chitosan and poly(vinylpyrrolidone). *Polymer* 46:1595–1600
- Menapace R, Skorpik C, Juchem M, Scheidel W, Schranz R (1989) Evaluation of the first 60 cases of poly HEMA posterior chamber lenses implanted in the sulcus. *J Cataract Refract Surg* 15:264–271
- Mishra RK, Datt M, Banthia AK (2008) Synthesis and characterization of pectin/PVP hydrogel membranes for drug delivery system. *AAPS J* 9:395–403
- Naghdeali MH, Adimi M (2015) Comparison between acrylic acid and methacrylamide on release and swelling properties for hydrogels based on PVP. *Biol Forum Int J* 7:304–308
- Okabe M, Lies D, Kanamasa S, Park EY (2009) Biotechnological production of itaconic acid and its biosynthesis in *Aspergillus terreus*. *Appl Microbiol Biot* 84:597–606
- Okay O, Gerlach G, Arndt KF (2009) General properties of hydrogels. In: Gerlach G, Arndt K-F (eds) *Hydrogel sensors and actuators*, Springer Series on Chemical Sensors and Biosensors. Springer, Berlin/Heidelberg, pp 1–14
- Pal K, Banthia AK, Majumdar DK (2009) Polymeric hydrogels: characterization and biomedical applications – a mini review. *Des Monomers Polym* 12:197–220
- Peppas NA, Sahlin JJ (1989) A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. *Int J Pharm* 57:169–172
- Peppas NA, Bures P, Leobandug W, Ichikawa H (2000) Hydrogels in pharmaceutical formulations. *Eur J Pharm Biopharm* 50:27–46
- Petruccioli M, Pulci V, Federici F (1999) Itaconic acid production by *Aspergillus terreus* on raw starchy materials. *Lett Appl Microbiol* 28:309–312
- Podkościelna B, Bartnicki A, Gawdzik B (2012) New crosslinked hydrogels derivatives of 2-hydroxyethyl methacrylate: synthesis, modifications and properties. *Express Polym Lett* 6:759–771
- Prasitsilp M, Siri Wittayakorn T, Molloy R, Suebsanit N, Siri Wittayakorn P, Veeranondha S (2003) Cytotoxicity study of homopolymers and copolymers of 2-hydroxyethyl methacrylate and some alkyl acrylates for potential use as temporary skin substitutes. *J Mater Sci Mater Med* 14:595–600
- Quitana JR, Valderruten NE, Katime I (2002) Mechanical properties of poly(N-isopropylacrylamide-co-itaconic acid) hydrogels. *J Appl Polym Sci* 85:2540–2545
- Rana P, Ganarajan G, Kothiyal P (2015) Review on preparation and properties hydrogel formulation. *WJPPS* 4:1069–1087
- Rashid Z, Ranjha NM, Raza H, Razzaq R, Mehmood A (2016) Preparation and evaluation of pH responsive poly (2-hydroxyethyl methacrylate-co-itaconic acid) microgels for controlled drug delivery. *Acta Poloniae Pharm-Drug Res* 73:1045–1055
- Ristić B, Popović Z, Adamović D, Devedžić G (2011) Izbor biomaterijala u ortopedskoj hirurgiji. *Vojnosanit Pregl* 67:847–855
- Rodríguez-Hernández J (2016) Antimicrobial hydrogels. In: *Polymers against microorganisms*, 1st edn. Springer, Cham, pp 179–204
- Roland CM (2013) Interpenetrating Polymer Networks (IPN): structure and mechanical behavior. In: Kobayashi S, Mullen K (eds) *Encyclopedia of polymeric nanomaterials*. Springer, Berlin, pp 1–9
- Sakthivel M, Franklin DS, Guhanathan S (2014) Investigation on itaconic acid based pH and salt-responsive biopolymeric hydrogels. *Int J Ad Chem Sci Appl* 2:20–22
- Salomé Veiga A, Schneider JP (2013) Antimicrobial hydrogels for the treatment of infection. *Biopolymers* 100:637–644
- Sanna R, Alzari V, Nuvoli DN, Scognamiglio S, Marceddu S, Mariani A (2012) Polymer hydrogels of 2-hydroxyethyl acrylate and acrylic acid obtained by frontal polymerization. *J Polym Sci Pol Chem* 50:1515–1520

- Sariri R, Jafarian V (2002) The effect of itaconic acid on biocompatibility of HEMA. *Eur Cells Mater* 4:41
- Serra L, Doménech J, Peppas NA (2006) Drug transport mechanisms and release kinetics from molecularly designed poly(acrylic acid-g-ethylene glycol) hydrogels. *Biomaterials* 27:5440–5451
- Shi Y, Xiong DS, Peng Y, Wang N (2016) Effects of polymerization degree on recovery behavior of PVA/PVP hydrogels as potential articular cartilage prosthesis after fatigue test. *Express Polym Lett* 10:125–138
- Singh P, Senthil Kumar SK, Keerthi TS, Tamizh Mani T, Getyala A (2012) Interpenetrating Polymer Network (IPN) microparticles an advancement in novel drug delivery system: a review. *Pharm Sci Monit Int J Pharm Sci* 3:1826–1837
- Singh G, Lohani A, Bhattacharya SS (2014) Hydrogel as a novel drug delivery system: a review. *J Fundam Pharm Res* 2:35–48
- Sohail K, Khan IU, Shahzad Y, Hussain T, Ranjha NM (2014) pH-sensitive polyvinylpyrrolidone-acrylic acid hydrogels: impact of material parameters on swelling and drug release. *Braz J Pharm Sci* 50:173–184
- Sperling LH (1981) An introduction to polymer networks and IPNs. In: *Interpenetrating polymer networks and related materials*. Springer US, New York, pp 1–10
- Sudarkodi C, Subha K, Kanimozhi K, Panneerselvam A (2012) Optimization and production of itaconic acid using *Aspergillus flavus*. *Adv Appl Sci Res* 3:1126–1131
- Tomar R, Sharma CR (2013) Fabrication and characterization of conducting polymer composite. *Int J Org Electron* 2:1–8
- Tomić SLj, Suljovrujić EH, Filipović JM (2006) Biocompatible and bioadhesive hydrogels based on 2-hydroxyethyl methacrylate, monofunctional poly(alkylene glycol)s and itaconic acid. *Polym Bull* 57:691–702
- Tu W, Zuo X, Liu H (2008) Study on the interaction between Polyvinylpyrrolidone and platinum metals during the formation of the colloidal metal nanoparticles. *Chin J Polym Sci* 26:23–29
- Wang W, Wang A (2010) Synthesis and swelling properties of pH – sensitive semi-IPN superabsorbent hydrogels based on sodium alginate-g-poly(sodium acrylate) and polyvinylpyrrolidone. *Carbohydr Polym* 80:1028–1036
- Wang W, Wang Q, Wang A (2011) pH-responsive carboxymethylcellulose-g-Poly(sodium acrylate)/polyvinylpyrrolidone Semi-IPN hydrogels with enhanced responsive and swelling properties. *Macromol Res* 19:57–65
- Wei QB, Fu F, Zhang YQ, Wang Q, Ren YX (2014) pH-responsive CMC/PAM/PVP semi-IPN hydrogels for theophylline drug release. *J Polym Res* 21:1–10
- Yanpeng J, Zonghua L, Shan D, Lihua L, Changren Z (2006) Preparation of biodegradable cross-linking agents and application in PVP hydrogel. *J Appl Polym Sci* 101:1515–1521

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