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HYDROGELS IN BIOMEDICINE: GRANULAR CONTROLLED RELEASE SYSTEMS BASED ON 2-HYDROXYETHYL METHACRYLATE COPOLYMERS. A REVIEW

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Abstract. The article analyzes and summarizes the latest achievements in the field of polymer systems for controlled release devices based on hydrogel materials. Possible directions of drug delivery are presented, including the use of granular hydrogels, which work on the principle of drug sorption − release in the body. The research on the synthesis regularities, structure, properties, and prospects for the use of granular hydrogels based on 2-hydroxyethyl methacrylate (HEMA) and its copolymers, in particular with polyvinylpyrrolidone (PVP), as systems for the controlled release of substances, in particular, drugs, is analyzed.

Keywords: drug prolongers; hydrogels; granular copolymers; HEMA; suspension polymerization; polyvinylpyrrolidone.

1. Introduction

One of the important areas of creating polymeric materials with special functional properties is the development of polymeric systems and devices for the controlled release of substances into the environment. The stimulus for the creation of such systems was the need of various fields of human activity for means of dosing chemically or biologically active substances in very small quantities for a long time[1,2]. This applies, in particular, to such industries as medicine and pharmacy, especially when it comes to the long-term continuous administration of small doses of drugs into the human or animal body at a constant rate.

It is known that the dosage forms used (tablets, capsules, ointments, solutions for injection) are mostly not optimal in terms of the functions they perform[3, 4]. They do not ensure a long and constant flow of drugs into the bloodstream and do not contribute to their targeted transportation to the diseased organ. In the body, this substance is distributed according to its physicochemical properties; it is often metabolized rapidly, and only a small part of the drug (usually less than 10−15 % of the administered amount) reaches the diseased organ. The remaining amount of the drug is useless at best, but in most cases, it is harmful as exhibits unnecessary physiological activity and causes toxic effects in other organs. The rapid elimination of drugs from the body necessitates their repeated administration to maintain the therapeutic effect, which further increases their harmful side effects.

Encapsulation of drugs with polymers that dissolve in the human or animal body can increase the effectiveness of drugs and reduce their negative effects[5, 6]. However, water-soluble polymers used for this purpose are still ineffective. After their dissolution, the process of substance release becomes uncontrolled, and there are problems with the excretion of the polymer or its metabolic products from the body.

A possible solution to this problem is the use of polymer hydrogels based on cross-linked polymers for a prolonged release system[7]. The chemically cross-linked structure in this method is formed due to the use of bifunctional monomer of similar nature in the reaction mass[8]. Crosslinking agents (CAs), which are used for the polymerization of monofunctional monomers, are bis(met)acrylates of glycols, bis-allyl esters, triallyl cyanurate, dialdehydes, polyethylene glycol dimethacrylates, and others. The number of CAs affects the degree of polymer matrix crosslinking and the molecular weight of intermolecular crosslinks Mn (Fig. 1). These polymers are capable of limited swelling in water and saline and contain up to 90 % water in the swollen state.

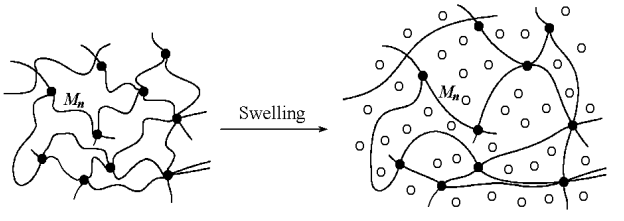

Fig. 1. Schematic diagram of hydrogel swelling: cross-linking node (●) and water molecule (○) [8]

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The advantages of hydrogels are their softness, high permeability to water and water-soluble substances, and transport characteristics, which are determined by the structural parameters of the network and can be controlled during synthesis.

Such materials are biocompatible, combining rigid and flexible chain characteristics for easy adjustment of physical properties (including porosity), as well as mechanical strength and specific sensitivity to external factors such as pH, temperature, biological components, and certain chemicals[9].

Hydrogels are one of the most promising technological platforms for therapeutic intervention in various diseases. They have been widely studied in tissue engineering and regenerative medicine,[10-15] pharmaceuticals, food additives, diagnostics, biosensors, biomaterials separation, *etc*.[16–19].

Hydrogels used as controlled-release systems can be classified according to their origin, preparation method, physical properties, ionic charges, swelling nature, crosslinking nature, sources, and biodegradation rate[20].

Over the past three decades, the development of hydrogel materials as smart tools for drug release with proper kinetics, in particular in the areas of oral, injectable, and transdermal drug delivery, has generally proceeded in two directions.

The first direction is the coating of solid particles with a polymeric hydrogel shell (encapsulation). In this case, the polymer coating performs a protective function in the dry state. After swelling, it acquires the properties of a membrane and can transport water and dissolved components through the structural network. The second direction is the creation of granular forms of polymers that work on the principle of drug sorption and release in the body.

This review will discuss various synthesized hydrogels in the form of spherical particles (nanoparticles) for use as drug prolongators[21].

Granular polymeric drug release systems allow[22-25]:

– to realize controlled release according to specific therapeutic needs;

– to prevent structural degradation of drugs in the gastrointestinal tract and increase contact with the mucous membrane and thus increase bioavailability;

– to provide the possibility of selecting the components of the granular carrier structure to achieve controlled release of the drug;

– to protect against environmental and physiological factors;

– to change the pharmacokinetics and biodistribution profiles;

– to modify the properties of microparticles, such as particle size, surface and porosity characteristics, and hydrophilicity to obtain the desired release effect;

– to choose the optimal routes of drug administration;

– to reduce or eliminate side effects.

Various methods for synthesizing different types of hydrogels of various shapes have been described and discussed[26].

Among the polymerization methods used to produce spherical microparticles are bulk polymerization, precipitation polymerization, dispersion polymerization, emulsion polymerization, and water-suspension polymerization. Suspension polymerization is one of the simplest and most versatile methods of producing spherical particles, which uses a small amount of reagents and simple reaction equipment; purification of the products is simple, and the cost of production is low[27].

Both natural[28–30] and synthetic[31–33] polymers can be used as a polymeric matrix for the synthesis of porous microparticles.

Natural hydrogels, such as proteins, peptides, natural gums, collagen, polysaccharides (alginates[34], cellulose[35], cellulosic materials, scleroglucans and xyloglucans[36]), as well as hyaluronic acid, are widely used for drug delivery. Synthetic hydrogels, on the other hand, include polyacrylic acid, polyhydroxyethyl methacrylate, polyvinyl alcohol, polyvinyl pyrrolidone, *etc*.

Chitosan/sodium dialdehyde alginate/magnetic dopamine hydrogel was investigated as a material for drugs delivery. The hydrogel was prepared from chitosan using sodium dicaldehyde alginate and dopamine by grafting, crosslinking, and compounding. The effect of dopamine dose on the performance of drug-filled hydrogels was studied. The drug delivery materials showed strong adhesion to the organ wall, hydrogel properties, antibacterial and antimicrobial ability (98 %), and biocompatibility (99 %), as well as significant potential for drug delivery and treatment of bladder cancer[37].

Hydrogel particles based on polysaccharides (PbHPs) are very promising carriers aimed at controlling and targeting the release of drugs with different physicochemical properties. Such delivery systems have advantages due to the proper encapsulation of many drugs (nonsteroidal and steroidal anti-inflammatory drugs, antibiotics, *etc*.), ensuring their proper release and targeting[38].

Among a wide range of ionic hydrogels for drug delivery and separation of ionic forms, hydrogels based on methacrylic acid (MAA) are intensively used[39, 40]. However, low mechanical strength, slow reaction to stimuli, and destruction in acidic environments are technical drawbacks for their use[41]. Due to the introduction of additional co-monomers into the polymer chain, wider controlled physical properties and, often, more efficient drug loading/release properties were induced.

The pH-sensitive polyampholytic microgels of poly(acrylic acid-co-vinylamine) (P(AA-co-VAm)) were

developed as hydrogels for controlled drug release. The P(AA-co-VAm) microgels were prepared by suspension polymerization of acrylic acid and *N*-vinylformamide followed by hydrolysis of poly(*N*-vinylformamide) (PNVF) chains of the resulting microgels under basic conditions. By using polyampholytic P(AA-co-VAm) microgels as an injectable hydrogel drug release system, a sustained drug release can be achieved, demonstrating the great potential of these pH-sensitive polyampholytic microgels for controlled drug delivery[42].

This article aims to analyze studies on the synthesis, properties, and prospects for the use of granular hydrogels based on hydroxyalkyl methacrylate copolymers, mainly hydroxyethyl methacrylate (HEMA), as controlled release systems for substances, in particular, drugs.

2. PolyHEMA-Based Drug Carriers

An important step in the development of hydrogel drug carriers was the use of nano– and microparticles of poly(HEMA) for this purpose. HEMA is a water-soluble monomer that can be easily polymerized into a water-insoluble polymer[43,44]. Typically, poly(HEMA) hydrogels have a water content of approximately 40 %, which can be changed to a certain extent by the crosslinking density[45,46]. Poly(HEMA) is biologically inert, resistant to degradation, has high chemical stability, and is not damaged under the action of high temperatures or pressures[47,48]. There are many potential applications for poly(HEMA) due to its water content and structure similar to living tissue[49].

Horak *et al*.[50] studied the HEMA suspension copolymerization with ethylene glycol dimethacrylate (EGDMA) in the presence of 1-dodecanol and cyclohexanol as inert substances. The authors investigated the effect of the solvent amount on the size and polydispersity of polymer particles, as well as the morphology and porosity of the synthesized particles. EGDMA is most commonly used as a crosslinker for methacrylate-based polymer particles[51–53]. Some other polyvinyl compounds, such as trimethylolpropan trimethacrylate[54], 2-oxypropyl-1,3-dimethacrylate[55], and 2,3-dihydroxybutyl-1,4-dimethacrylate[56] have been also successfully used. During the dispersion polymerization of hydrophobic methacrylic ester glycidyl methacrylate, pentaerythritol triacrylate, trimethylolpropane triacrylate and triethylolpropane trimethacrylate were used as crosslinkers[57].

Poly(HEMA-EGDMA-4-vinylbenzyl chloride) particles were obtained by suspension copolymerization of HEMA, EGDMA and 4-vinylbenzyl chloride in the presence of toluene, which was added to the polymerization composition to create a porous structure of the synthesized particles[58]. Polymer particles with a size of 150−350 μm were obtained by this method.

Also, spherical porous polymeric particles based on HEMA were similarly obtained during the polymerization of HEMA with EGDMA, which acts as a crosslinking agent, in a concentrated solution of NaCl in toluene[59]. It was found that magnesium hydroxide added to the dispersion medium improves the stabilization of polymer particles. The addition of toluene to the reaction system leads to a decrease in particle size.

Temperature and initiator are important factors that affect the properties of spherical polymers and copolymers. It is known that the typical step temperature of suspension polymerization is in the range of 60−80 °C[56,58]. The concentration of the initiator in the polymerization composition is about 1 wt. % of the monomer content. Jayakrishnan[59] investigated the effect of the initiator concentration and nature on the size of polymer particles. Benzoyl peroxide and 2,2-dinitrile-azo-bis-isobutyric acid are widely used as initiators for the copolymerization of methacrylates.

It is known that a stabilizer is used to prevent particle coalescence during the suspension polymerization. Synthetic and semi-synthetic water-soluble polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, polyacrylic acid, hydroxyalkyl cellulose, and others are often used as stabilizers in the suspension polymerization of methacrylates. Their molecular adsorption on the particle surface and the creation of a steric barrier prevent particle agglomeration[60]. Specific stabilizers also reduce the interfacial tension between the aqueous phase and the monomer droplets, thus promoting the formation of smaller particles.

One of the most common protective colloids is polyvinyl alcohol (PVA). Its stabilizing effect depends on such properties as molecular weight, degree of hydrolysis, distribution of hydroxyl and acetate groups in the chain, and the preparation method[61]. It has been shown that an increase in the PVA concentration in an aqueous medium allows the formation of smaller polymer particles[60]. Similar results were obtained during the suspension polymerization of methacrylates, in which high molecular PVP and polyacrylic acid were used as stabilizers[62,63].

The controlled release of several drugs, including hydrophilic anticancer agents, from poly(HEMA) nanoparticles was investigated[64]. HEMA-based nanoparticles have also been modified with an adsorbent for the purification of human serum albumin, antibodies, and DNA[65–67]. In many cases, polyHEMA particles are combined with other materials to give them the ability to respond to changes in pH or temperature[68–70].

An environmentally friendly process for the preparation of monodispersed spherical PHEMA particles was investigated. The dispersion polymerization of HEMA with ethylene glycol dimethacrylate (EGDMA) was carried out in supercritical carbon dioxide ($scCO_2$)[71]. Stabi-

lizers based on vinyl acetate (VAc) and vinyl pivalate (VPi) statistical copolymers P(VAc-stat-VPi) were used in such a way as to avoid the use of silicone or fluorine-based stabilizers, which are usually required in $scCO_2$. The effect of molecular weight and composition of P(VAc-stat-VPi) stabilizers on the size and shape of the obtained microparticles has been investigated. A copolymer stabilizer with a VAc : VPi molar composition of 56:□44 (Mn = 12.8 $kg \cdot mol^{-1}$) was the most effective, which made it possible to obtain monodispersed PHEMA particles with a diameter of 1.2 μm. The partial hydrolysis of the stabilizer ester groups located on the microparticles' surface leads to the formation of a hydrophilic surface with alcohol fragments and, therefore, facilitates the dispersion of the microparticles in water, which imparts valuable properties to the microgel particles.

PHEMA-based spherical macroporous particles with a certain porosity, swelling, and morphology were developed, which are suitable for creating drug prolongers, in particular for endovascular occlusion of various organs[72]. In contrast to cylindrical particles, spherical particles are especially suitable for transcatheter administration. Spherical particles with a size of 0.4–0.6 μm, a porosity of 60 % in water, and a specific surface area of 0.9 m^2/g in the dry state were obtained by suspension radical polymerization, in which the monomers were dissolved in a mixture of high-boiling alcohols and the solution was dispersed in water. The physicochemical and biomedical properties of the spherical particles were studied. Hematological studies have shown that residual amounts of monomers and other low molecular weight compounds, which are 10^{-5} g/g of polymer, were not toxic and contributed to irreversible platelet aggregation.

Spherical radiopaque hydrogel particles based on PHEMA, which are also intended for endovascular occlusion, were obtained by hydroxyl acylation of PHEMA spheres with low crosslinking with a non-toxic radiopaque compound based on triiodobenzoic acid without affecting their properties, which is an advantage in medical practice[73]. The effect of iodine content on the size of dry and swollen particles was determined, and it was found that the iodine content is approximately 25–30 wt. % to obtain an X-ray image that is easy to recognize. These particles facilitate immediate control of the embolus application and allow periodic testing of the polymer to verify the successful occlusion of the vessel. They also offer possibilities for further improving the method of endovascular occlusion.

Three series of porous microparticles based on glycidyl methacrylate, HEMA, and one of the following crosslinking agents: mono-, di-, or triethylene glycol methacrylate, were obtained by polymerization in water suspension[74]. By the reaction of grafting sodium hyaluronate to the existing epoxy groups on the surface of the microparticles, hybrid porous microparticles were obtained, which have a larger specific surface area, better swelling ability, and higher adsorption capacity for antimicrobial drugs (metronidazole) compared to the unmodified polymer. The reaction between metronidazole and hybrid microparticles was studied and the efficiency of the polymer systems was determined to select a polymer-drug system with the highest one. The release kinetics indicates that the release mechanism of metronidazole in the case of hybrid microparticles is a complex mechanism characterized by anomalous diffusion.

Poly(acrylic acid-co-2-hydroxyethyl methacrylate-co-2-acrylamido-2-methyl-1-propanesulfonic acid (AAc-HEMA-AMPS) microgels were synthesized using the inverse suspension polymerization technique[75]. The presence of propanesulfonic acid in the microgels caused a significant increase in water absorption. The synthesized microgels had an average particle diameter of 10 μm. Lidocaine (LD) and methylene blue (MB) were used as model drugs to study the behavior of drug release by microgels. Specific and nonspecific interactions between the microgel and the drug structure and pH of the dissolution medium were revealed. These hydrogels may be potential candidates for pH-sensitive applications.

A new polymeric nanomaterial based on poly(hydroxyethyl methacrylate-methacryloyl-amido-phenylalanine) was synthesized and characterized by mini-emulsion polymerization with a diameter of about 110 nm, and its potential suitability for the treatment of hypertension was demonstrated[76]. The binding of amlodipine (AML) was studied by changing the reaction conditions and the release rate of the drug bound to the nanopolymer under optimal conditions in the simulated gastrointestinal system at different pH values. AML-poly(HEMA-methacryloyl-amido-phenylalanine) nanomaterials facilitate less frequent drug administration, have higher bioavailability, and provide prolonged release with minimal side effects.

A new pH-sensitive controlled-release hydrogel carrier for the delivery of gut-specific drugs was prepared using ethylene glycol dimethacrylate (EGDMA) crosslinked with guar gum oleate, a poly(methacrylic acid) graft[77]. The release of the drug in buffer solutions of different pH was studied. It was confirmed that the guar gum oleate-graft-poly(methacrylic acid) hydrogel can be a potential pH-sensitive carrier for drug delivery to the colon.

A new multifunctional biocompatible system of superparamagnetic nanocarriers consisting of magnetic material in a polyHEMA solid polymeric matrix has been developed. For the development of these nanocarriers, polyHEMA nanoparticles were produced by a modified suspension polymerization method followed by co-precipitation of iron oxide inside the polyHEMA matrix[78]. Thus obtained superparamagnetic nanocomposite (mPHEMA) was char-

acterized by Fourier transform infrared spectroscopy (FTIR) and energy dispersive X-ray spectroscopy (EDAX), confirming the presence of Fe_3O_4 in polyHEMA nanoparticles. The biocompatibility was confirmed by *in vitro* cytotoxicity test following the extract-based method (ISO 10993-5, 2009), antihemolytic activity, and bovine serum albumin (blood protein) adsorption test. The water sorption behavior of the mPHEMA superparamagnetic nanocomposites was studied as a function of various factors such as the chemical composition of the nanoparticles, pH and temperature of the swelling bath, modeling of biological fluids, and applied magnetic field. The results showed that the superparamagnetic mPHEMA nanocomposite could be an excellent option for controlled and targeted delivery of anticancer drugs using an external magnetic field.

A passive delivery system based on pHEMA nanoparticles containing 5-fluorouracil as an anticancer drug was developed[79]. The main goal was to develop a drug delivery system with controlled swelling. The pHEMA nanoparticles in the range of 100−300 nm were obtained with a drug loading efficiency of more than 6 %. In this study, ethylene glycol dimethacrylate was used as a cross-linker.

A 5-fluorouracil-filled carrier composed of natural deep eutectic solvents and pHEMA was synthesized for cancer therapy. The physical structure proved to be porous with great potential for drug loading and sustained release. The carrier containing 5-fluorouracil effectively inhibited the spread of cancer cells[80].

The above works are mainly devoted to the study of hydrophilic drugs. Kumar *et al.*[81] conducted experiments with curcumin, which was a hydrophobic drug and was encapsulated through pHEMA. The drug loading efficiency was improved by the gel-like ionic liquid, obtaining a loading of 26.4 %. The *in vitro* cell toxicity was evaluated through ovarian cancer cells. The results imply that the ability of curcumin-loaded nanoparticles against cancer cells was higher than that of pure curcumin.

To improve the functionality of pHEMA, it was combined with other polymers to produce a multifunctional drug delivery system for simultaneous diagnosis and therapy. The pHEMA-poly(L-lactide)-poly(ethylene glycol) copolymer was developed for cancer therapy.[82] Doxorubicin was chosen as an anticancer drug and release studies showed that the drug release is pH dependent. Based on these results, the nanocarrier is promising in the theranostic treatment of cancer.

Poly(HEMA) nanoparticles containing timolol maleate (TM) were synthesized and characterized by precipitation polymerization[83]. Morphological observations using scanning electron microscopy and transmission electron microscopy confirmed the formation of nanoparticles with an average diameter of 128 nm under the appropriate synthesis conditions. The results of ultraviolet-visible (UV-Vis) spectrophotometry proved the controlled release of TM from the samples over a long period. The cytotoxicity of the samples on mesenchymal stem cells was evaluated, and the observations showed that they had no negative side effects on living cells.

Horak *et al.*[84] studied the regularities of methacrylate dispersion polymerization in the presence of a ferromagnetic filler to obtain monodisperse spherical particles of micron size. The authors investigated the effect of the main reaction parameters on the size and polydispersity of polymer particles. The use of the ferromagnetic filler improves the separation and purification of particles in a small volume. The homo– and copolymerization of methacrylate monomers (hydrophilic HEMA and hydrophobic glycidyl methacrylate (GMA)) was investigated in the presence of a magnetic colloid as a filler, in an inert medium − a mixture of 2-methylpropan-1-ol and toluene solvents. The authors substantiated and proposed a method for obtaining a ferromagnetic filler based on Fe_3O_4 by chemical deposition of iron salts of varying oxidation degrees and chose an effective dispersion medium: a mixture of ethanol and water in a ratio of 7.5:1 (w/w) for the GMA polymerization, and a mixture of 2-methylpropan-1-ol and toluene (1.3:1, w/w) for the polymerization of HEMA and its copolymerization with GMA. Using such a filler stabilized with oleic acid and PEG, granular polymer particles of homo– and copolymers were obtained. The optimal technological conditions for the preparation of microspheres based on HEMA and its mixture with GMA in the presence of a ferromagnetic colloid with a size of 0.2−20 μm and a polydispersity of 1.04−1.80 were determined. The influence of the main technological parameters of the dispersion polymerization process (polarity of the medium, temperature, nature and concentration of the monomer, stabilizer and initiator) on the average diameter of the particles and their polydispersity was established. Optimal conditions for obtaining monodisperse particles based on HEMA and its mixture with GMA were proposed. The better immobilization ability of spherical copolymeric particles containing ferromagnetic filler obtained in the medium of toluene/2-methylpropan-1-ol was found to be better compared with polymeric particles synthesized in the medium of ethanol/water. It was established that an increase in the content of hydrophobic GMA reduces the efficiency of peroxidase enzyme grafting.

3. Drug Carriers Based on Copolymers of HEMA with Polyvinylpyrrolidone

Despite the significant progress achieved recently in the development of technologies for the synthesis of granular HEMA polymers, they have the same type of

functionally active groups (=C=O and -OH) and limited possibilities for adjusting the composition and structural parameters of the network. The introduction of polyvinylpyrrolidone (PVP) into the HEMA composition provides a significant expansion of the carrier polymer properties due to additional highly polar, capable of hydration and ionization carbamate groups, which contribute to the improvement of the selective sorption-desorption properties of copolymers and increase their porosity[85]. PVP is effectively used in medicine and pharmacy[86], as well as as an active modifying agent in the synthesis of copolymers and the creation of polymer composite materials with special properties based on them[87–99]. Therefore, it is relevant to study the peculiarities of obtaining granular copolymers based on the HEMA-PVP composition *via* dispersion polymerization, as well as to establish their practical applicability for the creation of polymeric carriers of drugs controlled release.

3.1. Features and regularities of granular polymerization of HEMA in the presence of PVP

During the suspension copolymerization of water-soluble polymer-monomer systems, the use of water as a dispersion medium is complicated by the possible dissolution of the monomer (HEMA) and PVP in it. Therefore, the main problem for the successful synthesis of granular polymers was the choice of a solvent that, on the one hand, would dissolve water-soluble components (HEMA and PVP), and on the other hand, would not mix or would be partially soluble in water and prevent the diffusion of the components of the monomer-polymer composition into the aqueous phase. Therefore, studies were performed to select a suitable inert solvent added to the dispersing phase, for which the monomer distribution coefficient would be significantly higher than that for water[99,100].

Higher alcohols were used as solvents, in particular, cyclohexanol (CH), nonanol, decanol (DC), and their mixtures. The kinetic studies of monomer diffusion across the interface[99] revealed their insignificant transition to the aqueous phase. Moreover, after 1−1.5 h of limited dissolution, the diffusion practically stops. The introduction of PVP into the system reduces the rate of monomer diffusion from the organic phase into the aqueous phase. The highest dissolution of the monomer in water and an aqueous solution of PVP is observed when using DC as an organic phase, the lowest dissolution takes place using a mixture of CH-DC.

Based on the studies of diffusion, interfacial tension, coefficients of monomer distribution between the organic and aqueous phases, and the calculated solubility parameters, the CH-DC mixture was chosen as an inert solvent for the dispersed phase for the suspension polymerization of HEMA-PVP compositions[85]. For the compositions with another methacrylic ester (GMA), the monomer is a hydrophobic component, and PVP is a hydrophilic component, so a homogeneous composition may be formed only if PVP is well-dried under vacuum. For such compositions, a mixture of 1-decanol and toluene solvents proved to be the most effective[85, 101].

Suberlyak *et al.*[85, 99] investigated suspension copolymerization in an organic solvent of a polymer-monomer phase containing a monomer of different hydrophilicity, up to 10 % of EGDMA as a crosslinker (for HEMA), a polymerization initiator, and PVP dissolved in an organic solvent. The synthesis temperature was 348±3 K, and the stirring rate was maintained at 270±5 rpm. Freshly prepared fine colloids of magnesium hydroxide and barium sulfate, sodium tripolyphosphate, hydroxypropyl cellulose (HPC) with $MM=1\cdot10^5$, polyvinyl alcohol (PVA) with $MM=1.2\cdot10^5$ and 12 % of residual acetate groups, polyethylene glycol (PEG) with $MM=1.5\cdot10^3$, and PVP with $MM=3.6\cdot10^5$ were used as suspension stabilizers. The initiator (benzoyl peroxide (PB) or lauryl peroxide (PL) or azo-bis-isobutyric acid dinitrile (DAA)) was used in the amount of 0.5−2.5 wt. % relative to the monomer-polymer mixture.

The effect of PVP on the nature of the kinetic curves in suspension polymerization was similar to block polymerization and polymerization in solution: with an increase in PVP amount, the initial rate increases, and the so-called "limiting" monomer conversion decreases. At the same time, the researchers note a decrease or near absence of the induction period[102,103].

According to Suberlyak and Skorokhoda[85], the increase in the polymerization rate, as in the case of block polymerization and polymerization in solution, occurs due to the "matrix effect" accompanied by the formation of a charge transfer complex between the monomer molecule and the structural link of the PVP. As a result of the formation of such a complex, the electronic density of the monomer's double bond is redistributed and shifted, the dipole moment increases, and the activation parameters of the process decrease[104]. Monomer solvation, in addition to complexation, contributes to a local increase in its concentration and, consequently, the overall polymerization rate.

Based on the optimal composition of HEMA copolymers with PVP synthesized in the block and solution[85], in terms of both the technological properties of the initial composition (viscosity, fluidity, viability time, *etc*.) and the properties of copolymers (HEMA:PVP = 80:20, w/w), kinetic studies were performed for the mentioned ratio of components. The rate of suspension polymerization of the HEMA:PVP composition (80:20, w/w) in the CH-DC mixture is described by the kinetic equation (1) and the total effective activation energy is 51±3 kJ/mol.

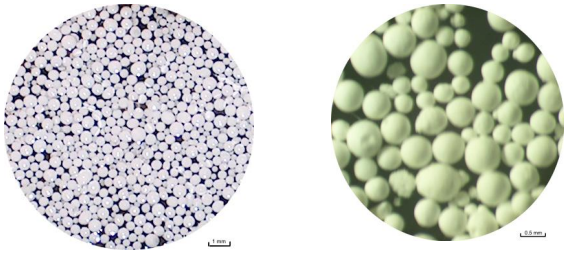
$$V = K\cdot[BP]^{0.7}\cdot[HEMA]^{2.0} \quad (1)$$

3.2. Influence of technological factors of suspension copolymerization of HEMA-PVP on the size and polydispersity of polymer particles

The main physical properties of polymer particles obtained by suspension polymerization, such as their size, polydispersity, surface area, and pore volume, depend on the physicochemical and hydrodynamic parameters and technological conditions of the synthesis. This group of parameters includes the nature and amount of monomers, crosslinker, initiator, stabilizer, temperature, ratio of organic phase to dispersion medium, stirring rate, and stirrer geometry. From a technological point of view, it was important to study the effect of these factors on the shape, size (diameter d_n), and polydispersity (polydispersity index (*PDI*)) of the granular particles.

Different types of stabilizers have been experimentally tested, namely high molecular stabilizers, such as PVP with $MM=3.6\cdot10^5$, PVA, hydroxypropyl cellulose (HPC), sodium tripolyphosphate, and low molecular stabilizers (magnesium hydroxide and barium sulfate)[85]. HPC in the amount of 0.5−5 wt. % of the initial composition proved to be unsuited for granular polymerization since at certain intervals the equilibrium was disturbed, coalescence of droplets, and the formation of polymer agglomerates and polymer particles of various sizes and shapes swollen in the solvent were observed. The use of sodium tripolyphosphate also did not give satisfactory results.

Using high molecular PVP and PVA as stabilizers, as well as $Mg(OH)_2$ during the suspension copolymerization of HEMA with PVA, particles of spherical shape and satisfactory polydispersity were obtained (Fig. 2).



a b

Fig. 2. Images of HEMA-PVP-based copolymers. Stabilizers: PVP (a) and $Mg(OH)_2$ (b)[85]

The use of magnesium hydroxide makes it possible to obtain spherical granules of larger sizes since it is a fine mineral powder and in proportionate concentrations creates a much less sterile effect than PVP and PVA. As a result, monomer particles are enlarged and larger granules are formed.

In the case of suspension polymerization of compositions based on the hydrophobic monomer GMA[101] using magnesium hydroxide as a stabilizer, suspensions of much larger sizes, wider polydispersity, with smoother surfaces were obtained compared to particles based on polyHEMA[85,102].

After optimization of the compositions and synthesis modes, the spherical particles of the highest quality were formed under the following technological conditions: HEMA:PVP = 80:20, w/w, [BP] = 1 wt. %, $[Mg(OH)_2]$ = 1 wt. %, CH:DC = 1:1, w/w, T = 348 K, stirring rate 150−240 rpm.

3.3. Sorption and desorption properties of granular HEMA-PVP copolymers

Usually, polymeric drug prolongers work on the principle of a substance sorption-release at a certain rate in the right place for a certain time. This makes it possible to prolong the terms of drug action and reduce its single dose. To establish the practical applicability of the synthesized copolymers, in particular for controlled drug release systems, the sorption and desorption of the model substance by polymeric materials of different compositions were investigated. The model substances were methylene blue (MB) and various drugs, namely diclofenac sodium, *p*-aminosalicylic acid (PASA), heparin, and carbamazine.

The study was carried out for copolymers based on both hydrophilic HEMA (PVP-graft-polyHEMA) and hydrophobic GMA (PVP-graft-polyGMA). Methylene blue (MB), which is also used as an antidote for poisoning with cyanide, carbon monoxide, hydrogen sulfide, nitrite, aniline, and its derivatives, was used as a model compound for the study. GMA-based particles were found to have a low sorption capacity[85,105]. The sorption rate and limiting levels of MS sorption by PVP-graft-polyHEMA polymers are almost 5 times higher than in the case of GMA-based copolymers. The authors attribute this to the presence of additional sorption centers in HEMA-based polymers − hydrophilic hydroxyl groups of methacrylate, which cause a stronger electrostatic interaction with the MB cation ($=N^+=(CH_3)_2$). The presence of such groups is the reason for the higher hydrophilicity and degree of swelling of PVP-graft-polyHEMA particles (water content 41−47 %) compared to PVP-graft-polyGMA (less than 10 %), and this fact further contributes to a better sorption capacity relative to MB. These differences may also indicate the high density of the macromolecular network in GMA-based polymers.

However, GMA-PVP-based polymeric particles, despite their lower sorption capacity, have the prospect of being used due to the possibility of their further modification by the epoxy group, which will expand the limits of their sorption properties.

The rate and value of MB desorption (G') by polymer particles depends on the medium pH. MB is released most intensively in an acidic medium, and a higher value of the limiting desorption is achieved. The maximum release of the dye by the copolymer suspension is only 38 %, which is obviously caused by the formation of a complex between the cation of the model substance and the functional groups (OH−, COO−) of the copolymer particles. In an acidic medium, the complex formed between the functional groups of MB and the copolymer is destroyed, resulting in a higher rate and maximum value of desorption.

The effect of synthesis conditions and composition of copolymers on drug sorption was studied on the example of diclofenac sodium, which is used as an anti-inflammatory, analgesic, and antipyretic agent, as well as carbamazine, which is used to treat filariasis and hookworm.

HEMA homopolymers have the lowest sorption capacity. Moreover, effective sorption is observed during the first 4−8 h of the process and remains practically unchanged thereafter. The introduction of PVP links into the copolymer composition significantly increases both the sorption rate and the maximum amount of sorbed drug. This is caused, according to Skorokhoda *et al.*[85,91], by several factors, the main ones being the introduction of additional functional groups of different natures into the copolymer, and an increase in the porosity of the granules themselves. It is known[104], that part of the PVP is capable of being washed out during hydration, and the formed space is filled with water or saline and substances dissolved in them. Thus, the introduction of PVP links into the copolymer composition allows changing the sorption properties of copolymers in the desired direction.

The synthesized copolymers desorb up to 40 % of the sorbed diclofenac sodium. The remaining amount was not released under the experimental conditions, except for polyHEMA-based granules. It should be noted that the amount of desorbed diclofenac sodium in all cases was within the therapeutic dose, which opens up the prospect of using synthesized hydrogels to create controlled release systems.

The issue of reducing the effective therapeutic dose in the case of carbamazine is particularly relevant because it has certain toxic properties. The reduction of dose can be achieved by creating sustained-release and controlled-release systems.

The effect of the copolymer composition and the presence of PVP links in its structure on the sorption of carbamazine has a similar dependence to the results obtained for diclofenac sodium. Sorption capacity of PVP copolymers is almost 2.5 times higher than that of polyHEMA. However, the desorption of carbamazine for the homopolymers is slow with a constant rate for almost 24 h.

The development of hemodialysis and hemofiltration materials, cardiovascular implants, drug prolongers, and other artificial organs has raised the problem of creating thromboreticulatory materials since the required thromboretic resistance is not always maintained with satisfactory biocompatibility. One of the effective ways to increase the thromboresistance of polymers is to immobilize the natural blood anticoagulant heparin on their surface. The main problem of heparin immobilization, in particular on polymeric particles, is its constant and minimized desorption during contact with blood.

The immobilization of heparin by synthesized hydrogel polymer particles based on copolymers of methacrylic esters with PVP was studied[85]. The materials for comparison were polymers based on modified cellulose and polyHEMA, which are used in practical medicine. The results of the study are presented in Table 1.

Table 1. Immobilization of heparin by polymeric spherical particles[85]

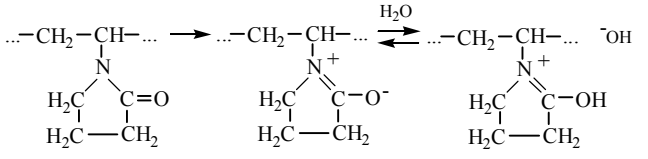
Polymer particles	τ, h	Sorption, 10^{-3} units/m^2	Desorption**, %		
			pH = 3	pH = 7	pH = 11
polyHEMA	1	45	0	1	9
	2	65	1	3	22
	3	96	2	4	38
	24	115*	5	9	86
PVP-graft-polyHEMA (20:80, w/w)	1	162	0	0	0
	2	263	0	0	1
	3	309	0	0	2
	24	550*	0	0	4
PVP-graft-poly(HEMA-GMA) (20:70:10, w/w/w)	24	546*	0	0	4

Notes: * – limiting value; ** – % relative to limiting value

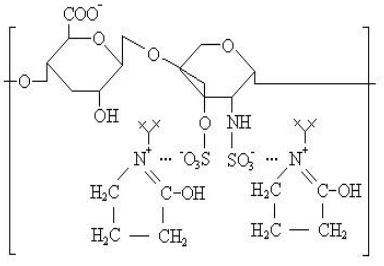
Since the heparin molecule is bulky and has a large molecular weight, most of it will be bound on the surface, so the immobilization results are presented as units of heparin per surface area unit.

Polymeric particles containing PVP links are characterized by an increased immobilization capacity relative to heparin, which only slightly decreases after replacing a part of HEMA with hydrophobic GMA, indicating the decisive influence of PVP on heparin immobilization. It should be noted that the most efficient sorption occurs in the first 2–4 h (~90 %) and then its rate decreases significantly up to the equilibrium value (Table 2).

The increased content of heparin on spherical particles with PVP is determined by the formation of ionic bonds between heparin and PVP macromolecules. When explaining the binding mechanism, it should be taken into account that the PVP linkage can exist either in the keto-form or in a form containing cationic nitrogen[85]:



Although the proportion of the cationic form is insignificant, these links allow the effective binding of heparin anions:



The formed PVP-heparin complex is so strong that when the polymers were kept in solutions with different pH for 24 h, heparin was practically not released (Table 2). The amount of heparin immobilized by polymer particles increases with sorption time, and the maximum value is reached after 24 h. The maximum saturation value of the particles with heparin is $550 \cdot 10^3$ units/m^2.

Regarding polyHEMA particles, a slight release of anticoagulant is observed in acidic and neutral media, while in alkaline media it increases to 38 %.

The obtained results show that heparin adsorbed by the surface of hydrogel polymer particles containing PVP is resistant to the action of saline for a long time. This implies stable antithrombogenic properties of hydrogels and their effective use in hemofiltration processes. Preliminary medical studies have confirmed the high thromboresistance of the synthesized polymers in contact with blood.

The synthesized polymeric particles are sufficiently chemically stable, can withstand sterilization in an autoclave, and can be used in contact with various physiological media[85].

The investigated two-stage method of obtaining granular drug prolongers, according to which granules are first synthesized and then saturated with drugs, has the significant drawback that the sorption capacity of hydrogels is limited and for this class usually does not exceed 0.01 g of drug per 1 g of polymer[106]. In this regard, a one-step method has been proposed that involves the synthesis of granular copolymers in the presence of drugs and allows increasing the drug content in the polymer carrier up to 30 %.

Thiotriazoline, omeprazole, isoniazid, and amlodipine benzoate were used as drugs. Long-term use of these drugs can change the blood formula. Therefore, it is important to create prolonged systems of such drugs that will significantly reduce the effective proportion of their use and minimize the negative effects of drugs on the mucous membrane of the esophagus and stomach.

The influence of these drugs on the suspension polymerization of HEMA compositions with PVP, as well as the particle size distribution of polymeric spherical particles, was studied. The monomer-soluble drugs were introduced into the polymer-monomer composition at the beginning of the synthesis.

In the presence of drugs, the suspension polymerization of HEMA compositions with PVP was successful, without changing the temperature and time. The spherical polymer particles were obtained, the sizes of which are given in Table 2.

The addition of isoniazid to the polymer-monomer composition leads to a decrease in the size of polymer particles. With an increase in the content of thiazolidinediones in the initial composition, the average particle diameter increases slightly, and the polydispersity index decreases, *i. e.*, more homogeneous particles of larger size are formed.

The experimental results of drug effect on the polydispersity of spherical composites are presented in the form of distribution curves showing the proportion of individual fractions in the material (Fig. 3). The most homogeneous spherical particles were formed with the content of omeprazole in the composition. Photographs of the obtained particles are shown in Fig. 4.

The experimental samples of drug-containing granules were studied for the release kinetics of the drugs. The results of the study confirm the possibility of synthesizing spherical polymer particles *via* suspension polymerization of HEMA-PVP compositions, particularly in the presence of drugs. The porosity, particle size, and particle size distribution are significantly influenced by the composition of the initial monomer-polymer mixture and the initiator nature and amount. This provides wide possibilities for tar-

geted control of the sorption-desorption properties of the synthesized copolymers when they are used as polymeric carriers for controlled release systems.

Based on the results of the research, a technology for obtaining granular HEMA-PVP copolymers and controlled-release systems based on them was developed.

Table 2. Influence of the nature and amount of drugs on the dispersive characteristics of microspherical particles based on HEMA-PVP composition (HEMA:PVP = 80:20, w/w, content of drug is 5 wt. %)[106]

Drug	d_n, mm	d_w, mm	*PDI*
Thiotriazoline	0.30/0.44*	0.67/0.63*	1.93/1.43
Omeprazole	0.31	0.36	1.14
Amlodipine benzoate	0.49	0.64	1.31
Isoniazid	0.19	0.37	1.92
–	0.55	0.62	1.13

* Value in denimonator is for thiotriazoline amount of 10 wt. %.

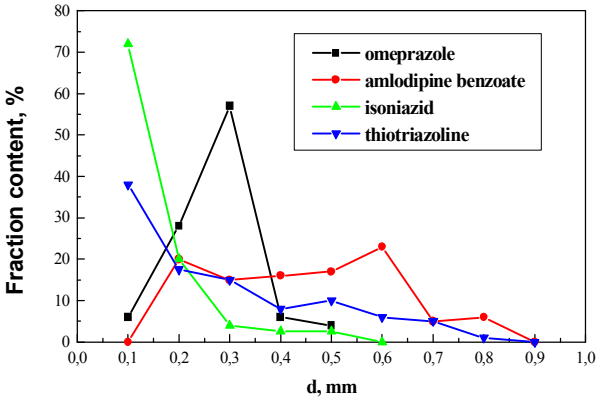


Fig. 3. Effect of the drug nature on the particle size distribution[106]

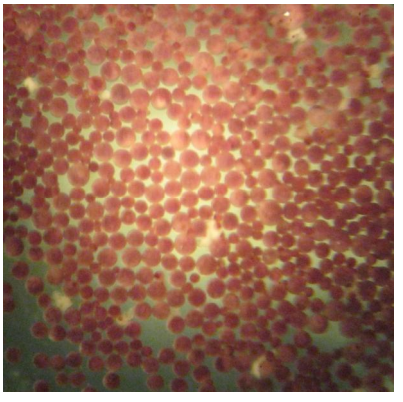


Fig. 4. Image of microspherical particles based on the HEMA-PVP composition synthesized in the presence of omeprazole[106]

Conclusions

The review deals with the problems of synthesis, properties, and application of hydrogels in the form of spherical nanoparticles based on hydroxyethyl methacrylate (HEMA) copolymers for use as drug prolongers. The main characteristics of such materials are discussed, namely the combination of rigid and flexible chains for easy adjustment of physical properties (including porosity), as well as mechanical strength and specific sensitivity to external factors such as pH, temperature, biological components, and certain chemicals. It has been shown that the synthesis of new carriers based on polyHEMA and its copolymers, including the synthesis in the presence of ferromagnetic nanofillers, opens up new prospects for this industry. In particular, researchers are interested in hydrogels that respond to external stimuli such as pH and temperature.

The peculiarities of obtaining hydrophilic functionally active fine-dispersed copolymers of methacrylic esters with PVP *via* suspension polymerization with the possibility of directed changes in their structure, particle size distribution, and selective sorption capacity during synthesis were investigated. The effect of technological factors on the properties of polymeric particles was examined. The regularities of sorption and desorption of model substances (methylene blue) and drugs (carbamazine, diclofenac sodium) by methacrylic esters-PVP copolymers were studied and the relationship between the nature of the copolymer functional groups, their dispersion characteristics and sorption properties was shown. The PVP copolymers exhibit an increased immobilization capacity for anionic substances, which are further released at different rates depending on the medium pH. The results were used to predict the composition of copolymers for the immobilization of a specific drug.

The possibility of obtaining granular drug prolongers *via* a one-step method involving the synthesis of granular copolymers in the presence of drugs has been confirmed, which allows increasing the drug content in the polymer carrier up to 30 %. In the presence of drugs (thiotriazoline, omeprazole, isoniazid, amlodipine benzoate), it was possible to carry out suspension polymerization of HEMA compositions with PVP without changing temperature and time and obtain spherical polymer particles with a size of 0.2−0.7 mm.

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ГІДРОГЕЛІ В БІОМЕДИЦИНІ: ГРАНУЛЬНІ СИСТЕМИ КОНТРОЛЬОВАНОГО ВИВІЛЬНЕННЯ НА ОСНОВІ (КО)ПОЛІМЕРІВ 2-ГІДРОКСІЕТИЛМЕТАКРИЛАТУ. ОГЛЯД

Анотація. *Проаналізовано й узагальнено останні досягнення в галузі створення полімерних систем для пристроїв контрольованого вивільнення речовин у середовище дії на основі гідрогелевих матеріалів. Представлено можливі напрями доставки ліків, зокрема за допомогою гранульних гідрогелів, які працюють за принципом сорбція лікарського засобу – вивільнення його в організмі. Проаналізовано дослідження закономірностей синтезу, структури, властивостей і перспектив застосування гранульних гідрогелів на основі 2-гідроксіетилметакрилату та його кополімерів, зокрема з полівінілпіролідоном, як систем контрольованого вивільнення речовин, зокрема ліків.*

Ключові слова: *пролонгатори ліків, гідрогелі, гранульні кополімери, 2-гідроксіетилметакрилат, суспензійна полімеризація, полівінілпіролідон.*