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Analytical review of mechanisms of controlled release of bioactive compounds from poly(2-hydroxyethylmethacrylate)/nanosilica composites

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The development of new functional composites for directed transport and controlled release of bioactive compounds (BACs) is one of the priority tasks of modern surface chemistry and pharmaceutical technology. The work analyzes hybrid organic/inorganic systems based on poly(2-hydroxyethyl methacrylate) (PHEMA) filled with nanosilica as stimulus-sensitive matrices for biomedical applications. It was established that the kinetics of BACs release from these composites is determined by a combination of their composition and structural parameters. The regulation of the desorption process of components is achieved by creating additional cross-links in the polymer matrix, introducing nanosilica as a filler and using water as a pore former. At the same time, the efficiency of BACs retention by the matrix and the rate of their diffusion significantly depend on the physicochemical parameters of the environment, in particular on the pH value, which is a key factor in modulating interactions in areas with different intensities of the inflammatory process. The presented analytical study summarizes the mechanisms of interaction of BACs with composites based on PHEMA and nanosilica. The limits of dominance of various types of influences, including electrostatic attraction, steric hindrance and the formation of hydrogen bonds during the binding and desorption of BACs, were determined. A comprehensive understanding of these fundamental processes allows us to transform approaches to creating innovative systems with controlled release of BACs in accordance with modern requirements of the pharmaceutical industry.

Keywords: composite systems, nanosilica, poly(2-hydroxyethyl methacrylate), bioactive compounds release.

Аналітичний огляд механізмів контрольованого вивільнення біоактивних сполук з композитів «полі(2-гідроксиетилметакрилат)/нанокремнезем».

І.В. Михайлова, І.І. Геращенко, О.С. Куколевська, Т.І. Ющенко

Розроблення нових функціональних композитів для спрямованого транспорту та контрольованого вивільнення біоактивних сполук (БАС) є одним із пріоритетних завдань сучасної хімії поверхні та фармацевтичної технології. У роботі аналізуються гібридні органо-неорганічні системи на основі полі(2-гідроксиетилметакрилату) (ПГЕМА), наповненого нанокремнеземом, як стимул-чутливі матриці для біомедичного застосування. Встановлено, що кінетика вивільнення БАС із цих композитів визначається кореляцією їхнього складу та структурних параметрів. Регулювання процесу десорбції компонентів

досягається створенням додаткових перехресних зв'язків у полімерній матриці, введенням нанокремнезему як наповнювача та використанням води в якості пороутворювача. Разом із тим, ефективність утримування БАС матрицею та швидкість їхньої дифузії суттєво залежать від фізико-хімічних параметрів середовища, зокрема від значення pH, що виступає ключовим чинником модуляції взаємодій у зонах із різною інтенсивністю запального процесу. У представленому аналітичному дослідженні узагальнено механізми взаємодії БАС із композитами на основі ПГЕМА і нанокремнезему. Визначено межі домінування різних типів впливів, серед яких електростатичне притягання, стеричні перешкоди та формування водневих зв'язків при зв'язуванні й десорбції БАС. Комплексне розуміння цих фундаментальних процесів дозволяє трансформувати підходи до створення інноваційних систем із контрольованим вивільненням БАС відповідно до сучасних вимог фармацевтичної галузі.

1. Introduction

Poly(2-hydroxyethyl methacrylate), known as PHEMA, is one of the most sought-after biomaterials in creating a versatile platform for biomedical applications due to its exceptional biocompatibility, cytocompatibility, and ability to elicit minimal immunological responses from the host tissue. Biomedical applications of PHEMA include hydrogel wound dressings, bone regeneration, cancer therapy, ocular drug delivery, artificial skin, artificial cornea, breast augmentation, catheters, intrauterine devices, and prostheses.

By its nature, PHEMA is a hydrophilic, optically transparent and non-biodegradable polymer. The chemical structure of PHEMA determines its unique amphiphilic character: the main carbon chain provides mechanical strength and resistance to hydrolysis, while the side chains contain hydroxyl (–OH) and ester (–COO–) groups (2-hydroxyethyl ester group). It is the presence of terminal (end) hydroxyl groups that determines the high hydrophilicity of the polymer and its ability to form a branched system of hydrogen bonds with water molecules and biologically active compounds (BACs) [1]. In the context of the interaction of PHEMA with antimicrobial cationic substances (such as decamethoxin), potential carboxyl groups (–COOH) could play a special role. Although pure PHEMA is nonionic, the presence of even a small amount of carboxyl groups (due to partial hydrolysis or as an impurity in the monomer synthesis) transforms the neutral matrix into a weak polyelectrolyte. This creates conditions for electrostatic binding of positively charged BACs molecules to negatively charged carboxylate anions, which directly affects the kinetics of their retention and prolonged release from the composite.

When in contact with an aqueous environment, the polymer quickly swells, turning into a flexible and soft hydrogel, which in its characteristics is similar to the natural extracellular matrix of the cell [2, 3]. The transparency of the PHEMA matrix, combined with its high permeability to oxygen, liquids and small molecules, has led to its historical use in the production of soft contact lenses and ophthalmic drug delivery systems.

Despite its significant list of advantages, pure PHEMA has certain limitations which forces the development of strategies for its modification [2]. In particular, this polymer is not biodegradable, which requires its combination with other materials depending on the ultimate goal of the therapy. In addition, PHEMA lacks its own antimicrobial properties. Since the implantation sites of biomedical devices are often prone to microbial infections, the inclusion of active additives such as silver nanoparticles, antibiotics or other antimicrobial agents in the matrix becomes critically important. Favorable physicochemical properties and high stability make PHEMA an ideal candidate for the creation of multicomponent systems. The prospects for the future use of this polymer are related to the development of new biomaterials for regenerative medicine, wound healing and stimulus-sensitive cancer therapy, where PHEMA acts as a stable and safe carrier for the delivery of BACs.

Physicochemical and biomedical studies of new composite materials based on PHEMA with controlled release of BACs not only confirmed their functional efficiency, high biocompatibility and stability in physiological environments [4–6], but also allowed us to trace the interaction of key factors governing the behavior of BACs in the structure of composites. The results of the observations indicate that the release of BACs from composites is a complex process that occurs slowly over a long time and is subject to a diffusion-kinetic mechanism. To effectively control such long-term kinetics, modification of the polymer matrix with nanosized inorganic fillers is often used. In particu-

lar, nanosized (highly disperse) silica (HDS) has a high specific surface area (150–380 m²/g), developed porosity, and a significant number of reactive silanol groups, which offers broad opportunities for the adsorption and controlled diffusional transport of BACs molecules. Furthermore, this material exhibits high chemical inertness and thermal stability, and modification of the matrix even within 1–5 wt % ensures the preservation of the structural integrity of the composite. At the same time, its high biocompatibility and ability to optimize interfacial interactions significantly enhance the physicochemical properties and functional stability of the resulting biomaterials.

For a deeper understanding of the mechanisms of retention and release of BACs from a polymer matrix, which contains HDS as a filler, it is necessary to consider in detail the interactions between all components of the composites. In addition to the electrostatic interaction of BACs with the silica surface, which is the main inhibitory factor of BACs release, these processes can also be significantly influenced by 1) the formation of hydrogen bonds between the functional groups of the polymer and the silica surface; 2) the presence of clusters of strongly bound water in the composite structure; 3) hydrophobic interactions of BACs with the silica surface and segments of the polymer matrix; 4) competitive ion exchange of the silica surface with the environment; and 5) steric resistance of the polymer matrix to the processes of diffusion and release of BACs. It should be added that the manifestation of the above-mentioned factors significantly depends on the parameters of the external environment: pH, ionic strength, temperature, etc.

2. Analysis of interaction mechanisms in composites

2.1. Polymer Matrix–Filler Interactions

A major research focus in the development of wound dressings and antimicrobial materials based on PHEMA and silica is the influence of the polymer matrix on BACs release from polymer composites. Experimental data demonstrate a direct relationship between polymer matrix architecture and the functional properties of the resulting materials. This relationship is manifested primarily through intermolecular interactions at the phase interface, particularly via the formation of hydrogen-bond networks between functional groups of the polymer network and the silica surface [7]. The interaction between HDS and the polymer matrix has been experimentally investigated using the model system HEMA(2-hydroxyethyl methacrylate)/HDS in aqueous media [8].

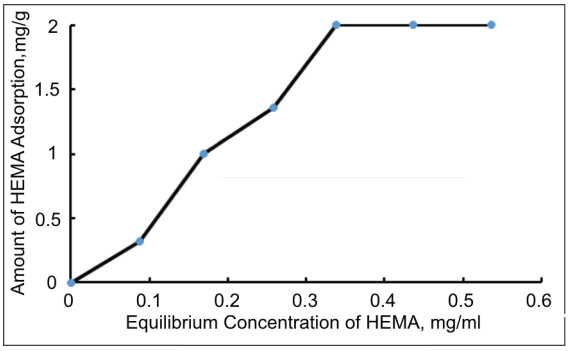


Figure 1. Adsorption isotherm of HEMA on the HDS surface (adopted from [8]).

The maximum adsorption of HEMA from aqueous solution onto HDS was found to be approximately 2 mg/g (~0.015 mmol/g) (Figure 1), corresponding to the placement of three monomer molecules per 100 nm^2 of the silica surface. This is confirmed by the following calculation: the specific surface area of highly dispersed fumed silica A-300 is on average 300 (m^2/g)=$300 \cdot 10^{18}$ nm^2/g, therefore, per 1 nm^2 of adsorbent surface there are $0.015 \cdot 10^{-3} \cdot 6.02 \cdot 10^{23}/(300 \cdot 10^{18})=0.0301$ HEMA molecules, which is equivalent to 3 molecules per 100 nm^2.

Analysis of IR spectra and quantum-chemical modeling of HEMA/SiO_2 adsorption complexes indicate [7] that adsorption occurs via hydrogen bonding between: a) the oxygen atoms of the HEMA carbonyl groups and silanol groups (Si–OH) on the silica surface; b) hydroxyl groups of HEMA and oxygen atoms of siloxane bridges on the silica surface (Si–O–Si) (Figure 2). As a result, each monomer unit of PHEMA may form up to three hydrogen bonds with the silica surface. In this case, a monolayer structure is formed, in which a HEMA molecule corresponds approximately to one Si–OH group.

Thus, due to hydrogen bonds between the filler (HDS) and the polymer matrix, an adsorption interaction occurs, which can significantly slow down the diffusion of BAC in the composite system.Therefore, the incorporation of BACs into polymer matrices together with nanosilica may be considered as an effective strategy for regulating the rate of BACs release.

The influence of the interfacial interaction of PHEMA/SiO_2 on the kinetics of the release of BACs is significantly depends on the degree of filling of the matrix with silica due to a change

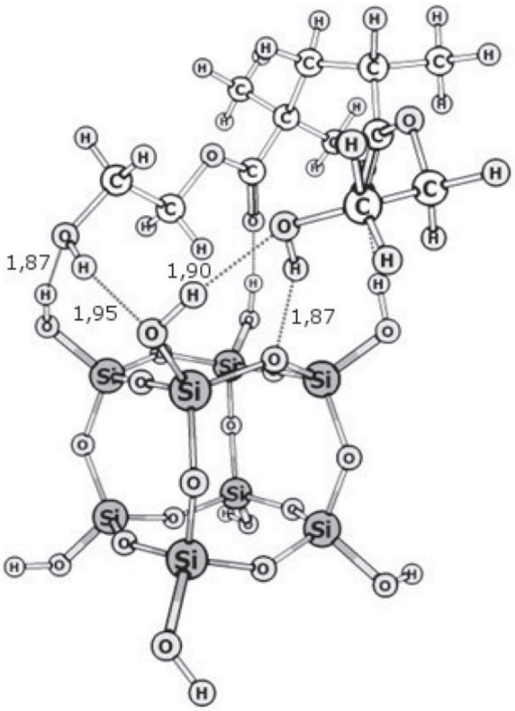


Figure 2. Optimized structure of the adsorption complex of a $(HEMA)_2$ dimer on the HDS surface (adopted from [7]).

in the diffusion regime. At low concentration (intense release mode), nanoparticles mainly act as hydrophilic centers that attract water and loosen the polymer network, facilitating the diffusion of BACs outward. At a high silica content (retention mode), nanoparticles form a continuous physical framework and numerous intermolecular hydrogen bonds with the matrix, which dramatically increase the cross-linking density of polymer chains and creates steric hindrances that "lock" the compound inside the matrix. The transition point depends on the specific surface area of the nanofiller and its ability to be uniformly distributed in the volume of the PHEMA matrix. Numerous studies show that to transition from release stimulation to retention, the optimal ratio in PHEMA/SiO_2 systems is typically 3–5 wt. % nanosilica. When the silica content is less than 3 %, the effect of matrix hydrophilization predominates, the pores of which remain accessible, and the release rate increases. In the range of 3–5 % silica content, a stable hydrated layer is formed, but the mechanical resistance of the network still allows swelling. At a silica content of more than 5–7 %, the retention mode is activated, when the filler creates a too dense physical framework, which sharply slows down diffusion. The vast majority of studies in the

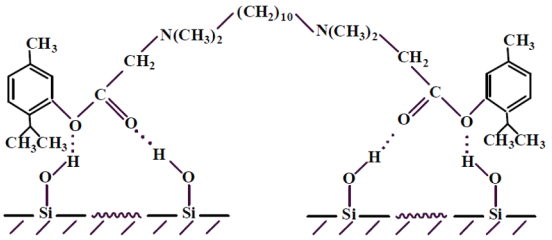


Figure 3. Schematic representation of DCM adsorption complexes on the silica surface (adopted from [10]).

field of creating biomedical materials focus on silica contents from 3 to 15 % [9].

Thus, the integration of silica nanoparticles into polymer matrices not only optimizes their mechanical properties, bioactivity, and hemocompatibility, but also affects the release profile of incorporated BACs, making such composites promising for the development of innovative materials in medical practice.

2.2. Adsorption of BACs on silica

The efficiency of deposition and subsequent release of biologically active compounds from composites depends on the adsorption capacity of BACs in relation to the silica surface. The highest adsorption rate on HDS among the studied BACs is demonstrated by the cationic surfactant antiseptic decamethoxin (DCM, 1,10-decamethylene-bis(N,N-dimethylmentoxycarbonylmethyl) ammonium dichloride, $C_{36}H_{76}N_2O_2$), which belongs to the derivatives of bis-quaternary ammonium compounds. As an antiseptic, DCM exhibits a wide spectrum of antimicrobial activity. In neutral and weakly alkaline solutions, adsorption occurs by an electrostatic mechanism due to the attraction between the positively charged quaternary nitrogen atoms of decamethoxin and the negatively charged residues of deprotonated silanol groups ($Si–O^-$) in accordance with the structure of the DCM molecule. In addition, the DCM molecule can form 4 hydrogen bonds with the HDS surface (Figure 3), which ensures reliable attachment during adsorption.

At the same time, the uncharged metronidazole molecule is able to form only 2 hydrogen bonds with the HDS surface (Figure 4), which explains its lower adsorption. The metronidazole molecule (1-(ß-oxyethyl)-3-methyl-5-nitroimidazole, $C_6H_9N_3O_3$) is a nitroimidazole derivative and contains a tertiary nitrogen atom and an alcoholic hydroxyl group, which have pronounced proton-accepting properties and can potentially participate in the formation

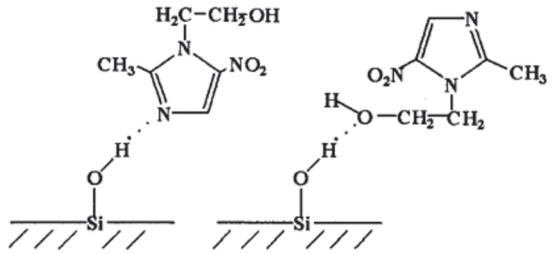


Figure 4. Schematic representation of metronidazole adsorption complexes on the silica surface (adopted from [11]).

of hydrogen bonds with the Si–OH groups of HDS.

A feature of PU(polyurethane)/PHEMA/SiO_2-based composites is also their ability to additionally stabilize BACs molecules, for example, DCM, due to hydrophobic interactions between long aliphatic chains of BACs and the silica surface and segments of the polymer matrix. This also contributes to the formation of a pH-independent fraction of adsorbed BACs, which remains stable even with significant changes in the acidity of the medium.

This nature of BACs retention is indirectly confirmed by the results of studying the stability of nanosilica suspensions in the presence of cationic surfactants: DCM, ethonium dichloride and cetyltrimethylammonium bromide (CTAB) [12]. In particular, it is shown that at concentrations close to the critical concentrations of micelle formation of cationic surfactants, a sharp increase in adsorption is observed; this can be explained by the aggregation of cationic surfactants on the surface of the adsorbent with the formation of hemimicelles (monolayer aggregates arising due to the lateral interaction between the hydrocarbon chains of cationic surfactants) and admicelles (multilayer structures with a hydrophobic core and a shell of charged functional groups). In this case, adsorption of cationic surfactants can occur on both charged and neutral adsorption centers within the framework of the monolayer model, especially at low pH values. The avalanche-like nature of this process correlates with the rapid loss of stability of suspensions. The question of whether aggregation of BACs molecules occurs inside water clusters in a polymer matrix based on PHEMA requires experimental clarification. If molecules assemble into micelles, their effective radius becomes larger than the pore radius, which can lead to a complete stop of release (the "trap" effect).

In addition, the effect of hydrophobic interaction of surfactants capable of micelle formation in the structure of composites is not only a possible factor in immobilization of BACs, but can also be a tool for the formation of anti-swelling properties of composites in the case of excessive water absorption by regulating the balance between hydrophilic and hydrophobic segments of composites [13]. During radical polymerization of HEMA in situ in the presence of silica, surfactant micelles act as stable structure-forming "nodes" that determine the architecture of the future PHEMA network. Acting as water-repellent locks, they strengthen the hydrophobic zones of the gel and prevent water from penetrating inside, which provides the anti-swelling effect.

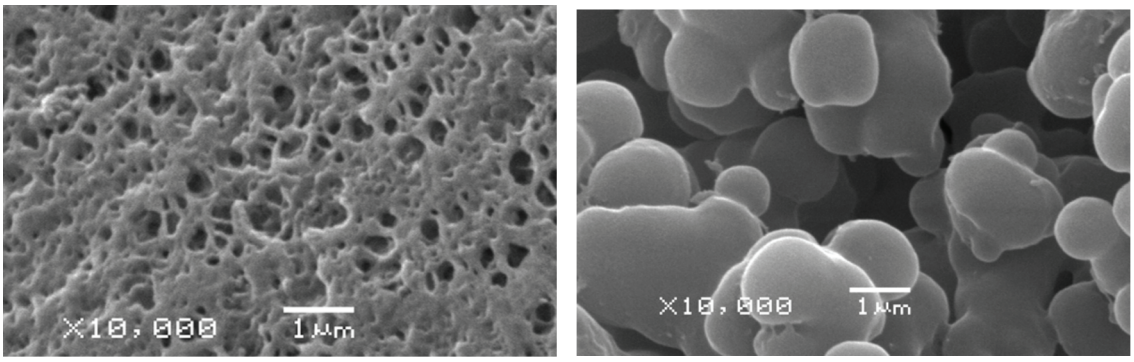
The adsorption of salts is mainly influenced by the degree of hydration of ions, which, for example, is energetically less favorable for Ag^+ ions (−464 kJ/mol) than for Zn^{2+} ions (−2050 kJ/mol), and this contributes to their better adsorption on the surface of HDS. As for amino acids, it has been proven that they are not adsorbed by the surface of HDS. This is probably due to the fact that in solution at pH 3–8 most amino acids are in the form of zwitterions, so the attraction of the $–NH^{3+}$ group and the repulsion of the $–COO^-$ group by the Si–OH group of the surface compensate each other [14].

3. Swelling of polymer matrix and diffusion properties of composites

3.1. The role of polymer matrix porosity

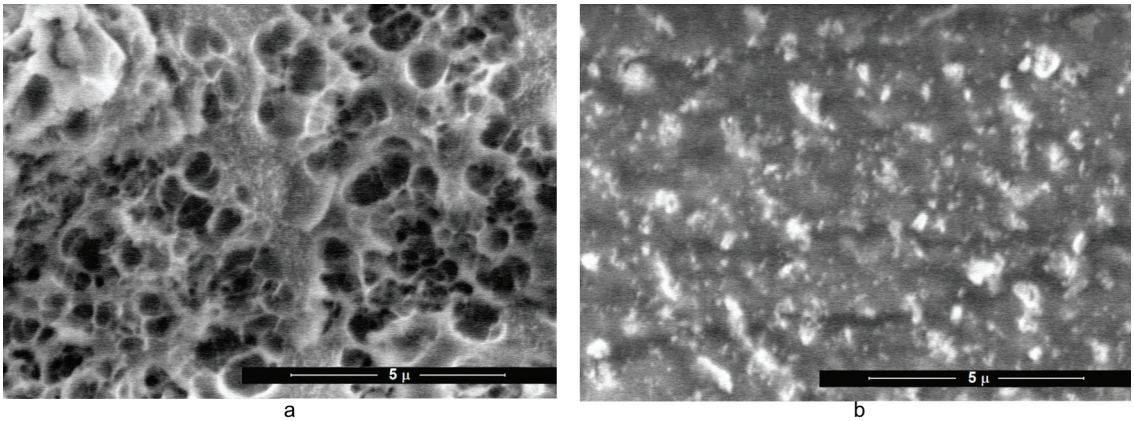
Another effective approach for modifying the physicochemical properties of PHEMA hydrogels is to form a branched pore system within the polymer structure. The pore size directly depends on the amount of water used as a pore former during composite synthesis. Increasing the amount of porogenic water leads to a significant increase in pore size and their openness (Figure 5). A decrease in sample porosity after the introduction of nanosilica (Figure 6) can be explained by the filling of pores with silica particles and possible contraction of pore walls due to chemical interactions between silica and PHEMA chains.

Studies have shown that the inclusion of silica nanoparticles in PHEMA at the polymerization stage leads to the formation of nanopores in the PHEMA matrix, which improves the mechanical properties of the composites and maintains their good hemocompatibility.



a b

Figure 5. SEM images of PHEMA synthesized with 66.7 % water (a) and 80 % water (b) (adopted from [8]).



a b

Figure 6. LVSEM images of PHEMA synthesized with 66.7 % water (a) and with 66.7 % water plus 10 % silica (b) (adopted from [8]).

Using the example of vitamin B_{12} diffusion, it was also shown that the release profile of molecules into the environment can be controlled by changing the concentration of both SiO_2 nanoparticles and the HEMA monomer during synthesis [15]. In [16], poly(ethyl methacrylate-co-hydroxyethyl acrylate)/nanosilica nanocomposites with a nanosilica content from 0 to 30 wt. %, were investigated with the prospect of their use as bone implants or for dentin regeneration. It was found that the optimal nanosilica content in the range of 10–20 wt. % ensures the formation of reinforcing structures and increases the bioactivity and wettability of the surface, while lower concentrations are ineffective, and higher concentrations lead to an increase in the stiffness of the material and a decrease in its controllability [17].

Thus, the introduction of BACs, either attached to HDS or simultaneously with it but separately, into a non-porous PHEMA matrix can significantly slow down the release of BACs into the aqueous environment. In porous systems synthesized with water as a porogen, however, BACs release profiles from materials containing silica and those without silica become similar. Thus, pore formation in the PHEMA matrix largely eliminates the retardation effect of silica on BACs release.

Despite this, it should be noted that the mechanical properties of the polymer matrix will be determined not only by the pore size and the presence of filler as a structure-forming agent, but also to a large extent by the properties of water in the structure of the composites.

3.2. The role of bound water in the composite structure

Analysis of the behavior of water in biomedical hydrogels has shown [18, 19] that at the beginning of the matrix swelling process, hydration of polar and hydrophilic groups leads to the appearance of “primarily bound water”; then due to interaction with hydrophobic areas of the matrix, “secondarily bound water” appears. These two fractions of water are often combined and called “total bound water”. After this, the matrix begins to absorb additional water due to osmosis: so-called “free water” (or “bulk water”) appears which fills the space between the chains of the polymer network, macropores or voids. The additional swelling is compensated by covalent or physical

"cross-links", which leads to elastic contraction (retraction) of the network, and thus the hydrogel reaches an equilibrium degree of swelling. Assessment of the state and relative amounts of free and bound water can provide a better understanding of the interactions that occur at the interface of a hydrogel with the biological environment. Detailed information about the morphology, molecular organization, specific intermolecular interactions, and internal mobility of hydrogel components can be obtained using nuclear magnetic resonance (NMR) [20].

^{1}H NMR spectroscopy showed that another factor significantly affecting the BACs release is the binding of water within interparticle spaces of the composite [21]. The PHEMA/SiO_2 matrix significantly changes the thermodynamic properties of water when it passes from the bulk state (free water) to the cluster state: the Gibbs free energy ($-\Delta G$) of water decreases, and water may remain in a liquid state even at temperatures well below 273 K (nonfreezing water). The change in ($-\Delta G$) when water freezes in a confined space allows us to assess how strongly the water is held in the matrix. High ($-\Delta G$) values correspond to strongly bound water (SBW) within small clusters. If BACs molecules are located ("hidden") within such clusters, they become surrounded by structured water, which shields the release process from external factors such as medium pH changes. This supports the hypothesis of a steric factor affecting the release process: BACs molecules become physically blocked (entangled) in rigid polymer domains, where the pH of the medium has a limited effect on the diffusion rate of BACs. Thus, zones are formed in the PHEMA/SiO_2 composite where water interacts with the polymer so strongly that it forms stable "capsules" for drugs.

Theoretical modeling of water behavior in hydrogels and a number of experimental methods, such as NMR, differential scanning calorimetry (DSC), dielectric relaxation spectroscopy (DRS), thermally stimulated depolarization current (TSDC), microscopy, thermogravimetric analysis (TGA) allow classifying it into several types [22]: 1) bound water, which consists of strongly bound (SBW, unfrozen at T<260–265 K), weakly bound (WBW, unfrozen at 260–265<T<273 K), and nonbound with almost bulk properties of water (NBW, frozen at 273 K); 2) associated water, which consists of strongly associated water (SAW, chemical shift δ_H>2 ppm, with 3D clusters and domains of various sizes) and weakly associated water (WAW, δ_H=1–2 ppm, 1D–2D clusters or individual molecules in a hydrophobic environment); 3) free water [23–25]. Thus, SBW corresponds to nonfreezing bound water, and WBW corresponds to freezing bound water.

Analysis of the state and amount of unfrozen water (both SBW and WBW) as a function of temperature below the normal freezing point of water allows us to study, in particular, the nanoporous structure of the walls of macropores in hydrogels [22]. It has been shown that the short-range order of water in lyophilized gels changes slightly compared to the long-range order. Studies of the diffusion of various solutes of low and high molecular weight in the macropores of hydrogels show that the state of water in the macropores is similar to the state of free water. However, if solutes are adsorbed on the surface of the macropores, this leads to changes not only in the diffusion of solutes, but also in the behavior of water, since the contributions of NBW, WBW and SBW change, and these effects are strongly dependent on temperature. The study of the characteristics of SBW and WBW in polymer-nanofiller systems using the example of composites with hyaluronic acid and nanosilica showed [25] that in a greater number of samples the SBW content is higher than the WBW content, which may be due to the hydrophilic properties of both fumed silica A-300 and hyaluronic acid.

In works substantiating the effectiveness of fumed silica as a carrier of drugs in composites, it has been shown that the presence of silica increases the bioactivity of adsorbed molecules, in particular, due to the effect of silica on the binding energy of water [26]. Indeed, the stronger the water binds to the surface of the carrier, the slower the desorption of BACs into the biological environment will occur, since BACs molecules on the diffusion path must overcome the near-surface layer of bound water. The binding of water in composite systems based on silica with chloramphenicol adsorbed on its surface in the presence of additives of hydrophobic components: solid – methyl silica and liquid – deuterochloroform was studied using the method of low-temperature ^{1}H NMR spectroscopy [27]. It has been shown that the immobilization of chloramphenicol causes a certain increase in hydrophilic properties and the degree of water binding. Replacing air with a liquid hydrophobic medium ($CDCl_3$) is accompanied by an increase in the interfacial energy by 0–30 %, and the

introduction of methyl silica into the SiO_2/chloramphenicol composite increases it by more than 4 times, which makes it possible to use such composite systems to create prolonged-acting drugs.

In the air environment, the spectrum of water is observed as a single signal, which decreases upon heating (210–285 K) from the value of the chemical shift δ_H from 7–9 ppm to 4.5–5 ppm; this is associated with a decrease in the degree of association of adsorbed water. In the $CDCl_3$ medium, signals of highly associated water and low-intensity signals of weakly associated water (δ_H=0–2 ppm) appear in the spectra. Processing of the dependence of the NMR signals of unfreezing water on temperature and the dependences of the change in Gibbs free energy on the concentration of unfreezing water obtained on their basis showed that the interfacial energy γ_s of the initial silica (7.7 J/g) slightly (9 J/g) when chloramphenicol is added, which means an increase in the binding energy of adsorbed water. (Chloramphenicol molecules contain several types of hydrophilic centers, so that when immobilized on the surface of silicon dioxide, some increase in its hydrophilicity can be expected). However, when chloramphenicol is released into the hydrophobic environment of $CDCl_3$, the binding energy of adsorbed water with the surface of silica not only does not decrease, but, on the contrary, increases (11.5 J/g). This paradoxical effect is explained by the confined space effect and clustering of water with a decrease in the radius of water clusters [21], which NMR records as an increase in the interfacial energy γ_s and the binding energy of water.

This effect is observed for most hydrogels [26]. Thus, in composite systems containing equal amounts of hydrophilic and hydrophobic silica, there is a possibility of significantly increasing water binding, which can be used to develop prolonged-release drugs.

Thus, the organization of water bound in hydrogels depends on many factors, and a comprehensive analysis of temperature and interfacial behavior of water provides a deeper understanding of the interfacial phenomena occurring in hydrogels at different degrees of hydration, different temperatures, and in the presence of different solutes. In addition, not only the type of bound water, but also its activity as a solvent, local (nanoclusters, nanodomains) and microscale (microdomains) structure, density, electrical conductivity, and other properties affect the behavior of hydrogels [23–25].

The influence of bound clustered water on the BACs release process can be attributed to another additional factor slowing down the diffusion of BACs, which manifests itself in composites with semi-interpenetrating polymer networks (semi-IPN) [9]. The presence of strongly bound water in narrow clusters of the polymer matrix correlates with a relatively low level of desorption, from 6 % for DCM to 30 % for metronidazole from semi-IPN PU/PHEMA [8]. In cases where the size of the water clusters becomes commensurate with the size of the BACs molecule, steric entanglement occurs, due to which the desorption rate ceases to depend on the external pH, since diffusion occurs exclusively through the narrow channels of the hydrated structure.

The interpretation of numerical calorimetric and spectroscopic data on the structure of water in hydrogels remains a subject of active scientific debate due to the dynamics of the system. The boundary between strongly, weakly bound and free water is blurred: water molecules constantly and very quickly change from one state to another. In particular, the ^1H NMR method has proven that there is an active exchange between water molecules in bound and free states, at a rate of approximately one H_2O molecule every 10^{-9} s. In addition, the influence of the matrix should be taken into account: even a minimal change in the composition of the composite completely changes the hydrogen bond network. Therefore, the structuring of water in composites is interpreted mainly within the framework of model approaches.

3.3. Mechanism of hydrogels swelling

Hydrophobic interactions and the water binding effect in the composite form the basis of the internal structure of the gel and act as critical factors regulating the mass transfer kinetics of BACs. The decisive stage of hydrogel activation is the process of swelling of the polymer matrix, during which the absorption of free water leads to the transition of the system to a highly elastic state and the expansion of diffusion channels. This is the most important property of the hydrogel, which determines its ability to retain water.

The swelling mechanism is explained in terms of the balance between two opposing forces: osmotic pressure and the resistance of the polymer matrix to expansion. Osmotic pressure (π_o), arising from the affinity of hy-

drophilic groups for water and the difference in concentrations of mobile ions between the gel and the external solution (the Donnan effect) [28], is the driving force of the process that leads to water penetration into the matrix. As the matrix swells, the polymer chains stretch, reducing their entropy and creating a force that resists further swelling (elastic retractive force, π_e). The phenomenon is called "The Swelling Paradox" (swelling without dissolution): hydrophilic functional groups (e.g., –OH, –COOH) provide the thermodynamic driving force for water uptake (hydration), however, crosslinks (covalent bonds or strong physical interactions) form an interpenetrating network that prevents the separation of individual polymer chains, thereby preventing complete dissolution.

Equilibrium swelling is achieved when the osmotic tendency to swell is balanced by the elastic resistance of the polymer matrix to stretching according to equation (1):

$$\pi_{total} = \pi_o - \pi_e = 0, \quad (1)$$

where π_{total} is the total swelling pressure, π_o is the osmotic pressure, π_e is the elastic retractive force.

Among the factors influencing the degree of swelling of hydrogels, the following most important ones can be distinguished:

• crosslink density; higher crosslink density (shorter chains between the connections) creates a denser network with higher π_e, which leads to a lower equilibrium swelling coefficient;

• polymer-water affinity; the more hydrophilic the polymer (e.g., PEG (polyethylene glycol), PAA (polyacrylic acid)), the higher π_o, and the larger the equilibrium swelling coefficient;

• ionic charge; polyelectrolyte gels swell much more than neutral gels due to the Donnan effect, since fixed charges on the polymer chain attract counterions, creating a large osmotic pressure difference. For example, an anionic gel (PAA) will swell strongly at high pH because its –COOH groups ionize to $-COO^-$.

The key parameter that determines the kinetics and degree of swelling of hydrogels is the presence of ionic charge on the polymer chains. Depending on the presence and nature of ionogenic groups in the polymer matrix, hydrogels are divided into nonionic, anionic, cationic and amphoteric, which fundamentally determines the mechanism of their swelling: from simple diffusion solvation to a complex osmotic response to changes in pH and ionic strength of the environment in polyelectrolyte systems. It should be added that the electrical charge of the polymer matrix is crucial for interaction with biomolecules (proteins, cells) and for stimuli-responsiveness [28]. Anionic hydrogels contain negatively charged groups (e.g., $–COO^-$ in alginate, PAA), so, they swell at high pH. Cationic hydrogels contain positively charged groups (e.g., $–NH_3^+$ in chitosan) and therefore swell at low pH. Neutral hydrogels do not contain charged groups (e.g., PEG, PHEMA), their swelling is less sensitive to pH. Ampholytic (zwitterionic) hydrogels contain both positive and negative charges in the same chain (e.g., phosphatidylcholine-mimicking polymers).

It should be noted that traditional theories of swelling of network polymers (for example, the Flory-Renner theory) are limited by the assumption of a linear dependence of the resistance force of the chains on the degree of their stretching. However, the study of charged hydrogels has shown [29] that with significant swelling, the polymer network passes into a state of nonlinear elasticity, where the elastic resistance increases exponentially due to the limited extensibility of the chains (the effect of finite elongation). Therefore, the thesis of anomalous growth of the elastic force in the polymer matrix can be crucial for the accurate determination of the thermodynamic equilibrium point during swelling.

Unlike charged hydrogels, where the degree of swelling is determined by a complex balance between the ionic osmotic pressure and the elastic resistance of the network (according to the approach of Nakajima [29]), in neutral PHEMA/SiO_2 composites the equilibrium shifts towards the dominance of the elastic forces of the matrix. The introduction of nanosilica creates additional physical crosslinking nodes, which increases the elastic resistance of the system and limits its expansion even with high hydrophilicity of the chains. This ensures high stability of the geometric dimensions of the gel in environments with different ionic strength, where the absence of the osmotic component described by Nakajima for polyelectrolytes makes the material insensitive to salt concentration [29].

3.4. The effect of hydrophobic association of surfactants

In the study [13], an anti-swelling hydrogel with adaptability to various environments was obtained based on hydroxyethyl methacrylate (HEMA), methacrylamide (MAm),

1-ethyl-3-methylimidazolium trifluoromethanesulfonate (TFSI) in the presence of nanosilica and hydrophobic associative micelles formed by sodium dodecyl sulfate (SDS), sodium chloride and divinylbenzene (DVB) in a binary solvent of deionized water and ethylene glycol (EG). The addition of SiO_2 led to the compaction of the structure and the formation of a large number of hydrogen bonds with the amide group of MAm and the hydroxyl group of HEMA, but when the proportion of SiO_2 solution exceeded 50 %, the excessive number of physical crosslinking and entanglement points led to the uneven distribution of the hydrogel network structure. The aggregation of hydrophobic DVB/SDS micelles promoted the chain entanglement, so that water molecules could not enter the hydrogel in excessive amounts, which improved the anti-swelling properties of the hydrogel [30]. Due to the high crosslinking density and the balance of hydrophilic and hydrophobic segments, the resulting MHES (MAm/HEMA/Ethylene glycol/SiO_2) hydrogel had excellent anti-swelling properties. It could maintain a dynamic swelling equilibrium for 67 days in various solvents and solutions.

In addition, the hydroxyl groups of ethylene glycol formed hydrogen bonds with water molecules, using ethylene glycol and water as a binary solvent, converting free water into bound water, thereby providing the MHES hydrogel with antifreeze and water-retaining properties. The positively charged imidazole cations and negatively charged TFSI anions enhanced the MHES hydrogel with electrical conductivity. Such an environmentally adaptable hydrogel could be a promising candidate for application as flexible electronic sensors, demonstrating significant potential in various practical scenarios [31, 32].

Another hydrogel prepared in the presence of hydrophobic associative micelles formed by the hydrophobic monomer myristyl methacrylate and the cationic surfactant CTAB also exhibited excellent anti-swelling properties (equilibrium water swelling coefficient of 25 % after soaking in water for 15 days) [33]. Therefore, the main strategies to solve the swelling problem of hydrogels mainly include hydrophobic association, synergistic effect of hydrophilic-hydrophobic segment, and regulation of the internal network structure. One strategy for increasing the adaptability and versatility of hydrogels under extreme conditions is to add high concentrations of electrolytes (LiBr, for example), which disrupt the structure of hydrogen bonds of water molecules and make it difficult for the gel to freeze [34]; this also improves the mechanical properties (elasticity) of the gel (the material demonstrates ultra-high elongation of over 1500 %), ensures their ionic conductivity and extraordinary adaptability to the environment.

3.5. Effect of ionic strength and pH on swelling

The ionic strength of the medium has practically no effect on the degree of swelling of pure PHEMA/SiO_2 composites, since such a system is a non-ionic hydrogel. The structure of the polymer matrix does not contain carboxyl or other groups capable of ionization; therefore, the material does not have excess osmotic pressure due to the difference in the concentrations of counterions inside and outside the polymer network. Unlike polyelectrolyte gels, the swelling of PHEMA/SiO_2 is mainly due to the hydrophilicity of the –OH groups and the crosslinking density, so a change in the concentration of salts in the solution does not cause a noticeable compression or expansion of the hydrogel pores. Although the Si–OH groups on the silica surface can dissociate to form a negative charge, ($Si–O^-$), their contribution to the overall sensitivity of the composite to the ionic strength of the medium remains minimal due to the specificity of interfacial interactions in the PHEMA/SiO_2 system. Most Si–OH groups form strong hydrogen bonds with hydroxyl and carbonyl fragments of the polymer, which sterically and energetically hinders their ionization and limits the access of salt ions to them. In addition, the surface charge density of nanosilica at neutral pH values is insufficient to create a significant osmotic gradient of counterions that could overcome the mechanical resistance of the crosslinked PHEMA matrix. Thus, unlike classical polyelectrolyte gels, where a change in ionic strength causes a sharp compression of the network due to charge screening, in this composite the dissociation of Si–OH is only local in nature and does not lead to a macroscopic change in the degree of swelling.

The effect of pH on the swelling of a pure PHEMA/SiO_2 composite is usually insignificant, since the polymer matrix does not contain ionogenic groups capable of protonation or deprotonation. However, at high pH values (in an alkaline environment), partial deprotonation of Si–OH on the silica surface may occur, which somewhat increases the hydrophilicity of the

system, but in the physiological pH range such gels remain stable, and their volume practically does not change, which significantly distinguishes them from pH-sensitive systems based on acrylic acid. PHEMA becomes pH sensitive when ionogenic components, such as methacrylic acid (for sensitivity to an alkaline environment) or 2-(dimethylamino)ethyl methacrylate (for sensitivity to an acidic environment), are added to the composite during synthesis process [28, 29].

Thus, nanosilica plays a dual role in the swelling process: it increases the overall affinity of the composite for water as a superhydrophilic agent, but at the same time acts as a structural restraint preventing excessive swelling of the system. This approach allows you to use the advantages of high hydrophilicity for biocompatibility, while avoiding uncontrolled stretching of the polymer network and "explosive" release of substances (burst release). The optimal concentration of nanosilica to achieve an anti-swelling effect is 3–5 % (wt.); at lower values, the restraining framework is not formed, whereas exceeding this limit leads to excessive matrix rigidity, which blocks the diffusion of BACs.

Such a limitation of swelling ensures the stability of the tortuosity of the diffusion pathways, preventing critical straightening of the channels, which allows you to maintain a prolonged release mode of BACs even under conditions of full hydration of the composite. However, most hydrogel applications are limited to aqueous environments and are susceptible to degradation in highly acidic or alkaline conditions, rendering the hydrogel unable to maintain long-term stability. Therefore, the creation of structurally stable and elastic composites with antiswelling properties and environmental adaptability – so-called antiswelling composites – is becoming critically important.

4. Kinetics of BACs release from composites

4.1. Mathematical modeling

The kinetics of release of BACs from dosage forms is a determining factor in their therapeutic activity. The study of the kinetic parameters of BAC release is a complex task that requires a deep understanding of the release mechanism and the use of mathematical models to describe the process. By predicting the behavior of drug delivery systems, mathematical models help to control the conditions for the effective and safe use of drugs. Among the factors affecting the kinetics of the release of substances from complex dosage forms, in particular, hydrogel composites, we can distinguish factors associated with: 1) the properties of BACs (solubility, content, molecular weight, molecular size); 2) the characteristics of the polymer (nature of the polymer, degree of crosslinking of the polymer network, pore size, degree of swelling, presence of hydrophilic or hydrophobic fillers and pore formers); 3) external conditions (pH of the medium, ionic strength, temperature). There are a number of mathematical models, including the zero-order release model, the first-order release model, the Higuchi model, the Hickson-Crowell model, the Korsmeyer-Peppas model, the Baker and Lonsdale model, the Weibull equation model, the Hopfenberg model, the Gompertz model, the regression model, and the Gallagher-Corrigan model [35]. Each model relies on key factors and assumptions that determine the release kinetics from a particular system.

4.1.1. Zero and first order release models

The zero-order release model describes the process of continuous long-term release of a biologically active substance from a delivery system regardless of the concentration of the substance and is used for non-disintegrating dosage forms (tablets, transdermal patches, implantable devices, intraocular implants, infusion systems) [36, 37]. In the case of long-term release of drugs, for example, from polymer films, when the release mechanism depends on the concentration of the substance, the first-order release model is used. In such systems with a decreasing concentration gradient over time, the amount of released substance decreases according to the first-order kinetic equation (2):

$$lnC_t = lnC_0 - kt, \quad (2)$$

where C_t is the concentration of the substance at time t, C_0 is the initial concentration of the substance, k is the reaction rate constant.

The first-order release model is used to describe release from tablets, capsules, and matrix systems, when the drug is distributed inside the polymer matrix and gradually diffuses down the concentration gradient, with a large amount of substance being released at the beginning, and the rate rapidly decreasing over time. Systems whose kinetics are subject to this model include elastomeric pumps, for example, insulin pumps.

4.1.2. Higuchi model

For systems with controlled sustained release of the active ingredient through a solid or semi-solid insoluble matrix, when the release can be described according to Fick's law for planar diffusion in heterogeneous media, Higuchi proposed a model in which the release rate decreases due to the lengthening of the diffusion path of the molecule through the matrix in proportion to the square root of time, as defined in equation (3):

$$M_t = K_H \sqrt{t}, \quad (3)$$

where M_t is the cumulative amount of drug released from the base (ointment film in the Higuchi model) at time t, K_H is the Higuchi constant, t is the release time.

In this case, the diffusion rate at any given time is linearly dependent on the concentration gradient (Fick's law for steady-state diffusion). However, since the gradient decreases continuously due to the lengthening of the path that the molecules have to travel to the surface of the carrier, the total amount of substance released becomes proportional to the square root of time (unsteady-state diffusion). Therefore, the Higuchi model can be used to predict the release rate for systems in which the drug release profile changes with time, namely, for hydrogels, microspheres (or) microcapsules, implantable drug delivery systems, ointments, creams, and gels that release the drug by diffusion from the matrix [38].

Thus, the key difference between first-order release models and the Higuchi model lies in the mass transfer mechanism: first-order kinetics typically describe dissolution processes where the rate depends on the residual substance, while the Higuchi model focuses on the leaching of the active ingredient from an insoluble matrix through a diffusion barrier. In PHEMA/SiO_2 composites, silicon dioxide nanoparticles, in particular, play the role of physical barriers that limit excessive swelling and create a tortuous path for diffusion [39–41].

The Higuchi model has had a profound impact on the field of advanced drug delivery and continues to influence the work of numerous research groups around the world [42]. The model mathematically describes, in particular, the process of BAC release from an insoluble matrix, where silica nanoparticles play the role of physical barriers that limit excessive swelling and create a tortuous path for diffusion. The Higuchi equation allows one to very easily calculate drug release from fairly complex systems, but care must be taken not to violate any of the assumptions on which the equation is based [43]. The model is based on a "pseudo-steady-state approach" that requires a high initial excess of drug and a stationary interface (no swelling or dissolution of the base). The equations also assume that the limiting factor is the transport of drug through the base, and that the diffusion coefficient of the drug in the base is constant and independent of time or position within the base.

It should be noted that other types of controlled drug delivery systems governed by release mechanisms different from those discussed by Higuchi may also be characterized by a proportionality between the total amount of drug released and the square root of time, which has led to misinterpretations and incorrect applications of the Higuchi model. An accurate indicator of the adequacy of the Higuchi model should be the very specific physical meaning of the Higuchi constant described by equation (4):

$$K_H = A\sqrt{2C_{ini}DC_s}, \quad (4)$$

where C_{ini} is the initial concentration of the drug in the base, C_s is the solubility of the drug, D is the diffusion coefficient, A is the total amount of drug substance divided by the surface area of the film in contact with the skin.

In some cases, for example, in the diffusion release of a drug from a thin planar carrier, when the drug is initially homogeneously distributed at a concentration below the maximum solubility limit, the square root dependence of the transport on time can also be observed at the initial stage [43]. However, this short-term approximation to the Higuchi model is only valid for the first 60 % of the total drug release, and the release process is better described as pure diffusion according to Fick's second law. It is noteworthy that in both cases, a dependence of drug transport on time $t^{1/2}$ is observed. Regarding Fick's diffusion law in this approximation, it should be noted that the diffusion coefficient is considered to be independent of concentration. Although this assumption is not conceptually correct, it is used to simplify the calculations.

In [43], a selective review of the different forms of the diffusion coefficient for different types of carriers is given and ways are discussed to improve the predictive power of the Fick diffusion theory in order to take into account the

dependence of the diffusion coefficient on concentration.

4.1.3. Korsmeyer-Peppas model

The Korsmeyer-Peppas theory is used, in particular, to describe drug transport in highly swollen, nonporous hydrogels, where drug release requires swelling (or) diffusion in the polymer matrix [44]. It offers a theoretical model that accurately predicts drug diffusion coefficients through the polymer matrix. The model is based on the free volume of the polymer matrix, assuming that the free volume of the polymer is the same as the free volume of the solvent. Over the years, the model has been modified for moderately, weakly swollen [45] and semi-crystalline hydrogels [46].

The model is based on the equation (5):

$$\frac{M_t}{M_\infty} = kt^n, \quad (5)$$

where M_t is the amount of drug released at time t; M_∞ is the total amount of drug available for release; k is the release rate constant; n is the release rate. In this equation, k is a parameter that includes geometric and structural characteristics of the matrix, while the exponent n is associated with the mechanism that controls the release kinetics.

In particular, for cylindrically shaped systems, as described in [47], the value of the release exponent n lies in certain intervals according to the expected release mechanisms. Namely, $0<n<0.45$ corresponds to hindered Fickian diffusion; $n=0.45$, Fickian diffusion (Case I), representing first-order kinetic where diffusion is the main release mechanism; $0.45<n<1$, anomalous transport characteristic of cases when, in addition to diffusion, other mechanisms also contribute to the drug release; $n=1$, non-Fickian transport (Case II) corresponding to zero-order kinetic and typical of kinetics governed by phenomena of polymer degradation and relaxation or degradation/dissolution of monolithic systems (tablets); $n>1$, super case II occuring where severe modifications in the matrix take place.

An analysis of mathematical models of drug release from various nanostructured systems showed that the power law model (Korsmeyer-Peppas model) is well suited to describe drug release from hydrogels [48]. This model is also used for systems in which release occurs by several kinetic mechanisms, or when the release mechanism is unclear [49]. It should be noted that the Korsmeyer-Peppas model shows the release behavior only for the first 60 % of the drug release [50].

Interpretation of the values of the exponent of the Korsmeyer-Peppas equation allows us to assume one or another release mechanism: $n\leq0.45$, Fickian diffusion (Case I diffusional); $0.45<n<0.89$, anomalous (non-Fickian) diffusion; $n=0.89$, zero order release (Case II transport) (controlled by relaxation of polymer chains); $n>0.89$, super case II transport (the accelerated release mechanism often associated with strong swelling or erosion of the polymer).

Despite the variety of approaches in the application of mathematical modeling of release, the Korsmeyer-Peppas model remains the most versatile tool for identifying the release mechanism from the calculated diffusion index [48].

In [41], diclofenac sodium was loaded as a model drug for release from PHEMA and cationic hydrogel p(HEMA-co-APTMACI) based on 3-acrylamidopropyltrimethylammonium chloride. The release index n was 0.84 for the PHEMA hydrogel and 0.76 for the p(HEMA-co-APTMACI) hydrogel, indicating a non-Fickian drug release mechanism for both hydrogels [51].

In mathematical modeling for the development and optimization of drug delivery systems, the choice of an appropriate model depends primarily on the geometry of the carrier and the nature of the polymer matrix [35]. Thus, the Baker-Lonsdale model was used to describe the release from spherical matrices (microcapsules), the Weibull model offered a universal empirical equation for the analysis of complex and non-standard dissolution profiles, the Hopfenberg model was a tool for predicting kinetics in reservoir systems with a constant surface area, the Gallagher-Corrigan model was justified for describing biodegradable systems, where the release depends simultaneously on diffusion and polymer degradation.

Today, the main challenge facing scientists is the development of mathematical models that simultaneously combine theories describing the phenomena of drug release and their effects during transportation to the human body. In other words, it is not easy to define models that take into account both diffusion phenomena and the cellular uptake reaction. The authors of a review of the ten most widely used drug delivery models developed or modified over the years showed that the frequency of use of the Higuchi and Korsmeyer-Peppas models is 33 and 27 %, respectively [52].

4.1.4. Approaches to predicting the diffusion coefficient of drugs

Given that most mathematical models assume that the diffusion coefficient is independent of concentration, release kinetics in complex matrices requires refinement of approaches to predicting diffusion parameters. To account for the physical limitations of diffusion in hydrogels, a number of attempts have been made [53] that take into account the structural characteristics of the polymer carrier. One approach, borrowed from the field of chemical engineering for transport phenomena in porous rocks and ion exchange resins, which are similar to drug diffusion through macro- or microporous polymers, proposes to replace the diffusion coefficient of the drug in the polymer, D_{ip} ("in polimer"), with the effective diffusion coefficient, D_{eff}, which depends on the concentration of the drug substance, to solve the Fick equation. In this case, the form of the concentration dependence of the diffusion coefficient is determined by the structural characteristics of the polymer carrier and is described, for instance, by equation (6):

$$D_{eff} = D_{ip} K_p K_r \frac{\varepsilon}{\tau}, \qquad (6)$$

where ε is the porosity, or pore volume fraction, which is a measure of the volume of pores available for diffusion; τ is tortuosity factor, which describes the geometric characteristics of the pores; K_p is the equilibrium partition coefficient, which, in the case where the drug is soluble in a polymer matrix, is determined by the ratio of its concentration inside the pore to the concentration outside it; K_r is a parameter describing the fractional reduction in diffusion within a pore when the solute diameter d_s is the commensurate in size with the pore diameter d_r.

In one of the semi-empirical equations for the diffusion of spheres through porous media, proposed by Faxen [43], the parameter λ (the ratio of the radius of the preparation, r_s, to the average pore radius, r_p) is used as a factor in the influence of the structural characteristics of the polymer on diffusion:

$$\frac{D_{ip}}{D_b} = (1-\lambda)\left(1+\alpha\lambda+\beta\lambda^3+\gamma\lambda^5\right), \qquad (7)$$

where D_{ip} and D_b are the diffusion coefficients of the sphere through the pore and in the volume, respectively; α, β and γ are constants.

As can be seen from the equation, as the size of the drug decreases relative to the pore size, the ratio D_{ip}/D_b approaches unity. However, a key structural factor used in numerous scientific works to correct theoretical models of drug release in real porous media is tortuosity.

One modification of the Higuchi equation, for example, can be adapted for systems of various shapes and geometries, in particular for a porous matrix saturated with a drug, taking into account the porosity and tortuosity coefficients [52]. However, all coefficients – diffusion, tortuosity and porosity – are considered constant and constitute the physical content of the Higuchi constant, K_H, according to equation (8):

$$\frac{M(t)}{M_\infty} = \sqrt{\frac{2C_0 D\varepsilon t}{\tau\pi}} = K_H\sqrt{t}, . \qquad (8)$$

where C_0 is the initial (or introduced) drug concentration.

This modified equation states that the fraction of drug released is proportional to the square root of the release time, and it is interesting to note that the release is directly proportional to the porosity and inversely proportional to the tortuosity factor.

Thus, there are essentially two effects that contribute to the reduction of the diffusion coefficient. First, since the drug cannot pass through the solid phase of the matrix, the cross-sectional area available for diffusion is proportional to the porosity factor ε (ε <1), and therefore the diffusion coefficient is reduced. Second, the pore channels are generally not straight, and the drug molecule needs to diffuse a longer distance on average to pass through the porous medium. The increase in path length can be taken into account by reducing the diffusion coefficient by the tortuosity factor τ. Taking both effects into account, the effective diffusion coefficient is often defined as in equation (9) [53]:

$$D_{eff} = D\cdot\frac{\varepsilon}{\tau} \qquad (9)$$

4.1.5. Tortuosity effect

It should also be taken into account that in addition to the structural characteristics of the polymer (porosity and pore size), the filler of the polymer matrix, in particular, nanosilica, whose particles form a "labyrinth" that enhances the "tortuosity effect" [21], contributes to the creation of additional steric hindrances for the release of BACs. Thus, due to geometric limitations, the actual distance that the BACs molecule overcomes before leaving the matrix becomes much greater than the thickness of the hydrogel film or the porous layer of the matrix. On the one hand, this allows for pro-

longed release of BACs molecules, and on the other hand, the degree of their release into the external environment can be reduced. This fact suggests that it is precisely through the "tortuosity" of the diffusion path that the time of drug release can be regulated: the more silica, the longer the path and the slower the release of BACs.

To take into account the effect of tortuosity in modeling diffusion processes, it is worth clarifying the physical meaning of the tortuosity coefficient and its relationship with the porosity and filler content in the matrix. Therefore, the tortuosity coefficient can be quantitatively estimated according to equation (10):

$$\tau = \frac{\Delta l}{\Delta x}, \quad (10)$$

where Δl is a real path of the molecule, Δx is the film thickness or the thickness of the layer that a molecule must overcome to get out (geometric straight path). Thus, the tortuosity value shows that the path of the molecule is lengthened by τ times.

Sometimes the tortuosity coefficient is defined as the square of this ratio, as defined in equation (11):

$$\tau = \left(\frac{\Delta l}{\Delta x}\right)^2, \quad (11)$$

which is also an experimentally confirmed approximation for calculating the effective diffusion coefficient.

Theoretical models usually outline the limits of using the tortuosity coefficient in the form of conditions satisfying the inequality (12) [54]:

$$\tau^2 \geq 1, \quad (12)$$

which simply means that the actual (average) path traveled by a molecule during diffusion in an interstitial fluid in a porous medium is longer than in the absence of a solid (matrix).

Secondly,

$$\lim_{\varepsilon \to 1} \tau = 1, \quad (13)$$

that is, in the absence of any (impermeable) solid, there are no obstacles to diffusion (in the original article, porosity (ε) is denoted by φ). Finally, $\tau \to \infty$ if and only if $\varepsilon \to 0$; that is, the tortuosity is finite for all non-zero values of porosity, so the obstacle is complete only when the pore space disappears. Porosity is then defined as the fraction of the volume of the system available for liquid diffusion.

A critical review of various empirical and theoretical models integrating the tortuosity coefficient into the diffusion coefficient for systems with solid particles has shown that one of the attempts to scale the diffusion coefficient along with the tortuosity is expressed by equation (14) [54]:

$$d_{\mathrm{m}}^{'} = \frac{d_{\mathrm{m}}}{\tau^2}, \quad (14)$$

where $d_{\mathrm{m}}^{'}$ is the scaled diffusion coefficient, d_{m} is the diffusion coefficient of a substance in the medium in the absence of matrix segments.

For the case where the tortuosity coefficient is determined by the square of the ratio $\left(\Delta l / \Delta x\right)^2$, the equation for scaling the diffusion coefficient taking into account the the tortuosity can be written as equation (15):

$$d_{\mathrm{m}}^{'} = \frac{d_{\mathrm{m}}}{\tau}. \quad (15)$$

It is obvious that these two equations for the effective diffusion coefficient ($d_m^{'}$) taking into account the tortuosity effect are equivalent.

Unlike ε, the parameter τ cannot be measured directly, but it has been shown that τ depends on ε. A collection of theoretical tortuosity-porosity relations satisfying the above conditions is presented in [54], with remarks on the type of physical system for which the relation is derived. Among them there are a number of equations relating the tortuosity coefficient to porosity, for example, equation (16):

$$\tau^2 = F\varepsilon, \quad (16)$$

where F is a form factor or structure factor that quantitatively describes how complex pore geometry (tortuosity) and porosity reduce the ability of a substance to diffuse or conduct electrical current through the material compared to a free liquid.

Another attempt to relate porosity and tortuosity is expressed by equation (17) [54]:

$$\tau = \varepsilon^{-\frac{2}{3}} \quad (17)$$

One of the well-known mathematical models of diffusion through porous electrodes with a high filler content used the Bruggeman equation (18) to estimate the tortuosity [55]:

$$\tau = \varepsilon^{-\alpha}, \quad (18)$$

where α is the Bruggeman index.

Knowing α, one can predict the tortuosity for a given porosity. The theory uses the Differential Effective Medium (DEM) approximation and offers a software tool to predict the Bruggeman index based only on the knowledge of the shape and orientation of the filler particles.

4.1.6. The relationship between tortuosity and filler volume fraction

It should be noted that tortuosity is not only the "walls" of the labyrinth, but also the zones of the compacted polymer around the silica particles, where diffusion becomes even slower. It is obvious that with increasing silica content, the free volume for diffusion decreases, however, based on a number of theoretical models, this dependence is nonlinear [56]. The main idea based on obstacle geometry is that the filler forces molecules to bypass solid particles, thereby lengthening their path, while diffusion depends on the geometric shape, polydispersity, orientation, type of packing, mode of addition and distribution of filler particles in the polymer matrix; all these factors can be taken into account using the mathematical modeling proposed in the work [56].

The classical Maxwell model, originally developed for the electrical conductivity of liquids, is ideally suited for diffusion in media with a low concentration of spherical obstacles (typically up to 20 % i.e., a volume fraction of dispersed filler φ_d <0.2). The model is based on the solution of the Laplace equation for the potential flow around a sphere and assumes that the filler particles are far apart and do not interact. The relationship between tortuosity and filler volume fraction is given by the equation (19):

$$\tau = 1 + \left(\frac{1}{2}\right)\varphi_d \qquad (19)$$

According to one of the first tortuosity models for predicting permeability in composite films, the tortuosity path is considered to be the longest distance traveled by a gas molecule diffusing through the entire thickness of the film, and for the appropriate geometry of the system, the tortuosity equation takes the form of equation (20) [57]:

$$\tau = 1 + \left(\frac{L}{2W}\right)\varphi_d, \qquad (20)$$

where L and W are the length and thickness of the filler plates.

The ratio L/W is called the aspect ratio (α). It is usually used as a characteristic geometric parameter of the filler to describe the reduction in gas flux through a composite film. The model is a function of the filler volume fraction and the aspect ratio.

To predict the permeability of composite films containing periodically arranged cylinders of infinite length and oriented parallel to the film surface, an even simpler equation has been proposed that is similar to the Maxwell model equation, namely, equation (21):

$$\tau = 1 + \varphi_d \qquad (21)$$

This approach is useful because at low filler concentrations (φ_d <0.2) the influence of the shape and size of the filler particles on the tortuosity effect can be considered significant.

Analysis of mathematical modeling of drug release from inert matrix systems has shown that overall drug release is the result of the combined effect of processes occurring at many different points along the pathway; therefore, drug release can be considered as a multiscale process. For inert porous matrices, modeling of the pore network can provide effective diffusion coefficients based on the pore structure (porosity, pore size distribution, and tortuosity), which can then be used in models of the overall release process [53].

4.2. The influence of external factors on the release of BACs

The study of the influence of external factors on the release of BACs showed that contact with electrolyte solutions can significantly affect non-covalent interactions in the composite. If the DCM cation and electrolyte ions compete for active centers at the interface ($Si–O^-$ groups or carbonyl groups of PHEMA), this may cause a charge screening effect: electrolyte ions weaken the electrostatic attraction between the polymer matrix and the DCM cation, which can facilitate its desorption. The presence of an electrolyte in the environment can significantly change the swelling kinetics of the polymer matrix, in particular, reduce the degree of its swelling, which will affect the diffusion of BACs.

This approach to explaining the mechanisms of BACs release into electrolyte solutions allows us to make an assumption about the mutual influence of two processes – ion exchange between the environment and the matrix and the electrostatic interaction of BACs ions and the electrolyte with the surface. It has been shown [58] that the release of BACs, in particular ibuprofen and diclofenac as weak electrolytes, from PHEMA-based hydrogels into phosphate buffers with pH 5.8 or 8.0 or NaCl solutions is stimulated by competition with ions of the medium; accordingly, during the first hours of the experiment, intensive diffusion of BACs into the medium is observed. This fact confirms the assumption about the predominant ionic nature of the bond between BAC molecules and

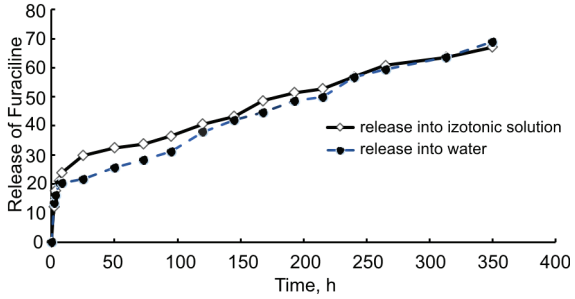


Figure 7. Release kinetics of furacilin from the polymer composite (adopted from [6]).

the silica surface. Competition of Na^+ ions for surface sorption centers (Si–O^- groups) can increase the lability of DCM/SiO_2 sorption complexes under isotonic conditions. When the pH decreases to 4.0–5.0, an increase in DCM release is observed. This is explained by the protonation of surface groups of silica, which leads to neutralization of the negative charge of the surface and weakening of the electrostatic attraction of DCM cations. At the same time, the preservation of hydrophobic interactions and the high polymer density of PHEMA-based hydrogels contribute to the maintenance of prolonged release of BACs for at least 24 hours; this allows the development of hydrogel-based delivery systems with a predicted release rate [58].

The assumption about possible competition of environmental ions for surface sorption centers correlates with data on the release of metronidazole and furacilin (nitrofural) (Figure 7), which, unlike DCM, are not ionized. The difference in the degrees of release, in particular, of furacilin into water and into an isotonic solution is small and has a random nature [6].

The effect of pH on the release of BACs from PHEMA composites remains undoubtedly critical and not fully understood. When the pH changes, the degrees of ionization of both the silica surface and the BACs molecules can change. In an acidic environment, the silica surface is poorly ionized, which weakens the electrostatic interaction of DCM with the surface and should promote the diffusion and release of BACs from the composite. In alkaline media, deprotonation of Si–OH groups of silica occurs, which can enhance the electrostatic interaction of DCM with the surface and slow down the diffusion of BACs. Issues such as the silica content at which the kinetics of BAC release from composites becomes pH-sensitive, as well as the contribution of ion exchange between the silica surface and the environment to this process depending on pH, require further clarification or experimental confirmation.

5. Interaction with the biological environment: formation of a "protein corona"

This aspect is becoming increasingly important in the field of medical device development, especially in view of their interaction with biological fluids. When the composite (PHEMA/SiO_2) comes into contact with wound exudate, instant adsorption of proteins (albumins, globulins) occurs, which leads to transformation of surface charges and pore architecture [59]. Thus, nonspecific adsorption of proteins with the formation of a protein corona becomes a key problem of biocompatibility of hydrogels, which changes the biological identity of the material and promotes the primary adhesion of microorganisms. The main reason for this phenomenon is the local hydrophobicity of PHEMA chains. Uncontrolled formation of a protein corona due to denaturation of proteins on hydrophobic areas of the surface creates an adhesive layer favorable for the attachment of bacteria. This leads to the recognition of the material as a foreign body, provoking the launch of inflammatory or immune processes or biofouling (nonspecific bioclogging) of the composite material [60, 61], which, in particular, is a critical drawback of hydrogel contact lenses.

Minimizing nonspecific adsorption ensures stable diffusion of biologically active substances through the open pores of the hydrogel, preventing blockage of the exit channels by biological plaque. An effective approach to solving this problem is to increase the hydrophilicity of the surface by introducing nanosilica. This contributes to the formation of a thermodynamically stable layer of energetically bound water due to strong hydrogen bonds. The hydrated shell acts as a physical barrier that prevents direct contact of biomolecules with the polymer matrix, preventing their adhesion and subsequent colonization by microorganisms.

It has been experimentally confirmed that the introduction of nanosilica at a concentration of 7 % into the material of contact lenses based on PHEMA provides a level of hydrophilicity sufficient to reduce the adsorption of lysozyme and bovine serum albumin by 65 and 57 %, respectively. At the same time, bacterial adhesion is reduced by 59 and 66 % compared to pure PHEMA hydrogel [62]. The formation of covalent Si–O bonds between nanoparticles and the polymer network was confirmed by IR and energy-dispersive X-ray spectroscopy

methods. The superhydrophilic composite PHEMA/NSCC (Nanosilica Covalent Coating) developed by the authors is a promising material for contact lenses with high resistance to tear fluid components and microorganisms.

Despite the effectiveness of nanosilica in improving the hydrophilicity of the polymer matrix, the issues of mechanical properties and long-term stability of the coatings remain challenging. Systematic studies in this field [63] show that a promising approach to increasing the stability of hydrophilic coatings may be a combination of oxygen plasma surface treatment and layer-by-layer self-assembly of polyelectrolyte and nanosilica. The formation of a nanosized coating by alternately applying layers with opposite charges – positively charged polyelectrolyte and negatively charged nanosilica particles – provides high thermodynamic stability of the hydrophilic layer due to the strong electrostatic attraction between the components, which allows you to reliably screen the local hydrophobicity of PHEMA and prevent uncontrolled adsorption of proteins.

It should be taken into account that when PHEMA/SiO_2 composites come into contact with a biological environment, the interaction of silica nanoparticles with proteins makes a significant contribution to the formation of a protein corona, affecting the functionality of the composite in biological environments. Comprehensive analysis using SAXS (X-ray scattering) and DLS (dynamic light scattering) reveals structural features of the protein–nanoparticle association, improving methods for characterizing hybrid systems [64].

Further investigation of how the protein corona modifies the diffusion pathways of BACs is key to predicting therapeutic response *in vivo*. Importantly, the protein corona evolves as nanoparticles traverse different microenvironments, leading to unpredictable biological behavior. A study [65] showed how physiological pH transitions affect protein corona dynamics, cellular uptake, and inflammatory responses. Understanding how changes in physiological conditions, especially pH changes associated with tumor targeting, affect protein corona composition and subsequent biointeractions is important for the biological fate and therapeutic efficacy of nanomedicines.

The presented analysis of protein corona formation allows modeling the biological behavior of composites as a whole – from nonspecific deposits on contact lenses to targeted drug delivery to tumors and use in purulent-inflammatory processes. In such cases, to predict the therapeutic efficacy of the material, it is extremely important to take into account the phased nature of the wound healing process and the physiological conditions of the environment. It should be noted that the therapeutic efficacy of composites in the treatment of purulent-inflammatory processes directly depends on the dynamics of the wound process, which is classically divided into three main phases: inflammation (exudation), proliferation (regeneration) and remodeling. Each phase is characterized by a unique proteomic profile of the exudate, which radically changes the composition of the protein corona on the surface of the composite. In terms of their drainage and kinetic properties, the developed materials are focused on the first phase of the wound process (inflammation and exudation), which requires intensive drainage of excess biological fluids and controlled release of BACs to suppress pathogenic microflora. The formation of protein corona is also significantly affected by environmental conditions, such as pH, ionic strength, temperature and protein concentration, while not only the identity of proteins, but also their conformation and orientation change [66].

It should be noted that the route of administration of nanomedicines for which they are intended also differs depending on the type of disease. As a result, nanomedicines can enter and pass through various biological environments. One important physiological parameter is pH, which varies depending on the location in the body and even on the location in the cell [67]. In addition, the pH of the environment varies depending on the stage of the disease. For example, the extracellular environment of malignant tumors is slightly acidic (pH 6.5–6.9), while tissues under normal physiological conditions are slightly alkaline (pH 7.2–7.4) [68]. The local environment in bacterial infections is also acidic [69], but the pH of the wound surface changes significantly after trauma compared to intact skin with its slightly acidic pH (4.0–5.5) [70]. The wound environment can become alkaline or acidic during the healing process, depending on the pathophysiology of the wound. At the initial stage of an acute wound, as a result of cell lysis and hypoxia, the environment is slightly acidified. However, when the process becomes chronic or when a pronounced bacterial infection develops, the pH of the wound surface shifts to the alkaline side (7.2–8.9), which

is a marker of persistent inflammation and delayed healing, while the gradual restoration of a slightly acidic profile indicates successful tissue regeneration [70].

Therefore, protein binding to the composite surface and protein structure change in response to pH, which can significantly alter the stability and biological activity of the composite [70]. Protein adsorption is best at its isoelectric point (pI) because electrostatic repulsion and protein–protein interactions are minimized, allowing compact protein molecules to pack tightly on the nanoparticle surface. Along with pH, ionic strength is an important parameter that significantly affects the architecture and biological activity of the protein corona. Ionic strength varies depending on location, for example, in blood it is 150 mM, and in bile it is 3–15 mM [66]. Therefore, understanding the role of pH and ionic strength in the formation and conformation of the protein corona is critical and should be considered during the development of nanomedicines.

To bridge the significant gap between experimental studies and clinical applications of nanomedicines, more and more studies are devoted to studying the influence of the protein corona on the biological functionality of nanoparticles. Conformational changes in the protein corona induced by nanoparticles can cause undesirable effects, such as induction of unwanted immune responses, disruption of enzyme activity, and reduction of colloidal stability of nanoparticles. At the same time, this can be used for therapeutic purposes, which may be a new era for preventing cancer progression or improving tissue regeneration [66].

Such a strategy can be used for cancer immunotherapy or even immunomodulated wound healing [71]. Although nonspecific adsorption of proteins initially "closes" the pores of the composite for the release of compounds, a controlled change in the conformation of the protein corona upon pH change (e.g., to pH 8 in alkaline wounds) transforms the protein corona from a barrier to an active transport element. This opens up the possibility of not just "releasing" drugs, but using the body's own proteins, bound to silica nanoparticles, to target metastasis, fibrosis, and wound healing. The understanding that a change in pH by just 0.5–1.0 units can radically change the status of the protein corona from "immunogenic" to "regenerative" makes the pH-sensitive composite (PHEMA/SiO_2) an ideal tool for such subtle modulation.

6. Current trends in the development of biomedical nanocomposites

The search for the most promising functional composites for targeted transport and controlled release of biologically active compounds has led to the rapid development of innovative trends and technologies [72–76].

6.1. Design of Multi-Responsive/Stimuli-Responsive Systems

Modern hydrogels are no longer simple inert sponges: they are designed to be "smart" or "intelligent", dynamically responding to environmental signals such as pH, temperature, light or certain biomolecules. In the field of creating such systems, a profound paradigmatic shift has occurred from "mono-sensitive" (pH-Responsive) to "multi-sensitive systems" (Multi-Responsive Systems) − hydrogels that respond not to a single factor (pH only), but to a combination of triggers characteristic of the pathological process, such as, for example, "pH/Temperature" (release is activated by an increase in wound temperature (inflammation) and a change in acidity) [72, 73]. This concept of the development of biomedical materials, in particular for the treatment of burns and wounds, shifts scientific interest towards the creation of Smart & Responsive Systems [77], which are able not only to respond to changes in the acidity of the environment, but also to adapt the kinetics of the release of BACs to the dynamic conditions of the inflammatory process, imitating the principles of biological feedback [78].

Over the past decade, the greatest efforts in the field of creating "smart" systems have been directed at the development of biomaterials for tissue engineering and regenerative medicine that respond to various stimuli (Stimuli-Responsive Hydrogels) [79, 80]. One of the main challenges in the application of tissue engineering is the development of biomimetic materials that can reproduce all the natural properties and functions of the extracellular matrix (ECM). This includes biocompatibility, the ability to support cell functions and behaviors such as cell signaling, adhesion, migration, proliferation, and differentiation, which are strongly regulated by the surrounding ECM. [81–83] These cell-matrix interactions are highly dynamic and remain challenging to reproduce, combining cells with traditional hydrogel-based biomaterials that lack adaptability. To dynamically tune the properties of biomaterials and thus bridge the gap with

true extracellular matrix (ECM) analogues, innovative stimuli-responsive smart hydrogel scaffolds are currently being developed. These stimuli-responsive hydrogels can respond to small changes in their microenvironment with highly specific changes in properties [84]. Dynamic changes can be triggered by a wide variety of signals, such as physical (temperature, light, sound, electric or magnetic fields [85]), chemical (pH, ionic strength or humidity) or biological (proteins, cells or enzymes [86–88]), as well as a combination of these factors. The examples of sensitivity of hydrogels to "stimuli" are the following:

pH-sensitivity

The mechanism of pH-sensitivity of hydrogels is related to the polyelectrolyte nature of hydrogels [85, 89]. Anionic gels (with –COOH groups) protonate and collapse at low pH. As pH increases, these groups are deprotonated ($–COO^–$), increasing charge repulsion and causing swelling. For example, a gel containing polyacrylic acid swells in the alkaline environment of the intestine (the –COOH groups are deprotonated to – $COO^–$, resulting in increased electrostatic repulsion), but remains folded in the acidic environment of the stomach. This is ideal, for example, for targeted drug release in the intestine (basic pH) instead of the stomach (acidic pH) [90, 91].

Cationic gels (with $–NH_2$ groups) do the opposite, swelling at low pH when protonated to $–NH_3^+$ [92].

Thermosensitivity

A gel, such as poly(N-isopropylacrylamide) (PNIPAAm), swells below ~32 °C and collapses above this temperature. This could be used for injectable drug delivery at temperatures close to body temperature [28]. The mechanism of thermosensitivity is determined by the lower critical solution temperature (LCST). For "smart" gels, this is the point at which their state switches: below the LCST, the polymer chains are hydrophilic (an ordered hydrated shell is formed), the gel absorbs water and swells; above the LCST, the polymer becomes hydrophobic (the entropic factor destroys hydrogen bonds between water and the polymer, which stimulates the strengthening of hydrophobic interactions in the polymer), expels water and sharply contracts (collapses).

Photosensitivity

A hydrogel with embedded photosensitive chromophore molecules (e.g., spiropyran, azobenzene) can swell or contract with ultra-precise spatiotemporal control using specific wavelengths of light, allowing for the fine control of microfluidic valves or the study of cell mechanics. Moreover, light-activated methods are increasingly based on visible light sources instead of ultraviolet radiation to avoid cell damage [93].

Bioreactivity

A hydrogel with immobilized enzymes or molecularly imprinted networks can respond to certain biomarkers. A classic example is an insulin delivery gel that responds to glucose and swells in the presence of high glucose levels, releasing insulin.

In this context, filling PHEMA matrices with functionalized nanosilica can serve as a powerful tool for programming such reactions, since silanol groups on the silica surface actively participate in modulating the sensitivity of the network and the interaction of the drug with the matrix.

6.2. Methods for Dynamic Modeling of Hydrogel Behavior

Traditional methods for designing hydrogels involve a tedious experimental process to determine the appropriate parameters, properties, and functionality of hydrogels. Computational approaches, including molecular dynamics simulations and advanced machine learning techniques, serve as powerful tools for investigating the physical and chemical interactions within hydrogels. Computational methods such as Density Functional Theory (DFT), Finite Element Analysis (FEA), Multiphysics Models, Molecular Dynamics (MD), and Computational Fluid Dynamics (CFD) enable rapid digital prototyping of materials and prediction of the behavior of stimuli-responsive hydrogels under the influence of external factors [94]. This paper presents a large selection of machine learning methods that have become powerful tools in the development of hydrogels.

The central idea of the DFT method is to use the electron density as a fundamental variable used to calculate the properties of a material, including the chemical interactions between the hydrogel network and its environment, as well as its mechanical properties. DFT can help to understand the dynamics of water absorption and diffusion, as well as how water

molecules are distributed in the polymer network. In the case of silica-filled hydrogels, DFT modeling can play a crucial role in calculating the hydrogen bonding energy between water molecules, the PHEMA matrix and the active silanol groups on the nanosilica surface, which directly controls the swelling of the matrix.

FEA is a computational method used to approximate the behavior of complex structures and systems by breaking them down into smaller, simpler parts called finite elements. The method predicts the characteristics and response of materials under different conditions and is ideally suited for modeling the swelling of hydrogels in response to different environmental conditions.

The method of MD simulation is used in materials science to study the molecular structures and properties of materials at the atomic level, and is particularly useful for studying diffusion in hydrogels to simulate the effect of "twisting" in real time. This method allows us to study in detail the mechanisms of BACs release from hydrogels at different degrees of crosslinking and bound water content.

Computational hydrodynamics based on discretization of the governing equations of hydrodynamics offers numerical methods for analyzing and predicting fluid flow, which for hydrogels can help optimize processes such as mixing and solidification, as well as predict the impact of scaling up hydrogel production.

6.3. Advanced methods for hydrogel fabrication

Topological engineering, used as a general strategy in the materials science of hydrogels, among the most current trends offers the design of so-called hierarchical structures from the nano- to macroscale, in particular, using three-dimensional (3D) printing. 3D printing technology is being widely investigated for the rapid design and production of hydrogels required for complex soft structures and devices.

Hydrogels are soft, viscoelastic materials consisting of 3D crosslinked polymer networks swollen by a solvent. 4D bioprinting adds time as a factor, where structures change their shape, behavior, or function over time in response to external stimuli such as temperature, pH, light, moisture, electric or magnetic fields. Hydrogels as basic bioinks are ideally suited for 4D bioprinting due to their high water content, biocompatibility, tunable mechanical and chemical properties, and responsiveness to stimuli.

Advanced strategies for fabricating such gels include [95, 96]:

- multi-material printing, where different hydrogels are printed in layers or zones to create regions with different responses;
- photocrosslinking techniques, where light is used to crosslink gels in precise areas for tunable stiffness and degradation;
- embedded printing, which consists of printing into a support medium to provide complex, unsupported geometries;
- shape memory integration, where hydrogels with shape memory properties return to a programmed shape upon stimulation.

In recent years, a number of exclusive, highly efficient and precise hydrogel synthesis technologies have been introduced, such as the droplet microfluidics method for the creation of polymer hydrogel particles [97]. This technique offers unprecedented control over various aspects of the particles, including their size, shape, functionalization, compartmentalization, and mechanics, which are difficult to achieve with other processing methods. Such efficient technologies also include the formation of core-shell structures in hydrogels [98]. Importantly, organic/inorganic systems such as PHEMA/nanosilica are perfectly suited for these advanced processing techniques, where the addition of the nanoreinforcement allows for the fine-tuning of rheological properties, viscosity, and structural integrity required for precise microfluidic and printing applications.

In the past few years, data-driven science, through the innovation of various algorithms and computational capabilities, has proposed the use of artificial neural networks (ANNs) to facilitate the investigation of the relationship between processing, structure, properties, and performance of materials [99]. Artificial neural networks are a real, active field of computer modeling in the materials science of hydrogels, based on the analysis of hundreds of experiments. The authors of the work showed that forming a database of scientific articles using ANNs allows creating algorithms for effectively predicting swelling and drug release profiles from hydrogels. Ultimately, applying these data-driven computational models to multicomponent silica-filled networks represents the next frontier, enabling the precise prediction and optimization of controlled release kinetics of BACs from functionalized PHEMA/nanosilica biomaterials.

7. Conclusions

Theoretical analysis of the mechanisms of binding and release of biologically active compounds from composites based on PHEMA and nanosilica allowed us to outline the boundaries of dominance of different types of intermolecular interactions between matrix components and the biological environment. It was established that the mechanism of release of biologically active compounds is determined by diffusion-controlled processes, the parameters of which directly depend on the structural characteristics of the polymer matrix and the properties of the environment. Research into the effectiveness of pH-sensitive systems based on polymer composites for directed transport and controlled release of biologically active compounds is the basis for the development of the next generation of biomedical materials: Multi-Responsive Systems and Smart&Responsive Systems. Such nanotechnological solutions will allow us to simulate biological feedback, adapting the therapeutic effect of the composite to dynamic changes in the area of inflammation, pathological focus or affected tissues of target organs in real time.

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