

THE STRUCTURE AND IMMOBILIZATION ACTIVITY OF POLYVINYLPIRROLIDONE CROSS-LINKED COPOLYMERS

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Relations between synthesis conditions, structure and sorption-desorption properties of polyvinylpyrrolidone cross-linked copolymers have been investigated.

The development of drugs prolonged and directed release systems is one of main directions in pharmaceutical and medical branches. Such systems allows to transfer medical substance directly to the active medium, as well as essentially reduces its one-time therapeutic doze [1]. Polymeric hydrogel carriers based on cross-linked copolymers of polyvinylpyrrolidone (PVP) with methacrylic esters, 2-hydroxyethylmethacrylate (HEMA) namely, are used for above-mentioned purposes. They are able to swell in water and physical solutions but are insoluble in such media and have controlled sorption-desorption properties due to the presence of different functional groups in their structures.

There are two researching directions concerning development of drugs prolonged release systems based on polymeric hydrogels at Department of Chemical Technology of Plastics Processing of Lviv Polytechnic National University. The first direction is covering of solid parts by polymeric hydrogel envelope (capsulation). The second one is development of granular forms operating by the following scheme: sorption of drug by polymer – drug release in the organism.

Synthesized copolymers are cross-linked compounds consisting of PVP molecules with grafted polyHEMA chains. They have functional groups with different polarities: C=O and –OH groups of monomer and N–C=O group of PVP. Moreover, in aqueous media PVP chain links may be in ketonic forms or forms with nitrogen cationic atom. Depending upon structure of initial mixture and synthesis conditions hydrogel composition and structural parameters may be varied (TABLE 1) [2]. All mentioned factors affect the sorption and diffusive-transfer properties of synthesized (co)polymers.

	Initial mixture composition, mass parts		f, %	P, %	Copolymer composition, mass parts	
	HEMA	PVP			polyH	PVP
1.	90	10	53	5	94,7	5,3
2.	80	20	52	10	89,6	10,4
3*	80	20	53	11	89,4	10,6
4**	80	20	49	10	90,2	9,8
5.	70	30	38	11	88,6	11,4
6***	70	30	42	13	87,4	12,6

BP - benzoyl peroxide; f - PVP graft effectiveness; P - graft degree;
* – for T=343 K; ** – for T=353 K; *** – [BP]= 0,75 mass %.

TABLE 1. Graft parameters and copolymer compositions (T = 348 K, [BP] = 1 mass %).

Copolymers so synthesized in the form of membranes were effective capsulated agents of solid drugs. In dry state while storing they act as protective envelope but while operation they are able to swell in the physical solution and become permeable. The scheme of components transfer from capsulated particles is following: copolymer swelling, molecular diffusion inside the capsule, mass transfer through polymeric membrane and mass delivery into ambient solution (FIG.1).

Spent capsule is removed out of organism by natural way without detriment to it.

In order to forecast the duration of drug removal from capsulated particle, as well as its end concentration in the solution, the model of mass transfer from globular particle enveloped with polymeric hydrogel has been developed (FIG.2).

The thickness of hydrogel envelope while swelling will change by following dependence:

$$\delta = \delta_n [1 + \alpha_{\max} (1 - e^{Kt})]$$

where: δ_n , δ – thickness of dry and swelled hydrogel envelope, [m]; t – swelling time, [s]; K – swelling rate constant, [s⁻¹]; α_{\max} – maximal value of swelling coefficient.

Concentration in the solution C is:

$$C = 4\pi(\rho_T - c_s)(r^3 - 3Rr^2 + 3Rr^2)/3W$$

$$\text{If } r=R, \text{ then } C = C_{\max} = 4\pi(\rho_T - c_s)R^3/3W$$

The change of particle mass at $\delta \ll R$ is equal to:

$$-dM/dt = 4\pi P^2 (c_s - c_1) / (\beta^{-1} + rD_1^{-1} + \delta D_2^{-1})$$

where: M – particle mass, [kg]; D_1, D_2 – diffusion coefficients in the solution inside the capsule and polymer, respectively, [m²/s]; R – particle radius, [m]; ρ_T – solid particle density, [kg/m³], c_s – concentration of the substance over the particle surface, [kg/m³]; r – reduction of particle radius; β – mass-transfer coefficient, [m/s]; W – liquid volume, [m³].

Maple v6.01 mathematical pack was used for the model numerical realization. Results so obtained allow to forecast the duration of drug removal from the particle, as well as its end concentration in the solution.

Investigated polymers also have been used for the development of drug delivery systems of another type, so called granular copolymers. Sorption properties of such copolymers are determined with net structural parameters and presence of different functional groups in the copolymer.

Initial mix design and kinetics investigation were fulfilled, what gave the possibility to substantiate the synthesis regimes of granulated copolymers and establish the effect of main factors on the granulometric composition and polymer properties [3]. The synthesis principles of PVP – HEMA granular copolymers have been developed. Such copolymers have controlled sizes of particles (from 0.1 to 2.0 mm) and polydispersity.

In order to establish the practical aptitude of copolymers so synthesized, the sorption and desorption processes were investigated using sodium diclofenac. This drug is used as solvent, analgesic and febrifuge, which is contra-indicated under stomach ulcer. Moreover, its long-term usage changes blood formula. Therefore, the development of prolonged systems, which essentially decrease the drug effective part and minimize its negative operation to the mucous membrane of gullet and stomach, is matter of great importance.

The experimental results show that homopolymers on the HEMA basis (FIG.3a, curve 1) have the least sorption ability. Effective sorption takes place during 6-8 h. and then practically does not change. The introduction of PVP links into the copolymer increases the sorption rate, as well as boundary amount of sorbed drug. Mentioned facts are caused, obviously, by introduction of additional functional groups of another nature into the copolymer composition (>N-C=O) and increase of granule porosity [4].

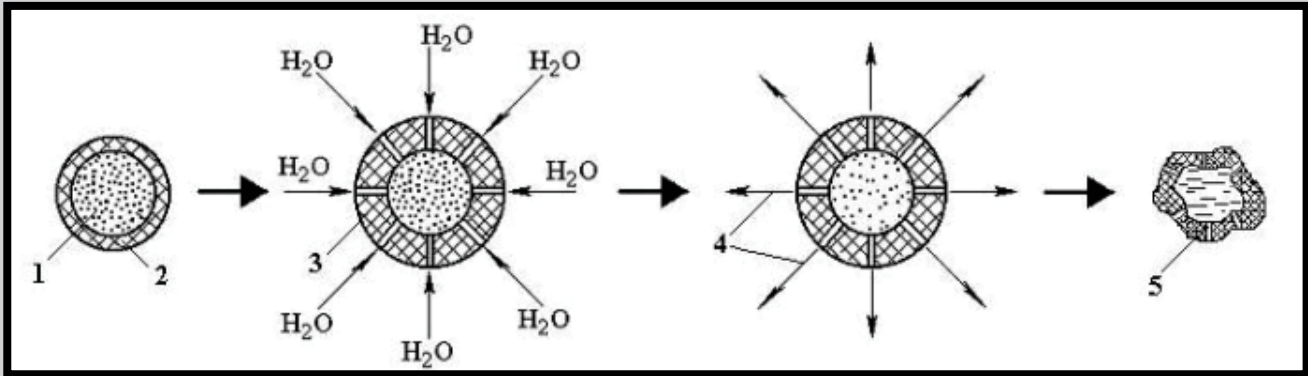


FIG.1. The scheme of components transfer from capsulated particles.
 1 – drug; 2 – solid polymer envelope; 3 – swelled cross-linked gel;
 4 – drug prolonged release; 5 – spent capsule.

We also examined the drug release by spherical particles because they model the behavior of prolonged drug while operation.

Synthesized copolymers were desorbed for 24 h. till 40% of maximum sorbed sodium diclofenac was achieved. The rest amount did not release under experimental conditions, except granules based on polyHEMA (FIG.3b, curve 3). Perhaps, in such a case sodium diclofenac is sorbed only due to the physical interacting forces which are weak and can not hold drug for a long time. In the presence of PVP functional groups in the copolymer structure both physical and chemical interaction forces take part in the sorption-desorption process. It should be noted that amount of desorbed sodium diclofenac was in the range of therapeutic doses in all cases.

Thus, we established the relationship between synthesis conditions, structure and sorption-desorption properties of PVP cross-linked copolymers, what offers the challenge of their application as carriers for the systems of drugs directional and controlled release.

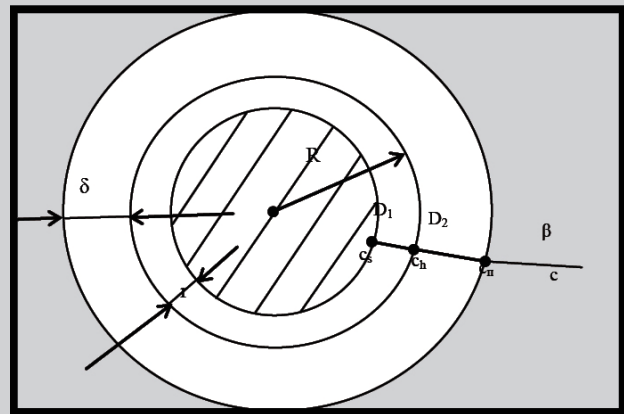


FIG.2. The scheme of mass transfer from solid particle with hydrogel envelope.

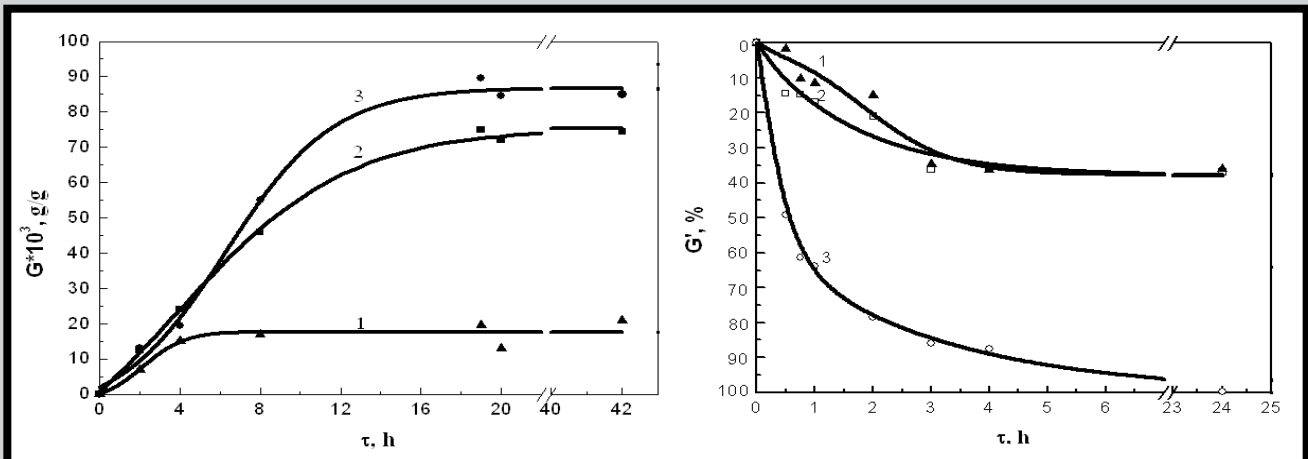


FIG.3. Kinetic curves of sodium diclofenac sorption (left) and desorption (right) by polymeric hydrogels, [HEMA]:[PVP], mass parts: 1-10:0 ($d_n=0,90\text{mm}$; PDI=1,27); 2-8:2 $d_n=0,64\text{mm}$; PDI=1,24); 3-7:3 ($d_n=0,73\text{mm}$; PDI=1,15).

References

- [1] Grygoryanc I.K., Tryhanova G.A. Polymer drug delivery systems // Chemistry abroad.-1984.-№9.-64 p.
 [2] Skorokhoda V., Semenyuk N., Suberlyak O. Structure and sorption ability of hydroxyethylmethacrylate copolymers with polyvinylpyrrolidone // Полімерний журнал.-2004.-№2.-P.86-92 (Ukraine).

- [3] Skorokhoda V., Semenyuk N., Lukan G., Suberlyak O. Influence of technological parameters on regularities of hydrophilic granular polyvinylpyrrolidone copolymers synthesis // Вопросы химии и химической технологии.- 2004.-№3.- С.88-91 (Ukraine).
 [4] Suberlyak O., Skorokhoda V., Thir I. Influence of complex formation on polymerization of hydroxyethylmethacrylate in presence of polyvinylpyrrolidone // Высокомолекулярные соединения.-1989.-V.5Б.-P.336-340 (Russia).