References

[1] S. Li, M. Vert, Encyclopedia of Controlled Drug Delivery, Mathiowitz, E., Ed., Wiley&Sons: New York, 1999, p. 71.
[2] S. Li, M. Vert, Macromolecules 36 (2003) 8008-8014.
[3] S. Li, J. Biomed. Mater. Res. 48 (1999) 342-353.
[4] Y. Hu, X. Jiang, Y. Ding, L. Zhang, C. Yang, J. Zhang, J. Chen, Y. Yang, Biomaterials 24 (2003) 2395-2404.
[5] G. Ruan, S.S. Feng, Biomaterials 24 (2003) 5037-5044.
[6] J. Matsumoto, Y. Nakada, K. Sakurai, T. Nakamura, Y. Takahashi, Inter. J. Pharm. 185 (1999) 93-101.
[7] T. Govender, T. Riley, T. Ehtezazi, M.C. Garnett, S. Stolnik, L. Illum, S.S. Davis, Inter. J. Pharm. 199 (2000) 95-110.
[8] I. Molina, S. Li, M.B. Martinez, M. Vert, Biomaterials 22 (2001) 363-369.
[9] S. Li and M. Vert, Macromolecules 36, 8008 (2003).
[10] X. Zhang, J. K. Jackson and H. M. Burt, Int. J. Pharm. 132, 195 (1996).
[11] K. Letchford, J. Zastre, R. Liggins and H. Burt, Colloids and Surfaces B: Biointerfaces 35, 81 (2004).
[12] B. Jeong, Y. H. Bae and S. W. Kim, Colloids and Surfaces B: Biointerfaces 16, 185 (1999).
[13] G. S. Kwon and K. Kataoka, Adv. Drug Del. Rev. 16, 295 (1995).
[14] Y. Dong and S. Feng, Biomaterials 25, 2843 (2004).
[15] G. Ruan and S. Feng, Biomaterials 24, 5037 (2003).

HIGH-HYDROPHILIC MEMBRANES FOR DIALYSIS AND HEMODIALYSIS

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Researches of high-hydrophilic and tromboresistive dialysis membranes have been carried out and possibility of their creation using polyvinylpyrrolidone has been confirmed.

Development of hemodialysis membranes, cardiovascular implants and other artificial organs put forward the problem of thromboresistive materials creation [1]. One of the effective ways of thromboresistance increase is immobilization of heparin, which is blood natural anticoagulant, over material surface. The main problem of heparin immobilization by polymeric membranes is its permanent minimal desorption at a contact with blood.

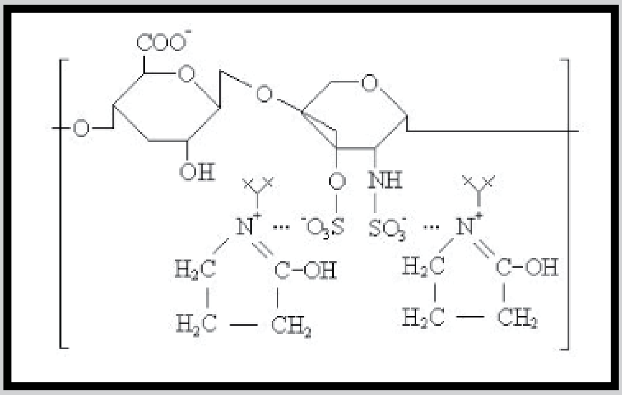
Researches concerning medical polymers syntheses and application are carried out at the Department of Chemical Technology of Plastics Processing of Lviv Polytechnic National University. These researches are directed mainly on the synthesis of new and modification of already existent polymers. Polyvinylpyrrolidone (PVP) was chosen as a base initial product after the protracted approbations. Originality of PVP properties and application is stipulated by its structure and physico-chemical properties. The presence of carbamate group favors high selective-sorption properties, complexation with iodine and other compounds and the formation of macromolecules ionic form in aqueous medium [2]. In addition to the foreseen PVP physiology activity and functional ability, it positively affects the kind of polymerization reaction at the synthesis of its copolymers.

Netted copolymers of oxyalkylenmethacrylates with polyvinylpyrrolidone [3] are perspective compounds for the production of dialysis membranes. The presence of PVP ionogenic groups in the composition of mentioned copolymers assumes the expansion of biochemical and sorption characteristics and obtaining of membranes with additional functions on their basis.

Hydrogel membranes were obtained by graft polymerization of 2-hydroxyethyl methacrylate (HEMA) over PVP (molecular mass was $10\text{-}50 \cdot 10^3$) in aqueous medium, what allowed to combine the synthesis stage and membrane swelling. Before the researches membranes were washed with the distilled water during 48 hours for the removal of unreacted products. The permeability of the synthesized hydrogel membranes in the dialysis process for the aqueous solutions of sodium chloride was determined at the special dialyzer with peristaltic pump. The saturation of membranes with heparin was realized in glycerin buffer solution (1M glycerin solution, pH=2,7), which contained 250000 units of heparin in 1 l. The amount of sorbed and desorbed heparin was determined by photocolorimetry, based on quantitative determination of heparin and methylene blue complex.

Synthesized hydrogel membranes with PVP links have advanced immobilization ability relative to heparin (TAB.1).

Increased content of heparin on membranes with PVP is assigned, to our opinion, by the formation of ionic connections between heparin and PVP macromolecules. Also it should be taken into account that PVP link may exist as ketoform or in the form that contains nitrogen cationic atom [2]:



In spite of the fact that part of cationic form is insignificant [2], mentioned links connect heparin anions efficiently. As a result, PVP-heparin complex is so strong, that heparin does not precipitated for 24 hours (see TABLE 1) at membranes keeping in solutions with different pH (glycin buffer solution with pH=2,7, physical solution with pH=7 and solution of sodium tetraboric acid with pH=9,1). Here the selective-transport characteristics of membranes are changed insignificantly. As for membranes based of polyHEMA and modified cellulose, there is an insignificant precipitation of anticoagulant in acid and neutral media, while in alkaline medium it grows to 80...95%.

We have established that the presence of –OH and N–C=O hydrophilic groups in the composition of membrane copolymers increases their sorption ability which is characterized with water content (TABLE 2). The increase of PVP content multiplies dialysis permeability (KNaCl) of hydrogel membranes based on HEMA-PVP, but their strength falls down (TABLE 2). Hence, changing hydrogel chemical structure it is possible to change permeability of membranes on the basis of HEMA-PVP copolymers.

High-hydrophilic membranes synthesized on the basis of HEMA-PVP copolymers sorb plenty of water and form polymeric hydrogels, possessing high elasticity. All these factors also create additional preconditions of successful coexistence with biological tissues similar to the physical

№	Material of membranes	Heparin sorption, [10^{-3} u/m^2]	Heparin desorption for 24 hr., [%]			$K_{NaCl}\cdot 10^5$, [mole·m^{-2}·h^{-1}]
			pH = 2,7	pH = 7	pH = 9,1	
1.	PHEMA	115	4	8	80	212/242*
2.	PVP-gr-PHEMA	550	0	0	2	848/865*
3.	Methyl cellulose [4]	126	8	5	95	–
K_{NaCl} is a permeability coefficient for NaCl; * - for heparinized membranes						

TABLE 1. Heparin immobilization by membranes surface and their permeability (membrane thickness is 200mcm).

№	Composition of (co)polymer membranes		Membrane tensile strength,[MPa]	Water content, [%]	K_{NaCl}, [mole·m^{-2}·h^{-1}]
	HEMA	PVP			
1.	100	—	0,53	40	127
2.	91	9	0,46	45	293
3.	82	18	0,40	48	412
4.	77	23	0,31	53	506
5.	69	31	0,22	61	611
K_{NaCl} is a permeability coefficient for NaCl					

TABLE 2. - Properties of hydrogel membranes based on HEMA-PVP, (membrane thickness is 200mcm).

№	Composition of PA6-PVP mixtures, [% mass.]		Membrane tensile strength, [MPa]	Water content, [%]	$K_{NaCl}\cdot 10^3$, [mole·m^{-2}·h^{-1}]
	PA6	PVP			
1.	99	1	21,0	22	0,36
2.	98	2	15,7	32	1,07
3.*	98	2	14,3	25	2,25
4.**	98	2	13,9	35	0,54
5.	95	5	15,4	32	0,96
6.	90	10	14,1	33	4,65
* solvent evaporation temperature 382 K; ** PA6/PVP:HCOOH: H_2O=7,2:77,6:15,2.					

TABLE 3. Properties of membranes based on PA6-PVP mixtures (PA6/PVP:HCOOH:H_2O=7,2:79,0:13,8; solvent evaporation temperature 353 K; membrane thickness is 20 mcm).

state. At the same time they have low strength sharply limiting their application.

It has been established that strength of hydrogels can be increased by introduction of additional polyfunctional monomers [5] to the initial composition, but in such a case their permeability and elasticity diminish substantially. Moreover, there is another strange fact. The introduction of monomers in some cases decreases mechanical strength of hydrogels. Therefore, the creation of membranes based on polyamides modified with PVP seems more perspective.

High hydrophily and also complex of valuable properties (high mechanical strength, in particular) assign perspective usage of polyamide-6 (PA6) for the obtaining of dialysis membranes. Membranes based on PA6 have high operational characteristics but unsatisfactory permeability, especially relative to water. PA6 hydrophysics is among the methods, which favors the considerable improvement of membranes permeability [6]. It is also necessary to pay attention to insufficient bio- and hemocompatibility of polyamides [7].

Membranes from PA6-PVP mixtures with high hydrophily were formed using solutions in the formic acid – water diluent system. Then prepared watering solutions were poured off [8].

We have established the possibility of ultrafine membranes formation on the basis of PA6-PVP mixtures with high hydrophily and permeability. We have confirmed the possibility of the controlled adjustment of membranes sorption ability and dialysis permeability by selection of initial polymeric mixture composition and membranes formation conditions (TABLE 3). High-hydrophilic membranes obtained on the basis of PA6-PVP are characterized with high strength (TABLE 3) which depends upon mixture composition, as well as the diluent system composition.

Previous medical researches confirmed the high thromboresistance of the synthesized high-hydrophylic PVP-containing membranes at their contact with blood.

Conclusion

Conducted researches confirm the formation of high-hydrophylic PVP-containing dialysis membranes based of HEMA-PVP and PA6-PVP systems. They are able to immobilize heparin on the surface and have the wide spectrum of selective-diffusive and strength characteristics. Heparin, adsorbed by membranes surface, is resistant to the action of physical solution for a long time, what foresees stable antithrombogenic properties. These properties together with high permeability and separating ability intend membranes effective application in the hemodialysis processes.

References

[1] Hennink W., Kim S. Inhibition of surface induced coagulation by preadsorption of albumin-heparin conjugation. // J. Biomed. Mat. Res. – 1984. – 18, vol. 8. – P. 911-926.

[2] Marutamutu M., Reddy J. Binding of fluoride onto poly(N-vinyl-2-pirrolidone). // J. Polym. Sci. – 1984. – 22, vol. 10. – P. 569-573.

[3] Thir I., Soshko A, Suberlyak O. About diffusion of electrolyte through hydrophilic polymer on the basis of monomethacrylate ethylene glycol and polyvinylpirrolidone. // Журнал прикладной химии. – 1983. – vol.10. – P. 2250-2253. (Russia)

[4] Schmitt E.,Holtz H. Heparin binding and release properties of DEAE cellulose membrane. // Biomaterials. – 1983. – 4, vol. 4. – P. 309-313.

[5] Suberlyak O., Skorokhoda V., Soshko A. The regularity of polymerization oligoesteracrylates on polyvinylpirrolidone. // Композиционные полимерные материалы. – 1986 . – 29. – P. 39-43. (Russia)

[6] Bryk M. The encyclopedia of membranes. – T. 1. – “Kyiv-Mogyla Academy” Publishing House. – 2005.

[7] Senoo Manabu. Polymer of medical application – Moscow: Medicine. – 1981.

[8] Suberlyak O., Melnyk J., Baran N. Modified of polyvinylpirrolidone polyamide membranes. // Наукові записки НаУКМА “Хімічні науки і технології”. – 2006. – 55. – P. 19-23. (Ukraine).