Modelling of controlled drug release from the solid phase through hydrogel membranes

Yuriy Melnyk, Iryna Dzyaman, Viktoria Antoniuk and Volodymyr Skorokhoda

Lviv Polytechnic National University, UKRAINE, Lviv,
S. Bandery street 12, E-mail: jourij_melnyk@polynet.lviv.ua

Abstract* – *The cross-linked copolymers of the 2-hydroxyethylmethacrylate with polyvinylpyrrolidone as granules and membranes were synthesized and their penetration and sorption-desorption properties were investigated. The mass-transfer model of hard soluble surface through the hydrogel shell was offered. The developed materials are able to creation as capsule and granule polymer forms of the substances prolonged freeing.

Key words – hydrogel, 2-hydroxyethyl methacrylate, polyvinylpyrrolidone, sorption, penetration.

I. Introduction

The development of polymer 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-hydroxyethyl methacrylate (HEMA) namely, are used for above-mentioned purposes. They are able to swell in water and physiological solutions but are insoluble in such media and have controlled penetration and sorption-desorption properties due to the presence of different functional groups in their structures [2].

II. Result and Discussion

There are two researching directions concerning development of drugs prolonged release systems based on polymeric hydrogels at the Department of Chemical Technology of Plastics Processing of Lviv Polytechnic National University. The first direction is capsulation of solid parts by polymeric hydrogel shell. The second one is development of granular forms operating by the following scheme: sorption of drug by polymer – drug release in the organism. The technological aspects of the both types of copolymers obtaining by the radical polymerization in the peroxides initiators presents are considered in accordance with [3] and [4].

Application of PVP-$FeSO_4$ complex as an initiating system instead of potassium persulphate allows to cut synthesis duration and considerably reduce the copolymers synthesis temperature (Table 1). The remaining monomer contents in order to the synthesis modes makes 0,5…2,5 *wt. p.* As it is foreseen to utilize the obtained polymers in medical practice, for the removing of the free monomer from the polymer in the technological scheme being contained the stage of polymer washing [3].

TABLE 1

THE COMPOSITION CONTENTS AND MODES OF FORMING INFLUENCE ON THE DEGREE OF REACTION COMPLETENESS*

№	Mixture composition, wt. p.				Forming mode	M_{rem}, %
	HEMA	PVP	H_2O	Initiator, % (catalyst)		
1.	90	10	100	0,3 PPS	333 K – 2 h, 343 K – 2 h	1,5
2.	80	20	100	0,3 PPS	333 K – 2 h, 343 K – 2 h	2,0
3.	80	20	50	0,05 $FeSO_4$	278 K – 1 h	2,5
4.	80	20	100	0,05 $FeSO_4$	323 K – 0,5 h	1,0
5.	80	20	300	0,05 $FeSO_4$	323 K – 0,5 h	1,0
6.	70	30	100	0,05 $FeSO_4$	323 K – 0,5 h	2,0

* – after remaining monomer contents (M_{rem}); PPS – potassium persulphate

TABLE 2

GRAFT PARAMETERS AND COPOLYMER COMPOSITIONS (T = 333 K)

№	Mixture composition, wt. p.		f, %	P, %	Copolymer composition, wt. p.	
	HEMA	PVP			PHEMA	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

f – PVP graft effectiveness; P – graft degree;
* – for T = 343 K; ** – for T = 353 K

TABLE 3

PROPERTIES OF HYDROGEL MEMBRANES

№	(Co)polymer composition, wt. p.		W, %	M_n, kg/mole	$D_2 \cdot 10^{12}$, m^2/s	$V \cdot 10^3$, mole/($m^2 \cdot s$)
	PHEMA	PVP				
1.	100	–	38	12	5,7/0,4*	1,3/0,11
2.	91	9	45	20	18,7	2,2
3.	82	18	48	24	28,0/2,2	3,0/0,21
4.	77	23	53	38	37,1	3,7

W – water content, M_n – molecular weight of net internodal fragment; V – rate of mass transfer (δ = 200 mkm); D_2 – diffusion coefficient (* – the numerator – for sodium chloride, the denominator – for sodium diclofenac)

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 cationic nitrogen [5]. The structural parameters and hydrogel composition contents may be direct changed by synthesis

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conditions. (Table 2) [6]. All above mentioned factors, of course, will affect on the sorption and diffusive-transfer properties of synthesized (co)polymers.

These factors will undoubtedly influence the sorption and diffusion-transport properties of the synthesized hydrogels (Table 3).

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

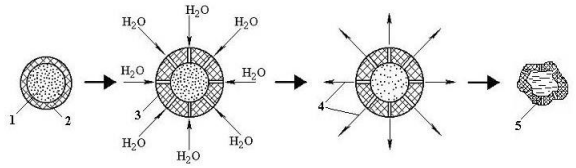

Fig. 1. The scheme of components transfer from capsulated particles:
1 – drug*; 2* – solid polymer shell*; 3* – swelled cross-linked gel*; 4* – drug prolonged release*; 5* – spent capsule

Used 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 which is shelled with the polymeric hydrogel has been developed (Fig. 2).

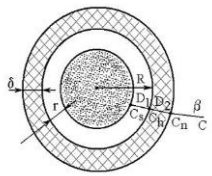

Fig. 2. The scheme of mass transfer from solid particle with hydrogel shell

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

$$\delta = \delta_n \left[1 + \alpha_{\max}\left(1 - e^{-Kt}\right)\right] \quad (2)$$

where δ_n, δ – thickness of dry and swelled hydrogel shell, m; t – swelling time, s; K – swelling rate constant, s^{-1}; α_{max} – maximal value of swelling coefficient.

Concentration in the solution C is:

$$c = \frac{4\pi \cdot (\rho_т - c_s)(r^3 - 3Rr^2 + 3Rr^2)}{3W}. \quad (3)$$

If $r = R$, then

$$c = c_{\max} = \frac{4\pi \cdot (\rho_т - c_s)R^3}{3W}. \quad (4)$$

The change of particle radius and mass at $\delta << R$ is equal to

$$\frac{dr}{dt} = \frac{(c_s - c)}{\left[\rho_т\left(\beta^{-1} + rD_1^{-1} + \delta D_2^{-1}\right)\right]}. \quad (5)$$

$$\frac{-dM}{dt} = \frac{4\pi \cdot R^2 (c_s - c)}{\left(\beta^{-1} + rD_1^{-1} + \delta D_2^{-1}\right)}. \quad (6)$$

where M – particle mass, kg; D_1, D_2 – diffusion coefficients in the solution inside the capsule and polymer, respectively, m^2/s; R – particle radius, m; $\rho_т$ – solid particle density, kg/m^3; c_s – concentration of the substance over the particle surface, kg/m^3; r – reduction of particle radius; β – mass-transfer coefficient, m/s; W – liquid volume, m^3.

The mathematic model and its verifying in detail are described in [7]. 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.

Synthesized copolymers are marked by chemical stability in slightly alkaline and slightly acid environments, sterilization is maintained in an autoclave.

Conclusion

The obtained results open the perspective of the use of the synthesized hydrogels polymers as the membranes and granules for creation of the drug delivery systems, carriers for chromatographic processes and immunological investigation.

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