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Chemistry

RESEARCHES OF AMPHIPHILIC PROPERTIES OF COPOLYESTERS WITH CHROMOPHORE GROUPS

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Abstract. The distribution coefficients of macromolecules of aminofunctional copolyesters with chromophore groups in the *n*-octanol–water system, as well as experimental and calculated characteristics of their hydrophilic-lipophilic balance (HLB) have been determined. A multiple regression analysis has been carried out and interpolation equation of the lipophilicity coefficient has been derived depending on the parameters characterizing the qualitative and quantitative composition of the copolyester. The factors which have the most significant influence on the lipophilicity factor and HLB of the obtained fluorescein-containing copolyester have been established.

Keywords: distribution coefficient, hydrophilic-lipophilic balance, copolyester, fluorescein, drug delivery systems.

1. Introduction

When creating drugs based on new classes of chemical compounds, one of the main issues is the mechanisms of their penetration into living cells and the interaction of these compounds with cell membranes. Ideal is the balanced ratio of the hydrophilic and lipophilic properties of the drug or its carrier, which makes it equally well soluble in both the aqueous and lipid environments. Assessment of compounds biodistribution on model systems is an important step in the creation and evaluation of the effectiveness of drugs delivery system so that they can reach the damaged places penetrating biological barriers.

Amphiphilic copolyesters, which combine the properties of hydrophilic polyoxyether diols and hydrophobically-modified natural dibasic amino acids (polymers of this type are also known as “pseudo-polyamino acids”), have considerable prospects for medical-biological application. Their biodegradability, non-toxicity of their degradation products and formation of stable dispersions with particles of 50–200 nm in aqueous solutions makes them interesting objects in terms of use as micro- and nanosized polymer carriers capable of immobilizing biologically active substances. Recently, there has been a tendency to provide additional functions to nanocarrier by introducing appropriate structural elements that would ensure a high degree of the carrier “targeting” and/or favors its detection in the body by accessible methods. Fluorescence spectroscopy is one of the most convenient and common detection methods.

Therefore, the actual task was to introduce a fragment – a marker capable of fluorescence into copolyester macromolecules, which would allow to detect them in the body tissues and thus to establish the effectiveness of nanocarriers on their basis. From the literature data, one can conclude that the fluorescence dyes of the xanthine series such as rhodamine, fluorescein and their derivatives are widely used in traditional and new areas of chemistry, biochemistry and medicine [1].

The aim of this work is to study the lipophilicity of new copolyesters in the binary system *n*-octanol–water, as well as to determine the effect of copolyester composition and structure on the lipophilicity and hydrophilic-lipophilic balance.

2. Experimental

2.1. Procedure for Obtaining Fluorescein Copolyesters *via* Steglich reaction

N-substituted glutamic acid (GLu-La-2-dodecanamino-pentadione or GLu-St-2-octadecanamino-pentadiene acid), comonomers of polyoxyether diols series (DEG, PEG-400, PEG-600, PEG-1000 and PEG-1500), dipropylene glycol (DPG), fluorescein and solvent were loaded into a two-necked reactor equipped with a stirrer and reflux condenser with a calcium chloride tube. The reaction mass was cooled to 280 K, and the pre-

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prepared solutions of 4-dimethylaminopyridine (DMAP) and dicyclohexylcarbodiimide (DCC) in a corresponding solvent were sequentially introduced under stirring. The temperature of the reaction mixture was raised to 288 K and the mixture was kept for 3 h, then at 308 K for another 3 h. After completion, the dicyclohexylurea (DCU) precipitated from the reaction mixture was separated by filtration. The filtrate was evaporated by a vacuum jet pump. After this the polymer was purified from unreacted monomers, activator, and catalyst. The resulting product was dried under vacuum to a constant weight.

2.2. Methods

2.2.1. Determination of the fluorescein content

The fluorescein content in the polymers was determined using spectrophotometry (spectrophotometer UNICO 1201) after their hydrolysis under the action of potassium hydroxide in methanol at the wavelength λ = 480 nm using a quartz cuvette of 5.0 mm thick. 10 % solution of KOH was added to a polymer solution prepared in methanol at the concentration of 0.07–0.08 %, then placed in a water bath at 333 K for 1 hour. The fluorescein concentration in the resulting solution was calculated using the dependence of optical density on the fluorescein concentration (standard line).

The distribution coefficient of fluorescein-containing copolyester is determined by the concentration ratio of fluorescein in octanol and water:

$$P = \frac{C_o}{C_w} \quad (1)$$

where C_o – the fluorescein concentration in octanol, %; C_w – the fluorescein concentration in water.

2.2.2. Definition of the distribution coefficient

The sample of fluorescein-containing copolyester was dispersed in water creating a concentration of 0.3–0.5 %. 1.00 ± 0.10 g of *n*-octanol were added to 1.00 ± 0.10 g of the formed dispersion and mixed for 24 h. In order to separate the phases, the resulting emulsion was centrifuged for 10 min at 10,000 s^{-1}. Fluorescein content was determined in each phase.

2.2.3. Determination of the hydrophilic-lipophilic balance (HLB) of copolyester

The experimental value of the hydrophilic-lipophilic balance (HLB_{exp}) was calculated from the concentration ratios of copolyester in different phases after redistribution in the water–octanol system using Davis formula [2].

$$HLB = 7 + 0.36 \ln \frac{C_w}{C_o} \quad (2)$$

where C_w, C_o is the copolyester concentration in the aqueous and hydrocarbon phases, respectively.

Calculated values of HLB_{calc} were obtained according to the additive scheme, taking into account the share of each fragment in the copolyester (^{1}H NMR spectroscopic data). In this case, the $\log P_{o/w}$ value for all fragments was obtained using the ACDLabs software [2].

^{1}H NMR spectra of monomeric fragments and fluorescein copolyesters were obtained in a deuterochloroform using a Bruker Nuclear Magnetic Resonance (NMR) Spectrometer at 400 MHz frequency under automatic scan mode. The spectra were analyzed according to the table of characteristic chemical shifts presented in [3], as well as by means of the ACDLabs software.

The average molecular weight, molecular weight distribution and polydispersion coefficient of the copolymers were obtained using Waters Corporation chromatograph with Waters 2998 refractometric detector and Waters 1515 Isocratic HPLCpump. Tetrahydrofuran was used as an eluent with the flow rate of 0.1 ml/min. Polystyrene with narrow molecular weight distribution were used as a standard.

3. Results and Discussion

By the procedure described in Subsection 2.1a series of amphiphilic copolyesters based on *N*-derivatives of glutamic acid and polyoxyether diols were synthesized *via* Steglich reaction of activated copolycondensation, in which fluorescein is included in the given amounts as a structural unit of the macromolecule (Fig. 1).

^{1}H NMR spectroscopic investigations of the obtained copolyester made it possible to assign the signals of protons and to calculate the content of each of the monomers in the macromolecule using intensity values [4].

The amphiphilic nature of the resulting polymers, provided by using monomers of different nature: lipophilic *N*-derivatives of glutamic acid (GluLa, GluSt) and hydrophilic polyoxyether dioles, assumes their surface activity [5].

Most of the resulting copolyesters form micellar solutions in water and reduce surface tension (s = 40–35 mN/m, Fig. 3). The decisive factor in choosing drug effective dosage is the ability to penetrate the cells membrane, which is determined by its lipophilicity [6]. To obtain numerical characteristics of copolyester lipophilicity, their distribution between 1-octanol (phospholipid membrane model) and water (intercellular fluid) was studied.

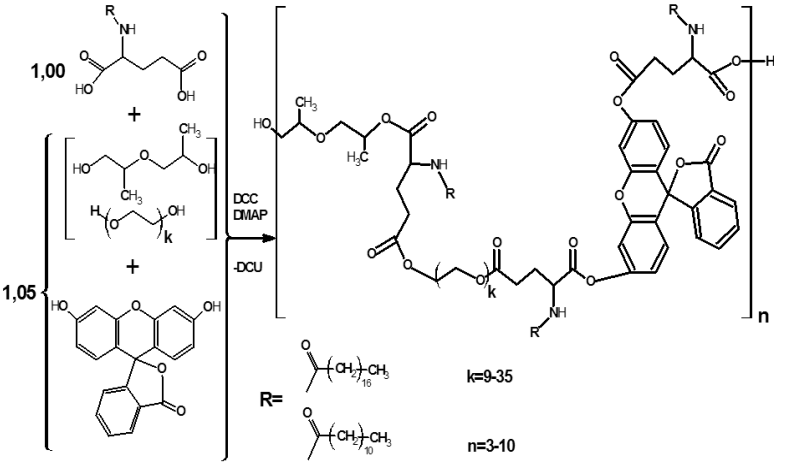

Fig. 1. Scheme for obtaining fluorescein-containing copolyester *via* Steglich reaction

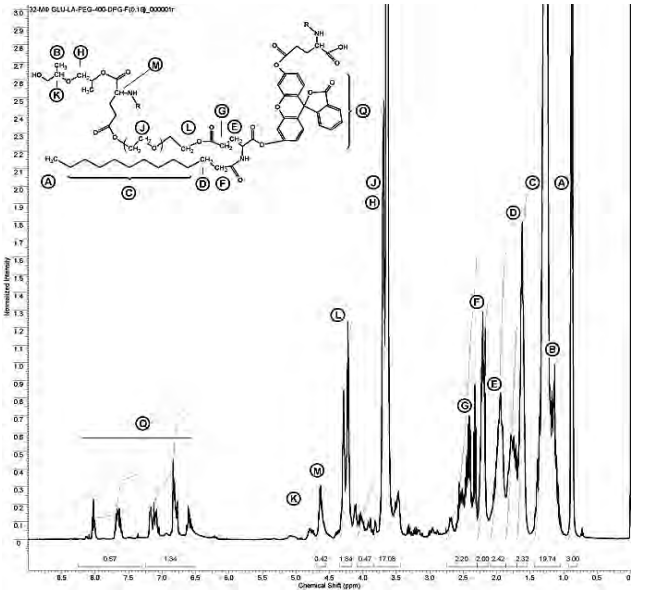

Fig. 2. ^{1}H NMR spectrum of copolyester GluLa-PEG400-DPG-F (fluorescein content C_F = 9.64 %)

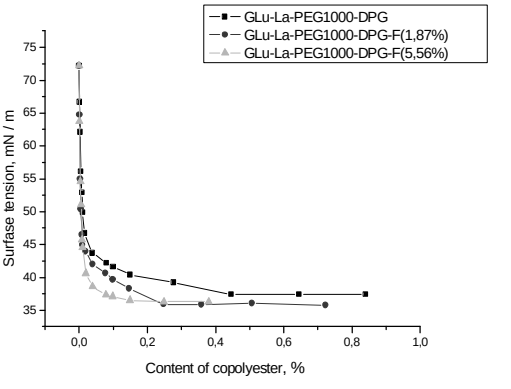

Fig. 3. Isotherms of surface tension of copolyester with different fluorescein contents

Table 1

Synthesis conditions and characteristics of copolyester based on *N*-substituted derivatives of glutamic acid, polyoxyether diols and fluorescein

Sample number	Generalized structural formula	Composition of monomer mixture, mole parts				Obtained in copolyester, mole parts				Content of *F* in the polymer, %	Average molecular mass of copolyester
		Acid*	PEG	DPG	Fluores-cein	Acid*	PEG	DPG	Fluores-cein		
1	GluLa-PEG400-DPG-F	0.5	0.307	0.137	0.0815	0.5	0.257	0.041	0.203	9.64	2950
2	GluLa-PEG600-DPG-F	0.5	0.274	0.137	0.116	0.5	0.262	0.049	0.189	13.07	3920
3	GluSt-PEG600-DPG-F	0.5	0.274	0.138	0.113	0.5	0.280	0.072	0.149	9.69	2540
4	GluLa-PEG1000-DPG-F	0.5	0.358	0.143	0.0265	0.5	0.31	0.095	0.095	1.87	5460
5	GluLa-PEG1000-DPG-F	0.5	0.337	0.134	0.052	0.5	0.301	0.043	0.156	3.75	3515
6	GluLa-PEG1000-DPG-F	0.5	0.307	0.13	0.083	0.5	0.261	0.062	0.177	5.56	4930

Note: * in accordance with the loading *N*-derivative of glutamic acid (GluLa or GluSt)

Table 2

Colloid-chemical characteristics of copolyester based on *N*-substituted derivatives of glutamic acid, polyoxyetherdiols and fluorescein

Sample number	Generalized structural formula	Content of *F* in the polymer, %	Experimental values			HLB_{calc}
			$P_{o/w}$	$\log P_{o/w}$	HLB	
1	GluLa-PEG400-DPG-F	5.53	2.03	0.31	6.75	6.15
2	GluSt-PEG400-DPG-F	4.67	2.83	0.45	6.63	4.84
3	GluLa-PEG600-DPG-F	5.20	2.85	0.45	6.63	6.58
4	GluSt-PEG600-DPG-F	4.03	2.86	0.46	6.72	5.38
4a	GluSt-PEG600-DPG	0	3.05	0.48	6.2	5.7
5	GluLa-PEG600-DPG-F	13.07	1.90	0.28	6.77	6.30
6	GluSt-PEG600-DPG-F	9.69	1.52	0.181	6.85	5.21
7	GluLa-PEG1000-DPG-F	3.75	1.45	0.16	6.87	7.39
7a	GluSt-PEG1000-DPG	0	0.06	-1.19	7.9*	6.37
8	GluSt-PEG1000-DPG-F	2.87	2.36	0.37	6.74	6.31
9	GluSt-PEG1000-DPG-F	5.87	0.68	-0.17	7.14	5.93
10	GluLa-PEG1000-DPG-F	5.56	1.45	0.16	6.86	7.045
11	GluLa-PEG1000-DEG-F	6.82	0.31	-0.58	7.48	7.62
12	GluLa-PEG1000-F	5.32	1.76	0.245	6.80	7.41
13	GluLa-PEG1500-DPG-F	3.182	6.05	0.78	6.35*	8.63

Note: * formation of trice emulsion/

In the case of covalent binding of the dye in the macromolecules structure, the concentration of the copolyester after redistribution explicitly correlates with the fluorescein content in each of the phases. It should be noted that in colloidal solutions of synthesized amphiphilic copolyester from fluorescein, the concentration in relation to free dye can be increased by more than an order of magnitude (C_F = 0.03 %) as compared to its own water solubility (C_{FH2O} = 0.005 %). This fact, as well as high molecular excitement factor of fluorescein (88000), allow to develop a method for analyzing copolyester content in each phase using relatively simple spectrophotometric equipment.

In the obtained copolyesters, the ratio of hydrophilic and lipophilic fragments molecular weight, which determines their colloidal-chemical properties and applications, is reflected by HLB [7].

Experimentally obtained values of the distribution coefficient ($P_{o/w}$) of the synthesized copolyesters (Fig. 1) and their values of HLB_{exp}, calculated by the formula (2) are given in Table 2.

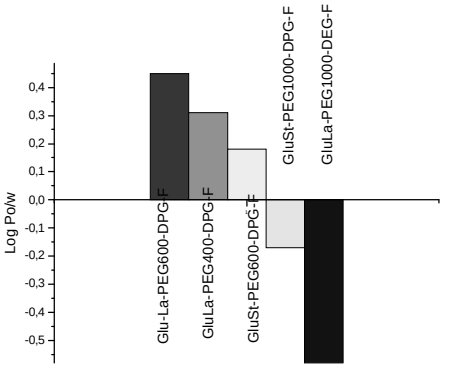

Fig. 4. Distribution coefficients (log$P_{o/w}$) for a series of copolyesters of different composition (samples 3, 1, 6, 9, 11, Table 2)

The results of determining the logarithm of the distribution coefficient for a number of copolyesters are shown in Fig. 4. A small range of changes in log$P_{o/w}$ values from -0.5 to 0.5 with a rather substantial change in the molar mass (400–1500 Da) of the polyoxyether diol hydrophilic fragment (PEG) in the copolyesters led to additional calculations that would rely on independent data. Table 2 also shows the values of HLB_{calc}, which are calculated based on the quantitative characteristics of the copolyester composition obtained by ^{1}H NMR spectroscopy (Table 1).

It is obvious that the calculated values of HLB are close to experimentally determined (Table 2). However, a satisfactory correlation between them is not observed. This is well illustrated by the scatter diagram of the experimental and calculated values of HLB, shown in Fig. 5. A significant deviation of the data from the diagram diagonal indicates the absence of correlation. The reason for such discrepancy is that when calculating the HLB according to the additive scheme for the elementary link of a polymer, such important factors as macrochain structure, its segmental mobility, functional and structural heterogeneity of the statistical copolyester, and the nature of the end groups are not taken into account. The simultaneous effects of several factors, which are not necessarily linear, complicate the analysis of HLB dependence on the composition of copolyester.

To identify the influence of all factors under such conditions and their importance, it would be appropriate to conduct a multiple regression analysis and construct an interpolation equation of the lipophilicity coefficient depending on the parameters which characterize the qualitative and quantitative composition of the copolyester.

As shown above, the calculated and experimental values of HLB are evaluated from the corresponding values of $P_{o/w}$ coefficient. Therefore, in order to reduce the accumulation of error, we used the values of $P_{o/w}$in the regression analysis, but not the values of HLB.

Since in this work we analyzed copolyesters [Glu(La, St)$_{0.5}$(PEG, DPG, F)$_{0.5}$], in which the amount of residues of glutamic acid *N*-derivatives, polyoxyether diol fragments and low molar mass diols not changed significantly, these factors can not be the parameters of regression analysis. Instead, such qualitative characteristic of these fragments as HLB may be the factor of the interpolation equation. The HLB numbers, equalled to 1.8 for Glu-St and 4.44 for Glu-La, are defined as parameter *G*, characterizing their influence on the lipophilicity coefficient in the interpolation equation. The fragment of polyoxyether diol in the copolyester is best characterized by the value of *P*, which is a coefficient proportional to its molar mass ($P = M_{PEG}/1000$). Low molecular diol, as a copolyester component, can be characterized by the parameter *N*, which is numerically equal to the value of the group contribution of its link in HLB according to the additive scheme. So, for the DPG residue $N = -0.15$ and for DEG $N = 0.3$ [6]. In the absence of low molecular diol $N = 0$. Only a fragment of fluorescein can be characterized by the parameter *F*, which corresponds to its percentage in copolyester (Table 2).

The type of interpolation equation of multiple regressions was selected by obtaining the maximum value of the multiplicative coefficient of linear correlation *R*. The maximum value of this coefficient $R = 0.9795$, is realized by an equation which has the following form:

$$P_{o/w} = a_0 + a_P \cdot P + a_{PP} \cdot P^2 + a_N \cdot N + \\ + a_G \cdot G + a_F \cdot F + a_{GF} \cdot GF \qquad (3)$$

The values of the coefficients of the interpolation equation (3) with their confidence intervals, estimated at 90% confidence level, are given in Table 3.

The received data allows us to conclude that all coefficients are significant in the selected confidence probability. The correlation quality can be estimated from the scatter diagram of the experimental values $P_{o/w}$(Fig. 6).

Eq. (3) is more convenient to be analyzed in its simplified form (Eq. (4)).

$$P_{o/w} = 7.2 - 10.7P + 7.0P^2 - 28N - \\ - 0.6G + (0.06G - 0.22) \cdot F \qquad (4)$$

The resulting expression is a predictive equation that describes the dependence of the distribution coefficient $P_{o/w}$on the molar mass of PEG fragments (*P*), the HLB values of *N*-derivatives of glutamic acid (*G*), the contributions of low molecular alcoholic components (*N*), the percentage content of fluorescein (*F*) and a mixed parameter of the factors *G* and *F*, which characterizes their synergistic effect.

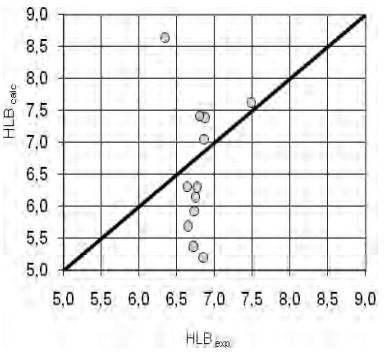

Fig. 5. Scatter diagram of the experimental values $P_{o/w}$ relative to their estimated values obtained by calculations

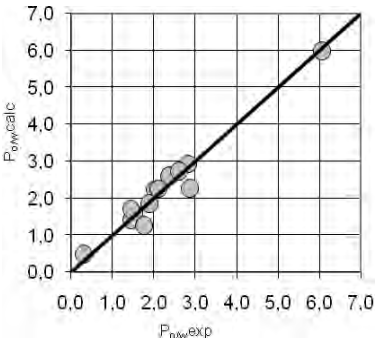

Fig. 6. Scatter diagram of the experimental values $P_{o/w}$ relative to their estimated values calculated by Eq. (3)

Table 3

Coefficients of regression equation with confidence intervals and relative errors

Coefficient	a_0	a_P	a_{PP}	a_N	a_G	a_F	a_{GF}
Value	7.2	-10.7	7.0	-2.8	-0.6	-0.22	0.06
Confidence interval*	±0.6	±1.0	±0.6	±0.6	±0.1	±0.06	±0.02
Relative error, %	8	10	9	20	18	24	25

Note: * confidence intervals are estimated at 90% confidence level

It was established that the selected parameters have different contributions in the obtained correlation dependence. This means that factors have a different impact on the copolyester distribution between phases. Parameter *P* has the largest (about 65 %) contribution to the regression; in Eq. (4) this parameter is represented by two terms – linear and quadratic ones, indicating the complex dependence of $P_{o/w}$ on the molar mass of PEG blocks. This effect is the main reason that complicates the establishment of a direct relationship between factors according to Table 2. The evaluation of PEG molar mass influence on the value of $P_{o/w}$ is shown in Fig. 7.

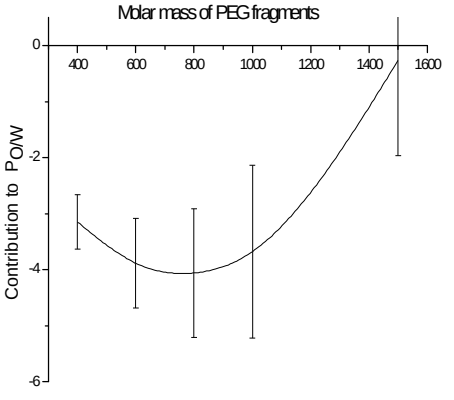

Fig. 7. $P_{o/w}$ values *vs.* the molecular weight of PEG in the copolyester macromolecule (according to Eq.(4))

One can see that the increase in PEG molar mass from 400 to 800 Da leads to a statistically significant decrease in $P_{o/w}$ values. It means that the introduction of PEG residues with a higher molar mass (within the mentioned range) into the copolyester composition leads to a logical increase in the share of copolyester which is redistributed to the aqueous phase. At the values of molar masses 800 or more the expected increase in hydrophilicity is not observed. In this case, for copolyester macromolecules with PEG molar mass of 1500 Da, the changes in redistribution are obviously related to the effects of microemulsion and the formation of a reverse micellar phase in octanol. Nevertheless, with the increase in PEG molar masses to 1500 Da, the ability of the copolyester dispersed phase particles for self-stabilization in the aqueous medium increases [8, 9]. Therefore, in terms of obtaining copolyester self-stabilized dispersions in the aqueous medium, it is expedient to use PEG fragments with a molar mass close to 1500 Da. In addition, such dispersions have the ability to redistribute into oleophase best of all.

The next by importance (20 %) contribution to the regression has the parameter *N*, which characterizes the nature of the low molecular diol used in the copolyester composition. As shown in Fig. 8, the presence or absence of dipropylene glycol in the fragment structure does not lead to significant changes in the copolyester HLB and it exhibits insignificant lipophilic properties (bars 2 and 3). However, the introduction of more hydrophilic diethylene glycol decreases the $P_{o/w}$ value and increases macromolecules HLB (bar 1). This fact is in a good agreement with the value predicted by the interpolation equation.

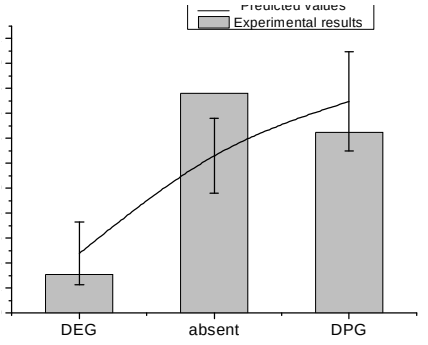

Fig. 8. Effect of low molecular diol on $P_{o/w}$ distribution coefficient: GluLa-PEG1000-DEG-F (1); GluLa-PEG1000-F (2) and GluLa-PEG1000-DPG-F (3)

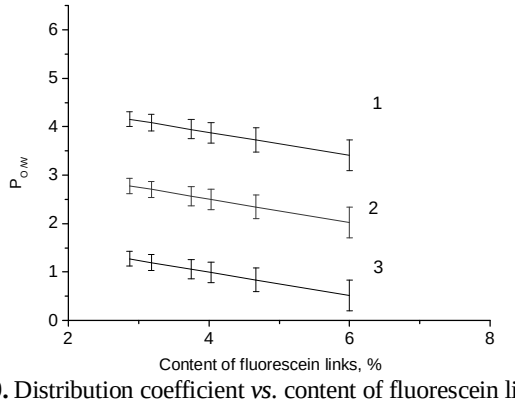

Fig. 9. Distribution coefficient *vs.* content of fluorescein links

Factor *G* has a similar effect. The increase in HLB value from 1.8 for GluSt to 4.44 for GluLa results in a proportional decrease in $P_{o/w}$ values and to the change in the copolyester redistribution between aqueous and oleophase in favor of water. However, the contribution of this parameter to the regression is relatively low and does not exceed 10 %.

The content of fluorescein fragments in copolyester (*F*) has the smallest, though statistically significant, contribution to regression. In the interpolation equation, its effect on the $P_{o/w}$ value is demonstrated by two terms – linear term *F* and mixed term *G*·*F*. The appearance of a mixed term in the interpolation equation is due to the fact that *F* is the only factor that quantitatively characterizes the copolyester composition. The total contribution of these terms does not exceed 5 %, but their exclusion from the interpolation equation reduces the coefficient of multiple correlation to 0.94, and most regression coefficients in this case retain their significance only at 80% confidence level. The influence of this factor is shown in Fig. 9 at *G* = 4.44 (GluLa, lines 1 and 3), and *G* = 1.8 (GluSt, line 2). The obtained dependences visually allow us to estimate the significance of this factor influence on the value of $P_{o/w}$ at different levels of factors *G* and *P*. In this regard, it should be noted that the increase in the content of the fluorescein fragment in all cases leads to a slight decrease in $P_{o/w}$ values.

The detected dependences and the evaluation of the significance of the copolyester fragments qualitative characteristics allows to predict the copolyester ability to be redistributed between the aqueous and the oleophilic phases more accurately than HLB calculated by the Davis formula.

4. Conclusions

Lipophilic fragments in the copolyesters structure can solubilise the drugs in the nanoparticles on their basis and interact with cell membranes, while the hydrophilic fragments of hydrated polyoxyether diols stabilize the dispersed phase in the aqueous medium and provide drugs delivery with the blood flow and intercellular fluid to target organs. The factors that have the most significant influence on the lyophilicity coefficient and HLB of the obtained fluorescein-containing copolyester were determined. The satisfactory coincidence of colloid-chemical characteristics which were obtained experimentally and calculated on the basis of the copolyester composition obtained using ^{1}H NMR spectroscopy allows to predict their properties, depending on the components choice at the synthesis stage. The insignificant influence of fluorescein in the macromolecules structure on their lyophilicity was established, which allows to create complex copolyester with adjusted properties and marked by fluorescent marker. Most of the investigated copolyesters characterized by logarithm values of the distribution coefficient ($\log P_{o/w}$ = -0.5–0.5) indicate their capability of equal distribution between the aqueous and lipid phases, which is one of the determining factors when creating the carrier material for drugs delivery systems.

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ДОСЛІДЖЕННЯ АМФІФІЛЬНИХ ВЛАСТИВОСТЕЙ КОПОЛІЕСТЕРІВ З ХРОМОФОРНИМИ ГРУПАМИ

Анотація. *Визначено коефіцієнти розподілу макромолекул амінофункційних кополістерів з хромофорними групами в системі н-октанол-вода та експериментальні і розрахункові характеристики їх гідрофільно-ліпофільного балансу(HLB). Проведено множинний регресійний аналіз та отримано інтерполяційне рівняння коефіцієнту ліпофільності від параметрів, які характеризують якісний та кількісний склад кополіестеру. Виявлено чинники, які мають найбільш суттєвий вплив на коефіцієнт ліпофільності та HLB одержаних флуоресцеїнвмісних кополіестерів.*

Ключові слова*: коефіцієнт розподілу, гідрофільно-ліпофільний баланс, кополіестери, флуоресцеїн, системи доставки ліків.*