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SURFACE-ACTIVE AGENTS FROM THE GROUP OF POLYOXYETHYLATED GLYCEROL ESTERS OF FATTY ACIDS. PART III. SURFACE ACTIVITY AND SOLUBILIZING PROPERTIES OF THE PRODUCTS OF OXYETHYLATION OF LARD (ADEPS SUILLUS, F.P. VIII) IN THE EQUILIBRIUM SYSTEM IN RELATION TO LIPOPHILIC THERAPEUTIC AGENTS (CLASS II AND III OF BCS)

MICHAŁ J. NACHAJSKI[1]*, JOWITA B. PIOTROWSKA[2], MICHAŁ K. KOŁODZIEJCZYK[1], MAREK LUKOSEK[3] and MARIAN M. ZGODA[1]

[1]Department of Drug Form Technology, Chair of Applied Pharmacy, Faculty of Pharmacy, Medical University in Lodz, Muszyńskiego 1, 90-151 Łódź, Poland
[2]Hospital Pharmacy – Cytotoxic Drug Laboratory, M. Kopernik Provincial Specialist Hospital in Lodz, Pabianicka 62 93-513 Łódź, Poland
[3]Institute of Heavy Organic Synthesis ICSO „ Blachownia" in Kędzierzyn Koźle, Poland

Abstract: Research was conducted into the solubilization processes of diclofenac, ibuprofen, ketoprofen and naproxen in equilibrium conditions in the environment of aqueous solutions of oxyethylated lard's fractions (Adeps suillus, Polish Pharmacopoeia VIII). The determined thermodynamic (cmc, ΔG_m^0) and hydrodynamic (R_0, R_{obs}, Ω, M_η) parameters characterizing the micelle of the solubilizer and the adduct demonstrate that lipophilic therapeutic agents are adsorbed in a palisade structure of the micelle due to a topologically created so-called "lipophilic adsorption pocket". This shows that the hydrophilicity of the micelle and the adsorption layer decreases at the phase boundary , which is confirmed by the calculated values of coefficients A_m and $r_{\cdot A}$. The results obtained indicate the possibility of making use of the class of non-ionic surfactants which are not ksenobiotics for the modification of the profile of solid oral dosage forms with lipophilic therapeutic agents from the II class of Biopharmaceutics Classification System (BCS).

Keywords: Surface activity, micellar solubilization, products of oxyethylation, lard, diclofenac, naproxen, ketoprofen, ibuprofen

Modern technology of drug forms applied on skin, cosmetics and solid oral dosage forms of preparations (tablets, capsules, implants) searches for new classes of excipients which would not be xenobiotics in relation to the human enzymatic system (1-5).

After fragmentary biodegradation on the surface of the skin or after biotransformation in the alimentary canal, fatty acids (6), vitamins (7-9) and sterols (10) compatible with sebum or nourishment are also expected to appear. They would also perform the function of promoters of mass exchange at the phase boundary (11).

The conducted chromatographic analysis (HPLC and GC) of the products of catalytic oxyethylation of lard's fractions (6), and above all the research on the structural level of hydrophilic-lipophilic balance as well as the viscosity of their aqueous solutions (12, 13), served as a basis for preformulation research on surface activity and the process of equilibrium micellar solubilization of lipophilic therapeutic agents (14).

Making use of the results of research conducted so far on the process of equilibrium solubilization of selected classes of lipophilic therapeutic agents of BCS class II and IV by aqueous solutions of the products of oxyethylation of lanolin (15), fatty acid methyl esters of rape-seed oil (16), cholesterol (17), cholic acid (18) and ursodeoxycholic acid (19), comparative experimental research was conducted on surface activity and micellar solubilization of lipophilic therapeutic agents and rutin (rutoside)

* Corresponding author: e-mail: michal.nachajski@umed.lodz.pl

(20) by the products of oxyethylation of lard's triglycerides fractions (6, 12).

The results of the research will serve as a basis for the modification of selected absorption and cosmetic bases with a possibility of creating model preparations applied on skin in the form of emulsive ointment preparations and cosmetics.

MATERIALS AND METHODS

Materials

Diclofenac, 2-(2,6-dichloranilino) phenylacetic acid, SIGMA, Germany, D 6899; ibuprofen, α-methyl-4-(2-methylpropyl)phenylacetic acid, (ibuprofen powder USP/Eph), Malinckrodt Chemical, Lot. B14188; ketoprofen, 3-benzoyl-α-methyl-2-naphthaleneacetic acid, SIGMA, USP Grade.

Some physicochemical and thermodynamic values of selected non-steroidal anti-inflammatory and analgesic drugs associated with their solubility in water (21) were juxtaposed in Table 1.

Basic values characterizing the products of catalytic oxyethylation of lard's fractions were included in publications (6, 12). Fractions with the declared content of $n_{TE} = 40$ and high solubility in water were selected for research on the process of equilibrium solubilization of lipophilic therapeutic agents (6, 12).

Surface activity of aqueous solutions of the products of oxyethylation of lard's triglycerides

The numerical value of the surface tension coefficient - γ^{25}, was determined in accordance with the Polish Standard (PN/ISO) by means of the stalagmometric method (22). It served as a basis to estimate the critical micellar concentration (cmc) for the solubilizer and its adducts with lipophilic therapeutic agents on the basis of the following equation:

$$\gamma^{25} = f\ (c, \log c; g \times 100\ cm^{-3}) \text{ (Table 1)}$$

The line equations at $p = 0.05$ and $r^2 \geq 0.9980$ were used to describe the relationship between the coefficient of surface tension - γ^{25} and log c within the range of low concentrations ($y = a_1 \times \log c + b_1$) and higher concentrations ($y_2 = a_2 \times \log c + b_2$) – (Fig. 1), which were juxtaposed in Table 2.

Both lines intersect at the identity point of solubilizer and its adduct's concentration range, which corresponds with the critical micellar concentration (cmc) and it is calculated on the basis of the following equation:

$$\log cmc = b_2 - b_1/a_1 - a_2$$

The numerical values of cmc (mol/dm^3) enabled also calculation of the thermodynamic potential for micelle formation (ΔG_m^0) on the basis of the equation:

$$\Delta G_m^0 = 2.303\ RT \times \log cmc$$

of a complex system - solubilizer and its adducts with lipophilic therapeutic agents.

The numerical value of a decrease of the surface tension coefficient - γ_{cmc}^{25} in the critical area was used to estimate the surface occupied by lyophilic segments of the solubilizer and the adduct - A_m at the phase boundary (water/air) on the basis of the surface state equation (23):

$$f \times A_m = k \times T,$$

where: $f = \gamma_{H_2O}^{25} - \gamma_{cmc}^{25}$.

The results obtained in the course of research are presented in Table 3.

Solubilization of lipophilic therapeutic agents

By means of the spectrophotometric method, in analogy to publications (15, 18, 19), the amount of the surfactant: diclofenac, ibuprofen, ketoprofen and

Table 1. Practical solubility $S_{(prac.)}(25)$, experimental $S_{(exp.)}(25)$ and theoretical S_W (25) of NSAIDs in water, the calculated melting entropy $\Delta H_{f(1)}$ and the mole fraction of the ideal solubility logxfor their structures.

Therapeutic agent	$T_m{}^oK$*	S_W mg/dm^3	$S_{(exp.)}$ mg/dm^3	$S_{(prac.)}$ mg/dm^3	logP**	$\Delta S_{f(1)}$	$\Delta H_{f(1)}$	$-\log x^i_{2\ (1)}$
Diclofenac	557.15	4.47	0.82	19.39	3.9	8.9235	4971.73	2.590
Ibuprofen	349.15	68.40	49.00	55.33	3.6	2.4832	867.03	0.510
Ketoprofen	367.15	21.30	51.00	129.21	3.2	3.1198	1145.46	0.690
Naproxen	426.15	51.00	15.9	63.83	2.8	5.0505	2152.28	1.280
Acetylsalicylic acid	408.15	1.46×10^3	4.6×10^3	-	1.4	4.4801	1828.58	1.100
Salicylic acid	431.15	1.13×10^3	2.24×10^3	-	-	5.2066	2244.86	1.330

* $T_m{}^oK = 273.15 + t^oC$, ** logP – partition coefficient logarithm

Table 2. Physicochemical values characterizing surface activity of the products of oxyethylation of lard's triglycerides fractions and their micellar adducts with non-steroidal anti-inflammatory drugs [NSAID].

Oxyethylation product Therapeutic agent	Approximation equation $-\gamma^{25}=f(\log c)$		log cmc	cmc $g \times 100cm^{-3}$	cmc $\times 10^{-4}$ $mol \times dm^{-3}$	ΔG^0_m kJ/dm^3	γ^{25}_{cmc} $mJ \times m^{-2}$	$A_m \times 10^{-19}m^2$	$r'_{A_1} \times Å$
	$y_1 = a_1x + b_1$	$y_2 = a_2x+b_2$							
1. Frisol 37R × n_{TE} = 40	y_1 = -8.6117x + 44.206	y_2 = -3.0736x + 47.606	-0.613	0.2432	5.9116	-18.4304	49.50	1.8311	2.4185
Diclofenac	y_1 = -12.009x + 34.105	y_2 = -3.3656x + 41.104	-0.8096	0.1550	3.7677	-19.5473	44.47	1.5017	2.1869
Ibuprofen	y_1 = -17.279x + 22.071	y_2 = -3.8348x + 34.979	-0.9227	0.1114	2.7078	-20.3662	38.70	1.2368	1.9846
Ketoprofen	y_1 = -11.792x + 36.224	y_2 = -3.4465x + 43.099	-0.8238	0.1501	3.6486	-19.6269	46.54	1.6180	2.2699
Naproxen	y_1 = -9.8986x + 39.836	y_2 = -3.8487x + 43.652	-0.6313	0.2337	5.6807	-18.5292	45.49	1.5539	2.2245
2. Frisol 50i × n_{TE} = 40	y_1 = -8.1698x + 51.839	y_2 = -3.6370x + 54.227	-0.5268	0.2973	9.9397	-17.1421	55.88	2.5567	2.8534
Diclofenac	y_1 = -16.3640x + 23.744	y_2 = -2.2371x + 39.745	-1.1326	0.07367	2.4630	-20.6012	41.80	1.3639	2.0841
Ibuprofen	y_1 = -17.0101x + 22.365	y_2 = -2.6200x + 36.484	-0.9812	0.1044	3.4904	-19.7368	39.43	1.2646	2.0068
Ketoprofen	y_1 = -11.0540x + 40.071	y_2 = -3.4218x + 45.610	-0.7257	0.1881	6.2888	-18.2771	47.59	1.6877	2.3183
Naproxen	y_1 = -10.8330x + 38.374	y_2 = -4.2830x + 43.737	-0.8188	0.1517	5.0718	-18.8103	46.50	1.6155	2.2682
3. Frisol 50i × n_{TE}=20	y_1 = -10.6210X + 51.812	y_2 = -2.4292X + 54.812	-0.3021	0.4988			55.18		
4. Friolehina FL6 × n_{TE} = 40	y_1 = -15.8060x + 40.273	y_2 = -6.0126x + 50.072	-1.0006	0.09987	4.4199	-19.1516	53.30	2.2024	2.6483
Diclofenac	y_1 = -13.2650x + 32.542	y_2 = -3.3664x + 41.109	-0.8655	0.1363	6.0319	-18.3805	44.46	1.4957	2.1825
Ibuprofen	y_1 = -16.1960x + 25.058	y_2=-4.4540x + 34.544	-0.8078	0.1556	6.8860	-18.0521	39.43	1.2646	2.0068
Ketoprofen	y_1 = -14.5120x + 28.963	y_2 = -2.2018x + 40.450	-0.9331	0.1166	5.1601	-18.7675	42.65	1.5057	2.1879
Naproxen	y_1 = -12.7710x + 34.231	y_2 = -3.6896x + 43.238	0.9919	0.1018	4.5051	-19.1041	46.44	1.6465	2.2898
5. Friolehina FL12i × n_{TE} = 40	y_1 = -11.3690x + 46.710	y_2 = -6.7895x + 49.625	0.6365	0.2309	8.1615	-17.6308	6 53.29	2.2025	2.6484
Diclofenac	y_1 = -14.2439x + 30.174	y_2 = -3.3655x + 41.104	-0.9931	0.1016	3.5912	-19.6662	44.46	1.4957	2.1825
Ibuprofen	y_1 = -16.0660x + 25.649	y_2 = -3. 7255x + 34.694	-0.7329	0.1849	6.5355	-18.1816	36.08	1.1466	1.9109
Ketoprofen	y_1 = -14.3710x + 29.958	y_2 = -2.2989x + 41.245	-0.9349	0.1162	4.0928	-19.3421	43.54	1.4474	2.1469
Naproxen	y_1 = – 13.2110x + 31.472	y_2 = -3.5159x + 41.923	-1.0779	0.08356	2.9431	-20.159	45.43	1.5504	2.2220
6. Friolehina FL 12N × n_{TE} = 40	y_1 = -10.9320x + 47.343	y_2 = -4.1441x + 50.636	-0.4851	0.3272	10.6476	-16.9715	53.29	2.2025	2.6484
Diclofenac	y_1 = -11.3530x + 35.518	y_2 = -2.5408x + 41.684	-0.7002	0.1995	6.4921	-18.1982	44.46	1.4957	2.1825
Ibuprofen	y_1 = -17.2380x + 21.941	y_2 = -3.7249x + 34.697	-0.9441	0.1137	3.7001	-19.5922	38.70	1.2103	1.9633
Ketoprofen	y_1 = -14.3710x + 29.718	y_2 = -2.4962x + 41.280	-0.9736	0.1063	3.4591	-19.7591	43.59	1.4035	2.1142
Naproxen	y_1 = -12.7320x + 33.099	y_2= -3.7471x + 41.461	-0.9441	0.1138	4.2761	-19.2335	43.60	1.6123	2.2659
7. Curtoil × n_{TE} = 40	y_1 = -11.1450x + 39.315	y_2 = -5.6554x + 44.668	-0.9751	0.1059	4.2761	-19.2335	49.70	1.8475	2.4256
Diclofenac	y_1 = -12.3240x + 34.967	y_2 = -1.7060x + 44.708	-0.9174	0.1209	4.8817	-18.9051	46.44	1.6117	2.2655
Ibuprofen	y_1 = -17.1340x + 17.604	y_2 = -2.8138x + 33.876	-1.1362	0.07306	2.9501	-20.1538	37.97	1.2103	1.9632
Ketoprofen	y_1= -12.3460x + 31.921	y_2 = -3.0921x + 39.557	-0.8251	0.1496	6.0406	-18.3769	42.65	1.4028	2.1136
Naproxen	y_1 = -12.9961x + 34.073	y_2 = -1.8653x + 44.517	-0.9383	0.1153	4.6556	-19.0226	46.45	1.6123	2.2660

Table 3. Basic viscosity values characterizing the process of micellar solubilization by oxyethylated lard's fractions at n_{TE} = 40 in equilibrium system.

Solubilizer Therapeutic agent	GLL [η]	M_η	n_S *	$R_o \times 10^{-7}$ cm	$R_{obs.} \times 10^{-8}$ cm	$\Omega \times 10^{-20}$ cm^3	c_S mg dm^3	K_w^m
1. Friolehina FL6 × n_{TE} = 40 + Diclofenac	0.101813	2513.58	2.62	4.2085	3.4362	1.6995	117.0956	5.0389
2. Friolehina FL 12i × n_{TE} = 40 + Diclofenac	0.189333	7021.07	17.89	7.2886	5.9510	8.8283	118.6844	5.1209
3. Friolehina FL 12N × n_{TE} = 40 + Diclofenac	0.111681	2929.93	3.95	4.5679	3.7295	2.1731	244.2008	11.5941
4. Frisol 37R × n_{TE} = 40 + Diclofenac	0.105614	2671.11	3.15	4.3475	3.5496	1.8735	125.0397	5.4486
5. Frisol 50i × n_{TE} = 40 + Diclofenac	0.098506	2380.11	2.15	4.0874	3.3876	1.5571	134.5726	5.9403
6. Curtoil × n_{TE} = 40 + Diclofenac	0.103533	2580.55	2.85	4.2716	3.4876	1.7771	296.6317	14.2981
$n_s \cdot = \frac{M_h - M_{cz.\,so\,lub.}}{295.11}$								
1. Friolehina FL6 × n_{TE} = 40 + Ibuprofen	0.241138	10478.72	42.35	9.0287	7.3717	16.7811	3042.8015	53.9937
2. Friolehina FL 12i × n_{TE} = 40 + Ibuprofen	0.257767	11701.96	48.28	9.5778	7.8201	20.0324	3081.7120	54.6969
3. Friolehina FL 12N × n_{TE} = 40 + Ibuprofen	0.270672	12687.72	52.94	10.0011	8.1656	22.8073	3859.9220	68.7618
4. Frisol 37R × n_{TE} = 40 + Ibuprofen	0.373193	21593.74	96.23	6.1686	10.8509	53.5191	3354.0856	59.6196
5. Frisol 50i × n_{TE} = 40 + Ibuprofen	0.309748	15861.57	68.43	11.2691	9.2009	32.6288	3431.9066	61.0261
6. Curtoil × n_{TE} = 40 + Ibuprofen	0.218134	8876.00	34.59	8.2619	6.7457	12.8584	3782.1011	67.3553
$n_s \cdot = \frac{M_h - M_{cz.\,so\,lub.}}{206.3}$								
1. Friolehina FL6 × n_{TE} = 40 + Ketoprofen	0.102719	2550.98	3.18	5.2438	3.4633	1.7402	687.6574	4.3220
2. Friolehina FL 12i × n_{TE} = 40 + Ketoprofen	0.130523	3792.76	8.07	5.2438	4.2815	3.2876	675.0629	4.2245
3. Friolehina FL 12N × n_{TE} = 40 + Ketoprofen	0.145734	4552.14	10.96	5.7813	4.7203	4.4058	648.2997	4.0174
4. Frisol 37R × n_{TE} = 40 + Ketoprofen	0.150378	4794.80	12.01	5.9441	4.8532	4.7882	890.6028	5.8926
5. Frisol 50i × n_{TE} = 40 + Ketoprofen	0.131167	3823.76	8.18	5.2667	4.3001	3.3309	951.9911	6.3677
6. Curtoil × n_{TE} = 40 + Ketoprofen	0.118721	3241.94	5.91	4.8218	3.9369	2.5561	712.8463	4.5169
$n_s \cdot = \frac{M_h - M_{cz.\,so\,lub.}}{254.3}$								
1. Friolehina FL6 × n_{TE} = 40 + Naproxen	0.124591	3511.65	7.69	5.0323	4.1088	2.9056	365.8559	4.7317
2. Friolehina FL 12i × n_{TE} = 40 + Naproxen	0.144681	4497.78	11.97	5.7443	4.6901	4.3219	355.3648	4.5673
3. Friolehina FL 12N × n_{TE} = 40 + Naproxen	0.122105	3396.37	7.08	4.9433	4.0361	2.7542	335.3356	4.2535
4. Frisol 37R × n_{TE} = 40 + Naproxen	0.146479	4590.71	12.37	5.8075	4.7416	4.4658	446.9241	6.0017
5. Frisol 50i × n_{TE} = 40 + Naproxen	0.149507	4748.91	13.05	5.9136	4.8283	4.7152	454.5541	6.1213
6. Curtoil × n_{TE} = 40 + Naproxen	0.150295	4790.43	13.25	5.9412	4.8508	4.7815	436.4329	5.8374
$n_s \cdot = \frac{M_h - M_{cz.\,so\,lub.}}{230.3}$								

naproxen, solubilized in equilibrium conditions in aqueous solutions was determined.

Approximation equations describing the relationship between the concentration - c_{exp} and the measured value of absorbance – A for tested lipophilic therapeutic agents – included in publications (15, 18, 19) after transformation to the form – $c_S = A – a/b$ made it possible to calculate the amount of the solubilized agent.

The obtained results served as a basis for calculation of the numerical value of the micellar partition coefficient - K_W^m (Table 3).

Viscosity of aqueous solutions of the product of oxyethylation of lard's triglycerides and their adducts after equilibrium micellar solubilization

The limiting viscosity number GLL, [η] of aqueous solutions of solubilizers and their adducts after equilibrium micellar solubilization was determined according to the Polish Standard by means of an Ubbelohde's viscosimeter (24).

The value served as a basis, as in publications (16-19), for calculating some viscosity values: M_η, R_o, R_{obs}, Ω and the solubilization indexes - n_S.

DISCUSSION

The research results presented in Table 2 indicate that in aqueous micellar solutions of Frisol 37R × n_{TE} = 40, Frisol 50i × n_{TE} = 40, Friolehina FL12i × n_{TE} = 40 and Friolehina FL12N × n_{TE} = 40, the thermodynamic potential for the adduct's micelle formation - ΔG_m^0 (add.) is lower by 2-3 kJ in relation to the solubilizer's ΔG_m^0.

This experimental fact supports the increase of thermodynamic stability of the adduct with lipophilic therapeutic agents (II class of BCS) in relation to the solubilizer's micelle:

ΔG_m^0 (add.) < ΔG_m^0 (solubilizer's micelle).

However, in the case of the Curtiol's*n_{TE} = 40 and Friolehina's FL6* n_{TE} = 40 micelles, the thermodynamic stability of the micelle of the adduct with diclofenac, ketoprofen, ibuprofen and naproxen is

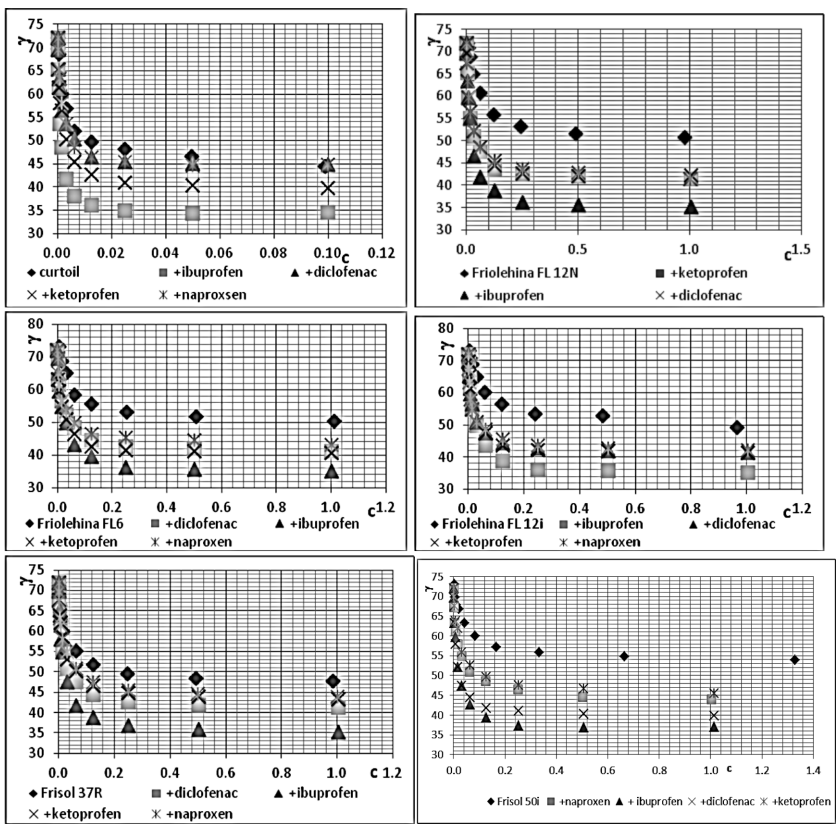

Figure 1 The relationship between the coefficient of surface tension γ^{25} [mN/m] and the concentration [mg/100 mL] of solubilizers (n_{TE} = 40) and their micellar adducts with diclofenac, ibuprofen, ketoprofen and naproxen

considerably diverse; ΔG_m^0 (add.) > ΔG_m^0 (solubilizer's micelle). The exception in those systems is the ibuprofen adduct with the Curtiol's micelle × n_{TE} = 40.

In addition, on the basis of the research results included in Table 3, it should be stated that after equilibrium solubilization of NSAIDs the calculated effective volume of the adduct is basically higher (while maintaining the order of magnitude) than the effective volume of the solubilizer's micelle: Ω(add.) > Ω(solub.).

In this situation, regardless of the process mechanisms (including its complexity), it appears that the adsorption in a topological niche of the micelle of lyophilic therapeutic agent molecules (II class of BCS) results in the increase of the adduct's hydrophilicity. It is reflected in the regression of the numerical value of A_m coefficient (while maintaining the order of magnitude) (Fig. 2).

In order to define the preferences of the NSAIDs' structure for a topological space and the

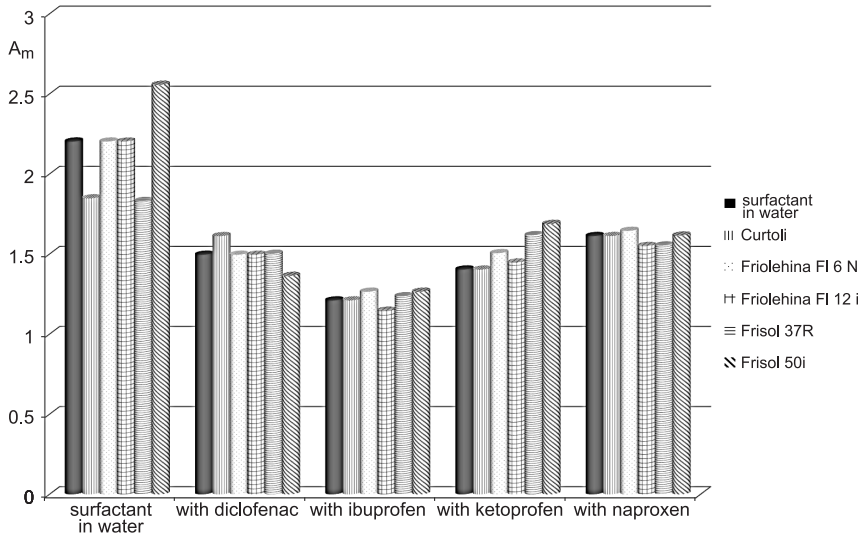

Figure 2. Calculated A_m values for micellar solubilizers (n_{TE} = 40) and their adducts with diclofenac, ibuprofen, ketoprofen and naproxen

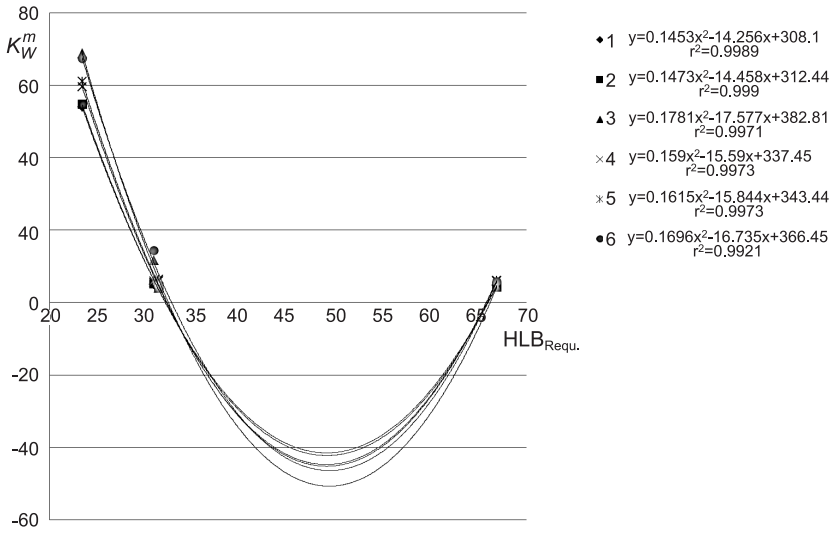

Figure 3. The relationship between the partition coefficient K_w^m and the soluble value of HLB_{requ}

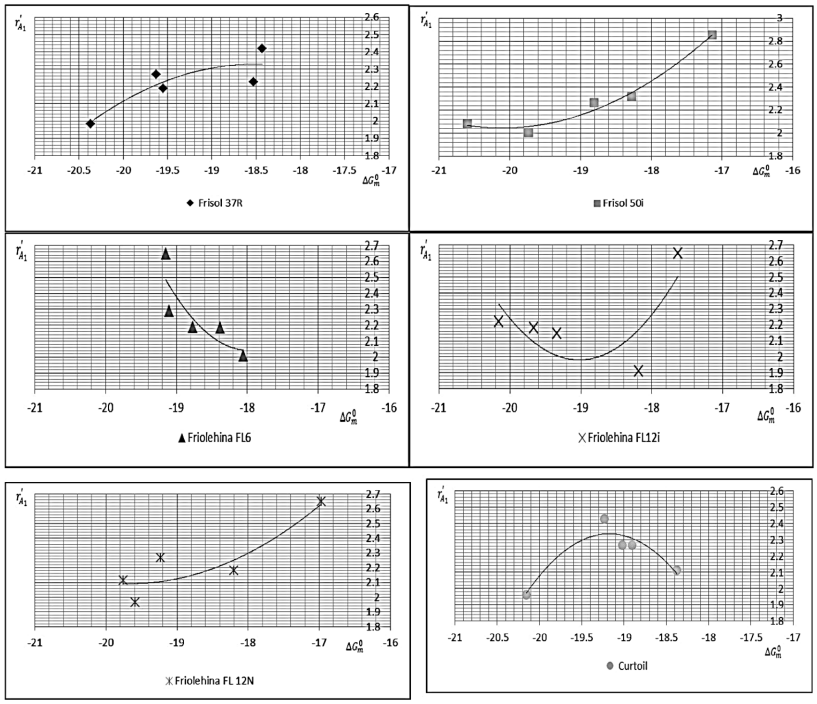

Figure 4. Relationship between r'_{A_1} and ΔG_m^0

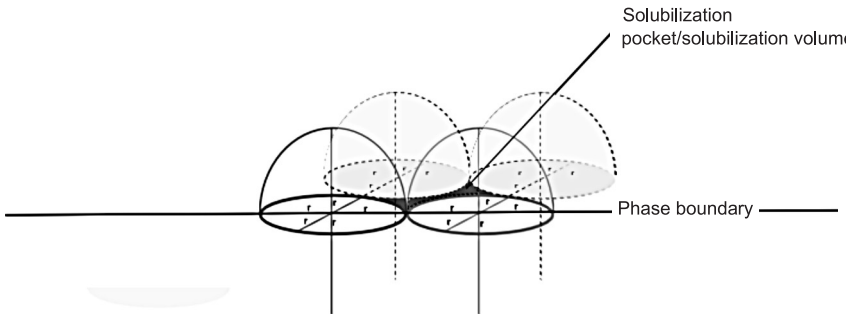

Figure 5. Model of solubilizing space of the products of oxyethylation of lard's fractions at $n_{TE} = 40$ at the phase boundary

adsorption layers of the solubilizer's micelle, the course of dependence between K_W^m (micellar, soluble partition coefficient) and $HLB_{Requ.}$: $K_W^m = f(HLB_{Requ.})$ was investigated on the basis of the data juxtaposed in Tables 3, 4 and Figure 3.

Taking into account the small number of the class (n = 4), the course of dependence between K_W^m (y) and $HLB_{Requ.}$ (x) for the process of equilibrium solubilization in the environment of non-ionic surfactants – fig. 3, was drawn as a trend line and at p = 0.05, $r^2 \geq 0.9920$ described with quadratic polynomial equations of the type: $y = cx^2 - bx + a$ for:

(1) Aqueous solution of Friolehina FL6 $n_{TE} = 40$
$y = 0.145x^2 - 14.256x + 308.10$

(2) Aqueous solution of Friolehina FL12i $n_{TE} = 40$
$y = 0.147x^2 - 14.458x + 312.44$

(3) Aqueous solution of Friolehina FL12 $n_{TE} = 40$
$y = 0.178x^2 - 17.577x + 382.81$

(4) Aqueous solution of Curtiol $n_{TE} = 40$

$y = 0.159x^2 - 15.590x + 337.45$

(5) Aqueous solution of Frisol R37R $n_{TE} = 40$

$y = 0.161x^2 - 15.844x + 343.44$

(6) Aqueous solution of Frisol 50i $n_{TE} = 40$

$y = 0.169x^2 - 16.735x + 366.45$

The course of the above dependences shows that the solubilizing preferences of the surfactant's micelle result not only from the type of fatty acids (particularly those with double bonds –HC=CH- (cis/trans isomerism)) in a triglyceride's molecule, but they are also the consequence of the thermodynamic value of $HLB_{Requ.}$ of a therapeutic agent.

The ideal surface state equation (23) in an application version – $f(\pi)A_1 = kT$ enables calculation of the A_1 value i.e., the mean surface per one surfactant's molecule at the phase boundary.

Simultaneously, at low surface pressure values, the surfactant's – solubilizer's molecule – behaves as two-dimensional ideal gas at the phase boundary. Thus, the A_1 value enables estimating from the relationship $A_1 = \pi r^2$; $r'_{A_1} \cdot \sqrt{A/\pi}$ - the mean radius of the topological volume occupied by lipophilic fragment of a surfactant's molecule ("fishing float rule" – uplift over the phase boundary), which determines efficiency of the solubilization process (an increase of the actual solubility). Calculated numerical values of r'_{A_1} are presented in Table 2.

This situation through the investigation of the relationship between (Å) and for the micelle of the solubilizer's adduct with diclofenac, ibuprofen, ketoprofen and naproxen enables estimating (Fig. 4) the solubilization mechanism including application durability of the adduct .

The course of the above dependence at $p = 0.05$ was described with quadratic polynomial equations of the type $y = cx^2 + bx + c$ for:

(7) Micellar solution of Frisol 37R $n_{TE} = 40$ at $r^2 = 0.7521$ ($r = 0.8672$)

$y = -0.0984x^2 - 3.6451x - 3.4360$

(8) Micellar solution of Frisol 50i $n_{TE} = 40$ at $r^2 = 0.9801$ ($r = 0.9900$)

$y = 0.0920\ x^2 + 3.6982x + 39.2240$

(9) Micellar solution of Friolehina FL6 $n_{TE} = 40$ at $r^2 = 0.7160$ ($r = 0.8461$)

$y = 0.3294\ x^2 + 11.8550x + 108.6800$

(10) Micellar solution of Friolehina FL12i $n_{TE} = 40$ at $r^2 = 0.5527$ ($r = 0.7430$)

$y = 0.2718\ x^2 + 10.3390 + 100.3200$

(11) Micellar solution of Friolehina FL12N $n_{TE} = 40$ at $r^2 = 0.8180$ ($r = 0.9040$)

$y = 0.0741\ x^2 + 2.9140x + 30.7560$

(12) Micellar solution of Curtiol $n_{TE} = 40$ at $r^2 = 0.8836$ ($r = 0.9400$)

$y = -0.37988\ x^2 - 14.5660x - 137.3300$

From the course of the above relationships it appears that in the environment of micellar solutions of Frisol 37R $n_{TE} = 40$, Frisol 50i $n_{TE} = 40$ and Friolehina FL12i $n_{TE} = 40$ with the increase of the stability of a micellar adduct ΔG^0_m (of the adduct) < ΔG^0_m (H_2O) the numerical value decreases. However, in the environment of the micellar solution of Friolehina FL6 $n_{TE} = 40$, a case in which ΔG^0_m (of the adduct) > ΔG^0_m (H_2O) is noted with the regression of r'_{A_1} value, analogical as in the solubilization process mentioned above

For micellar solutions of Friolehina FL12, $n_{TE} = 40$ and Curtiol $n_{TE} = 40$ an asymptotically regressive character of the changes between r'_{A_1} and ΔG^0_m was noted.

Supplementing the above with the analysis of hydrodynamic parameters of the solubilizer's micelle and its micellar adduct with diclofenac, ibuprofen, ketoprofen and naproxen (R_0, $R_{Obs.}$, Ω and M_η) it should be emphasized – despite the complexity of the problem – that essentially in the environment of all tested oxyethylated derivatives, the regularity R_0, $R_{Obs.}$,Ω (of the adduct) > R_0, $R_{Obs.}$,Ω (of the solubilizer) is observed.

Concluding the research results and calculations, it can be stated that the effective micellar solubilization of lipophilic therapeutic agents from the II class of BCS is accompanied with the increase of hydrodynamic parameters (Table 3) together with the increase of hydrophilic structure of the micelle, which is observed as the A_1 and r'_{A_1} numerical value decrease.

This situation is influenced by the content of unsaturated fatty acids in a molecule of oxyethylated triglyceride (cis-trans isomerism) which was determined as the numerical value of an iodine number $L(I_2)$ (12).

CONCLUSIONS

1. The products of oxyethylation of lard's fractions with the declared content of oxyethylated segments – $n_{TE} = 40$ turned out to be selective solubilizers in relation to lipophilic therapeutic agents from the II class of BCS: diclofenac, ibuprofen, ketoprofen and naproxen. Ibuprofen is solubilized by the micellar solution of a surfactant in the most effective way , which is confirmed by the numerical value of the micellar partition coefficient K^m_W . In the quantitative approach, the solubilization process of diclofenac, ketoprofen and naproxen also enables the preformulation research on forming model solid dosage forms with modified pharmaceutical availability.

2. The estimation of a trend line between K_W^m and the thermodynamic value of HLB $_{requ}$ enables identification of the relationship between the level of HLB balance of the structure of the lipophilic therapeutic agent (diclofenac, ibuprofen, ketoprofen and naproxen), as well as properties of the structure of the solubilizers' micelle, which influences quantitive preferences in solubility progression. The results of the preformulation research indicate the possibility of using the products of oxyethylated lard's fractions at $n_{TE} = 40$ for creating a solid oral dosage form of the drug with ibuprofen (because of high K_W^m values) with an expected pharmaceutical availability profile.

3. Hydrodynamic parameters of the micelle of the surfactant and the adduct with diclofenac, ibuprofen, ketoprofen and naproxen, as well as calculated A_m and r'_{A_i} coefficients together with the equation of ideal surface state indicate that the adsorption of a therapeutic agent takes place in a palisade layer of the micelle – Fig. 5 at the increase of R_0, R_{obs}, Ω values of the micelle and with simultaneous decrease of its lipophilicity. However, it has an individual reference to its thermodynamic stability – ΔG_m^0.

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