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PHARMACEUTICAL TECHNOLOGY

USEFULNESS OF ROSEN'S POSTULATE FOR STUDYING THE RELATIONSHIP BETWEEN THE STRUCTURE OF CHOLIC ACID OXYETHYLATION PRODUCTS AND THE PROCESS OF SOLUBILIZATION OF LIPOPHILIC THERAPEUTIC AGENTS (BCS CLASS II AND IV) IN AQUEOUS SOLUTIONS IN EQUILIBRIUM

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Abstract: We verified the usefulness of "Rosen's postulate", i.e., the logarithm of reciprocal concentration of surfactant $-\log(1/c_{\pi=20})$ by which the surface tension of a solution can be decreased by 20 mJ/m^2 in relation to water (physiological value γ^{25} = 48–52 mJ/m^2) in the evaluation of the applicatory properties of cholic acid oxyethylation products. Moreover, the values of ΔG^0_m for solubilizers and their micellar adducts with diclofenac, naproxen, and loratadine constituted the basis for estimating the thermodynamic value of "Rebinder's effect", associated with change in the state of matter of therapeutic agent. We determined critical micellar concentration for the aqueous products of oxyethylation and for micellar adducts with diclofenac, naproxen, and loratadine, and used these values to calculate (thermodynamic potential of micelle formation).

Keywords: oxyethylation, cholic acid, oxyethylates of cholic acid, surfactants, Rosen's postulate

Rosen is known for implementing p value to the analysis of the surface activity of surfactants. This value is the logarithm of reciprocal concentration by which the surface tension of water can be decreased by 20 mN/m (1). Revealing the linear relationship between $\log(1/c_{\pi=20})$ and the number of carbon atoms in the lipophilic radical [(n_c)] of the homological structures of ionic and non-ionic surfactants constitutes the basis for using the directional coefficients of correlation equation to calculate the energy of transport to the phase boundary of lipophilic radical – $\Delta G_{tr(1)}[F_w\uparrow]$, as well as to the hydrophilic part of surfactant molecule – $\Delta G_{tr(h)}[F_c\downarrow]$.

Previous application studies of the surface activity and solubilization properties of the aqueous solutions of Pluronics and Rokopols (2), M-PEG (3, 4), and Rokanols and Rokacets (5, 6) constituted the basis for calculating $\log(1/c_{\pi=20})$ value and analyzing its relationship with the number of oxyethylated segments (CH_2CH_2O) in surfactant structure (7). The calculated values of transport energy, $\Delta G_{tr(h)}$ for hydrophilic segments $(CH_2CH_2O)_{n=1}$ and $\Delta G_{tr(1)}$ for lipophilic radicals allowed, in response to Laughlin's postulate (8), to propose H/L ΔG_{tr}(h/l) ratio as the thermodynamic version of hydrophilic-lipophilic balance (H/L, HLB). The previously published (9) thermodynamic approach to the hydrophilic-lipophilic balance H/L (ΔG_{tr}) of surfactants can explain the process of the micellar solubilization of lipophilic therapeutic agent (solid body) in equilibrium by the micellar solution of surfactant ($c_{exp} \geq$ cmc) at phase boundary. These findings constituted the basis for verifying the possibility of using "Rosen's postulate" not only to determine the surface activity of the aqueous solutions of cholic acid oxyethylation products with n_{TE} = 20–70, but also to explain the so-called Rebinder's effect, which in thermodynamic approach accompanies the process of the solubilization of lipophilic therapeutic agents (BCS class II and IV) in equilibrium in the aqueous solutions of surfactant with $c_{exp} \geq$ cmc (critical micellar concentration) (10–14).

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Table 1. Correlation formulas describing relationship: $\gamma^{25}_{roz} = f(c, mol/dm^3)$, constituting the basis for calculating "Rosen's postulate" – $\log(1/c_{\pi=20})$, along with the determined number of n_{TE} and HLB^{1HNMR} for solubilizer and its micellar adducts with diclofenac, naproxen, and loratadine.

Solubilizer Cholic acid Therapeutic agent	**Determined n_{TE}**	**HLB^{1HNMR}**	**ΔG^0_m kJ/mol**	**Correlation formula: $\gamma^{25}_{roz.} = f(c, mol/dm^3)$ $c_{\pi=20}$**			**$\times 10^4$ mol/dm^3**	**$\log[1/c_{\pi=20}]$**
				r^2	a ± da[$\gamma^{25}_{gram.}$]	b ± db		
1. Cholic acid n_{TE} = 20	23.79	12.85	–19.7647	0.9708	69.7142 ± 3.6484	–175235.2 ± 79491.3	1.0125	3.9945
2. Cholic acid n_{TE} = 30	29.88	13.14	–19.6345	0.9901	70.3569 ± 1.2116	–179686.4 ± 47059.3	1.0232	3.9900
3. Cholic acid n_{TE} = 40	42.66	15.01	–19.8823	0.9918	71.2818 ± 0.9700	–180235.1 ± 42488.9	1.0714	3.9700
4. Cholic acid n_{TE} = 50	50.11	16.59	–20.2497	0.9755	70.7455 ± 1.8763	–242231.4 ± 100258.7	1.1342	3.9453
5. Cholic acid n_{TE} = 60	57.28	17.79	–20.5486	0.9761	69.5929 ± 2.1544	–149315.4 ± 61096.9	1.1802	3.9280
6. Cholic acid $n_{T E}$ = 70	73.57	19.22	–21.8211	0.9803	66.4608 ± 1.0527	–110624.0 ± 40920.2	1.3099	3.8828
Diclofenac – adduct								
1. Cholic acid n_{TE} = 20	20.37	15.59	–19.4925	0.9921	69.8262 ± 1.1407	–194765.3 ± 45202.7	0.9168	4.0377
2. Cholic acid n_{TE} = 30	28.01	16.54	–19.5131	0.9901	70.5182 ± 1.4522	–227375.0 ± 59239.5	0.8157	4.0884
3. Cholic acid n_{TE} = 40	39.11	17.38	–20.2899	0.9919	69.8224 ± 1.1555	–223134.0 ± 52425.8	0.8001	4.0968
4. Cholic acid n_{TE} = 50	51.85	17.95	–20.7147	0.9808	68.7459 ± 1.4252	–244641.0 ± 89154.6	0.6857	4.1638
5. Cholic acid n_{TE} = 60	57.22	18.12	–21.0969	0.9523	69.1569 ± 2.4991	–332979.1 ± 195952.1	0.5161	4.2872
6. Cholic acid n_{TE} = 70	67.09	18.37	–21.7467	0.9779	70.7762 ± 1.9292	–395400.7 ± 155289.6	0.4756	4.3272
Naproxen – adduct								
1. Cholic acid n_{TE} = 20	19.22	16.66	–19.7322	0.9842	71.0299 ± 1.7985	–238866.8 ± 78829.1	0.7979	4.0980
2. Cholic acid n_{TE} = 30	30.09	16.74	–19.7898	0.9919	69.8225 ± 1.1555	–223134.0 ± 52425.8	0.8001	4.0968
3. Cholic acid n_{TE} = 40	40.77	17.44	–20.1698	0.9811	69.3128 ± 1.4891	–2217841.4 ± 78742.7	0.7961	4.0990
4. Cholic acid n_{TE} = 50	51.01	17.64	–20.7838	0.9565	70.3319 ± 2.6044	–314868.7 ± 176413.8	0.5831	4.2342
5. Cholic acid n_{TE} = 60	56.61	18.11	–20.9758	0.9921	69.5545 ± 1.1025	–347707.3 ± 80695.2	0.5057	4.2961
6. Cholic acid n_{TE} = 70	65.29	18.33	–21.5748	0.9374	67.2716 ± 2.6267	–347344.5 ± 237046.9	0.4405	4.3560
Loratadine – adduct								
1. Cholic acid n_{TE} = 20	22.21	15.85	–19.6127	0.9803	66.4607 ± 1.0528	–110624.0 ± 40920.2	1.3099	3.8227
2. Cholic acid n_{TE} = 30	31.39	16.85	–19.2241	0.9991	70.1485 ± 0.3937	–176915.3 ± 13117.5	1.0275	3.9882
3. Cholic acid n_{TE} = 40	42.98	17.58	–20.6948	0.9792	70.7474 ± 2.3500	–261099.0 ± 99251.3	0.7191	4.1431
4. Cholic acid n_{TE} = 50	51.99	17.64	–20.9836	0.9565	70.3319 ± 2.6044	–314868.0 ± 80695.2	0.5831	4.2348
5. Cholic acid n_{TE} = 60	56.28	18.09	–20.5157	0.9547	64.9535 ± 1.9643	–336857.9 ± 192723.6	0.3854	4.4140
6. Cholic acid n_{TE} = 70	69.81	18.42	–21.9692	0.9927	65.4909 ± 0.7084	–943116.9 ± 209107.7	0.1433	4.38435

Table 2. Correlation formulas describing "Rosen's postulate", and the energy required to transport the oxyethylated segment $[CH_2CH_2O]_{n=1}$ and lipophilic segment (adduct with therapeutic agent) from solution to interphasic interface: aqueous solution – air.

Solubilizer Cholic acid n_{TE} Therapeutic agent	**Type of correlation formula**	**Directional coefficients of the formulas**			**$\Delta G_{tr}[CH_2CH_2O]_{n=1}$(h) hydrophilic segment [KJ/mol]**	**ΔG_{tr} [R–] (l) lipophilic segment [KJ/mol]**
		r^2	a ± da	b ± db		
1. Cholic acid	$y = a + b \times n_{TE}$	0.9879	4.0576 ± 0.0251	$-2.2905 \times 10^{-3} \pm 0.5109 \times 10^{-3}$	0.71073	0.401205×10^{-3}
n_{TE} = 20–70	$\log y = a + b\,\gamma \times n_{TE}$	0.9862	0.6084 ± 0.0028	$-2.5231 \times 10^{-4} \pm 0.5743 \times 10^{-4}$		
2. Cholic acid· n_{TE} = 20–70 + Diclofenac	$y = a + b \times n_{TE}$	0.9491	3.0576 ± 0.1334	$-6.1701 \times 10^{-3} \pm 2.8445 \times 10^{-3}$	0.68232	1.08068×10^{-3}
	$\log y = a + b\,\gamma \times n_{TE}$	0.9508	0.5914 ± 0.0136	$6.4118 \times 10^{-4} \pm 2.9028 \times 10^{-4}$		
3. Cholic acid n_{TE} = 20–70 + Naproxen	$y = a + b \times n_{TE}$	0.9178	3.9281 ± 0.1718	$-6.1240 \times 10^{-3} \pm 3.6904 \times 10^{-3}$	0.68800	1.072611×10^{-3}
	$1/y = a + b \times n_{TE}$	0.9178	0.2535 ± 0.0096	$-3.4546 \times 10^{-4} \pm 2.0744 \times 10^{-4}$		
4. Cholic acid n_{TE} = 20–70 + Loratadine	$y = a + b \times n_{TE}$	0.9594	3.3759 ± 0.3776	$1.9117 \times 10^{-2} \pm 0.7797 \times 10^{-2}$	0.59128	3.348320×10^{-3}
	$1/y = a + b \times n_{TE}$	0.9758	0.2836 ± 0.0155	$-1.0331 \times 10^{-3} \pm 0.3205 \times 10^{-3}$		

Table 3. Values of $H/L(\Delta G_{tr})$ ratio determined for cholic acid oxyethylation products and for micellar adducts with diclofenac, naproxen, and loratadine.

Equilibrium system Cholic acid n_{TE} Therapeutic agent	**$H/L(\Delta G_{tr}) \times 10^3$**			
	Solubilizer with diclofenac	Micellar adduct with naproxen	Micellar adduct with loratadine	Micellar adduct
1. Cholic acid·n_{TE} = 20	42.1082	12.9682	12.3281	3.9220
2. Cholic acid·n_{TE} = 30	52.9220	17.6849	19.3005	5.5433
3. Cholic acid·n_{TE} = 40	75.5716	24.6932	26.1509	7.5898
4. Cholic acid·n_{TE} = 50	88.7692	32.7371	32.7192	9.1809
5. Cholic acid·n_{TE} = 60	101.4708	36.1275	36.3110	9.9384
6. Cholic acid·n_{TE} = 70	130.3284	42.3593	41.8786	12.3279
$H/L(\Delta G_{tr}) = n_{TE} \cdot \Delta G_{tr(h)} / \Delta G_{tr(l)}$				

Table 4. Correlation formulas describing relationship between G_m^0 and HLB^{1HNMR} for solubilizer and its micellar adducts with therapeutic agents as a function of n_{TE}.

Solubilizer Cholic acid˙n_{TE} Therapeutic agent	**Type of correlation formula for function**	**Directional coefficients of the formulas**		
		r^2	**a ± da**	**a ± da**
	$\Delta G_m^0 = f(n_{TE})$			
1. Cholic acid˙n_{TE} = 20–70	y = a + b × x	0.9262	–18.4190 ± 1.1394	$-4.1065 \times 10^{-2} \pm 2.3193 \times 10^{-2}$
2. Cholic acid˙n_{TE} = 20–70 + Diclofenac	y = a + b × x	0.9768	–18.5966 ± 0.5766	$-4.0485 \times 10^{-2} \pm 1.2297 \times 10^{-2}$
3. Cholic acid˙n_{TE} = 20–70 + Naproxen	y = a + b × x	0.9691	–18.7013 ± 0.6763	$-4.1135 \times 10^{-2} \pm 1.4526 \times 10^{-2}$
4. Cholic acid˙n_{TE} = 20–70 + Loratadine	y = a + b × x	0.9567	–17.6187 ± 2.2685	$-5.6061 \times 10^{-2} \pm 4.6846 \times 10^{-2}$
	$HLB^{1HNMR} = f(n_{TE})$			
1. Cholic acid˙n_{TE} = 20–70	y = a + b × x	0.9896	9.3678 ± 1.3698	01384 ± 0.0278
2. Cholic acid˙n_{TE} = 20–70 + Diclofenac	y = a + b × x	0.9644	14.7743 ± 1.0342	0.0581 ± 0.0221
3. Cholic acid˙n_{TE} = 20–70 + Naproxen	y = a + b × x	0.9788	15.7706 ± 0.5291	0.0391 ± 0.0113
4. Cholic acid˙n_{TE} = 20–70 + Loratadine	y = a + b × x	0.9609	15.0441 ± 0.9988	0.0515 ± 0.0206

Consequently, the values of cmc determined for the aqueous solutions of the oxyethylation products and micellar adducts with diclofenac, naproxen, and loratadine were used to calculate ΔG_m^0 (thermodynamic potential of micelle formation). Moreover, the total solids obtained after the evaporation of water (~ 37°C) from saturated micellar solutions formed in the process of solubilization in equilibrium constituted the basis for determining the content of oxyethylated segments, n_{TE} and HLB^{1HNMR}, using ^{1}HNMR method. The results of these studies, along with the aggregates formed as a result of evaporating water from saturated micellar solutions formed during the micellar solubilization of diclofenac, naproxen, and loratadine in equilibrium, constituted significant material deliverables of the verification of the usefulness of "Rosen's postulate" for the thermodynamic estimation of energy required to change the state of matter at phase boundary: therapeutic agent (solid body) – micellar solution of surfactant with $c_{exp} \geq$ cmc. The aim of the research reported here was to confirm the usefulness of Rosen's proposal for estimating the solubilizing properties and the thermodynamic stability of the micellar adduct.

EXPERIMENTAL

Materials

Product of the catalytic oxyethylation of cholic acid with declared molar content of ethylene oxide – n_{TE} = 20–70. Structural characteristics and aqueous solutions of the novel class of surfactants were described in our previous publication (10). Diclofenac: 2-{2-[(2,6-dichlorophenyl)amino]phenyl}acetic acid, pure for analysis (Sigma, Germany). Naproxen: 2-(6-methoxy-2-naphthyl)propionic acid, pure for analysis (Zydus Cadila – Cadila Healthcare Ltd., India). Loratadine: 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2b]pyridin-11-ylidene)-1-piperidine-1-carboxylic acid ethyl ester, pure for analysis (Zydus Cadila – Cadila Healthcare Ltd., India). All the substances used in the course of research have a low level of water solubility and belong to BCS Class II.

Equipment

Stalagmometers with V = 28.20 cm^3 and V = 45.0 cm^3 (Tropfen Wasser type) with MLW-U2C type thermostatic system of measurement area (Medingen Sitz Freital, Germany).

Research methodology

The surface activity of aqueous solutions of the products of cholic acid oxyethylation and their

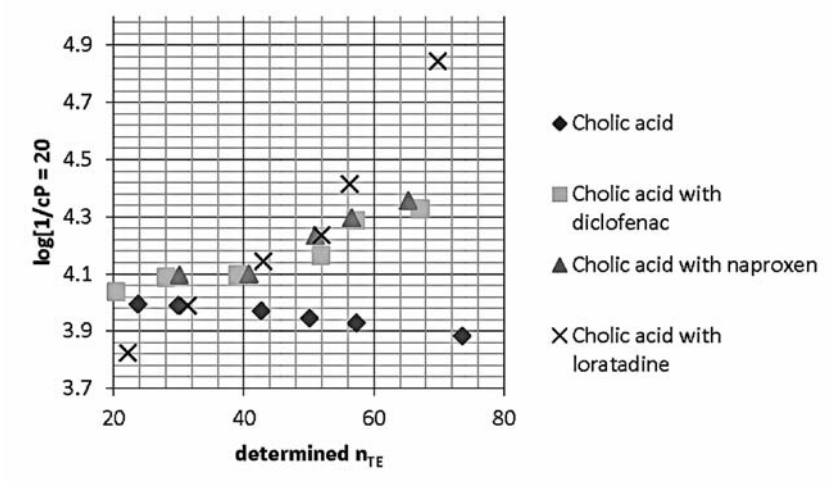

Figure 1. Graphic illustration of relationship: $\log(1/c_{\pi=20}) = f(n_{TE})$

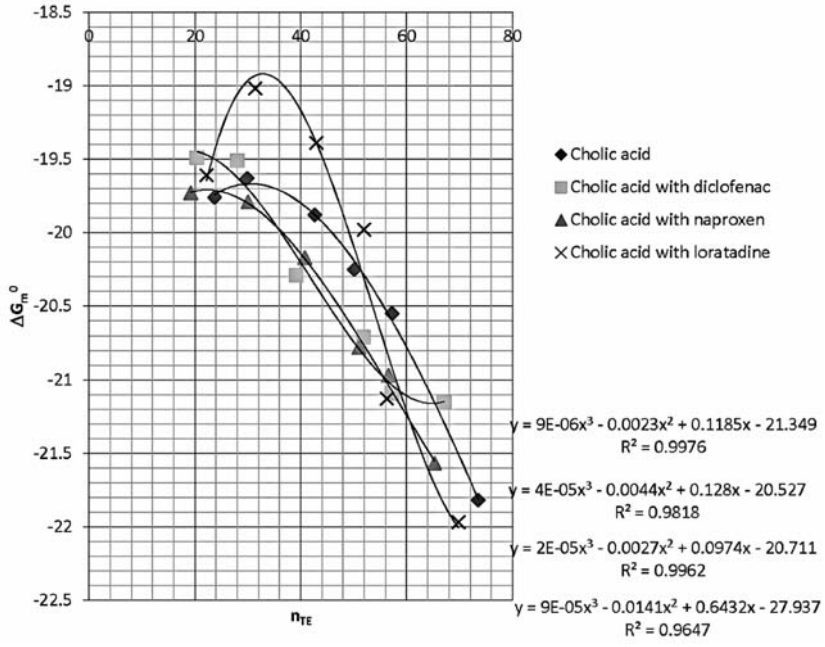

Figure 2. Graphic illustration of relationship: $DG_m^0 = f(n_{TE})$

adducts formed as a results of the micellar solubilization of diclofenac, naproxen, and loratadine in equilibrium was determined on the basis of changes in surface tension. The surface activity of the aqueous solutions of solubilizers and their micellar adducts with the lipophilic therapeutic agents was determined with the stalagmometric method in accordance with the Polish Standard (15).

Determination of cmc

The determined value of critical micellar concentration (cmc) allowed for the calculation of the thermodynamic potential of micelle formation (Δ) based on the following equation:

$$\Delta G_m^0 = 2.303RT \cdot \log(cmc)$$

The relationship $\gamma^{25} = f(c, mol/dm^3)$ in the examined range of concentrations, i.e., for the val-

ues below cmc, was described with regression equations at p = 0.05. The correlation equations presented in Table 1 allowed us to calculate $c_{\pi=20}$ and $\log(1/c_{\pi=20})$ values of "Rosen's postulate" (16).

Determination of HLB parameter

The saturated solutions of therapeutic agents (diclofenac, naproxen, loratadine) obtained after exposure to 25°C in the aqueous solution of solubilizer with c_{exp} = cmc were subjected to condensation at 37°C, dried, and transformed into the solid phase. The ^{1}HNMR spectra of resultant micellar solid dispersions in $CDCl_3$ were obtained as previously described (10, 11). They were used to calculate the hydrophilic-lipophilic balance (HLB) on the basis of the following equation:

$$HLB^{1HNMR} = 15 \times A_h / 0.05(15 \times A_h + 10 \times A_l)$$

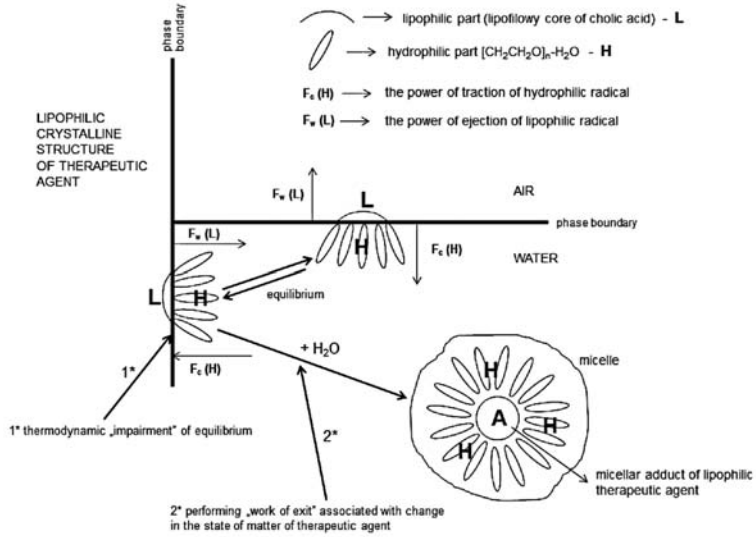

Figure 3. Lipophilic crystalline structure of therapeutic agent

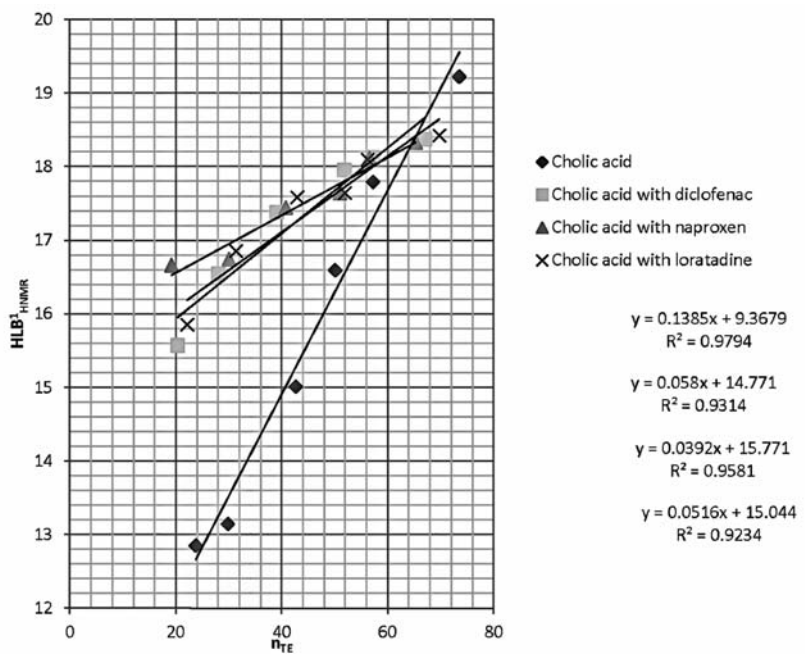

Figure 4. Graphic illustration of relationship: $HLB^1_{HNMR} = f(n_{TE})$

Determination of the overall number of lipophilic protons $\Sigma H_1 = 36$ in the structure of the molecule of cholic acid made it possible to calculate the content of oxyethylated segments (CH_2CH_2O) in dry micellar adduct after solubilization in equilibrium on the basis of the following equation:

$$n_{TE} = (36 \times A_h / A_l - 3) / 4$$

The determined values of n_{TE} and HLB^{1HNMR} are presented in Table 1.

RESULTS AND DISCUSSION

The values of $1/c_{\pi=20}$, HLB^{1HNMR}, and n_{TE} presented in Table 1 point to significant variability in the surface activity of the micellar adduct of solubilizer with diclofenac, naproxen, and loratadine, as well as to the variability of ΔG^0_m, the thermodynamic potential of micelle formation, in relation to the exposure solution of derivative of the oxyethylation of cholic acid with $n_{TE} = 20–70$ (Table 1). The n_{TE} and HLB^{1HNMR} of the solubilizer and its micellar adduct also suggest individual variability in the value of "Rosen's postulate", $\log 1/c_{\pi=20}$).

We analyzed the relationship between $\log 1/c_{\pi=20}$) and the determined number of oxyethylated segments, n_{TE} (Table 1, Fig. 1), to estimate the character of thermodynamic interactions occurring at phase boundary. Correlation equations describing the abovementioned relationship at $p = 0.05$ are presented in Table 2. The directional coefficients of the correlation equations (Table 2) allowed us to calculate the value of transport energy to the phase boundary of the lipophilic part of solubilizer, [F↑] ($\Delta G_{tr(l)}$), as well as the value of the transport energy of hydrophilic oxyethylated segment, $[CH_2CH_2O]_{n=1}$ [F↓] ($\Delta G_{tr(h)}$), using the following formulas:

$$\Delta G_{tr(l)} = a/2.303 \times R \times T$$

$$\Delta G_{tr(h)} = b/2.303 \times R \times T$$

Presented in Table 2 values of the energy of transport $\Delta G_{tr(l)}$ and $\Delta G_{tr(h)}$, in all conditions described by Loughlin allowed us to calculate the ratio:

$$H/L(\Delta G_{tr}) = n_{TE} \cdot \Delta G_{tr(h)} / \Delta G_{tr(1)}$$

which can constitute our thermodynamic interpretation of hydrophilic-lipophilic balance at phase boundary. The results are presented in Table 3.

The calculated values of $H/L(\Delta G_{tr})$ ratio (Table 3) suggest that individual progression of this parameter is determined by the method and place of the solubilization of therapeutic agent and significant thermodynamic stability (ΔG^0_m) of micellar adduct. The values of $H/L(\Delta G_{tr})$ presented in Table 3 inspired us to analyze the relationship $\Delta G^0_m = f(n_{TE})$ and to estimate "Rebinder's effect", i.e., the value of energy required to transform the molecule of therapeutic agent from solid body to micelle (molecular state of dispersion). The correlation equations for $\Delta G^0_m = f(n_{TE})$ formula, obtained at $p = 0.05$, are presented in Table 4. The directional coefficient "a" of the correlation equation $y = a + b \cdot x$ by $n_{TE} = 0$ can refer to $\Delta G^0_{m(gr)}$ of the lipophilic core of cholic acid and its micellar adducts with lipophilic therapeutic agents, i.e., diclofenac ($\Delta G^0_{m(gr)}D$), naproxen ($\Delta G^0_{m(gr)}N$), and loratadine ($\Delta G^0_{m\,(gr)}L$).

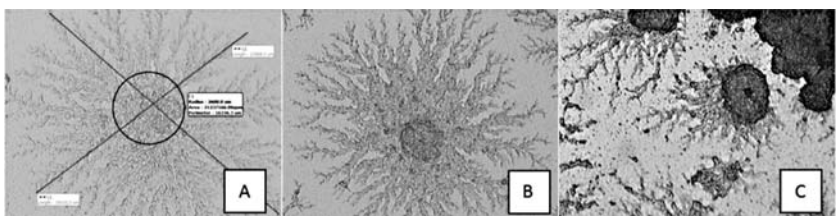

Figure 5. Microscopic structure of the solutions of solubilizers with $n_{TE} = 70$ and the solutions of adducts after the loss of volatile components (evaporation of solvent): A – solution of surfactant, B – adduct with diclofenac, C – adduct with loratadine

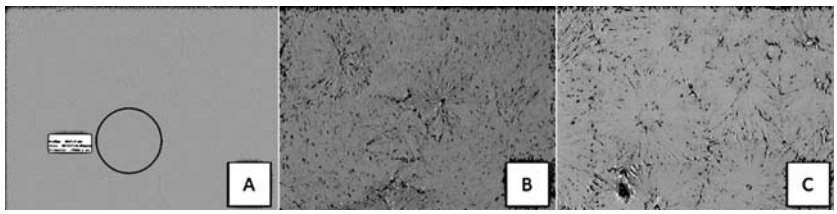

Figure 6. Microscopic structure of the solutions of solubilizers with $n_{TE} = 50$ and the solutions of adducts after the loss of volatile components (evaporation of solvent): A – solution of surfactant, B – adduct with diclofenac, C – adduct with loratadine

In such a state, due to the proposed experimental model, one can estimate the level of energy (or work) of "Rebinder's effect" required to transport the molecules of therapeutic agent (following complete moistening) from the surface of solid body to micellar structure, and to form the thermodynamically stable adduct. The values of $\Delta G^0_{m(gr)}$ coefficients presented in Table 4 allowed us to estimate the energy of transport required to change the state of matter on the basis of the following formula:
Δ("Rebinder's effect" eR) = $\Delta G^0_{m\,(gr)}$ D,N,L – $\Delta G^0_{m(gr)}$ of cholic acid

The values of eR calculated on the basis of the abovementioned formula equaled to:

for diclofenac: Δ"eR" = –0.1776 kJ/mol
for naproxen: Δ"eR" = –0.2823 kJ/mol
for loratadine: Δ"eR" = –0.8003 kJ/mol

The thermodynamic stability of solubilizer's micelle and the adduct with lipophilic therapeutic agents at phase boundary (air/water) was confirmed by the values of H/L(ΔG_{tr}) ratio (Table 3) and the relationship $HLB^{1HNMR} = f(n_{TE})$ presented in Figure 4.

On the basis of the abovementioned relationships, we observed that the solubilization of lipophilic therapeutic agent is associated with an increase in the hydrophilicity of the adduct (obtained in solid phase). This was suggested by the values of the directional coefficients of correlation equations presented in Table 4, which varied significantly depending on solubilizers, i.e., the oxyethylation products of cholic acid with n_{TE} = 20–70. We revealed that the products (solid dispersions) obtained upon the micellar solubilization of diclofenac, naproxen, and loratadine in equilibrium, and subsequent dehydration (drying at 37°C) have HLB^{1HNMR}, which suggests their significant hydrophilicity, irrespective of being the adducts of the lipophilic therapeutic agents.

Analyzing the microscopic structure of compounds obtained upon the loss of the volatile components of the solutions of solubilizer with $c_{exp} \geq$ cmc and the saturated solutions of adducts, we found the important material explanation for the abovementioned statement (Figs. 5, 6) as the therapeutic agents were located in the core, that is to say, in the central part of solubilization space (micelle).

CONCLUSIONS

1. Analyzing an array of homologous structures of cholic acid oxyethylation products with n_{TE} = 20–70, as well as their micellar adducts with lipophilic therapeutic agents: diclofenac, naproxen, and loratadine, we confirmed the relationship between "Rosen's postulate" [$\log(1/c_{\pi=20})$] and the content of oxyethylated segments (n_{TE}). The calculated values of transport energy, $G_{tr(h)}$ and $G_{tr(1)}$, constituted the base for determining H/L(G_{tr}) ratio, being the thermodynamic characteristic of hydrophilic-lipophilic balance at the phase boundary.
2. The values of $\Delta G^0_{m(gr)}$ for solubilizer and its micellar adducts with diclofenac, naproxen, and loratadine, which were calculated with approximation formulas, constituted the basis for estimating "Rebinder's effect" associated with the energy required to transform the molecule of therapeutic agent into the state of molecular dispersion. The value of $\Delta G^0_{m(gr)}$ points to thermodynamic stability and to the possibility of estimating the energy of transport associated with changing the state of matter.
3. The structural character of interaction occurring at phase boundary between the micellar solution of solubilizer and solid body (dispersed therapeutic agent) was confirmed by the values of $\log(1/c_{\pi=20})$, $\Delta G^0_{m(gr)}$, HLB^{1HNMR}, and H/L(G_{tr}), as well as by the documentation obtained after evaporating water from saturated solution formed as a result of the solubilization of lipophilic therapeutic agent in equilibrium.
4. The results of this study confirm the possibility of comprehensive utilization of "Rosen's postulate" for the evaluation of solubilization properties of cholic acid oxyethylation products. Moreover, they allow for the thermodynamic estimation of „Rebinder's effect" associated with the energy of transport required for changing the state of matter of lipophilic therapeutic agent. The results of the research facilitate the application of Rosen's proposal for the assessment of the usefulness of solubilizers and the stability of the systems obtained.

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