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SURFACE ACTIVITY OF NOVEL SURFACE ACTIVE COMPOUNDS, PRODUCTS OF CATALYTIC OXYETHYLATION OF CHOLIC ACID AND THEIR MICELLAR ADDUCTS WITH SELECTED LIPOPHILIC THERAPEUTIC AGENTS

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Abstract: The aim of this study was to determine the surface activity parameters of novel surface active compounds, products of catalytic oxyethylation of cholic acid, and their micellar adducts with selected lipophilic therapeutic agents (diclofenac, loratadine, naproxen and rutin). High solubility of lipophilic naproxen was observed in the environment of aqueous solutions of the cholic acid oxyethylation products as suggested by determined factual solubility and the value of micellar partition coefficient (K_w^m). Determined surface activity of surfactants described by various physicochemical characteristics (γ_{cmc}^{25}, cmc, ΔG_m^o and A_m) suggested their compatibility with physiological values of the surface activity of plasma (48.0-52.0 mJ/m^2) and lacrimal fluid (46.0-52.0 mJ/m^2). Calculated values of $HLB^1{}_{HNMR}$ and n_{TE} of the micellar adduct in solid phase (solid dispersion) corresponded to an increase in its hydrophilicity, and, therefore, suggested possible mechanisms and site of diclofenac, loratadine, naproxen and rutin solubilization in the micellar structure (core or palisadic layer).

Keywords: solubilization, surface activity, diclofenac, loratadine, naproxen, rutin, ethoxylation products of cholic acid

Products of the catalytic oxyethylation of cholic acid in molecular fragmentation state, a new group of novel surface-active compounds, are characterized by marked physicochemical compatibility with bile "A" (duodenal content). Additionally, these compounds are not recognized as xenobiotics by the human immune system (1-7).

As was confirmed previously *in vitro*, the marked solubilizing properties of the lipophilic therapeutic agents exhibited by the cholic acid oxyethylates have substantiated further preformulation research on the possible implementation of these derivatives as formulations in the solid oral drug forms. Following the disintegration, further dissolving and effective transport of such formulation could occur independently from the physiological value of the lithogenolithic index of bile "A" (duodenal content) (8-13).

Previous viscosity (η) analyses and determination of the surface activity (γ) of bile "A" in healthy subjects and patients with various biliary tract disorders (4) constituted a base for further studies of the surface activity of the aqueous solutions of the cholic acid oxyethylates with n_{TE} = 20-70, (n_{TE} = number of oxyethylene segments) and their micellar adducts with lipophilic therapeutic agents (BCS class II and IV) (14).

Determination of selected parameters: critical micelle concentration - cmc, thermodynamic potential of micelle formation - ΔG_m^o, the size of the lipophilic core uplift above the phase boundaries - A_m, surface tension at the critical area - γ_{cmc}^{25}, characterizing surface activity of the novel class of non-ionic surfactants and their adducts with the lipophilic therapeutic agents enabled the assessment of their potential application in solid oral drug formulations and injections (15, 16).

The aim of this study was to determine the surface activity parameters of novel surface active compounds, products of the catalytic oxyethylation of cholic acid, and their micellar adducts with selected lipophilic therapeutic agents. The results of this

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study may constitute a base for further original and novel research on formulating solid oral forms of drugs (non-coated tablets, prolonged release tablets, matrix tablets with variable core viscosity) or parenteral formulations (injections, intravenous infusions). These formulations should be characterized by established, stable pharmaceutical and biological availability independent of pathological changes in the solubilizing properties of bile "A" (duodenal content).

EXPERIMENTAL

Materials

Diclofenac; 2-{2-[(2,6-dichlorophenyl)amino] phenyl}acetic acid, pure for analysis (Sigma, Germany); rutin (rutoside), pure for analysis (Sichuan Xieli Pharmaceutical Co. Ltd., China); loratadine, pure for analysis (Zydus Cadila – Cadila Healtcare Ltd., India); naproxen, pure for analysis, serial no. 381936 (Medana, Poland); products of the

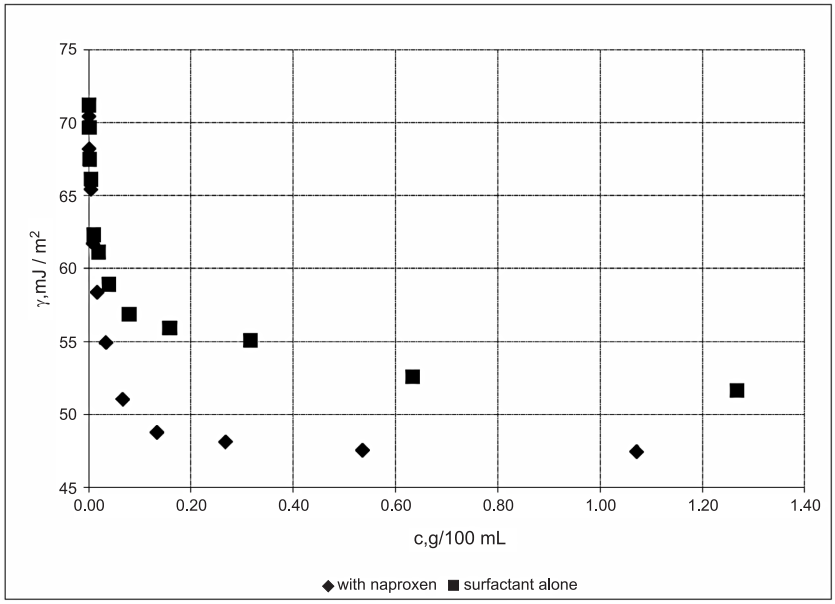

Figure 1. Relationship between the surface activity (g, mJ/m^2) and the concentration of surfactant (c, g/100 mL; oxyethylated cholic acid n_{TE} = 50)

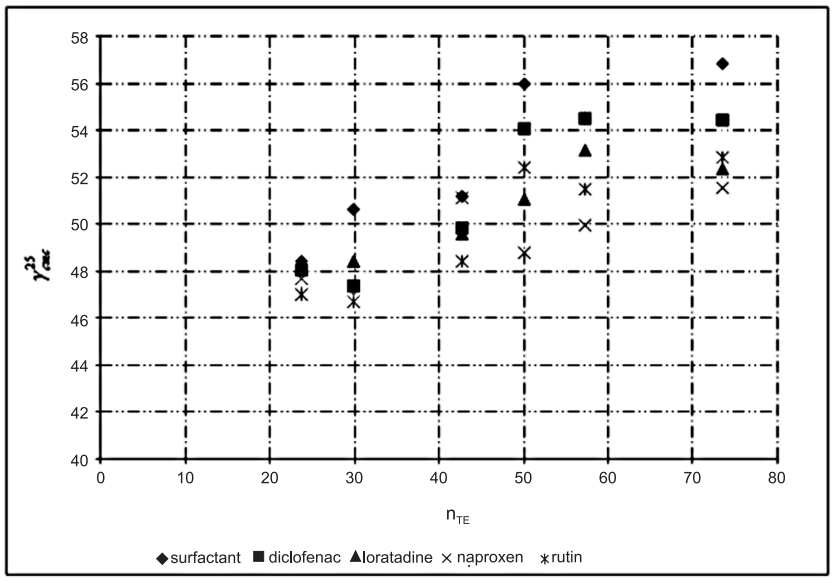

Figure 2. Relationship between surface activity in "critical area" (γ_{cmc}^{25}) and the number of oxyethylated segments (n_{TE}) in surfactant

Table 1. Basic viscosity and hydrodynamic characteristics of the aqueous solutions of cholic acid oxyethylation products solubilizing naproxen[1,2].

Cholic acid oxyethylation roduct Mη	C_{exp} [g × 100 cm^{-3}]	GLL [η]	$M_{\eta\,adduct}$	$R_o \times 10^{-7}$ [cm]	$R_{obs} \times 10^{8}$ [cm]	$\Omega \times 10^{-20}$ [cm]	c/n_o* [mg × dm^{-3}]	K_w^{m*}
1. Cholic acid n_{TE} = 20 Mη = 1981.7	1.0220	0.0835679	1826.6	3.5427	1.5011	1.0137	534.42	32.61
2. Cholic acid n_{TE} = 30 Mη = 1877.5	1.0274	0.0854125	1879.5	3.6026	2.9414	1.0661	556.99	34.03
3. Cholic acid n_{TE} = 40 Mη = 2108.5	1.0119	0.0928375	2157.6	3.8785	3.1667	1.3302	528.78	32.25
4. Cholic acid n_{TE} = 50 Mη = 2730.7	1.0711	0.1115816	2925.6	4.5642	3.7266	2.1679	675.51	41.48
5. Cholic acid n_{TE} = 60 Mη = 2662.15	1.0075	0.1126817	2973.5	4.6041	3.7591	2.2251	782.73	48.22
6. Cholic acid n_{TE} = 70 Mη = 3011.1	1.0103	0.1280905	3676.4	5.1572	4.2107	3.1274	816.59	50.35

[1] theoretical solubility in water $c_{t\,(o)}$ = 51.0 mg/dm^3; [2] determined solubility in water c_{ht} = 15.9 mg/dm^3; * – calculated in relation to the determined solubility ~c_{ht}

catalytic oxyethylation of cholic acid in molecular fragmentation state with declared molar content of ethylene oxide, n_{TE} = 20-70.

Structural characteristics of the novel class of surfactants were described in our previous publication (12).

Determination of oxyethylated segment content (n_{TE}) and hydrophilic-lipophilic balance $HLB_{^1HNMR}$ of dry adduct (solid dispersion) after micellar solubilization in equilibrium

The ^{1}HNMR spectra of the adduct of lipophilic therapeutic agents after micellar solubilization in equilibrium in solid phase (solid dispersion) were obtained as described previously (1, 3, 5, 8).

They were used to calculate the hydrophilic-lipophilic balance on the basis of the following equation:

$$HLB_{^1HNMR} = \frac{15 \cdot A_h}{0.05\,(15 \cdot A_h + 10 \cdot A_l} \quad (1)$$

Where A_h = number of hydrophilic protons, A_l = number of lipophilic protons

Determination of the overall number of lipophilic protons $\Sigma\,^1H = 36$ in the structure of the molecule of cholic acid made it possible to calculate the content of oxyethylated segments in dry micellar adduct after solubilization in equilibrium, on the basis of the following equation:

$$n_{TE} = \frac{(36 \cdot \frac{A_h}{A_l} - 3)}{4} \quad (2)$$

Surface activity and viscosity of aqueous solutions of the products of cholic acid oxyethylation and their adducts resulting from micellar solubilization in equilibrium

The surface activity of aqueous solutions of the products of cholic acid oxyethylation and their micellar adducts with the lipophilic therapeutic agents was determined with the stalagmometric method in accordance with the Polish Standard (17).

Determined value of critical micellar concentration (cmc) enabled the calculation of the thermodynamic potential of micelle formation (ΔG_m^o) based on the following equation:

$$\Delta G_m^o = 2.303 \cdot RT \log cmc \quad (3)$$

where: ΔG_m^o = the thermodynamic potential of micelle formation, R = gas constant (8.314J/mol·K), T = temperature.

The numerical value of the decrease in the surface activity coefficient in critical area (γ_{cmc}^{25}) enabled the calculation of the "average area per

surfactant molecule" on phase boundary (minimal value of A_m per 1 molecule corresponds to approximately 20×10^{-16} cm^2) on the basis of the equation:

$$f(\pi) \cdot A_m = k \cdot T, \quad (4)$$

where: $f(\pi) = \gamma^{25}_{H_2O} - \gamma^{25}_{cmc}$ (5), A_m = the size of the lipophilic core uplift above the phase boundaries, $\gamma^{25}_{H_2O}$ = the surface tension of water, γ^{25}_{cmc} = the surface tension at the critical area, k = constant, T = temperature which was further transformed into the following application version:

$$A_m = \frac{k \cdot T}{\gamma^{25}_{H_2O} - \gamma^{25}_{cmc}}. \quad (6)$$

This aforementioned relationship results from the mathematical transformation of Gibbs formula:

$$T = \frac{c}{RT} \cdot \frac{\pi}{c}, \quad (7)$$

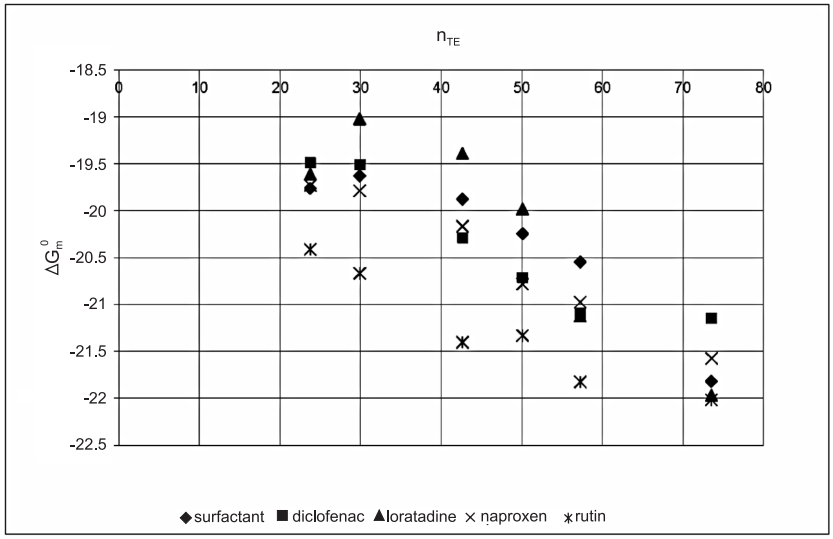

Figure 3. Relationship between the thermodynamic potential of micelle formation (ΔG^o_m) and the number of oxyethylated segments (n_{TE}) in surfactant

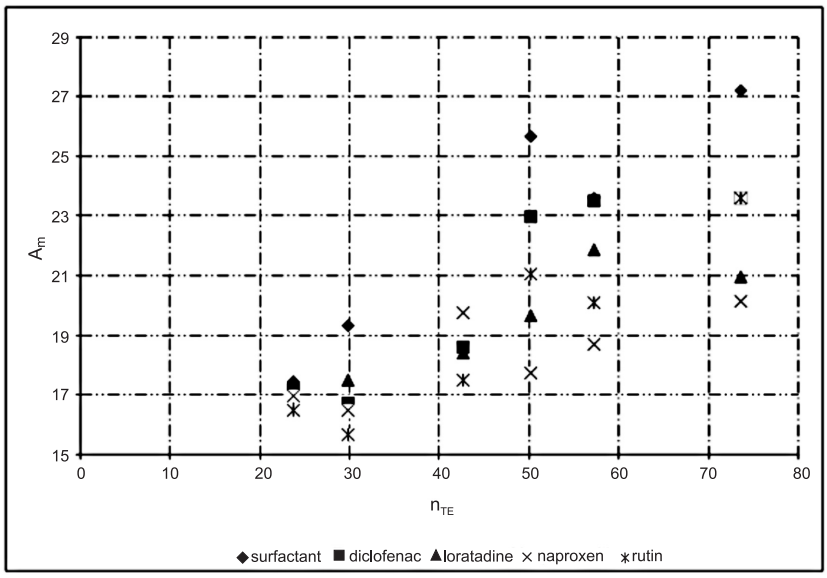

Figure 4. Relationship between the surface of lipophilic core upthrust over the phase boundary (A_m) and the number of oxyethylated segments (n_{TE}) in surfactant

Table 2. Basic surface activity characteristics of novel surface active compounds, products of catalytic oxyethylation of cholic acid and their micellar adducts with selected lipophilic therapeutic agents.

Surfactants	γ_{cmc}^{25} [mJ × m^{-2}]	cmc [g × 100 cm^{-3}]	cmc × 10^{-4} [mol × dm^{-3}]	ΔG_m^o [kJ × mol^{-1}]	$A_m \times 10^{-20}$ [m^2]
1. Cholic acid n_{TE} = 20	48.41	5.0243 × 10^{-2}	3.4514	-19.7647	17.4646
2. Cholic acid n_{TE} = 30	50.65	6.2741 × 10^{-2}	3.6374	-19.6345	19.2985
3. Cholic acid n_{TE} = 40	51.16	7.5306 × 10^{-2}	3.2915	-19.8823	19.7714
4. Cholic acid n_{TE} = 50	55.94	7.4248 × 10^{-2}	2.8381	-20.2497	25.6634
5. Cholic acid n_{TE} = 60	54.52	7.3762 × 10^{-2}	2.5158	-20.5486	23.5897
6. Cholic acid n_{TE} = 70	56.85	5.4959 × 10^{-2}	1.5059	-21.8211	27.2069
Diclofenac					
1. Cholic acid n_{TE} = 20	48.05	7.0487 × 10^{-2}	3.8519	-19.4925	17.2018
2. Cholic acid n_{TE} = 30	47.35	7.3248 × 10^{-2}	3.8199	-19.5131	16.7129
3. Cholic acid n_{TE} = 40	49.86	7.4628 × 10^{-2}	2.7845	-20.2899	18.6094
4. Cholic acid n_{TE} = 50	54.07	7.5247 × 10^{-2}	2.3528	-20.7147	22.9838
5. Cholic acid n_{TE} = 60	54.47	7.6124 × 10^{-2}	2.0166	-21.0969	23.5089
6. Cholic acid n_{TE} = 70	54.53	8.9918 × 10^{-2}	1.9766	-21.1467	23.5897
Loratadine					
1. Cholic acid n_{TE} = 20	47.07	7.0487 × 10^{-2}	3.6696	-19.6127	16.5251
2. Cholic acid n_{TE} = 30	48.42	7.5006 × 10^{-2}	4.6528	-19.0241	17.4720
3. Cholic acid n_{TE} = 40	49.60	7.5663·× 10^{-2}	4.0067	-19.3948	18.3850
4. Cholic acid n_{TE} = 50	51.05	7.9244 × 10^{-2}	3.1596	-19.9836	19.6675
5. Cholic acid n_{TE} = 60	53.14	7.2758 × 10^{-2}	1.9934	-21.1257	21.8493
6. Cholic acid n_{TE} = 70	52.33	6.0724 × 10^{-2}	1.4185	-21.9692	20.9486
Naproxen					
1. Cholic acid n_{TE} = 20	47.69	6.3875 × 10^{-2}	3.4969	-19.7322	16.9469
2. Cholic acid n_{TE} = 30	47.01	6.4215 × 10^{-2}	3.4166	-19.7898	16.4854
3. Cholic acid n_{TE} = 40	51.13	6.3243 × 10^{-2}	2.9311	-20.1698	19.7429
4. Cholic acid n_{TE} = 50	48.77	6.6943 × 10^{-2}	2.2881	-20.7838	17.7355
5. Cholic acid n_{TE} = 60	49.95	6.2968 × 10^{-2}	2.1176	-20.9758	18.6854
6. Cholic acid n_{TE} = 70	51.54	6.1144 × 10^{-2}	1.6631	-21.5748	20.1389
Rutin					
1. Cholic acid n_{TE} = 20	47.01	10.5487 × 10^{-2}	2.6668	-20.4149	16.4854
2. Cholic acid n_{TE} = 30	46.67	7.5062 × 10^{-2}	2.3962	-20.6694	15.6458
3. Cholic acid n_{TE} = 40	48.42	7.0486 × 10^{-2}	1.7821	-21.4035	17.4720
4. Cholic acid n_{TE} = 50	52.41	7.1248 × 10^{-2}	1.8345	-21.3331	21.0342
5. Cholic acid n_{TE} = 60	51.48	7.2758 × 10^{-2}	1.5019	-21.8277	20.0801
6. Cholic acid n_{TE} = 70	52.85	6.7438 × 10^{-2}	1.3921	-22.0174	23.5897

where: c = the molar concentration of the solute, T = surface concentration
and Szyszkowski formula:

$$\pi = \gamma_o - \gamma = a \cdot (1 + b \cdot c), \quad (8)$$

with the resulting following equation:

$$\pi \cdot A_m = R \cdot T. \quad (9)$$

This aforementioned equation is the "surface equation of state". After the bilateral dividing by the Avogadro constant, it can be transformed into the following equation:

$$f = (\pi) \cdot A_m = k \cdot T. \quad (10)$$

The estimated and calculated values are summarized in Table 2.

The limiting viscosity number (LVN, η) of aqueous solutions after micellar solubilization of naproxen by the cholic acid oxyethylation products was estimated on the basis of the Polish Standard by means of the Ubbelohde viscosimeter (18). The estimated LVN was used to calculate several viscosity parameters: viscosity average molar masses - M_η, the end of mean square distance between chain terminals - R_o, hydrodynamic value of micelle radius - $R_{obs,}$ and effective volume - Ω. The results are summarized in Table 1.

RESULTS AND DISCUSSION

Micellar solubilization of lipophilic therapeutic agent in equilibrium in the environment of aqueous solutions of cholic acid oxyethylation

The formerly described spectroscopic method (11-13) was employed to determine the amount of

Table 3. Content of oxyethylated segments (n_{TE}) and the value of hydrophilic-lipophilic balance (HLB_{HNMR}) of micellar adduct in solid dispersion determined by means of ^{1}H NMR.

Surfactant	Determined n_{TE}	HLB^1_{HNMR}	Micellar adduct of cholic acid n_{TE} = 20-70							
			Diclofenac		Loratadine		Naproxen		Rutin	
			HLB^1_{HNMR}	$n_{TE\,(X)}$	HLB^1_{HNMR}	$n_{TE\,(X)}$	HLB^1_{HNMR}	$n_{TE\,(X)}$	HLB_{HNMR}	$n_{TE\,(X)}$
1. Cholic acid n_{TE} = 20	23.77	12.85	15.57	20.37	15.85	22.21	16.66	19.22	14.63	15.59
2. Cholic acid n_{TE} = 30	29.88	13.14	16.54	28.01	16.85	31.39	16.74	30.09	16.22	25.05
3. Cholic acid n_{TE} = 40	42.66	15.01	17.38	39.11	17.58	42.98	17.44	40.77	17.30	37.82
4. Cholic acid n_{TE} = 50	50.11	16.59	17.95	51.85	17.64	51.99	17.64	51.01	17.74	46.54
5. Cholic acid n_{TE} = 60	57.28	17.79	18.12	57.22	18.09	56.28	18.11	56.61	18.19	59.86
6. Cholic acid n_{TE} = 70	73.57	19.22	18.37	67.09	18.42	69.81	18.33	65.29	18.33	65.44

lipophilic therapeutic agent solubilized in equilibrium conditions in aqueous solutions of novel surface active agents with $c_{exp} \geq$ cmc.

Approximation equation describing the relationship between the concentration of the therapeutic agent (naproxen; c, mg × 100 cm^{-3}) and the measured value of absorbance (A) at λ = 262 nm wavelength, p = 0.05 and r = 0.9982, i.e.:

$$A = 0.0923 + 0.1722 \cdot C, \qquad (11)$$

and the following transformation of the equation:

$$c = A - \frac{0.0923}{0.1722}, \qquad (12)$$

made it possible to calculate the amount of the solubilized therapeutic agent.

The results of the calculation were used to estimate the value of the micellar partition coefficient (K^m_w, Table 1).

Hydrodynamic parameters characterizing the process of naproxen solubilization in equilibrium (Table 1) suggest that their progression occurs proportionally to the value of micellar partition coefficient (K^m_w).

These aforementioned findings suggest that population based content of naproxen (250 mg or 500 mg per drug unit; tablet or suppository) in combination with approximately 1% of the content of the cholic acid oxyethylation products in these formulations, enable the complete solubilization of the active substance irrespective of the physiological value of the lithogenolithic index of bile "A" (duodenal content).

Similarly to previous studies (1, 3, 5, 8), the value of cmc was determined based on the formulation:

$$\gamma^{25}_{cmc} = (c, \text{g/100 cm}^3, \text{Fig. 1}), \qquad (13)$$

along with the decrease in the value of surface activity coefficient in the critical region (γ^{25}_{cmc}).

Table 2 summarizes the values of surface activity of aqueous solutions of the cholic acid oxyethylation products and their micellar adducts with lipophilic therapeutic agents (diclofenac, loratadine, naproxen and rutin).

The observed relationship between γ^{25}_{cmc} and n_{TE} (Fig. 2) suggests that the surface activity coefficient in the critical area (cmc) does not decrease below 46 mJ/m^2.

Conferring observed values of γ^{25}_{cmc} to the physiological range of the surface activity of body fluids (γ = 46.0 (48.0) – 52 mJ/m^2) suggests potential safety of the cholic acid derivatives used as excipients in drug formulation technology (solid oral forms, eye drops, infusions and injections). This finding is particularly interesting since the structure of cholic acid is not recognized as xenobiotic by the human immune system.

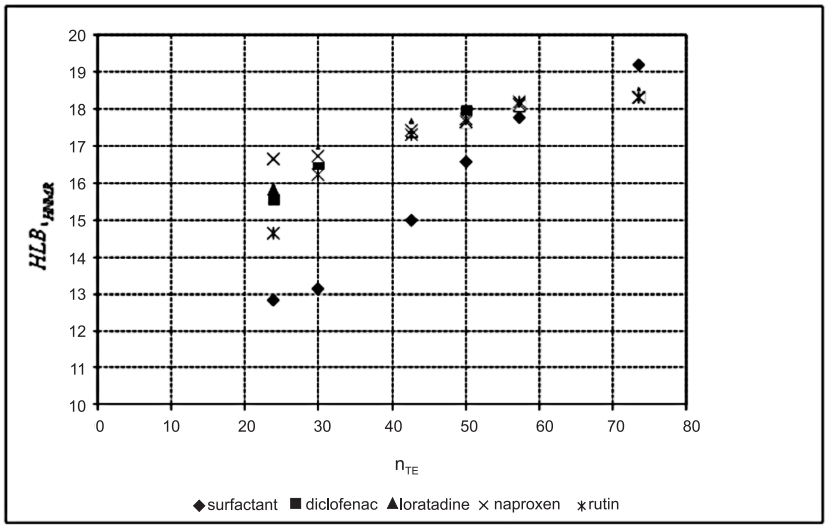

Figure 5. Relationship between micellar level of hydrophilic-lipophilic balance of adduct and solubilizer and the number of oxyethylated surfactant segments determined in equilibrium

Table 4. Approximation equations describing the relationship: $\Delta G_m^o = f(n_{TE})$ for the cholic acid derivatives and their micellar adducts.

Solubilizer / Micellar adduct	Type of equation	"r"	Directional coefficients	
			"a"	"b"
1. Cholic acid*	y = a + bx 1/y = a + bx	0.9246 0.9324	-18.4256 -5.3725×10^{-2}	-4.0949×10^{-2} 9.5953×10^{-5}
2. Cholic acid + diclofenac	y = a + bx y = a + b/x	0.9394 0.9641	-18.6459 -22.0796	-3.8233×10^{-2} 66.6786
3. Cholic acid + loratadine	y = a + bx 1/y = a + bx	0.8996 0.8974	-17.6089 -5.5801×10^{-2}	-5.5745×10^{-2} 1.3272×10^{-4}
4. Cholic acid + naproxen	y = a + bx 1/y = a + bx	0.9862 0.9861	-18.6832 -5.3122×10^{-2}	-3.9409×10^{-2} $9.3072 \cdot 10^{-5}$
5. Cholic acid + rutin	y = a + bx y = a + blogx	0.9629 0.9818	-19.7440 -15.7254	-3.3186×10^{-2} -3.3972

* cholic acid n_{TE} = 20-70

Analyzing the relationship between the calculated value of the thermodynamic potential of micelle formation by solubilizer (ΔG_m^o) or its adducts with lipophilic therapeutic agents, and the determined content of oxyethylated segments (n_{TE}): $\Delta G_m^o = f(n_{TE})$ revealed significant variability of changes of various adducts in comparison to the ΔG_m^o of solubilizer whose homologous line was characterized by specific content of n_{TE} (Fig. 3). This finding indicates the necessity of further detailed analysis of the course of relationship $\Delta G_m^o = f(n_{TE})$ for analyzed lipophilic therapeutic agents.

The course of relationship between the surface of lipophilic core upthrust over the phase boundary (A_m) and the number of oxyethylated segments (n_{TE}) in surfactant (solubilizer, Fig. 4) is specific for the site and topologic micellar structure of adduct's solubilizer.

As suggested by the course of this relationship, solubilized adduct is more hydrophilic (as confirmed by significant decrease in the value of A_m) than the micellar structure of surfactant (solubilizer).

This finding was additionally confirmed by the fact that the calculated values of A_m for solubilizer

Table 5. Approximation equations describing the relationship between $HLB_{^1HNMR}$ of dry adduct and solubilizer as a function of n_{TE}* by p = 0.05: $HLB_{^1HNM} = f(n_{TE})$.

Solubilizer / Micellar adduct	Type of equation	"r"	Directional coefficients "a"	Directional coefficients "b"
1. Cholic acid**	y = a + bx logy = a + blogx logy = a + b/x	0.9896 0.9853 0.9559	9.3678 0.5658 1.3504	0.1384 0.3837 6.3006
2. Cholic acid + diclofenac	y = a + bx logy = a + b/x	0.9651 0.9995	14.7713 1.2946	5.8039×10^{-2} -2.1034
3. Cholic acid + loratadine	y = a + bx logy = a + b/x	0.9608 0.9916	15.0441 1.2919	5.1573×10^{-2} -2.0530
4. Cholic acid + naproxen	y = a + bx 1/y = a + bx	0.9655 0.9643	15.8221 6.2739×10^{-2}	3.8736×10^{-2} -1.2746×10^{-4}
5. Cholic acid + rutin	y = a + bx logy = a + b/x	0.9478 0.9992	14.1899 1.2923	6.8998×10^{-2} -2.0039

* n_{TE} was determined in total solids left after evaporating water from the solution of solubilizer and micellar adduct; ** cholic acid n_{TE} = 20-70

(Fig. 4) were located under the plot of function $A_m = f(n_{TE})$.

Surprisingly, this finding was also confirmed by the course of relationship between micellar level of hydrophilic-lipophilic balance of adduct and solubilizer, calculated by means of ^{1}HNMR method (HLB^1_{HNMR}) and the number of oxyethylated surfactant segments determined in equilibrium: $HLB_{^1HNMR} = f(n_{TE})$ (Fig. 5).

The values of $HLB_{^1HNMR}$ and n_{TE} for solubilizer and studied adducts are summarized in Table 3.

Approximation equations presented in Table 4, describing the relationship between ΔG^o_m and determined content of n_{TE} by p = 0.05, suggest that the "a" coefficient for solubilizers ($\Delta G^o_{m(aprox)} = -18.4256$ kJ/mol) is comparable to those for micellar adducts with diclofenac (– 18.6459 kJ/mol) and naproxen (– 18.6832 kJ/mol).

Slight decrease in micellar stability of adduct was observed in case of loratadine ($\Delta G^o_{m\ (aprox)} = -17.6039$ kJ/mol), whereas the micellar stability of rutin adduct ($\Delta G^o_{m(aprox)} = -19.7440$ kJ/mol) increased surprisingly despite a significant rise in the effective molecular volume.

The ΔG^o_m value for adduct, as well as quantitative characteristics of solubilization by homologous structures of the new class of surfactants, raises the possibility of formulating model preparations for parenteral use.

Gradients of lines that illustrate the relationship between $HLB_{^1HNMR}$ along with the number of oxyethylated segments (n_{TE}, Table 5) for solubilizers and their micellar adducts suggest that (by $n_{TE} = 0$) the value of $HLB_{^1HNMR(0)}$ for molecular adducts of cholic acid derivatives with diclofenac, loratadine, naproxen and rutin ranges from 14.1899 (rutin) to 15.8221 (naproxen). This in turn, suggests their surprisingly high solubility in water and isotonic solutions when compared to cholic acid whose $HLB_{^1HNMR(0)}$ (by $n_{TE} = 0$) was found to be 9.3698.

The increase in $HLB_{^1HNMR}$ value of adduct that was observed in this study suggests indirectly the possible mechanism and site of diclofenac, loratadine, naproxen and rutin solubilization by the micelle of cholic acid oxyethylation products. Moreover, it suggests that structural and quantitative characteristics of this process depend on the amount of oxyethylated segments (n_{TE}) in the molecule of surfactant.

CONCLUSIONS

High solubility of lipophilic naproxen was observed in the environment of aqueous solutions of the cholic acid oxyethylation products as suggested by determined factual solubility and the value of micellar partition coefficient (K^m_w).

Determined surface activity of surfactants (new class of derivatives) described by various physicochemical characteristics (γ^{25}_{cmc}, cmc, ΔG^o_m and A_m) suggests their compatibility with physiological values of the surface activity of plasma (48.0-52.0 mJ/m^2) and lacrimal fluid (46.0-52.0 mJ/m^2). This finding establishes the possible application of the

cholic acid oxyethylation products as excipients (solubilizers) in formulations of solid drug forms containing lipophilic therapeutic agents.

Calculated values of HLB_{HNMR} and n_{TE} of the micellar adduct in solid phase (solid dispersion) corresponded with an increase in its hydrophilicity (Table 3), and, therefore, suggested possible mechanisms and site of diclofenac, loratadine, naproxen and rutin solubilization in the micellar structure (core or palisadic layer).

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