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EXPERIMENTAL PAPER

Solubility and solubilizing capabilities of aqueous solutions of *Extractum Taraxaci e radix cum herba aqu. siccum* in light of selected values of general Hildebrand-Scatchard-Fedors theory of solubility

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Summary

Introduction: The general Hildebrand-Scatchard theory of solubility supplemented by Fedors' solubility parameter $-\delta^{\frac{1}{2}}$ was used to estimate the real solubility by -log x_2 (log of the mole fraction) of phytochemicals contained in *Ext. Taraxaci e radix cum herba aqu. siccum*. Surface activity of aqueous solution of extracts was determined and quantified – solubilizing capabilities of solutions of $c_{exp.} \geq$cmc in relation to cholesterol particle size of Ø=1.00 mm, as well as of ketoprofen were defined. **Objective:** The calculated value -log x_2 collated with the polarity of extraction medium ε_M allows to estimate the optimal solubility of phytochemicals that determine the viscosity of the aqueous extract of dandelion and above all its surface activity and the ability to solubilize lipophilic therapeutic agents (ketoprofen). **Methods:** Viscosity of water model solutions of dandelion extracts and exhibition solutions after the effective micellar solubilization of cholesterol and ketoprofen was measured using Ubbelohde viscometer in accordance with the Polish Standard. The surface tension of aqueous solutions of extract and exhibition solutions after solubilization of cholesterol and ketoprofen was measured according to the Polish Standard with stalagmometric method. **Results:** The calculated factual solubility, and mainly the determined and calculated hydrodynamic size mean, that despite the complex structure of the micelle, it solubilizes cholesterol (granulometric grain of diameter Ø=1.00 mm) and ketoprofen (state of technological fragmentation) in equilibrium conditions. Equilibrium solubilization of ketoprofen also occurs in an environment of model gastric juice (0.1 mol HCl). **Conclusions:** The obtained results indicate that after the administration (and/or dietary supplementation) with *Ext. Taraxaci e radix cum herba aqu. siccum*, the physiological parameters of gastric juice would not be measured and its presence (phytosurfactant) in the body of the duodenum (bile A) increases abilities of solubilizing lipophilic therapeutic agents and cholesterol accounting for its use in the treatment of liver diseases and cholesterol gall bladder stones.

Key words: *Taraxacum officinale, dry extract, solubility, solubilizing capability*

INTRODUCTION

Dandelion (*Taraxacum officinale* coll., *Asteraceae*), collected as a herb with root and inflorescence (*Taraxaci officinalis herba cum radice* FP IX), is a rich source of phytochemicals, which in galenic forms have been used in bile ducts, gall bladder and urological diseases – among others in nephrolithiasis (oxalate and phosphate) [1, 2].

Comprehensive studies on *T. officinale* extraction product, methanol, chloroform and ethyl acetate [3] confirmed their high anti-inflammatory activity, whereas sterile lyophilized "decoctum" from *Taraxaci* effectively affected the progression of immune parameters in mice [4].

In vivo and *in vitro* evaluation of aqueous extract from dandelion root (*T. officinale radix*) showed significant hepatoprotective and antioxidant properties against alcohol (ethanol)-induced liver damage [5], whereas its water-ethanol extract (80%) exhibited anti-fibrotic activity in CCl_4-induced severe bile ducts and gall bladder dysfunction in mice [6, 7].

In separate, alternative studies on water and ethyl acetate fractions derived from dandelion flower extract (*T. officinale flos*), high content of chlorogenic and caffeic acid was detected. Luteolin and its glycosidic conjugates are responsible for cholagogic, cholepoietic, antioxidant and cytotoxic activity [8].

Complex studies on liquid water-ethanol extracts (50–80%) from the dandelion herb (*T. officinale herba*), at programmed temperature progression, allowed to optimize the extraction process and quantitative caffeic and cichoric acid secretion [9].

Searching for alternative components for the preparation of nutrients, a hydrolysis of minced dandelion root (*T. officinale radix*) was performed with a culture of *Lactobacillus casei* and sugar alcohols were identified in a separated and purified product by spectroscopic methods [10].

A comprehensive review made by Schütz *et al*. of phytochemical composition of the extracts from dandelion and, above all, the resulting direction of application, pointed to the significant and growing role of this plant in rational phytotherapy [11].

Determination of the structure and melting temperature (°C) of biologically active phytochemicals isolated from dandelion (*T. officinale: folium, flos, radix, herba*) was the basis for calculation (by Fedors' method [12]) of the solubility parameter and the required numerical value of HLB_{Requ} [13, 14].

The above was the basis for the calculation, from the Hildebrand-Scatchard equation, the predicted solubility in water and in extraction mixtures with ethanol [15, 16] by the mole fraction of the solubilized substance -log x_2; triterpenes, sesquiterpene lactones, derivatives of taraxacoside, taraxacolide β-D-glucoside and tetrahydroridentin B [17].

Comparison of calculated value -log x_2 of phytochemicals with the polarity of the extracting medium – E_M enables to estimate their optimal solubility, which determines the viscosity of the aqueous extract and, above all, the surface activity of water-soluble phytochemicals that in turn decide about the solubilizing capability of lipophilic therapeutic agents.

The carried out preformulation studies, which are the subject of this publication, will be the basis for estimating the pharmaceutical availability of phytochemicals from a solid oral dosage form, which has *Ext. Taraxaci e radix cum herba aqu. siccum* in its composition to model acceptor fluids [18].

MATERIAL AND METHODS

Material

Dry extract from dandelion root and herb – *Ext. Taraxaci e radix cum herba aqu. siccum*; S:040901 Europlant Group – Phytopharm Klęka S.A. Poland

Ketoprofen: 3-benzoyl-α-methylphenylacetic acid, SIGMA, Germany

Cholesterol, AR, Polish Chemical Reagents Gliwice, Poland

For solubilization tests cholesterol was prepared by amorphous form wet granulation with ethanol (AR). The granules were sieved through Erweka sieve set. After drying to a constant weight, separation of grain was made using HAVER EML 200 digital T analyzer, Analysesiebmaschine Test Sieve Shaker (Haver & Boecker, Germany) and a set of sieves in numerical order from Ø=1.60 mm to Ø=0.160 mm. The prepared cholesterol granulated mass of bulk density and granule density comparable to cholesterol gallstones (cholesterol content higher than 84%) was the subject of equilibrium micellar solubilization in model solutions (water, 0.1 mol HCl, phosphate buffer, pH=6.88) prepared from *Ext. Taraxaci e radix cum herba aqu. siccum*.

Solubility of phytochemicals in medium of variable polarity – E_M of the extraction medium

Hildebrand-Scatchard equation was supplemented by Fedors' method [15, 19], which allows to calculate the solubility parameter of the extraction medium and phytochemical parameters. Despite application reservations, it is a fundamental tool for estimating the predicted solubility of chemical compounds, including therapeutic agents in real solution.

The equation in the form:

$$-\log x_2 = \frac{\Delta H_f^{app}}{2.303 \cdot R \cdot T} \cdot \frac{T_m - T}{T_m} + \frac{V^2 \cdot \varphi^2}{2.303 \cdot R \cdot T} \cdot (\delta_1 - \delta_2)^2$$

where: ΔH_f^{app} – apparent molar entalphy of fusion, R – gas constant, T – temperature in °K (273.15+t°C), V_2 – molar volume of the phytochemical of defined structure and melting temp., φ – solvent volume fraction, δ_1 and δ_2 – medium (1) and phytochemical (2) solubility, allows to calculate the solubility in the form of a molar fraction $-\log x_2$.

Apparent enthalpy of fusion – ΔH_f^{app} was calculated from the equation:

$$\Delta H_f^{app} = \frac{0.01(T_m - T) \cdot R}{\log T_{m/T}} \cdot T_m$$

where: T_m – melting temperature of the dissolved substance, T – temperature at which solubility is to be determined.

The solubility parameter – $\delta^{\frac{1}{2}}$ was calculated from the equation given by Fedors [12]:

$$\delta^{\frac{1}{2}} = \sqrt{\Sigma E_i / \Sigma V_i}$$

The calculated numerical value of solubility using a molar fraction – x_2 can be expressed in mol/dm^2 with the equation:

$$S_{|z|} = \frac{1000}{M_{cz}\left(\frac{1}{x_2} - 1\right)}$$

where: M_{cz} – molecular mass of the solvent.

Phytochemical solubility parameter – $\delta^{\frac{1}{2}}$ allows to calculate from the equation

$$HLB_{Requ} = \left[\left(\delta^{\frac{1}{2}} + 7\right)/8\right]^4$$

the so called required level of hydrophilic-lipophilic balance.

The calculated values $\sum \Delta E_i$, $\sum \Delta V_i$, $\delta^{\frac{1}{2}}$, ΔH_f^{app}, and -log x_2 are presented in table.

Viscosity and surface tension of model aqueous solutions of *Ext. Taraxaci e radix cum herba aqu. siccum*

The viscosity measurements of aqueous solutions of *Ext. Taraxaci e radix cum herba aqu. siccum* in 0.1 mol HCl and in phosphate buffer of pH=6.88 were performed acc. to the Polish Standard using Ubbelohde viscosimeter. They were the basis for calculating from the equation [20]:

$$LVN[\eta] = \left[\eta_{wB} + 3 \cdot \ln\left(\eta_{roz} / \eta_{o\ H_2O}\right)\right] / 4 \cdot c$$

the limiting viscosity number [η] as well as the selected hydrodynamic values: Mη, R_o, R_{abs}, Ω and solubilization index – n_s.

The obtained results of determinations and calculations are presented in table. The surface tension of model aqueous solutions – γ_{sol}^{25} of *Ext. Taraxaci e radix cum herba aqu. siccum* were determined by stalagmometric method acc. to the Polish Standard [21]. The critical micellar concentration (cmc) was calculated as described in publication [22]. The numerical value of cmc (g/100 cm^3, mol/dm^3) was the basis for calculating from the equation:

$$\Delta G_m^o = 2.303\ R \cdot T \cdot \log\ cmc$$

the thermopotential for the formation of micelles – ΔG_m^o. The value of the decrease of the surface tension coefficient in the critical area – γ_{roz}^{25} was the basis for calculating from the equation:

$$A_m = K \cdot T / \gamma_{roz}^{25} - \gamma_{cmc}^{25}$$

'the average area per one molecule of the surfactant' – A_m at phase boundary.

The above dependence results from dividing both sides of 'the equation of state of perfect areas' ~ $\Delta p \cdot A = R \cdot T$ by Avogadro number leading to the equation – $f(\Delta p) \cdot A_m = K \cdot T$, where $f(\Delta p) = \gamma_{H20}^{25} - \gamma_{cmc}^{25}$.

The determined and calculated values are demonstrated in table.

Micellar solubilization of cholesterol granules and ketoprofen in model solutions of *Ext. Taraxaci e radix cum herba aqu. siccum*

The process of micellar solubilization was performed in a container of V=100 cm^3 into which there were weighed not less than 0.350 g of homogeneous cholesterol granules of φ=1.00 mm, in the case of ketoprofen the weighed quantity did not exceed 0.3530 g. Then, 25.0 cm^3 of the aqueous solution of the extract was pipetted into 0.1 mol HCl and phosphate buffer of pH=6.88. The containers were fixed in EIPIN+375 water bath shaker at bath temp. 37.0 ±0.1°C. After 24 h of exposure, saturated micellar solution of solubilized cholesterol and ketoprofen was separated from the excess of granules on the Eurochem BCD-12/5 quantitative filter.

To measure viscosity (η) and surface tension (γ_{cmc}^{25}), the solutions were filtered through a sterile filter used in a disposable set for magistral ophthalmic topical drop preparations – Machery-Nagel, Chromafil CA-45/255, Cell acetate 0.45 μm.

Solutions of solubilized ketoprofen were prepared for quantitative determinations by spectrophotometric method (UV). After the measurement of absorbancy (A) of model solutions post exposure, the approximation equation applied in [23] allowed to calculate from the dependence $c_{|sol|} = A \cdot a/b$ the amount of the solubilized therapeutic agent. The obtained results are summarized in table.

Ethical approval: The conducted research is not related to either human or animal use.

RESULTS AND DISCUSSION

The structure of phytochemicals [2, 17, 25], supplemented with selected physicochemical values, was the basis for calculating by Fedors' method [12] thermodynamic values: $\sum \Delta E_i$ (cal/mol) and $\sum \Delta V_i$ (cm^3/mol) that are needed to estimate the

solubility parameter – ψ. This part of the research was supplemented with alternative HLB value calculated by Davies' method [25] from the equation – $HLB_D = 7 + \sum W \cdot h(+) + \sum W \cdot l(-)$, the numerical value of hydrophilic-lipophilic balance (HLB) the value of which is demonstrated in table 1.

Table 1.

Calculated thermodynamic values and the level of hydrophilic-lipophilic balance HLB_{Requ} HLB_D of phytochemicals contained in *Ext. Taraxaci e radix cum herba aqu. siccum*

Phytochemicals	MW [g·mol^{-1}]	Melting temp. [°C]	$\Sigma\Delta E_i$ [cal/mol]	$\Sigma\Delta V_i$ [cm^3/mol]	$\delta^{\frac{1}{2}}$	HLB_{Requ}	HLB_D
1. Taraxinic acid glucosyl ester lactone $C_{21}H_{28}O_9$	424.44	84–86	57625	210.0	16.565	7528	615
2. Taraxacoside lactone $C_{18}H_{22}O_{10}$	398.36	178–180	55800	178.2	17.695	90.80	12.50
3. Taraxolide-1-*O*-*β*-D-glucopyranoside lactone $C_{21}H_{32}O_9$	428.47	192	30825	123.6	15.792	65.88	9.65
4. 4.11.13.15-Tetrahydrorident B lactone $C_{15}H_{24}O_4$	268.34	141–142	21140	135.9	12.47	35.09	6.725
Triterpene							
5. Oleanolic acid $C_{30}H_{48}O_3$	456.70	305–310	33295	303.8	11.35	27.67	0.075
6. Taraxerol $C_{30}H_{50}O$	426.72	282–283	34120	334.9	0.09	20.84	–4.40
7. Taraxasterol $C_{30}H_{50}O$	426.72	225.5–226	33875	308.3	10.48	22.80	–2.50
8. ψ-Taraxasterin $C_{30}H_{50}O$	426.72	217–219	33523	312.0	110.36	22.20	–4.875
9. Taraxeron $C_{30}H_{18}O$	424.71	240–241	29980	355.9	9.17	16.72	–5.025
10. Taraxeren $C_{30}H_{50}$	410.72	238–239	27360	311.5	9.37	17.53	–6.775

Using the extraction medium polarity – ε_η for water: ethanol extraction system and its solubility parameter $\delta^{\frac{1}{2}}$ [16], a numerical value of the predicted solubility of phytochemicals contained in the *Ext. Taraxaci e radix cum herba aqu. siccum* was calculated by Hildebrand-Scatchard method by -log x_2.

Values characterizing the structure, predicted solubility (-log x_2) and hydrophilic-lipophilic balance (HLB_{Requ}, HLB_D) of selected phytochemicals are presented in table 2.

Table 2.

Calculated expected solubilities - log x_2 of phytochemicals depending on solubility parameter $\delta^{\frac{1}{2}}$ of extraction medium at ethanol concentration progression

Medium H_2O	$\delta^{\frac{1}{2}}$ – medium	ε_M – medium	-log x_2					
			Oleanolic acid	Taraxerol	Taraxasterol	Taraxeron	Taraxeren	ψ–Taraxasterin
1. H_2O	24.52	78.50	47.9692	6.8607	47.0454	63.9672	55.2453	48.3108
2. 50% Ethanol	18.57	49.00	18.6336	4.7994	17.3604	25.5916	22.1676	17.8999
3. 70% Ethanol	16.19	38.00	11.3083	8.8393	9.9145	15.4279	13.4584	10.2636
4. 90% Ethanol	13.81	281.0	6.5119	15.6564	5.0572	8.1775	7.3384	5.2193
5. 100% Ethanol	12.63	24.30	5.0458	42.6365	15.6312	9.2385	5.3692	4.3822
6. ΔH_f^{app}			11260.46	10457.75	8771.47	9311.08	9255.48	8689.52

Table 2.cont.

Medium H_2O	$\delta^{\frac{1}{2}}$ – medium	ε_M – medium	-log x_2			
			Taraxinic acid glycosyl ester	Taraxacoside	Taraxacolide -1-*O*-*β*-D-glucopyranoside	4.11.13.15–Tetrahydroridentin B
1. H_2O	24.52	78.50	10.4128	7.9777	9.0079	15.8311
2. 50% Ethanol	18.57	49.00	1.2789	2.6643	2.8053	5.0856
3. 70% Ethanol	16.19	38.00	0.6818	2.1904	2.1189	2.7586
4. 90% Ethanol	13.81	281.0	1.8149	3.8638	2.4583	1.5593
5. 100% Ethanol	12.63	24.30	3.0251	5.2489	3.0099	1.4248
6. ΔH_f^{app}			5384.98	7625.29	7997.52	6701.41

They are the basis for tracing the relationship between the predicted solubility (-log x_2) and the polarity of extraction medium (ε_M); (-log x_2)=f(ε_M), (fig. 1 and 2).

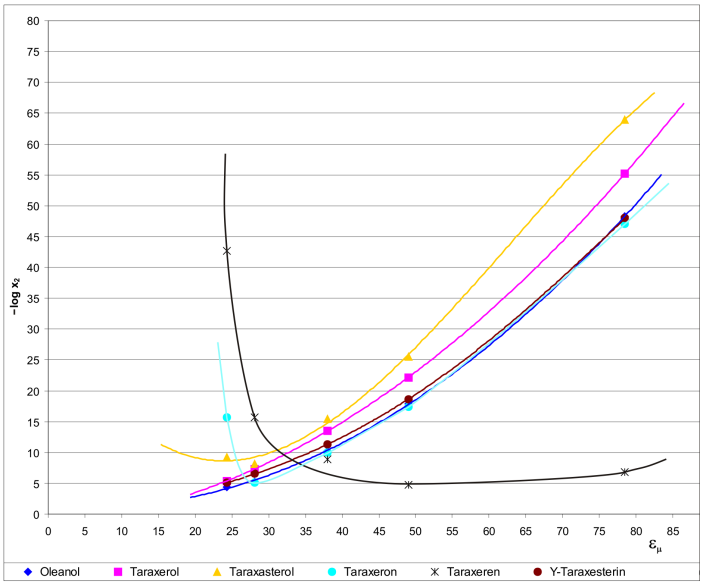

Figure 1.

The course of the dependence between -log x_2 of triterpenes and dielectric constant ε_μ of the water:ethanol system of solvents

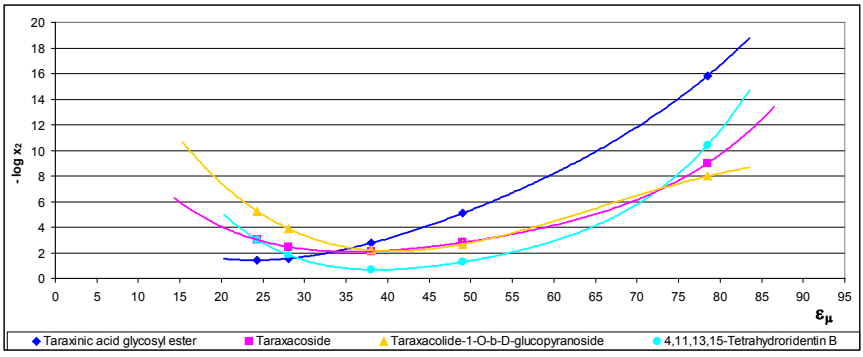

Figure 2.

The course of the dependence between -log x_2 of hydrophilic structures of *Ext. Taraxaci e radix cum herba aqu. siccum* and dielectric constant ε_μ of the water:ethanol system of solvents

It results from the course of the dependence $(-\log x_2)=f(\varepsilon_M)$, figure 1, that the predicted solubility of triterpenic structures: oleanolic acid, taraxasterol, taraxerol, taraxeren and ψ-taraxasterin increases asymptotically with the decrease of polarity of the extraction medium $-\varepsilon_M$ (increase of % ethanol).

Only taraxerol is characterized by significant predicted solubility (-log x_2) in water (tab. 2, fig. 1) and in 50% aqueous solution of ethanol, but with the increase of ethanol concentration (decrease the medium polarity) its solubility decreases (increase of numerical value -log x_2).

However, it results from similar functional equation, Fig. 2, for taraxacoside, tetrahydroridentin B, taraxacolide β-D-glucoside and taraxinum acid β-D-glucoside that these structures obtain optimal predicted solubility at 70% ethanol concentration.

Predicted solubility -log x_2 of taraxacoside, taraxacolide β-D-glucoside and taraxinum acid β-D-glucoside in water is sufficient to form with taraxerol triterpenic structure (-log x_2=6.8607) in aqueous solution, in complex spatial system micelles, which decreasing surface tension at phase boundary will solubilize, in their own specific way, lipophilic therapeutic agents.

The course of the dependence between -log x_2 in the function of dielectric constant of the extraction system – ε_M at p=0.05 was described by correlation equations which are presented in table 3. They reflect the solubility preferences of phytostructures contained in *Ext.Taraxaci e radix cum herba aqu. siccum* that determine the therapeutic efficacy of preparations produced on the basis of dry extract of *T. officinale*.

Table 3.

Correlation equations describing the relationship at p=0.05 between the calculated predicted solubility – log x_2 and medium polarity – ε_M; -log $x_2=f(\varepsilon_M)$

Phytochemicals	Equation type	r	a ± da	b ± db
1. Oleanolic acid	1. $y=a+b\cdot x$	0.9880	–17.0134 ± 10.9785	0.8009 ± 0.2301
	2. $y=a+b\cdot\log x$	0.9476	–113.9555 ± 82.1600	82.4144 ± 51.0288
2. Taraxerol	1. $\log y=a+b\cdot\frac{1}{X}$	0.8859	0.2741 ± 0.8046	28.7639 ± 27.6606
	2. $y = a_1\times x^2 + a_2\times x + b$	1.0000	a_1 = 0.0081 a_2 = 0.0822	– 1.4268
3. Taraxasterol	1. $y=a+b\cdot x$	0.9121	–10.9985 ± 27.1467	0.6883 ± 0.5688
	2. $y = a_1\times x^2 + a_2\times x + b$	0.9980	a_1 = 0.0117 a_2 = 0.1678	+ 5.1515
4. Taraxeran	1. $y=a+b\cdot x$	0.9849	–21.1820 ± 16.1481	1.04779 ± 0.3383
	2. $y=a+b\cdot\log x$	0.9416	–147.4379 ± 113.6603	
5. Taraxeren	1. $y=a+b\cdot x$	0.9912	–19.7726 ± 10.8741	0.9290 ± 0.2278
	2. $y=a+b\cdot\log x$	0.9545	–132.8290 ± 88.6672	95.9755 ± 55.0704
6. ψ–Taraxasterin	1. $y=a+b\cdot x$	0.9866	–17.0134 ± 10.9785	0.8009 ± 0.2301
	2. $y=a+b\cdot\log x$	0.9447	–113.9555 ± 82.1600	82.4144 ± 51.0288
7. Taraxinic acid glucosyl ester	1. $y = a_1\times x^2 + a_2\times x + b$	0.9999	a_1 = 0.0040 a_2 = – 0.1453	+ 2.5310
	2. $y = a \times \ln x - b$	0.8544	11.9820	– 38.8060
8. Taraxacoside	1. $y = a_1\times x^2 + a_2\times x + b$	0.9980	a_1 = 0.0041 a_2 = 0.3062	+ 7.9425
	2. $y = a \times \ln x - b$	0.6264	4.8950	– 14.1520

Phytochemicals	Equation type	r	a ± da	b ± db
9. Taraxacolide–1–*O*–*β*–D–glucopyranoside	1. y=a+b·x	0.8836	–1.2320 ± 5.4499	0.1173 ± 0.1122
	2. $y = a_1 \times x^2 + a_2 \times x + b$	0.9777	$a_1 = 0.0056$ $a_2 = -0.5164$	+ 14.1880
10. 4.11.13.15–Tetrahydrorident B	1. y=a+b·x	0.9756	–6.4979 ± 5.3555	0.2714 ± 0.2278
	2. y=a+b·log x	0.9243	–38.8050 ± 33.6956	27.5884 ± 20.9280

Surface tension γ_{roz}^{25} of aqueous model solutions of *Ext.Taraxaci e radix cum herba aqu. siccum*

It results from numerical values – γ_{roz}^{25} demonstrated in table 4 that surface activity of model solutions of *Ext.Taraxaci e radix cum herba aqu. siccum* is above physiological value $\gamma_{(f)}^{25}$ =48–52 mJ/m^2 of human body fluids.

Table 4.

Physicochemical parameters characterizing surface activity of model aqueous solutions of *Ext.Taraxaci e radix cum herba aqu. siccum*

Extract type Medium	% of extract solubility in water	cmc [g · 100 cm^{-3}]	cmc [mol · dm^{-3}]	ΔG_m^{o} * [kJ · mol^{-1}]	γ_{cmc}^{25} [kJ · m^{-2}]	$A_m \cdot 10^{-19}$ ** [m^2]
Ext.Taraxaci e radix cum. herba aqu. siccum						
1. Aqueous solution	87.76	0.6750	$3.4861 \cdot 10^3$	–14.0247	63.50	4.8537
2. Solution in 0.1 mol HCl	90.12	0.7000	$4.7637 \cdot 10^3$	–13.2508	64.25	5.3246
3. Solution in phosphate buffer of pH=6.88	76.41	0.8500	$3.6189 \cdot 10^3$	–13.9321	63.75	5.0012

* ΔG_m^{o} =5.7065 kJ/mol·log cmc

** $A_m = 411.5990 \cdot 10^{-20} / 71.98 \cdot \gamma_{cmc}^{25}$

Relatively low value of ΔG_m^{o} (kJ/mol) for water (- 14.0247 kJ/mol) for 0.1 mol HCl (– 13.2508 kJ/mol) and (– 13.9321 kJ/mol) for phosphate buffer of pH=6.88 indicates not very high thermodynamic stability of the micellar system. Numerical values of ΔG_m^{o} (kJ/mol) and coefficient Am (m^2) point to relatively high bioavailability of phytochemicals forming a topological structure of the micelles and, above all, to the difficult to identify solubilizing capabilities with respect to compatible structures of phytochemicals and therapeutic agents. Practically – basing on the results obtained *in vitro* – it can be concluded that the so-called

drug-induced gastroduodenal reflux during the therapy with solid oral form of preparation (tablet) will not occur.

Viscosity of model and exposure- after cholesterol solubilization – solutions with *Ext.Taraxaci e radix cum herba aqu. siccum*

It results from calculated viscosity values presented in table 5 that the concentration of hydrogen ions – $pH_{(aH+)}$ has a significant impact on the viscometric order of magnitude ([η], M_η) as well as on the calculated hydrodynamic values (R_o, R_{abs}, Ω) that characterize a complex micellar system.

Low value of ΔG_m^o, that is the thermodynamic potential for micelle formation, in combination with hydrogen ion activity and osmotic pressure (water ~0 m Osm/dm^3, 0.1 mol HCl – 200 m OSm/dm^3, phosphate buffer –m Osm/dm^3) makes that cholesterol capabilities to solubilization from granulometric grain of Ø=1.00 mm are confirmed only for the aqueous solution; cholesterol n_{lsl} = 1.6518 ($n_{lsl} = \frac{M_\eta add - M_\eta mic}{386,67}$). Regression of viscosity and hydrodynamic parameters during cholesterol exposure makes micellar adduct lose the hydration layer (solvation), which, considering the adsorption of cholesterol molecules, is not significantly reflected in the order of their magnitude. It results from the above that system of phytochemicals topologically constructed in micelles contained in a dry *Ext.Taraxaci e radix cum herba aqu. siccum* and soluble in water does not undergo decomposition during micelar solubilization.

This was an inspiration for carrying out the equilibrium solubilization of ketoprofen; a therapeutic agent with much lower molecular weight than cholesterol; ketoprofen MW=254.3 g/mol. The determination of the amount of solubilized ketoprofen was performed by spectrophotometric method (UV) and the results are summarized in table 5.

Unexpectedly, it appeared that the complex micellar system preserves significant solubilization capacity in water and also in a solution of 0.1 mol of HCl; determined at 25±0.1°C real solubility of ketoprofen in water – c_{lnl}=12.9214 mg·100 cm^{-3}. The obtained results indicate that the introduction of *Ext.Taraxaci e radix cum herba aqu. siccum* into the therapy in an oral dosage form (tablet, capsule) can complement the Lindblad lythogenolythic index in duodenal contents (0.700 = $\sum$cholesterol/$\sum$cholid acids-H^2/Na^+ + $\sum$lecithins; $\frac{mol}{mol}$(24h)) and promote solubilization of cholesterol as well as lipophilic therapeutic agents BCS class II and IV. This aspect is important in pharmaco- and phytotherapy of liver diseases – especially cholesterol lithiasis and also in the process of stimulating the secretion of hepatic bile (bile C) and shaping its physiological properties, especially in patients after cholecystectomy [26-28].

Table 5.

Basic viscosity values of model aqueous solutions of *Ext.Taraxaci e radix cum herba aqu. siccum* before and after equilibrium solubilization of cholesterol of Ø=1.00 mm

Extract type Medium	Weighed amount g·100 cm^{-3}	GLL; [η]	M_η	$R_o \cdot 10^{-7}$ [cm]	$R_{obs} \cdot 10^{-8}$ cm	$\Omega \cdot 10^{-20}$ cm^{-3}	c_{isl} η_{isl}
Ext. Taraxaci e radix cum herba aqu. siccum							c_{isl} * ketoprofen mg·100 cm^{-3}
1. Aqueous solution	1.8524	0.086961	1936.25	3.6604	2.9886	1.1182	107.4138
2. 0.1 mol HCl solution	2.0276	0.073614	1469.44	3.1564	2.5784	0.7183	36.9746
3. Phosphate buffer of pH=6.88	1.8669	0.097721	2348.78	4.0586	3.3137	1.5243	-
Ext. Taraxaci e radix cum herba aqu. siccum							$\eta_{isl\ chol}$ mol:mol
1. Aqueous solution	1.8524	0.10331	2574.98	4.2631	3.4807	1.7665	1.6518
2. 0.1 mol HCl solution	2.0276	0.071243	1391.92	3.0682	2.5051	0.6585	-
3. Phosphate buffer of pH=6.88	1.8669	0.093032	2165.16	3.8857	3.1726	1.3377	-

* ketoprofen solubility in water – $c_{|sol|}$ = 12.9214 mg/100 cm^3 at temp. 25.0 ±0.1°C

CONCLUSIONS

1. The use of the general Hildebrand-Scatchard theory of solubility supplemented by Fedors' solubility parameter $-\delta^{\frac{1}{2}}$ is an application method for estimating the real solubility by $-\log x_2$ (log of the mole fraction) of phytochemicals contained in *Ext. Taraxaci e radix cum herba aqu. siccum*. The numerical value $-\log x_2$ related to ε_M extraction medium allows to estimate quantitatively the solubility of phytochemicals and, first of all, physicochemical properties of the extract solutions in water, in the solution 0.1 mol HCl and in phosphate buffer of pH=6.88.
2. The measurement of surface tension coefficient – γ_{sol}^{25} of monophasic, real solutions of the extract in water allowed to calculate basic thermodynamic values: cmc, ΔG_m^o, γ_{cmc}^{25}, A_m, which point to predictable nature of biological interactions with plasma morphotic elements and, above all, to solubilization capability of complex micelle in model body fluids. It results from the calculated values of ΔG_m^o (kJ/mol) that only a micelle consisting of phytochemicals has equilibrium solubilization capacity at phase boundary exclusively in aqueous solution. The level of the decrease of surface tension coefficient γ_{cmc}^{25} indicates that the administration of a tablet with an extract of pharmacopoeial disintegration time after its disintegration in the gastric juice does not disturb its physiological

value [27]. Therefore, after administration of the preparation (and/or dietary supplement) with an *Ext. Taraxaci e radix cum herba aqu. siccum*, physiological parameters of gastric juice will not alter and thus the so-called "drug-induced gastric reflux" will not occur.

3. It results from the determined and calculated viscosity and hydrodynamic values that the complex structure of micelles in aqueous solution solubilizes cholesterol from granulometric grain of Ø=1.00 mm and ketoprofen. Ketoprofen solubilization equilibrium also takes place in aqueous solution of an extract in 0.1 mol HCl (200 mOsm/dm^3).

The above proves the topological stability of the micelle structure, although ΔG_m^o is in the range of (–13.2508 kJ/mol) – (–14.0247 kJ/mol). The calculated hydrodynamic values (R_o, R_{obs}, Ω) testify to the stability of the hydration layer of complex micellar adduct after the cholesterol solubilization. The obtained results confirm the possibility of using *Ext. Taraxaci e radix cum herba aqu. siccum* in the treatment of diseases of the liver and cholesterol cholelithiasis [27, 28].

Conflict of interest: Authors declare no conflict of interest.

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ROZPUSZCZALNOŚĆ I ZDOLNOŚCI SOLUBILIZACYJNE WODNYCH ROZTWORÓW *EXTRACTUM TARAXACI E RADIX CUM HERBA AQU. SICCUM* W ŚWIETLE WYBRANYCH WIELKOŚCI OGÓLNEJ TEORII ROZPUSZCZALNOŚCI HILDEBRANDA-SCATCHARDA-FEDORSA

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S t r e s z c z e n i e

Wstęp: Ogólną teorię rozpuszczalności Hildebranda-Scatcharda uzupełnioną przez Fedorsa o parametr rozpuszczalności $-\delta^{\frac{1}{2}}$ wykorzystano do oszacowania rozpuszczalności rzeczywistej na sposób -log x_2 (log ułamka molowego) fitozwiązków wchodzących w skład *Ext. Taraxaci e radix cum herba aqu. siccum*. Oznaczono aktywność powierzchniową wodnych roztworów ekstraktów, a także określono ilościowo zdolności solubilizacyjne roztworów o $c_{exp.} \geq$ cmc w stosunku do cholesterolu w formie granulometrycznego ziarna o Ø = 1,00 mm, a także ketoprofenu. **Cel:** Wyliczone wartości -log x_2 zestawione z polarnością medium ekstrakcyjnego ε_M umożliwiają oszacowanie optymalnej rozpuszczalności fitozwiązków, które decydują o lepkości wodnego roztworu ekstraktu z mniszka lekarskiego, a przede wszystkim o jego aktywności powierzchniowej i zdolności do solubilizacji liofilowych środków leczniczych (ketoprofenu). **Metody:** Lepkość wodnych, modelowych roztworów ekstraktów z mniszka lekarskiego i roztworów ekspozycyjnych po efektywnej solubilizacji micelarnej cholesterolu i ketoprofenu zmierzono wiskozymetrem rozcieńczeniowym metodą Ubbelohde'a zgodnie z Polska Normą. Napięcie powierzchniowe wodnych roztworów ekstraktu i roztworów ekspozycyjnych po solubilizacji cholesterolu i ketoprofenu zmierzono wg Polskiej Normy metodą stalagmometryczną. **Wyniki:** Z wyliczonej rozpuszczalności rzeczywistej, a przede wszystkim z wyznaczonych i wyliczonych wielkości

hydrodynamicznych wynika, że mimo złożonej struktury miceli solubilizuje ona w warunkach równowagowych cholesterol (ziarno granulometryczne o Ø=1,00 mm) i ketoprofen (o technologicznym stanie rozdrobnienia). Równowagowa solubilizacja ketoprofenu zachodzi również w środowisku modelowego soku żołądkowego (0,1 mol HCl). **Wnioski:** Uzyskane wyniki wskazują, że po podaniu preparatu (i/lub suplementu diety) z *Ext. Taraxaci e radix cum herba aqu. siccum* nie zostaną zmierzone parametry fizjologiczne soku żołądkowego, a jego obecność (fitosurfaktantu) w treści dwunastnicy (żółć A) zwiększy zdolności solubilizacyjne liofilowych środków leczniczych i cholesterolu co uzasadnia jego wykorzystanie w leczeniu schorzeń wątroby i kamicy cholesterolowej woreczka żółciowego.

Słowa kluczowe: *Taraxacum officinale, suchy ekstrakt, rozpuszczalność, zdolność solubilizacyjna*