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

ZBIGNIEWS MARCZYŃSKI¹*, SŁAWOMIRA NOWAK², JERZY JAMBOR³, MARIAN MIKOŁAJ ZGODA⁴

¹Department of Pharmacy
Chair of Applied Pharmacy
Faculty of Pharmacy
Medical University
Muszyńskiego 1
90-151 Łódź, Poland

²Department of Pharmacognosy
Chair of Pharmacognosy
Faculty of Pharmacy
Medical University
Muszyńskiego 1
90-151 Łódź, Poland

³Europlant Group
Phytopharm Klęka SA
Klęka 1
63-040 Nowe Miasto n. Wartą, Poland

⁴Extramural Doctoral Studies
Chair of Applied Pharmacy
Medical University
Muszyńskiego 1
90-151 Łódź, Poland

*Corresponding author: phone/fax: +4842 6779240,
e-mail: zbigniew.marczynski@umed.lodz.pl
Summary

Introduction: The general Hildebrand-Scatchard theory of solubility supplemented by Fedors' solubility parameter $\delta^2$ 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 $c_{exp.} \geq \text{cmc}$ in relation to cholesterol particle size of $\varnothing = 1.00$ mm, as well as of ketoprofen were defined. Objective: The calculated value $-\log x_2$ collated with the polarity of extraction medium $\varepsilon_M$ 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 $\varnothing = 1.00$ 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 CCl4-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<sub>requ</sub> [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 x₂, triterpenes, sesquiterpene lactones, derivatives of taraxacoside, taraxacolide β-D-glucoside and tetrahydroridentin B [17].

Comparison of calculated value -log x₂ of phytochemicals with the polarity of the extracting medium – Eₘ 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 $\varnothing=1.60\text{ mm}$ to $\varnothing=0.160\text{ mm}$. 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:

$$-\log x_2 = \frac{\Delta H_{f}^{\text{app}}}{2.303 \cdot R \cdot T} \cdot \frac{T_m - T}{T_m} + \frac{V_2 \cdot \varphi^2}{2.303 \cdot R \cdot T} \cdot (\delta_1 - \delta_2)^2$$

where: $\Delta H_{f}^{\text{app}}$ – apparent molar enthalpy of fusion, $R$ – gas constant, $T$ – temperature in $^\circ\text{K}$ (273.15+to$^\circ\text{C}$), $V_2$ – molar volume of the phytochemical of defined structure and melting temp., $\varphi$ – solvent volume fraction, $\delta_1$ and $\delta_2$ – 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 – $\Delta H_{f}^{\text{app}}$ was calculated from the equation:

$$\Delta H_{f}^{\text{app}} = \frac{0.01(T_m - T) \cdot R}{\log T_m / T} \cdot T_m$$

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

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

$$\delta^2 = \frac{\Sigma E_i}{\Sigma V_i}$$
The calculated numerical value of solubility using a molar fraction – $x_2$ can be expressed in mol/dm$^2$ with the equation:

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

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

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

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

the so called required level of hydrophilic-lipophilic balance.

The calculated values $\sum \Delta E_i$, $\sum \Delta V_i$, $\delta^{\frac{1}{2}}$, $\Delta H_f^{\text{app}}$, 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]:

$$\text{LVN}[\eta] = \left[ \eta_{\text{wb}} + 3 \cdot \ln \left( \frac{\eta_{\text{fo}}}{\eta_0 \cdot \text{H}_2\text{O}} \right) \right] / 4 \cdot c$$

the limiting viscosity number $[\eta]$ as well as the selected hydrodynamic values: $M_\eta$, $R_o$, $R_{\text{abs}}$, $\Omega$ and solubilization index – $n_s$.

The obtained results of determinations and calculations are presented in table. The surface tension of model aqueous solutions – $\gamma_{\text{sol}}^{25}$ 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:

$$\Delta G_m^0 = 2.303 \, \text{R} \cdot \text{T} \cdot \log \text{cmc}$$
the thermopotential for the formation of micelles – $\Delta G_m^0$. The value of the decrease of the surface tension coefficient in the critical area – $\gamma_{roz}^{25}$ 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’ $\sim \Delta p \cdot A = R \cdot T$ by Avogadro number leading to the equation

$- f(\Delta p) \cdot A_m = K \cdot T$, where $f(\Delta p) = \gamma_{H2O}^{25} - \gamma_{cmc}^{25}$.

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 were weighed not less than 0.350 g of homogeneous cholesterol granules of $\phi = 1.00$ mm, in the case of ketoprofen the weighed quantity did not exceed 0.353 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 ($\eta$) and surface tension ($\gamma_{cmc}^{25}$), 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 $c_{kol} = A \cdot a/b$ 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 – $\psi$. This part of the research was supplemented with alternative HLB value calculated by Davies’ method [25] from the equation – $\text{HLB}_D = 7 + \sum W \cdot h(+) + \sum W \cdot l(-)$, 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$_{\text{Requ}}$, HLB$_D$ of phytochemicals contained in Ext. Taraxaci e radix cum herba aqu. siccum

<table>
<thead>
<tr>
<th>Phytochemicals</th>
<th>MW [g·mol$^{-1}$]</th>
<th>Melting temp. [$^\circ$C]</th>
<th>$\Sigma \Delta E_i$ [cal/mol]</th>
<th>$\Sigma \Delta V_i$ [cm$^3$/mol]</th>
<th>$\delta^\phi$</th>
<th>HLB$_{\text{Requ}}$</th>
<th>HLB$_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Taraxinic acid glucosyl ester lactone C$<em>{21}$H$</em>{28}$O$_9$</td>
<td>424.44</td>
<td>84–86</td>
<td>57625</td>
<td>210.0</td>
<td>16.565</td>
<td>7528</td>
<td>615</td>
</tr>
<tr>
<td>2. Taraxacoside lactone C$<em>{18}$H$</em>{22}$O$_{10}$</td>
<td>398.36</td>
<td>178–180</td>
<td>55800</td>
<td>178.2</td>
<td>17.695</td>
<td>90.80</td>
<td>12.50</td>
</tr>
<tr>
<td>3. Taraxolide-1-O-β-D-glucopyranoside lactone C$<em>{21}$H$</em>{26}$O$_9$</td>
<td>428.47</td>
<td>192</td>
<td>30825</td>
<td>123.6</td>
<td>15.792</td>
<td>65.88</td>
<td>9.65</td>
</tr>
<tr>
<td>4. 4.11.13.15-Tetrahydrorident B lactone C$<em>{15}$H$</em>{24}$O$_4$</td>
<td>268.34</td>
<td>141–142</td>
<td>21140</td>
<td>135.9</td>
<td>12.47</td>
<td>35.09</td>
<td>6.725</td>
</tr>
<tr>
<td><strong>Triterpene</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Oleanolic acid C$<em>{30}$H$</em>{48}$O$_3$</td>
<td>456.70</td>
<td>305–310</td>
<td>33295</td>
<td>303.8</td>
<td>11.35</td>
<td>27.67</td>
<td>0.075</td>
</tr>
<tr>
<td>6. Taraxerol C$<em>{30}$H$</em>{50}$O</td>
<td>426.72</td>
<td>282–283</td>
<td>34120</td>
<td>334.9</td>
<td>0.09</td>
<td>20.84</td>
<td>–4.40</td>
</tr>
<tr>
<td>7. Taraxasterol C$<em>{30}$H$</em>{50}$O</td>
<td>426.72</td>
<td>225.5–226</td>
<td>33875</td>
<td>308.3</td>
<td>10.48</td>
<td>22.80</td>
<td>–2.50</td>
</tr>
<tr>
<td>8. ψ-Taraxasterin C$<em>{30}$H$</em>{50}$O</td>
<td>426.72</td>
<td>217–219</td>
<td>33523</td>
<td>312.0</td>
<td>110.36</td>
<td>22.20</td>
<td>–4.875</td>
</tr>
<tr>
<td>10. Taraxeren C$<em>{30}$H$</em>{50}$</td>
<td>410.72</td>
<td>238–239</td>
<td>27360</td>
<td>311.5</td>
<td>9.37</td>
<td>17.53</td>
<td>–6.775</td>
</tr>
</tbody>
</table>

Using the extraction medium polarity – $\varepsilon_\eta$ for water: ethanol extraction system and its solubility parameter $\delta^\phi$ [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 x₂) and hydrophilic-lipophilic balance (HLB_{Requ}, HLB_D) of selected phytochemicals are presented in table 2.

Table 2.

Calculated expected solubilities - log x₂ of phytochemicals depending on solubility parameter δ\(^\perp\) of extraction medium at ethanol concentration progression

<table>
<thead>
<tr>
<th>Medium</th>
<th>δ(^\perp) - medium</th>
<th>ε(_M) - medium</th>
<th>-log x₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(_2)O</td>
<td>24.52</td>
<td>78.50</td>
<td>47.9692</td>
</tr>
<tr>
<td>50% Ethanol</td>
<td>18.57</td>
<td>49.00</td>
<td>18.6363</td>
</tr>
<tr>
<td>70% Ethanol</td>
<td>16.19</td>
<td>38.00</td>
<td>11.3083</td>
</tr>
<tr>
<td>90% Ethanol</td>
<td>13.81</td>
<td>281.0</td>
<td>6.5119</td>
</tr>
<tr>
<td>100% Ethanol</td>
<td>12.63</td>
<td>24.30</td>
<td>5.0458</td>
</tr>
<tr>
<td>ΔH(<em>f)(</em>{app})</td>
<td>11260.46</td>
<td>10457.75</td>
<td>8771.47</td>
</tr>
</tbody>
</table>

Table 2. cont.

<table>
<thead>
<tr>
<th>Medium</th>
<th>δ(^\perp) - medium</th>
<th>ε(_M) - medium</th>
<th>-log x₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(_2)O</td>
<td>24.52</td>
<td>78.50</td>
<td>10.4128</td>
</tr>
<tr>
<td>50% Ethanol</td>
<td>18.57</td>
<td>49.00</td>
<td>1.2789</td>
</tr>
<tr>
<td>70% Ethanol</td>
<td>16.19</td>
<td>38.00</td>
<td>0.6818</td>
</tr>
<tr>
<td>90% Ethanol</td>
<td>13.81</td>
<td>281.0</td>
<td>1.8149</td>
</tr>
<tr>
<td>100% Ethanol</td>
<td>12.63</td>
<td>24.30</td>
<td>3.0251</td>
</tr>
<tr>
<td>ΔH(<em>f)(</em>{app})</td>
<td>5384.98</td>
<td>7625.29</td>
<td>7997.52</td>
</tr>
</tbody>
</table>

They are the basis for tracing the relationship between the predicted solubility (-log x₂) and the polarity of extraction medium (ε\(_M\)); (-log x₂) = f(ε\(_M\)), (fig. 1 and 2).
Solubility and solubilizing capabilities of aqueous solutions of *Extractum Taraxaci e radix cum herba aqu. siccum...*

- **Figure 1.**
  The course of the dependence between $-\log x_2$ of triterpenes and dielectric constant $\varepsilon_\mu$ 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 $\varepsilon_\mu$ of the water:ethanol system of solvents

It results from the course of the dependence $(-\log x_2)=f(\varepsilon_\mu)$, figure 1, that the predicted solubility of triterpenic structures: oleanolic acid, taraxasterol, taraxerol, taraxeren and $\psi$-taraxasterin increases asymptotically with the decrease of polarity of the extraction medium $-\varepsilon_\mu$ (increase of % ethanol).
Only taraxerol is characterized by significant predicted solubility (-log x₂) 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 x₂).

However, it results from similar functional equation, Fig. 2, for taraxacside, tetrahydrodridentin 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 x₂ of taraxacside, taraxacolide β-D-glucoside and taraxinum acid β-D-glucoside in water is sufficient to form with taraxerol triterpenic structure (-log x₂=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 x₂ in the function of dielectric constant of the extraction system – εₓ at p=0.05 was described by correlation equations which are presented in table 3. They reflect the solubility preferences of phytosturctures 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.**

<table>
<thead>
<tr>
<th>Phytochemicals</th>
<th>Equation type</th>
<th>r</th>
<th>a ± da</th>
<th>b ± db</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Oleanolic acid</td>
<td>1. y=a+b·x</td>
<td>0.9880</td>
<td>-17.0134 ± 10.9785</td>
<td>0.8009 ± 0.2301</td>
</tr>
<tr>
<td></td>
<td>2. y=a+b·log x</td>
<td>0.9476</td>
<td>-113.9555 ± 82.1600</td>
<td>82.4144 ± 51.0288</td>
</tr>
<tr>
<td>2. Taraxerol</td>
<td>1. log y=a+b·\frac{1}{x}</td>
<td>0.8859</td>
<td>0.2741 ± 0.8046</td>
<td>28.7639 ± 27.6606</td>
</tr>
<tr>
<td></td>
<td>2. y = a₁·x² + a₂·x + b</td>
<td>1.0000</td>
<td>a₁ = 0.0081</td>
<td>a₂ = 0.0822</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-1.4268</td>
</tr>
<tr>
<td>3. Taraxasterol</td>
<td>1. y=a+b·x</td>
<td>0.9121</td>
<td>-10.9985 ± 27.1467</td>
<td>0.6883 ± 0.5688</td>
</tr>
<tr>
<td></td>
<td>2. y = a₁·x² + a₂·x + b</td>
<td>0.9980</td>
<td>a₁ = 0.0117</td>
<td>a₂ = 0.1678</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ 5.1515</td>
</tr>
<tr>
<td>4. Taraxeran</td>
<td>1. y=a+b·x</td>
<td>0.9849</td>
<td>-21.1820 ± 16.1481</td>
<td>1.04779 ± 0.3383</td>
</tr>
<tr>
<td></td>
<td>2. y=a+b·log x</td>
<td>0.9416</td>
<td>-147.4379 ± 113.6603</td>
<td></td>
</tr>
<tr>
<td>5. Taraxeren</td>
<td>1. y=a+b·x</td>
<td>0.9912</td>
<td>-19.7726 ± 10.8741</td>
<td>0.9290 ± 0.2278</td>
</tr>
<tr>
<td></td>
<td>2. y=a+b·log x</td>
<td>0.9545</td>
<td>-132.8290 ± 88.6672</td>
<td>95.9755 ± 55.0704</td>
</tr>
<tr>
<td>6. ψ–Taraxasterin</td>
<td>1. y=a+b·x</td>
<td>0.9866</td>
<td>-17.0134 ± 10.9785</td>
<td>0.8009 ± 0.2301</td>
</tr>
<tr>
<td></td>
<td>2. y=a+b·log x</td>
<td>0.9447</td>
<td>-113.9555 ± 82.1600</td>
<td>82.4144 ± 51.0288</td>
</tr>
<tr>
<td>7. Taraxinum acid glucosyl ester</td>
<td>1. y = a₁·x² + a₂·x + b</td>
<td>0.9999</td>
<td>a₁ = 0.0040</td>
<td>a₂ = -0.1453</td>
</tr>
<tr>
<td></td>
<td>2. y = a xl n x – b</td>
<td>0.8544</td>
<td>11.9820</td>
<td>-38.8060</td>
</tr>
<tr>
<td>8. Taraxacoside</td>
<td>1. y = a₁·x² + a₂·x + b</td>
<td>0.9980</td>
<td>a₁ = 0.0041</td>
<td>a₂ = 0.3062</td>
</tr>
<tr>
<td></td>
<td>2. y = a xl n x – b</td>
<td>0.6264</td>
<td>4.8950</td>
<td>-14.1520</td>
</tr>
</tbody>
</table>
Solubility and solubilizing capabilities of aqueous solutions of *Extractum Taraxaci e radix cum herba aqu. siccum*...

<table>
<thead>
<tr>
<th>Phytochemicals</th>
<th>Equation type</th>
<th>r</th>
<th>a ± da</th>
<th>b ± db</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Taraxacolide–1–O–β-D-glucopyranoside</td>
<td>1. ( y=a+b\cdot x )</td>
<td>0.8836</td>
<td>-1.2320 ± 5.4499</td>
<td>0.1173 ± 0.1122</td>
</tr>
<tr>
<td></td>
<td>2. ( y = a_1\cdot x^2 + a_2\cdot x + b )</td>
<td>0.9777</td>
<td>( a_1 = 0.0056 )</td>
<td>( a_2 = -0.5164 ) + 14.1880</td>
</tr>
<tr>
<td></td>
<td>10. 4.11.13.15–Tetrahydrorident B</td>
<td>1. ( y=a+b\cdot x )</td>
<td>0.9756</td>
<td>-6.4979 ± 5.3555</td>
</tr>
<tr>
<td></td>
<td>2. ( y=a+b\cdot \log x )</td>
<td>0.9243</td>
<td>-38.8050 ± 33.6956</td>
<td>27.5884 ± 20.9280</td>
</tr>
</tbody>
</table>

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

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

**Table 4.**

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

<table>
<thead>
<tr>
<th>Extract type</th>
<th>Medium</th>
<th>% of extract solubility in water</th>
<th>cmc ([\text{g} \cdot 100 \text{ cm}^{-3}])</th>
<th>cmc ([\text{mol} \cdot \text{dm}^{-3}])</th>
<th>( \Delta G_m^o ) ([\text{kJ} \cdot \text{mol}^{-1}])</th>
<th>( \gamma_{cmc}^{25} ) ([\text{kJ} \cdot \text{m}^{-2}])</th>
<th>( A_m \cdot 10^{-19} ) ([\text{m}^2])</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Ext. Taraxaci e radix cum. herba aqu. siccum</em></td>
<td>1. Aqueous solution</td>
<td>87.76</td>
<td>0.6750</td>
<td>3.4861·10^3</td>
<td>-14.0247</td>
<td>63.50</td>
<td>4.8537</td>
</tr>
<tr>
<td></td>
<td>2. Solution in 0.1 mol HCl</td>
<td>90.12</td>
<td>0.7000</td>
<td>4.7637·10^3</td>
<td>-13.2508</td>
<td>64.25</td>
<td>5.3246</td>
</tr>
<tr>
<td></td>
<td>3. Solution in phosphate buffer of pH=6.88</td>
<td>76.41</td>
<td>0.8500</td>
<td>3.6189·10^3</td>
<td>-13.9321</td>
<td>63.75</td>
<td>5.0012</td>
</tr>
</tbody>
</table>

\( \Delta G_m^o = 5.7065 \text{ kJ/mol·log cmc} \)

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

Relatively low value of \( \Delta G_m^o \) (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 \( \Delta G_m^o \) (kJ/mol) and coefficient Am \((\text{m}^2)\) 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_{aft+} 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^o_m, 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_{ins} = \frac{M_{add}}{M_{mic}} - \frac{1.6518}{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 micellar 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_{ins} = 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 \text{cholesterol/\sum cholid acids-H2/Na}^+ + \sum \text{lecithins; 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

<table>
<thead>
<tr>
<th>Extract type</th>
<th>Medium</th>
<th>Weighed amount g·100 cm⁻³</th>
<th>GLL: [n]</th>
<th>M_η</th>
<th>R_η·10⁻⁷ [cm]</th>
<th>R_θη·10⁻⁸ cm</th>
<th>Ω·10⁻²⁰ cm⁻³</th>
<th>c_isI</th>
<th>c_isI * ketoprofen mg·100 cm⁻³</th>
<th>n_isI chol mol:mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ext. Taraxaci e radix cum herba aqu. siccum</td>
<td>1. Aqueous solution</td>
<td>1.8524</td>
<td>0.086961</td>
<td>1936.25</td>
<td>3.6604</td>
<td>2.9886</td>
<td>1.1182</td>
<td>107.4138</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. 0.1 mol HCl solution</td>
<td>2.0276</td>
<td>0.073614</td>
<td>1469.44</td>
<td>3.1564</td>
<td>2.5784</td>
<td>0.7183</td>
<td>36.9746</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Phosphate buffer of pH=6.88</td>
<td>1.8669</td>
<td>0.097721</td>
<td>2348.78</td>
<td>4.0586</td>
<td>3.3137</td>
<td>1.5243</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ext. Taraxaci e radix cum herba aqu. siccum</td>
<td>1. Aqueous solution</td>
<td>1.8524</td>
<td>0.10331</td>
<td>2574.98</td>
<td>4.2631</td>
<td>3.4807</td>
<td>1.7665</td>
<td>1.6518</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. 0.1 mol HCl solution</td>
<td>2.0276</td>
<td>0.071243</td>
<td>1391.92</td>
<td>3.0682</td>
<td>2.5051</td>
<td>0.6585</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Phosphate buffer of pH=6.88</td>
<td>1.8669</td>
<td>0.093032</td>
<td>2165.16</td>
<td>3.8857</td>
<td>3.1726</td>
<td>1.3377</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ketoprofen solubility in water – c_isI = 12.9214 mg/100 cm³ 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 $\varepsilon_m$ 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 $-\gamma_{sol}^{25}$ of monophasic, real solutions of the extract in water allowed to calculate basic thermodynamic values: cmc, $\Delta G_m^{\circ}$, $\gamma_{cmc}^{25}$, $A_m$, 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 $\Delta G_m^{\circ}$ (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 $\gamma_{cmc}^{25}$ 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 \( \Phi = 1.00 \) mm and ketoprofen. Ketoprofen solubilization equilibrium also takes place in aqueous solution of an extract in 0.1 mol HCl (200 mOsm/dm³).

The above proves the topological stability of the micelle structure, although \( \Delta G_m^o \) is in the range of \((-13.2508 \text{ kJ/mol}) – (-14.0247 \text{ kJ/mol})\). The calculated hydrodynamic values \( (R_o, R_{obs}, \Omega) \) 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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ZBIGNIEW MARCZYŃSKI1*, SŁAWOMIRA NOWAK2, JERZY JAMBOR3, MARIAN MIKOŁAJ ZGODA4

1Zakład Farmacji Aptecznej
Katedra Farmacji Stosowanej
Wydział Farmaceutyczny
Uniwersytet Medyczny
ul. Muszyńskiego 1
90-151 Łódź

2 Zakład Farmakognozji
Katedra Farmakognozji
Wydział Farmaceutyczny
Uniwersytet Medyczny
ul. Muszyńskiego 1
90-151 Łódź

3 Europlant Group
Phytopharm Klęka SA
Klęka 1
63-040 Nowe Miasto n. Wartą

4 Niestacjonarne Studium Doktoranckie
Katedra Farmacji Stosowanej
Uniwersytet Medyczny
ul. Muszyńskiego 1
90-151 Łódź

*autor, do którego należy kierować korespondencję: tel/fax: +4842 6779240,
e-mail: zbigniew.marczynski@umed.lodz.pl

Streszczenie

Wstęp: Ogólną teorię rozpuszczalności Hildebranda-Scatcharda uzupełnioną przez Fedorasa na parametr rozpuszczalności - δ_{1} wykorzystano do oszacowania rozpuszczalności rzeczywistej na sposób -log x_{2} (log ulamka molowego) fitozwiązków wchodzących w skład Ext. Taraxaci e radix cum herba aqu. siccum. Oznaczało aktywność powierzchniową wodnych roztworów ekstraktów, a także określono ilościowo zdolności solubilizacyjne roztworów o c_{exp.} ≥ 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 rozcieńczonym metodą Ubbelohde’a a zgodnie z Polską 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 $\Omega = 1,00 \text{ mm}$) i ketoprofen (o technologicznym stanie rozdrobnienia). Równowagowa solubilizacja ketoprofenu zaczęła 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