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EXPERIMENTAL PAPER

Litogenolitic and solubility properties of products obtained from common ivy extract (*Hederae helicis e folium*) and medium of diversified polarity (ε_M)

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Summary

Introduction: Common ivy (*Hedera helix*) is a plant used successfully in the treatment of various ailments. This is possible owing to the unique set of substances contained in it such as large amount of saponins, flavonoids, phenolic acids and phytosterols as well as polyacetylenes and coumarins. All these substances

have been used in the production of cosmetic and medicinal preparations. Clinical trials on the efficacy and safety of dry ivy leaf extract have shown its high efficacy, comparable to synthetic medications, and better tolerance of herbal drugs.

Objective: Investigations were performed on model ivy leaf (*Hedera helix*) extracts which were created using a medium of diversified polarity (ε_M). Measurements of viscosity and surface activity on phase boundary were performed. During preformulation studies attention was drawn to the possibility of micellar solubilization of cholesterol and selected structures of nonsteroidal anti-inflammatory drugs (NSAIDs) – ketoprofen.

Methods: Viscosity measurements of *Extractum Hederae helicis e folium* aqueous solutions and in 0.1 mol HCl were performed according to the Polish Standard with Ubbelohde dilution viscometer. The surface tension of aqueous solutions – $\Delta\gamma_{sol}^{25}$ of *Hederae helicis e folium* extracts was determined according to the Polish Standard with stalagmometric method . Critical micellar concentration (cmc) was calculated. This enabled to evaluate the dependence $\Delta G_m^0 = 2.303\ RT \times \log cmc$ of the thermodynamic potential of micelle formation (ΔG_m^0). Results: It has been confirmed in the conducted comparative studies that aqueous solutions of *Extr. Hederae helicis e folium* created with maltodextrin as well as with SiO_2 – maltodextrin result in micellar solubilization. The increase of granulometric size of cholesterol particle to ø 1.60 mm decreased the amount of solubilized cholesterol but solubility preferences of the extracts were maintained.

Conclusions: Model extracts produced from *Hederae helicis e folium* with diversified polarity of the extraction medium (water – ethanol) are characterized by appropriate solubility of the components which results not only from the presence of chlorophyll and its derivatives in the extract but also from the technique used for spray drying of the extract.

Key words: ***Hedera helix, dry extract, cholesterol, hederasaponin C***

Słowa kluczowe: ***Hedera helix, suchy ekstrakt, cholesterol, hederasaponina C***

INTRODUCTION

Preformulation studies performed on model dry extracts obtained from maidenhair tree (*Ginkgo bilobae*) leaves with diversified polarity (ε_M) of the extracting medium enabled to assess their technical preferences in the light of requirements stated in the Biopharmaceutics Classification System [1].

Obtained results constituted an inspiration for conducting supplementing and comparative tests on extracts obtained from common ivy leaves (*Hederae helicis e folium*), as these should contain triterpenoid saponins known for their substantial biological activity that is already commonly used in medical treatment and cosmetology [2, 3].

Clinical studies performed on preparations created on the basis of extracts obtained from common ivy leaves confirmed their spasmolytic and anti-spasmodic [4, 5], antimicrobial and anthelmintic [4, 6-8], anti-inflammatory [4, 9] and analgesic [4, 10, 11], antineoplastic as well as antimutagenic and anticoagulant biological activity [4, 12].

Clinical trials confirmed the suitability of the following preparations: drops (35 mg/d – 42 mg/d), syrup (105 mg/d) and suppositories (160 mg/d), created basing on dry extract obtained from common ivy leaves, in the treatment of chronic and bacterial upper respiratory tract infections in children [13].

Common ivy leaf extracts, available in the form of pharmaceutical and cosmetic formulations (ointments, creams, hydrogels), are used in treating skin inflammatory conditions and cellulite [14-16].

Phytochemical analyses concerning common ivy fruits (*Hederae helicis fructus*) revealed that these fruits are going to be the material secreting triterpenoid saponins as well as helixosides A and B by means of selective extraction [17].

The increasing role of triterpenoid saponins, in particular hederasaponin C, next to monodesmosidal saponins, which are produced along with preparation of the raw material for extraction, was the reason underlying the creation of model dry extracts with medium of diversified polarity (ε_M), anticipated for creating a solid oral form of the medication [18, 19].

Presence of bidesmosidal triterpenoid saponin in the dry extract – namely hederasaponin C and products of its structural transformations constitute application inspiration to estimate solubility and litogenolitic capacities in model aqueous solutions of model extracts in the equilibrium system.

Preformulation tests emphasise the possibility of micellar solubilisation of cholesterol and selected

structures of non-steroidal anti-inflammatory drugs (NSAIDs) – ketoprofen [20].

MATERIAL AND METHODS

Extracts

1. *Extractum Hedreae helicis e folium spir. siccum* 30% (*v/v*) – 100% native,
2. *Extractum Hederae helicis e folium aq. siccum* with 50% share of maltodextrin,
3. *Extractum Hederae helicis e folium spir. siccum* 95% (*v/v*) with 47% share of MD maltodextrin and 3% SiO_2 silica,
4. *Extractum Hederae helicis e folium spir. siccum* 70% (*v/v*) – 100% native was produced with the help of a standard industrial technology in Phytopharm Klęka S.A., Poland.

Reference extract

1. *Extractum Hederae helicis e folium spir. siccum* 30% (*v/v*) (Finzelberg Martin Bauer Group, Germany).
2. Cholesterol p. a. grade (Avantor Performance Materials, former PoCh, Gliwice, Poland).
Cholesterol used for solubility tests was prepared by means of wet granulation – with ethanol (p. a. grade) of amorphous cholesterol using mechanical devices (ERWEKA). Granulate was passed through a proper set of sieves. After drying to a solid mass, granulate was separated with HAVER EML 200 digital T, Analysensiebmaschine Test Sieve Shaker (Haver and Boecker, Germany) and a set of sieves in the following numerical sequence: ø 1.60 mm – 0.160 mm. Cholesterol granulate prepared in such manner with saturated weight and density comparable with cholesterol gallstones constituted the subject of micellar equilibrium solubility in the environment of aqueous solutions prepared with *Extractum Hederae helicis e folium*.
3. Ketoprofen; 3-benzoil-α-methylphenyl acetic acid (SIGMA, Germany).

Methods and equipment

Viscosity and surface tension in aqueous solutions of *Extractum Hederae helicis e folium*. Viscosity measurements concerning aqueous solutions and in 0.1 mol of HCl *Extractum Hederae helicis e folium* were conducted according to the Polish Standard with Ubbelohde Dilution Viscometer [21]. These constituted the basis for conducting the limiting viscosity number [η], as well as selected hydrodynamic values: M_η, R_o, R_{obs}, Ω and the $n_{|s|}$ solubility index, according to η following formula [22]:

$$GLL, [\eta]=[\eta_{prop}+31n(\eta_{sol}/\eta_{0_{H_2O}})]/4\times c$$

Surface tension of aqueous solutions – γ_{sol}^{25} of extracts obtained from *Hederae helicis e folium* were marked with stalagmometric method, according to Polish Standard [23]. Critical micellar concentrations /cmc/ were calculated analogically to the manner used in the publication [20]. This enabled to evaluate $\Delta G_m^0=2.303\ RT\times\log cmc$, namely the thermodynamic potential of micelle formation (ΔG_m^0). Numerical values presenting the decrease in the – γ_{sol}^{25} surface tension coefficient in the critical area constituted the basis to use the following equation:

$$A_m=k\times T/\ \gamma_{H_2O}^{25}-\gamma_{cmc}^{25}$$

to calculate "the average surface per one molecule of the surfactant" – A_m on phase boundary.

The abovementioned relation stands as a consequence of bilateral division of "equation for the condition of perfect surfaces" – $\pi\times A_m=R\times T$ by the (constant) Avogadro number, which provides the equation above with the following application form: $f(\pi)A_m=k\times T$, where

$$f(\pi)=\gamma_{H_2O}^{25}-\gamma_{cmc}^{25}$$

Micellar solubilisation of cholesterol and ketoprofen granulates in *Extractum Hederae helicis e folium* solution

Micellar process of cholesterol (granulate with ø 1.00 mm and 1.60 mm) and ketoprofen solubilisation was conducted in a container of V=100 cm^3, with not more than 0.3550 g of cholesterol granulate weighed into the container. In case of ketoprofen, the weighed amount did not exceed 0.3529 g. This was followed by the addition of 0.25 cm^3 of aqueous solution of extracts obtained from *Hederae helicis e folium* with a pipette. Solubilisation of ketoprofen in solution of extracts in 0.1mol HCl with the following exposure concentration was $c_{exp} \geq$ cmc.

Containers were mounted in EIPIN + 375 (water bath shaker type 357) with bath temperature of 37.0±0.1°C.

After 24 hours of exposure, saturated micellar solution of solubilised cholesterol and ketoprofen solution was separated on the quantitative filter of the EUROCHEM BCD-12/5 type from the excess of cholesterol and ketoprofen granulate (standard degree of fragmentation used in the technology of solid oral drug form).

Solutions used for the measurement of viscosity (η) and surface tension $-\gamma_{sol}^{25}$ were filtered through a sterile filter used in the set anticipated for preparing MACHERY-NAGEL, Chromafil CA- 45/25 s, cell, acetate 0.45 mm type of eye drops.

Solutions of solubilised ketoprofen anticipated for quantitative spectrophotometric indications (UV), which were conducted in a manner analogical to the one used in the publication [24], were prepared similarly.

Approximating equation quoted in [24], describing the relation between the concentration of ketoprofen (c, g×100 cm^{-3}) and the measured absorbance level (A) after the transformation to $c_{|sol.|} = A - a/b$, enabled to calculate the amount of solubilised medicinal substance. Obtained results constituted the basis to the calculation of the micellar coefficient of division $-K_w^m$.

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

RESULTS AND DISCUSSION

Viscosity of exposure solutions and adducts after micellar stabilisation of cholesterol.

During the process of drying common ivy (*Hederae helicis*) leaves, bidesmosidal triterpenoid saponins (hederasaponins C) present in these leaves are transformed into a proper monodesmoside (α-hederine), through the process of hydrolysis (fig. 1) [2].

Taking into consideration the solubility preferences of triterpenoid saponin structures (hederagenin), the process related to the extraction of the raw material was conducted with medium of extremely diversified polarity (ε_M) with water, ethanol and their pharmacopoeial mixtures. Fundamental data concerning triterpenoid saponin – hederagenine, along with supplementing calculations, were performed on the basis of the publication by Fedors [26]. The numerical value of solubility parameter – $\delta^{1/2}$ and the solubility level of hydrophilic-lipophilic balance – HLB_{Requ} were estimated. Viscosity measurements concerning aqueous solutions of extracts made the estimation of the limiting of viscosity number [η] possible which constituted the basis to calculate selected hydrodynamic parameters, which are enumerated in table 1. Table 1 also presents the compilation of experimentally indicated true solubility of components from the tested extracts. The considerably diversified solubility of components

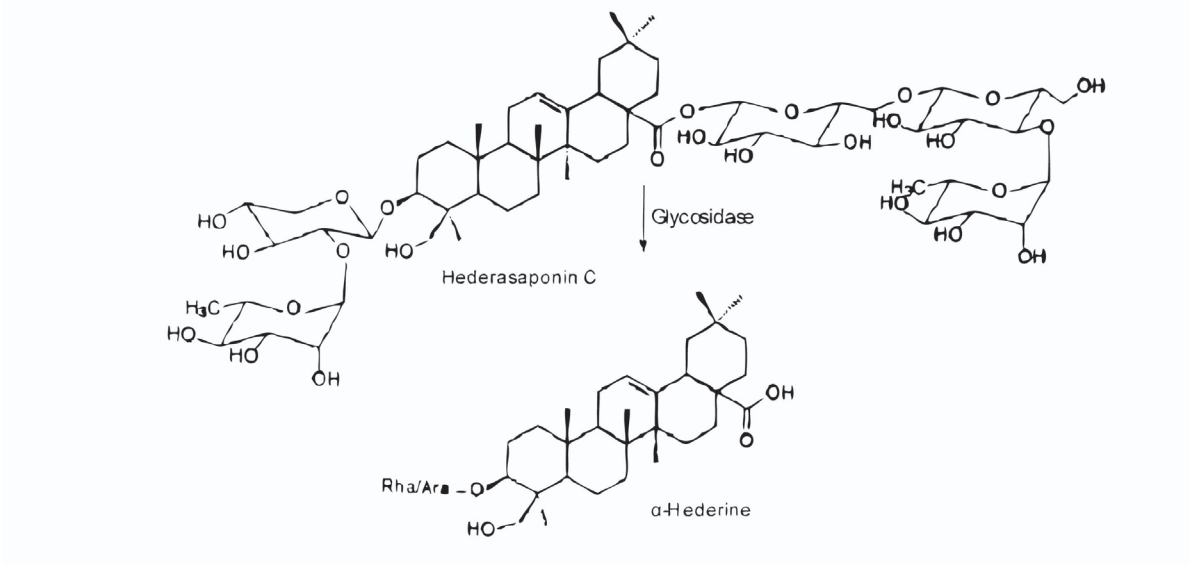

Figure 1

Example of bidesmosidal triterpenoid saponin (hederasaponin C) which has been transformed into a corresponding monodesmoside (α-hederine) [2]

Table 1

Regression equation describing the course of the following relation: $\gamma_{sol}^{25} = f(c, mol \times dm^3)$ with p=0.05, constituting the basis to calculate the critical micellar concentration (cmc) and Rosen's postulate – $\log (1/c)_{\pi=20}$

Type of extract	Correlation equation $-\gamma_{sol}^{25} = f(c, mol \times dm^3)$					$\log (1/c)_{\pi=20}$
Producer: medium	HLB_{1HNMR}	Type of equation	r^2	a ± da	b ± db	
1. *Hederae helicis e folium spir.* 30% (*v/v*) *siccum* 100% nativee Phytopharm Klęka SA Aqueous solution	16.56	$\log y_1 = a + b \times x_1$ $\log y_1 = a + b \times \log x_2$ $\log y_2 = a + b \times x_2$ $\log y_2 = a + b \times \log x_2$	0.9319 0.9567 0.9644 0.9934	$1.7356 \pm 2.7631 \times 10^{-2}$ $1.5011 \pm 5.4326 \times 10^{-2}$ $1.8522 \pm 3.0875 \times 10^{-2}$ 1.5102 ± 0.1081	-30.6626 ± 22.0068 $-6.6710 \times 10^{-2} \pm 3.7470 \times 10^{-2}$ -1198.2140 ± 997.1006 $-6.6044 \times 10^{-2} \pm 2.2853 \times 10^{-2}$	3.9437
2. *Ext.Hederae helicis e folium spir.* 30% (*v/v*) *siccum* Finzelberg Martin Bauer Aqueous solution	15.36	$\log y_1 = a + b \times x_1$ $\log y_1 = a + b \times \log x_1$ $\log y_2 = a + b \times x_2$ $\log y_2 = a + b \times \log x_2$	0.9808 0.9939 0.9584 0.9954	$1.7383 \pm 1.8765 \times 10^{-2}$ $1.3842 \pm 5.9399 \times 10^{-2}$ $1.8581 \pm 1.5373 \times 10^{-2}$ $1.6059 \pm 3.9257 \times 10^{-2}$	-70.2765 ± 25.2422 $-9.5329 \times 10^{-2} \pm 1.8479 \times 10^{-2}$ -1631.9920 ± 888.9944 $-4.5492 \times 10^{-2} \pm 7.7054 \times 10^{-3}$	4.0595
1. *Hederae helicis e folium spir.* 30% (*v/v*) siccum 100% nativee Phytopharm Klęka SA 0.1 mol HCl	15.32	$\log y_1 = a + b \times x_1$ $\log y_1 = a + b \times \log x_1$ $\log y_2 = a + b \times x_2$ $\log y_2 = a + b \times \log x_2$	0.9512 0.9918 0.9891 0.9708	$1.7086 \pm 2.2221 \times 10^{-2}$ $1.4681 \pm 4.7090 \times 10^{-2}$ $1.8487 \pm 9.1581 \times 10^{-2}$ 1.5786 ± 0.1115	-26.8420 ± 15.8865 $-7.0161 \times 10^{-2} \pm 1.6025 \times 10^{-2}$ -1025.9820 ± 280.3895 $-5.1028 \times 10^{-2} \pm 2.3132 \times 10^{-2}$	3.8876
2. *Ext. Hederae helicis e folium spir.* 30% (*v/v*) *siccum* Finzelberg Martin Bauer 0.1 mol HCl	13.45	$\log y_1 = a + b \times x_1$ $\log y_1 = a + b \times \log x_1$ $\log y_2 = a + b \times x_2$ $\log y_2 = a + b \times \log x_2$	0.9912 0.9957 0.9705 0.9877	$1.6892 \pm 6.8352 \times 10^{-2}$ $1.5248 \pm 2.3397 \times 10^{-2}$ $1.8484 \pm 1.5658 \times 10^{-2}$ $1.5507 \pm 7.8908 \times 10^{-2}$	-15.9834 ± 3.9841 $-4.8856 \times 10^{-2} \pm 8.2258 \times 10^{-2}$ -1722.6040 ± 785.6925 $-5.4212 \times 10^{-2} \pm 1.5677 \times 10^{-3}$	4.1136
1. *Hederae helicis e folium aq. Siccum* + 50% MD* Phytopharm Klęka SA Aqueous solution	14.48	$\log y_1 = a + b \times x_1$ $\log y_1 = a + b \times \log x_1$ $\log y_2 = a + b \times x_2$ $\log y_2 = a + b \times \log x_2$	0.9779 0.9931 0.9842 0.9859	$1.6555 \pm 1.1313 \times 10^{-2}$ $1.4058 \pm 0.3533 \times 10^{-2}$ $1.8543 \pm 1.5427 \times 10^{-2}$ 1.6133 ± 0.1157	-23.5087 ± 6.9615 $-7.4728\ 1 \times 10^{-2} \pm 1.2272 \times 10^{-2}$ -621.7130 ± 346.8218 $-4.7860 \times 10^{-2} \pm 2.5302 \times 10^{-2}$	3.6426
Solubilisation of cholesterol with ø=1.00mm	13.75	$\log y_1 = a + b \times x_1$ $\log y_1 = a + b \times \log x_1$ $\log y_2 = a + b \times x_2$ $\log y_2 = a + b \times \log x_2$	0.9972 0.9892 0.9990 0.9336	$1.6725 \pm 5.0433 \times 10^{-3}$ $1.3489 \pm 5.6553 \times 10^{-2}$ $1.8576 \pm 4.7146 \times 10^{-3}$ 1.4681 ± 0.2478	-31.3614 ± 3.1282 $-9.6452\ 1 \times 10^{-2} \pm 1.9641 \times 10^{-2}$ -683.4652 ± 59.1623 $-7.8983 \times 10^{-2} \pm 5.5712 \times 10^{-2}$	3.6830
Solubilisation of cholesterol with ø=1.60mm	12.97	$\log y_1 = a + b \times x_1$ $\log y_1 = a + b \times \log x_1$ $\log y_2 = a + b \times x_2$ $\log y_2 = a + b \times \log x_2$	0.9926 0.9912 0.9841 0.9734	$1.6881 \pm 4.0989 \times 10^{-3}$ $1.5278 \pm 2.4743 \times 10^{-2}$ $1.8495 \pm 1.1039 \times 10^{-3}$ $1.5994 \pm 9.8008 \times 10^{-2}$	-15.3195 ± 2.4991 $-4.7884 \times 10^{-2} \pm 8.6174 \times 10^{-3}$ -417.1380 ± 138.5385 $-5.1018 \times 10^{-2} \pm 2.2104 \times 10^{-2}$	3.4878
2. *Ext. Hederae helicis e folium spir.* 70% (*v/v*) *siccum* + 100% nativee Phytopharm Klęka SA Aqueous solution	13.93	$\log y_1 = a + b \times x_1$ $\log y_1 = a + b \times \log x_1$ $\log y_2 = a + b \times x_2$ $\log y_2 = a + b \times \log x_2$	0.9926 0.9933 0.9766 0.9700	1.7565 ± 0.1314 $1.4103 \pm 6.1337 \times 10^{-2}$ $1.8532 \pm 1.0990 \times 10^{-2}$ $1.6595 \pm 5.9320 \times 10^{-2}$	-30.9804 ± 6.8259 $-0.1041 \pm 2.1900 \times 10^{-2}$ -552.2972 ± 250.5701 $-3.7564 \times 10^{-2} \pm 1.7170 \times 10^{-2}$	4.0196
Solubilisation of cholesterol with ø=1.00 mm	13.57	$\log y_1 = a + b \times x_1$ $\log y_1 = a + b \times \log x_1$ $\log y_2 = a + b \times x_2$ $\log y_2 = a + b \times \log x_2$	0.9635 0.9918 0.9887 0.9763	$1.7511 \pm 2.0313 \times 10^{-2}$ $1.5095 \pm 4.9249 \times 10^{-2}$ $1.8427 \pm 6.1501 \times 10^{-3}$ $1.6754 \pm 6.2902 \times 10^{-2}$	-20.7909 ± 10.6222 $-7.3267 \pm 1.7544 \times 10^{-2}$ -482.0673 ± 140.2199 $-3.2397 \times 10^{-2} \pm 1.3416 \times 10^{-2}$	3.7988
Solubilisation of cholesterol with ø=1.60 mm	12.20	$\log y_1 = a + b \times x_1$ $\log y_1 = a + b \times \log x_1$ $\log y_2 = a + b \times x_2$ $\log y_2 = a + b \times \log x_2$	0.9926 0.9933 0.9766 0.9700	1.7565 ± 0.1314 $1.4103 \pm 6.1337 \times 10^{-2}$ $1.8532 \pm 1.0990 \times 10^{-2}$ $1.6595 \pm 5.9320 \times 10^{-2}$	-30.9804 ± 6.8259 $-0.1041 \pm 2.1900 \times 10^{-3}$ -552.2972 ± 250.5701 $-3.7564 \times 10^{-2} \pm 1.7170 \times 10^{-2}$	3.6045
3. *Ext. Hederae helicis e folium spir.* 95% (*v/v*) *siccum*+ 47% MD + 3% SiO_2 Phytopharm Klęka SA Aqueous solution	16.25	$\log y_1 = a + b\ x_1$ $\log y_1 = a + b\ x \log x_1$ $\log y_2 = a + b\ x_2$ $\log y_2 = a + b\ x \log x_2$	0.9987 0.9904 0.9654 0.9887	$1.7442 \pm 5.5572 \times 10^{-2}$ 1.3694 ± 0.1391 $1.8525 \pm 2.2969 \times 10^{-2}$ 1.5780 ± 0.1145	-89.3374 ± 10.7991 $-9.9547 \times 10^{-2} \pm 4.2014 \times 10^{-2}$ -1198.5970 ± 982.7578 $-5.1978 \times 10^{-2} \pm 2.3687 \times 10^{-2}$	3.9429
Solubilisation of cholesterol with ø=1.00 mm	15.72	$\log y_1 = a + b \times x_1$ $\log y_1 = a + b \times \log x_1$ $\log y_2 = a + b \times x_2$ $\log y_2 = a + b \times \log x_2$	0.9999 0.9811 0.9720 0.9839	$1.7785 \pm 2.7990 \times 10^{-2}$ 1.3693 ± 0.1298 $1.8511 \pm 1.0645 \times 10^{-2}$ $1.6484 \pm 6.1815 \times 10^{-2}$	-127.0349 ± 5.9622 $-0.1039 \pm 3.7880 \times 10^{-2}$ -1081.9440 ± 487.2778 $-3.7195 \times 10^{-2} \pm 1.2381 \times 10^{-2}$	3.9029
Solubilisation of cholesterol with ø=1.60 mm	14.48	$\log y_1 = a + b \times x_1$ $\log y_1 = a + b \times \log x_1$ $\log y_2 = a + b \times x_2$ $\log y_2 = a + b \times \log x_2$	0.9992 0.9841 0.9555 0.9963	$1.7821 \pm 2.9735 \times 10^{-2}$ $1.5139 \pm 6.0128 \times 10^{-2}$ $1.8485 \pm 1.1525 \times 10^{-2}$ $1.6590 \pm 2.5186 \times 10^{-2}$	-81.9653 ± 6.7465 $-6.8346 \times 10^{-2} \pm 1.7451 \times 10^{-2}$ -1870.2240 ± 1054.541 $-3.3015 \times 10^{-2} \pm 4.7588 \times 10^{-2}$	4.1490

found in extracts is worth noticing, and mostly the order of magnitude relating the viscosimetrically average molecular mass M_η. Moreover, this also results in an increased percentage share of solubility in components of these extracts. Presence of sugar alcohols in the solution increases the ability of the structure to hydrotropic solubility of lipophilic components found in the extract. The list of viscosity and hydrodynamic parameters given in tables 2, 3 and 4 revealed that as far as the quantity is concerned, the process of solubilising cholesterol with seed surface of ø 1.00 mm proceeds in a better manner, which is indicated by the calculated value of solubility index – $n|s|_{sol.}$Preferences towards a significant cholesterol solubility are maintained by solutions of extracts obtained at the extreme medium polarity.

Conducted comparative studies confirmed that aqueous solutions of maltodextrin, as well as maltodextrin with the percentage of SiO_2 resulted in micellar solubilisation of cholesterol from the granulometric form. Increased granulometric size of the cholesterol seed to ø 1.60 mm, which caused considerable reduction of solubility surface, which can be seen in calculated values of solubility indices – $n|s|_{sol}$. Summarising obtained results, it is worth mentioning that all extract separated and prepared from *Hederae helicis e folium* used to create a solid, oral form of the drug (direct compression) with the direct compression technique, maintained the ability to solubilise cholesterol from granulometric form, which makes possible the preparation of the drug form (dietary supplement) supporting litogenolitic index of duodenal matter (bile A) in subjects with a preference (diagnosed) towards cholesterol lithiasis.

Surface tension of aqueous extract solutions and their adducts after equilibrium solubilisation with cholesterol

Segment of physical and chemical tests with determining solubility capacities of model extracts from *Hederae helicis e folium* has been preceded with assessment of surface activity revealed by aqueous solutions, as well as in 0.1 mol HCl environment. The numerical value of – γ_{sol}^{25} surface tension coefficient was evaluated according to Polish Standard (SN) also for micellar adduct from cholesterol. The relation between γ_{sol}^{25} = f (c, mol·dm^{-3}) within the scope of data (x_1) and small (x_2) concentrations was described on the level of p=0.05 with correlation equations listed in table 5. They constitute the basis to calculate the critical micellar concentration (cmc) from the following relation: cmc = a_2-a_1/b_1-b_2. As far as such a set is concerned, this enabled to estimate the ΔG_m^0 thermodynamic potential concerning the creation of micelles and adduct with cholesterol after micellar solubilisation on phase boundary from the following relation: ΔG_m^0=2.303 RT×log cmc (conversion version ΔG_m^0=5.7065 kJ/mol x log cmc).Calculated numerical value of decreased surface tension coefficient in the critical area (γ_{cmc}^{25}) made it possible to calculate the area covered on phase boundary (air/water) basing on the following equation:

$$A_m = k \times T / \gamma_{H_2O}^{25} - \gamma_{cmc}^{25}$$

(conversion version: $A_m = 411.5990 \times 10^{-20} / 71.88 - \gamma_{cmc}^{25}$

Physical and chemical properties revealed by aqueous solutions of model extracts – as far as the application aspect is concerned, were supplemented with the calculated numerical value, the so-called Rosen's postulate – $\log (1/c)_{\pi=20}$, namely the lowering of surface tension coefficient by 20 mJ/m^2 when compared to $\gamma_{H_2O}^{25}$(mJ/m^2) at a temperature of 25±0.1°C, calculated from the equation: $\log y_2 = a + b \times x_2$.

Calculated values are presented in table 5.

Directional coefficients of approximation equations type $\log y_2 = a + b \times \log x_2$ demonstrated in table 5 constituted the basis to calculate the work load associated with lifting (lipophilic core uplift force F↑) above the phase boundary of lipophilic segment of triterpenoid saponin from the relation: $\Delta G_{tr}(l) = a/2.303\ R \times T$.

The equilibrium pulling force (F↓) of hydrophilic (sugar) segment of triterpenoid saponin deep into the structures of aqueous solution was analogically calculated from the following relation: $\Delta G_{tr}(h) = b/2{,}303\ R \times T$.

Calculated and marked values characterising aqueous solutions of model extracts from *Hederae helicis e folium* are presented in table 6.

According to test results presented in tables 5 and 6, created model extracts from *Hederae helicis e folium* – regardless of the polarity of the medium extracting in aqueous solution, are characterised by high surface activity, as compared to classic cmc and ΔG_m^0 values [26].

With the whole dependence of the process in the equilibrium system, viscosity measurements confirmed significant solubilising capacity of triterpenoid saponins in relation to lipophilic cholesterol (HLB_{1HNMR} = 1.0).

The ΔG_m^0 calculated for micellar adduct, indicates its high thermodynamic stability, which may have an effect on practical use of extracts when

Table 2

Basic viscosity values of aqueous solutions of *Extractum hederae helicis e folium siccum*– saturated solutions

Type of extract medium	Producer	% solubility [x]* in water	Weighed amount ** g × 100 cm^{-3}	GLL, [η]	M_η	$R_o \times 10^{-7}$ [cm]	$R_{obs} \times 10^{-8}$ [cm]	$\Omega \times 10^{-21}$ [cm^3]
1. *Extractum Hederae helicis e folium spir.* 30% *siccum* -100% native	Phytopharm Klęka S.A.	96.32	2.1254	0.0713855	1396.52	3.0736	2.5095	6.6207
2. *Extractum Hederae helicis e folium spir.* 30% *siccum* -100% native	Finzelberg Martin Bauer Group	98.18	2.4017	0.0882049	1982.32	3.7067	3.0264	11.6121
3. *Extractum Hederae helicis e folium aq. siccum* with 50% MD	Phytopharm Klęka S.A.	87.46	1.4125	0.0551647	911.46	2.4466	1.9976	3.3392
4. *Extractum Hederae helicis e folium spir.* 95% *siccum* with 47% MD and 3% SiO_2	Phytopharm Klęka S.A.	89.59	2.6832	0.1351554	4018.17	5.4082	4.4157	36.0669
5. *Extractum Hederae helicis e folium spir.* 70% *siccum* - 100% native	Phytopharm Klęka S.A.	90.72	1.7409	0.0567965	956.45	2.5105	2.0554	3.6077

[x]* with 5-7 gravimetric measurements; ** really marked solubility of hydrophilic extract components

Table 3

Basic viscosity values of aqueous solutions of *Extractum hederae helicis e folium siccum* in 0.1 mol HCL – saturated solutions

Type of extract medium	Producer	% solubility [x]* in 0.1 mol HCl	Weighed amount ** g × 100 cm^{-3}	GLL, [η]	M_η	$R_o \times 10^{-7}$ [cm]	$R_{obs} \times 10^{-8}$ [cm]	$\Omega \times 10^{-21}$ [cm^3]
1. *Extractum Hederae helicis e folium spir.* 30% *siccum* -100% native	Phytopharm Klęka S.A.	92.54	2.9016	0.0642869	1174.19	2.8015	2.2873	5.0131
2. *Extractum Hederae helicis e folium spir.* 30% *siccum* -100% native	Finzelberg Martin Bauer Group	87.54	3.1635	0.0764064	1562.87	3.2642	2.6652	7.9305
3. *Extractum Hederae helicis e folium aq. siccum* with 50% MD	Phytopharm Klęka S.A.	54.96	1.5356	0.0663450	1237.08	2.8809	2.3520	5.4503
4. *Extractum Hederae helicis e folium spir.* 95% *siccum* with 47% MD and 3% SiO_2	Phytopharm Klęka S.A.	94.97	2.7540	0.0505814	789.47	2.2657	1.8499	2.6520
5. *Extractum Hederae helicis e folium spir.* 70% *siccum* - 100% native	Phytopharm Klęka S.A.	94.92	2.7188	0.0555093	920.84	2.4601	2.0086	3.3946

[x]* with 5-7 gravimetric measurements; ** really marked solubility of hydrophilic extract components

Table 4

Basic viscosity values of aqueous solutions of *Extractum hederae helicis e folium* after equilibrium cholesterol solubilisation with the size of granulometric seed ø=1.00mm (saturated solution) [solubilisation of cholesterol with ø=1.00 mm]

Type of extract medium	Producer	Weighed amount ** g × 100 cm^{-3}	GLL, [η]	M_η	$R_o \times 10^{-7}$ [cm]	$R_{obs} \times 10^{-8}$ [cm]	$\Omega \times 10^{-21}$ [cm^3]	$^*n_{\|s\|}$ [mol/mol]
1. *Extractum Hederae helicis e folium spir.* 30% *siccum* -100% native	Phytopharm Klęka S.A.	2.1254	0.0877978	1967.19	3.6915	3.0141	11.4703	1.4759
2. *Extractum Hederae helicis e folium spir.* 30% *siccum* -100% native	Finzelberg Martin Bauer Group	2.4017	0.1086446	2799.20	4.4577	3.6396	20.1971	2.1126
3. *Extractum Hederae helicis e folium aq. siccum* with 50% MD	Phytopharm Klęka S.A.	2.2516	0.2039798	7942.89	7.7856	6.3567	107.6002	18.1845
4. *Extractum Hederae helicis e folium spir.* 95% *siccum* with 47% MD and 3% SiO_2	Phytopharm Klęka S.A.	2.7208	0.1703293	5893.14	6.6371	5.4191	66.6627	4.8490
5. *Extractum Hederae helicis e folium spir.* 70% *siccum* - 100% native	Phytopharm Klęka S.A.	2.6009	0.066691	1247.78	2.8941	2.3629	5.5265	0.7534

$^*n_{|s|}=M_{\eta adduct} - M_{\eta sol}/386.67$; M of cholesterol molecule = 386.67 g/mol; ** really marked solubility of hydrophilic extract components

Table 5

Basic viscosity values of aqueous solutions of *Extractum hederae helicis e folium* after equilibrium cholesterol solubilisation with the size of granulometric seed η=1.60 mm (saturated solution).

Type of extract medium	Producer	Weighed amount ** g × 100 cm^{-3}	GLL, [η]	M_η	$R_o \times 10^{-7}$ [cm]	$R_{obs} \times 10^{-8}$ [cm]	$\Omega \times 10^{-21}$ [cm^3]	$^*n_{\|s\|}$ [mol/mol]
1. *Extractum Hederae helicis e folium spir.* 30% *siccum* -100% native	Phytopharm Klęka S.A.	2.4017	0.1050345	2646.88	4.3256	3.5318	18.4543	0.9291
2. *Extractum Hederae helicis e folium spir.* 30% *siccum* -100% native	Finzelberg Martin Bauer Group	2.1254	0.0819927	1756.55	3.4746	2.8371	9.5649	1.7186
3. *Extractum Hederae helicis e folium aq. siccum* with 50% MD	Phytopharm Klęka S.A.	2.2516	0.106765	2719.47	4.3894	3.5838	19.2824	4.6758
4. *Extractum Hederae helicis e folium spir.* 95% *siccum* with 47% MD and 3% SiO_2	Phytopharm Klęka S.A.	2.7208	0.204426	5060.44	8.4466	6.8966	34.3512	2.6955
5. *Extractum Hederae helicis e folium spir*. 70% *siccum* - 100% native	Phytopharm Klęka S.A.	2.6009	0.0719395	1414.51	3.0947	2.5268	6.7581	1.1846

$^*n_{|s|}$= cholesterol solubility index; $n_{|s|} = M_{\eta adduct} - M_{\eta sol}/386.67$; M of cholesterol molecule = 386.67 g/mol; ** really marked solubility of hydrophilic extract components

Table 6

Physical and chemical properties characterising the surface activity of model extracts from *Hederae helicis e folium* and micellar adduct from cholesterol

Type of extract Producer: medium	cmc log cmc [mol× dm^3]	ΔG_m^0 [kJ × mol^{-1}]	γ_{cmc}^{25} [mJ/m^2]	$A_m \times 10^{-20}$ [m^2]	ΔG_{tr} (l) * [kJ × mol^{-1}]	ΔG_{tr} (h) ** [kJ × mol^{-1}]
1. *Hederae helicis e folium spir.* 30% (*v/v*) *siccum* 100% nativee Phytopharm Klęka SA Aqueous solution	9.9867×10^{-5} – 4.0006	–22.8295	52.10	20.7042	12.472	209.880
2. *Ext. Hederae helicis e folium spir.* 30% (*v/v*) *siccum* Finzelberg Martin Bauer Aqueous solution	7.6710×10^{-5} – 4.1151	–23.4833	53.98	22.8666	12.633	285.861
1. *Hederae helicis e folium spir.* 30% (*v/v*) *siccum* 100% nativee Phytopharm Klęka SA 0.1 mol HCl	1.4022×10^{-5} – 3.8531	–21.9884	48.95	17.8722	12.363	179.711
2. *Ext. Hederae helicis e folium spir.* 30% (*v/v*) *siccum* Finzelberg Martin Bauer 0.1 mol HCl	9.3288×10^{-5} – 4.0302	–22.9985	48.25	14.3264	12.354	301.732
1. *Hederae helicis e folium aq. siccum* + 50% MD* Phytopharm Klęka SA Aqueous solution	3.3233×10^{-4} – 3.4784	–19.8499	43.70	14.5544	12.523	108.899
Solubilisation of cholesterol with ø=1.00mm	2.88386×10^{-4} –3.5469	–20.2406	46.10	15.9041	12.523	119.716
Solubilisation of cholesterol with ø=1.60mm	4.0167×10^{-4} –3.3961	–19.3802	48.40	17.4554	12.386	73.066
2. *Ext. Hederae helicis e folium spir.* 70% (*v/v*) *siccum* + 100% nativee Phytopharm Klęka SA Aqueous solution	1.8549×10^{-4} – 3.7316	–21.2901	55.10	24.3833	12.492	96.741
Solubilisation of cholesterol with ø=1.00 mm	1.9857×10^{-4} –3.7021	–21.1261	55.30	24.6762	12.194	84.439
Solubilisation of cholesterol with ø=1.60 mm	1.8549×10^{-4}	–21.2901	55.70	25.2824	12.492	96.741
3. *Ext. Hederae helicis e folium spir.* 95% (*v/v*) *siccum*+ 47% MD + 3% SiO_2 Phytopharm Klęka SA Aqueous solution	9.7632×10^{-5} – 4.0104	–22.8856	54.80	23.9580	12.472	209.947
Solubilisation of cholesterol with ø=1.00 mm	7.6023×10^{-5} –4.1190	–23.5054	58.20	29.8693	12.431	189.513
Solubilisation of cholesterol with ø=1.60 mm	3.7130×10^{-5} –4.4303	–25.2815	60.05	34.5012	12.357	327.592

*hydrophilic segment on phase boundary
**lipophilic segment on phase boundary

producing oral form of the drug supplementing bile A litogenicity in patients who underwent cholecystectomy and with diagnosis of cholesterol lithiasis of the gallbladder.

Calculated, comparable value of $\Delta G_{tr}(l)$ F↑ in table 6 indicates the structural stability of lipophilic segment in triterpenoid saponin contained in extracts from *Hederae helicis e folium,* regardless of the polarity of the extracting medium, whereas, diverse numerical values of $\Delta G_{tr}(h)$, F↓ presented in table 6 indicate a considerably diversified hydrophilicity in the sugar segment of triterpenoid saponin, which additionally indicates the division of hydrophilic segment in creation of the topological structure favouring cholesterol solubilisation on the boundary from its granulometric form (ø1.00 mm and ø1.60 mm). The indicated Rosen's postulate (tab. 5) and γ^{25}_{cmc}, which stands for surface tension within the critical area, principally fall within the physiological segment of decreasing the surface tension coefficient, which equals 48.0–52.0 mJ/m^2.

This fact constitutes a significant condition to use them in solid forms of the drug, galenic forms and in herbal mixtures for brewing.

Solubility of ketoprofen in solutions of model extracts in pharmacopoeial artificial gastric juice – 0.1 mol HCL

Confirmed surface activity of triterpenoid saponins included in model extracts in 0.1 mol HCl solution was an inspiration for estimating – with the whole complexity of the issue, the true solubility of lipophilic ketoprofen and micellar adduct created on phase boundary. The 0.1 mol HCl environment constituted an analytical guarantee, ensuring that acidic dissociation of carboxylic group in ketoprofen would be inhibited (non-dissociated molecules would be solubilised in the solution), and most of all, the ability to create hydrotropic connections with the so-called ballast bodies included in tested extracts, as well as Freundlich adsorption on compound chlorophyll complex, would be eliminated.

Measurement of – γ^{25}_{sol} surface tension, the value of which stood as an unexpected phenomenon on phase boundary, enabled to follow the γ^{25}_{sol} relation, for tested solutions of extracts from *Hederae helicis e folium* obtained with extreme polarity of the extracting medium (ε_m).

The course of γ^{25}_{sol}=f (c, g×100 cm^{-3}) relation, was described with p=0.05 with correlation (regression) equations for big (x_1) and small (x_2) concentrations before and after ketoprofen exposure. Correlation equations listed in table 7 enabled to calculate critical micellar concentration (cmc), as well as ΔG^0_m which is the thermodynamic potential concerning the creation of micelle and its adduct with ketoprofen. Analogically to the publication [25], spectrophotometric method (UV) was used to determine the amount of ketoprofen extract dissolved in true solution (tab. 8), as well as conversion flavonoid content.

Indicated numerical value of the - γ^{25}_{cmc} surface tension coefficient in the critical area constituted the basis to calculate numerical value of the A_m coefficient, which characterises the thermodynamic nature of lesions on sorption surface on phase boundary before and after ketoprofen solubilisation.

Quantities characterising solutions of extracts in 0.1 mol HCl are presented in table 8.

Tables 7 and 8, presenting physical and chemical values, prove that as far as the environment of the artificial gastric juice (0.1 mol HCl) is concerned, triterpenoid saponins decrease the γ^{25}_{sol} surface tension coefficient in the profile close to classic non-ionic surfactants in the presence of balance substances (structures). This – with whole complexity of the issue, favours ketoprofen solubility, which may give rise to combining the selected type of extract from *Hederae helicis e folium* with ketoprofen or with other lipophilic medicinal agents in the form of preparation (tablet, capsule).What is unique from the physiological point of view, is the fact that the order of magnitude relating the decrease of the – γ^{25}_{cmc} surface tension coefficient in the critical area fall above 48–52 mJ/m^2 physiological segment, which may lead to lack of haemolytic capacity towards blood cell remaining in blood vessels in stomach, duodenum and small intestine. Solutions of model extracts – aqueous and 95% (*v/v*) ethanol in 0.1 mol HCl, as well as micellar adduct of triterpenoid saponins with ketoprofen are characterised by stable value of ΔG^0_m,whereas what concerns 70% (*v/v*) ethanol extract we can observe significant lowering of numerical value of the ΔG^0_m to the benefit of the adduct with ketoprofen.

The data presented in table 8 allow to state that as far as physiological conditions are concerned, micellar adduct of ketoprofen can be active in the process of mass exchange on phase boundary.

CONCLUSIONS

1. Model extracts produced from *Hederae helicis e folium* with diversified polarity of the extraction

Table 7

Correlation equations describing the course of γ_{sol}^{25} =f (c, g × 100 cm^{-3}) relation within the scope of big (x_1) and small (x_2) concentrations, as well as calculated critical micellar concentration (cmc)

Type of extract	Correlation equation $-\gamma_{sol}^{25}$ =f(c, g × 100 cm^{-3})				cmc [g × 100 cm^{-3}]
Producer: medium	Type of equation	r^2	a ± da	b ± db	
1. *Ext. Hederae helicis e folium aq. siccum* + 50% M.D. Phytopharm Klęka SA 0.1 mol HCl	$y_1 = a + b \times x_1$	0.9942	47.1313±1.0964	–1.5766±0.5127	0.436617
	$\log y_1 = a + b \times \log x_1$	0.9944	1.6744±1.0168 × 10^{-2}	–0.0566±4.7555 ×10^{-3}	
	$y_2 = a + b \times x_2$	0.9854	72.7569±1.6137	–1198.2140±997.1006	
	$\log y_2 = a + b \times \log x_2$	0.9853	1.8621±9.7152 ×10^{-2}	–0.3753±0.1905	
0.1 mol HCl + ketoprofen	$y_1 = a + b \times x_1$	0.9927	55.0931±11.7421	–2.2003±0.8149	0.414718
	$\log y_1 = a + b \times \log x_1$	0.9949	1.7426±1.3759×10^{-2}	0.0189±6.4367 ×10^{-3}	
	$y_2 = a + b \times x_2$	0.9576	68.1282±1.6841	–33.6316±18.5474	
	$\log y_2 = a + b \times \log x_2$	0.9612	1.8334±1.0642 × 10^{-2}	–0.2236±0.1174	
2. *Ext. Hederae helicis e folium spir. siccum* 95% (*v/v*) + 47% MD + 3% SiO_2 Phytopharm Klęka SA 0.1 mol HCl	$y_1 = a + b \times x_1$	0.9871	60.0962±1.7623	–2.9517±0.8747	0.301292
	$\log y_1 = a + b \times \log x_1$	0.9585	1.7809±1.3252 × 10^{-2}	–2.3608±6.5781 × 10^{-3}	
	$y_2 = a + b \times x_2$	0.9585	71.8071±3.8557	–41.8206±37.8393	
	$\log y_2 = a + b \times \log x_2$	0.9602	1.8565±2.3884 × 10^{-2}	–0.2674±0.2343	
0.1 mol HCl + ketoprofen	$y_1 = a + b \times x_1$	0.9941	55.3021± 0.9229	–2.2997±0.4581	0.290478
	$\log y_1 = a + b \times \log x_1$	0.9971	1.7442±7.4425 × 10^{-3}	–1.9688±3.6941 × 10^{-3}	
	$y_2 = a + b \times x_2$	0.9529	68.8743±2.4154	–49.0233±17.4103	
	$\log y_2 = a + b \times \log x_2$	0.9558	1.8381±0.0152	–0.3193±0.2992	
3. *Ext. Hederae helicis e folium spir. siccum* 70% (*v/v*) 100% native Phytopharm Klęka SA 0.1 mol HCl	$y_1 = a + b \times x_1$	0.9997	57.5318±0.5501	–4.5855± 0.3114	0.105135
	$\log y_1 = a + b \times \log x_1$	0.9994	1.7633 ±5.5632 × 10^{-3}	–3.9613 ± 3.1502 ×10^{-2}	
	$y_2 = a + b \times x_2$	0.9993	70.5052±0.3920	–127.9820 ± 13.8576	
	$\log y_2 = a + b \times \log x_2$	0.9983	1.8486±3.2746 × 10^{-3}	–0.8322 ± 0.1157	
0.1 mol HCl + ketoprofen	$y_1 = a + b \times x_1$	0.9989	55.2973±1.5394	–6.2779±0.8716	0.268712
	$\log y_1 = a + b \times \log x_1$	0.9967	1.7508±2.6271 × 10^{-2}	–6.0412±1.4876 × 10^{-2}	
	$y_2 = a + b \times x_2$	0.9886	64.8657±2.1918	–41.8863±19.3701	
	$\log y_2 = a + b \times \log x_2$	0.9831	1.7361±4.8218 × 10^{-2}	–4.6743 × 10^{-2}±2.6901 × 10^{-2}	

Table 8

Selected quantities characterising flavonoid content (c_1, c_2), solubility of ketoprofen and surface activity of extracts in 0.1 mol HCl

Type of extract Producer	Environment	c_1 [mg × 100 cm^{-3}]	c_2 [mg × 100 cm^{-3}]	$c_{\|s\|}$ [mg× 100 cm^3]	cmc × 10^{-3} [mol ×dm^{-3}]	ΔG_m^0 [kJ ×mol^{-1}]	$A_m \times 10^{-20}$ [m^2]
1. *Ext. Hederae helicis e folium aq. siccum* +50% MD Phytopharm Klęka SA	0.1 mol HCl	70.3827	147.9208	18.5104	3.5294	-13.9942	15.9658
	0.1 mol HCl + ketoprofen				3.3524	-14.1217	23.1756
2. *Ext. Hederae helicis e folium spir. siccum* 95% (*v/v*) 47% MD + 3% SiO_2	0.1 mol HCl	113.5079	249.8633	17.8813	3.8163	-13.8004	32.4604
	0.1 mol HCl + ketoprofen				3.6779	-13.8910	23.9580
3. *Ext. Hederae helicis e folium spir. siccum* 70% (*v/v*) 100% native	0.1 mol HCl	115.7557	254.9293	8.4684	1.1417	-16.7912	25.0061
	0.1 mol HCl + ketoprofen				2.9181	-14.4655	22.1528

medium (water - ethanol) are characterised by appropriate solubility of components, which results not only from the presence of chlorophyll and its derivates in the extract but also from the technique used for spray drying (of the extract). Unexpectedly, it turned out that obtaining granulometrically optimal and stable extract as an extraction medium; water and 95% (*v/v*) ethanol, requires introducing maltodextrin (MD) and SiO_2, since only the participation of these above-mentioned excipients enables to maintain technologically required humidity (decreased hygroscopic properties of components in the extract) and flow. Form of an extract prepared in this way gives the possibility to create a solid form of the drug with selected extracts with the use of direct compressing of the tablet mass granulate.

2. Indicated viscosity and hydrodynamic properties of tested extracts for the aqueous environment and comparable in 0.1 mol HCl aqueous solution indicate that during exposure in a solution with $pH_{(aH+)}$=1.30, a hydrolysis of hydrophilic sequence of sugar alcohols is observed, hence as far as viscosity is concerned, the average molecular mass – M decreases. This is of considerable significance when evaluating the unique solubilisation process by natural surfactants present in the composition of model cholesterol extracts from the surface of the granulometric form with ø=1.00 mm and ø=1.60 mm.
   Thermodynamic outcome of the process related to the change in the physical state of γ_{sol}^{25} cholesterol: the solid/molecular degree of fragmentation reveals a considerable increase in viscosity values ([η], $[M_\eta]$) and hydrodynamic values (R_o, R_{obs}, Ω) of the micellar adduct. Marked solubility index characterises the qualitative course of the solubilisation process and most of all indicates this type of extract, where the content of triterpenoid saponins may be an inspiration to create such a form of the drug, which will considerably improve the litogenolitic index of bile A (duodenal matter).
3. The measurement of – γ_{sol}^{25} surface tension in aqueous solutions and in 0.1 mol HCl of model extracts which were characterised by high solubility indices as compared with granulometric form of cholesterol, was also described with correlation equations. They constituted the basis for calculating the critical micellar concentration (cmc) and thermodynamic potential for creating micelles – ΔG_m^0 and adduct with cholesterol. Values presented in Tables 5 and 6 reveal that cholesterol is solubilised in the palisade micellar layer with stable ΔG_m^0 value. Unexpectedly, it turned out that the model extract from *Hederae-helicis folium spir. siccum* 70% (*v/v*) – 100% native has the most stable thermodynamic values among all tested solutions.
4. Surface activity of solutions of extracts in 0.1 mol HCl, and most of all the indicated thermodynamic values characterising the cholesterol solubilisation process, as well as equilibrium of phase boundary (air/water) were an inspiration to test the solubility of ketoprofen (II class BCS).

   Obtained results presented in table 8 indicate that there takes place the process related to the solubility of ketoprofen, whereas the qualitative course of the above-mentioned process may in the future be used to create a solid form of the mixed-ketoprofen type of drug + selected target type of extract, in which triterpenoid saponin components will play the role of the so-called solubility agent in physiological conditions.

   The suggestion mentioned above, prejudges the determined values characterising the above-mentioned processes presented in table 8 and the type of extract with determined granulometric preferences.

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