EXPERIMENTAL PAPER

Selected physicochemical and solubilization properties of pharmacopeal solutions of dry green tea leaf extract (*Ext. Camellia sinensis* L. *folium aqu. siccum*)

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Summary

Introduction: Green tea offers not only pleasant, delicate flavor, but also provides health benefits. The extract contains, among others, polyphenols responsible for antioxidant and anti-inflammatory properties.

They reduce the risk of cancer and their presence exerts preventive activity against cardiovascular diseases.

Objective: Analysis of selected physicochemical and solubilizing properties of pharmacopoeial-true solutions of dry green tea extract.

Methods: The caffeine content was determined in the extract and in dry residue after solubilization by high performance liquid chromatography. The process of micellar solubilization of cholesterol granules and ketoprofen was carried out in model solutions of green tea extract.

Results: The obtained results indicate that the prepared 'ex tempore' leaf green tea infusion subjected to short thermal exposure will be characterized by significant solubilization abilities.

Conclusions: The outcomes of the research pointed to the possibility of developing a solid oral dosage form with titrated dry green tea extract of expected pharmacotherapeutic profile.

Key words: *Camellia sinensis, phytochemicals, solubilization, ketoprofen, caffeine, cholesterol*

INTRODUCTION

Nowadays, selected classes of phytochemicals e.g. polyphenols such as flavonoids, proanthocyanidins, catechins including epigallocatechin gallate are used in the prevention of civilization diseases. They are administered in the form of extracts. As introduced into the periodic or daily diet, they reduce the risk of diseases or significantly slow down the course of those initiated by free radicals i.e. cancer and cardiovascular and neurodegenerative diseases [1-3].

Chromatographic methods (HLPC, UPLC, MSA, DAD) were applied to determine the content of fundamental classes of phytochemicals i.e. phenolic acids and their derivatives, catechins, xanthine alkaloids (purine), proanthocyanidins and flavonols, flavones and forms of O-glycosides and their acetyl derivatives [4-9] in extracts from tea brands available in the market (green, white, pu erh), which decides on effective antioxidant and pharmacological activity [10, 11].

Special attention should be paid to quantitative relation between levels of caffeine and catechins when the application profile of tea brands and their extracts is determined [12].

The studies on the solubility of phytochemicals contained in the dry green tea leaf extract *(Ext. Camellia sinensis* L. *folium aqu. siccum)* [13] were the inspiration for determining the physicochemical properties of aqueous solutions of the extract and, above all, for the determination of caffeine in exposure solutions after equilibrium solubilization in the medium of specific osmotic pressure of ketoprofen and granulometrically modified cholesterol [14, 15].

The obtained results enable to develop an oral solid dosage form containing dry green tea extract *(Ext. Camellia sinensis* L. *aqu.siccum)* of expected pharmacotherapeutic profile which takes into account (Lindblat index) the effective micellar or hydrotropic solubilization of lipophilic medicinal agents in the gastrointestinal tract [16].

MATERIAL AND METHODS

Material

Dry aqueous extract from green tea leaves: *Extractum Camellia sinensis* L. *folium aqu. siccum* (100% native) – Europlant Group Phytopharm Klęka S.A., Poland; Koffein wasserfrei Pulver (caffeine anhydrous powder) – BASF, Pharma Chemikalien GmbH Co KG (Germany), Lot. 694661AX10.

Determination of caffeine content in extract and dry residues after solubilization was performed by high performance liquid chromatography (HPLC).

Apparatus

Hewlett-Packard liquid chromatograph 1100 series including 1311A pump, HP 1322A degasser, 20 μl injector (Rheodyne 7725i, Cotati. CA, USA) and HP 1314A variable wavelength UV/VIS detector was used to determine the amount of caffeine in the dry green tea leaf extract and model dry residues by reverse phase high-performance liquid chromatography (RP-HPLC) method. The extracts were separated using MN (Macherey Nagiel) (250x4 mm) column packed with Nucleodur C18 solid phase carrier of particle size 5 μm with 4x4 mm guard column (Hypersil ODS, 5 mm, Germany).

Chromatographic procedure

Extracts (~ and dry residues after solubilization) were separated by gradient elution using solvents as follows: A: water – phosphoric acid (99.5:0.5) and B: methanol (MeOH). Separation conditions: 0–10 min: 25% B in A, 10–20 min: 85% B in A, 20–25 min: 25% B in A. The separation was performed at room temperature at a flow rate of 1 ml/min and detection in UV light at 272 nm (sensitivity 0.05 AUFS). HPLC-grade solvents were used: methanol (Merck, Germany), ortophosphoric acid (Sigma Aldrich), redistilled water.

The reference substance – caffeine – was Caffein anhydrous powder (Koffein wasserfrei pulvis) from BASF, Germany. Identification of caffeine in the extract was performed by RP-HPLC method by comparing the retention time of the obtained signal with retention time of the reference substance.

The prepared extracts were injected into a column consecutively six times (n=6) in the volume of 10 μl.

Calibration of measurement system

Caffeine standard solution (0.0154 g/50 ml) was prepared in 25% MeOH and a final concentration of 0.308 mg/ml was obtained. Calibration curves for caffeine were prepared in a concentration range of 18.48-308 μg/ml for 6 declared concentrations. Calibration curves for caffeine are described by the equation:

y = 9E + 0.7x – 65923 at correlation coefficient r=0.9996.

The results were expressed in g/100 g of dry extract weight (%).

Viscosity and surface tension of model aqueous solutions of *Ext. Camellia sinesis* L. *folium aqu. siccum*

The viscosity measurements of aqueous solutions of *Ext. Camellia sinensis* L. f*olium aqu. siccum* in 0.1 mol HCl and in phosphate buffer of pH=6.88 were performed according to the Polish Standard [16] using Ubbelohde viscosimeter. They were the basis for calculating from the equation

$$[\eta], GLL = \frac{[\eta_{sp} + 3\ln(\eta_{sol.}/\eta_{oH_2O})]}{4 \times c}$$

calculating the limiting viscosity number [η] as well as selected hydrodynamic values: M_η, R_o, R_{abs} and Ω [17]. Critical micellar concentration (cmc) was calculated analogically to that of publication [17].

The surface tension of model aqueous solutions – $\gamma_{sol.}^{25}$ of *Ext.Camellia sinensis* L. *folium aqu. siccum* were determined by stalagmometric method acc. to the Polish Standard [17]. The numerical value of cmc (g/100 cm³; mol/dm³) was the basis for calculating from the equation:

$$\Delta G_m^o = 2.303\ RT\ \log cmc$$

the thermopotential for the formation of micelles – ΔG_m^o.

After substituting the physicochemical values and multiplying them as well as simplifying and converting to kJ, finally ΔG_m^o was calculated from the equation:

$$\Delta G_m^o = 5.709043 \cdot \log cmc \ \ [kJ/dm^3]$$

The value of the decrease of the surface tension coefficient in the critical area – γ_{cmc}^{25} was the basis for calculating from the equation –

$$A_m = \frac{k \cdot T}{\gamma_{sol.}^{25} - \gamma_{cmc}^{25}}$$

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 – $\pi \cdot A_m \cdot R \cdot T$ by Avogadro number (constant) leading to the equation

$$f(\pi) \cdot A_m = k \cdot T$$

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

After substituting the physicochemical values to the above equation and then after multiplying and simplifying the following equation is obtained:

$$A_m = \frac{411.6410 \cdot 10^{-20}\ m^2}{71,98 \cdot \gamma_{cmc}^{25}}.$$

Micellar solubilization of cholesterol granules and ketoprofen in model solutions of *Ext. Camellia sinensis* L. *folium aqu. siccum*

The process of micellar solubilization was performed in a container of V=100 cm³ into which there were

weighed not less than 450 g of homogeneous cholesterol granules of Φ=0.5 mm, in the case of ketoprofen (technological form of lipophilic therapeutic agent) the weighed quantity did not exceed 0.400 g.

After equilibrium solubilization of cholesterol and ketoprofen the solutions were prepared for viscosity (η) and surface tension ($\gamma_{sol.}^{25}$) measurements similarly to the patent publication [15].

Calculated basic viscosity and hydrodynamic values allowed to estimate in the equilibrium system from the equations:

(1)

$$n_{(s,k)} = \frac{M_\eta add. - M_{\eta(sol.)}}{254.3}$$

and

(2)

$$n_{(s,chol)} = \frac{M_\eta add. - M_{\eta(sol.)}}{386.64} .$$

the numerical values of solubilization indices – $n_{(s,k)}$ and $n_{(s,chol)}$ for ketoprofen and cholesterol.

The surface activity of the micelles at the phase boundary was estimated by calculating the A_m coefficient for the exposure and saturated solutions after equilibrium solubilization of ketoprofen and cholesterol.

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

RESULTS AND DISCUSSION

The physicochemical properties of classes of phytochemicals contained in the green tea leaf extract (*Ext. Camellia sinensis* L. *folium aqu. siccum*) [13] have been the inspiration for conducting preformulation studies on the surface activity and solubilization capacities in equilibrium system in model solutions of acceptor fluids (water, 0.1 mol HCl, phosphate buffer of pH$_{(a_{H^+})}$ = 6.88).

It results from the basic viscosity and hydrodynamic values presented in table 1 that the complex solubilization process of lipophilic ketoprofen was most effective in aqueous solution, whereas in 0.1 mol HCl and phosphate buffer solution of pH$_{(a_{H^+})}$ = 6.88 was significantly decreased to the level of solubilization index – $n_{(s,k)}$ ≤0.3 (mol/mol).

Unexpectedly, the process of solubilization of cholesterol granulometric form (granule diameter Φ=0.50 mm) was effective quantitatively in the aqueous solution of the extract and in the aqueous solution of 0.1 mol HCl as evidenced by the

calculated from the viscosimetric measurements - numerical values of the solubilization indices – $n_{(s,chol)}$=2.8437 and 2.3686 (mol/mol).

The amount of solubilized cholesterol in phosphate buffer medium of pH$_{(a_{H^+})}$ = 6.88 decreased significantly by about 50%. The obtained results of preformulation studies are presented in table 1.

The thermodynamic assessment of the solubilization capabilities of phytochemicals contained in the green tea leaf extract was performed by determining the critical micelle concentration (cmc) and by calculating the thermodynamic potential for micelle formation (ΔG_m^o) as well as A_m coefficient which determines the lipophilic stability and size of the lipophilic uplift of the micellar adduct above the phase boundary (tab. 2).

It results from table 2 that the significant application increase in the stability of the complex micellar adduct took place in case of solubilization of the granulometric form of cholesterol, as it was evidenced by the numerical value of ΔG_m^o from – 18.8094 kJ in phosphate buffer of pH$_{(a_{H^+})}$ = 6.88 (model duodenal contents – bile "A") to –21.1219 kJ in 0.1 mol HCl (model gastric juice). Also in the environment of the aqueous extract solution, the solubilization process is efficient and the stability of the adduct is determined by ΔG_m^o = –19.9779 kJ (tab. 2).

The process of lipophilic ketoprofen solubilization is characterized by a stable value of ΔG_m^o in the range of –17.5499 kJ for 0.1 mol HCl to –18.2731 kJ for the phosphate buffer of pH$_{(a_{H^+})}$ = 6.88 at similar value – 18.1402 kJ for the aqueous extract (tab. 2).

The fact that the numerical value of A_m coefficient for the micellar adduct is a value characteristic of itself for solubilized structure of ketoprofen (– regression of the A_m value) and cholesterol (– deep variation of A_m value due to pH$_{(a_{H^+})}$ and osmolarity of the model solution) is significant and characteristic for the thermodynamic course of the process of ketoprofen and cholesterol solubilization in model solutions of the extract.

This indicates that oral preparations containing dry extract of green tea leaves (*Ext. Camellia sinensis* L. *folium aqu. siccum*) significantly complement the lythogenolythic index in duodenal contents (bile "A") which is responsible for the process of lipophilic structure mass exchange on phase boundary - in the small intestine in the gastrointestinal tract [19, 20].

The physicochemical phenomenon that needs clarification is the active role of caffeine in the form of physicochemical structural interactions (~ with sugar alcohols) in the process of solubilization of ketoprofen and cholesterol lipophilic structures [21-24].

Table 1

Viscosity and hydrodynamic parameters of model solutions of green tea leaf dry extracts – *Ext. Camellia sinensis* L. *folium aqu. siccum* in water, in 0.1 mol HCl and in phosphate buffer of $pH_{(a_{H^+})} = 6.88$ solubilizing in equilibrium conditions ketoproten and cholesterol

Exposure solutions *Ext. Camellia sinensis* L. *folium aqu. siccum*	c_{exp} g·100 cm³	$[\eta]$	M_η	$R_o \cdot 10^{-7}$ cm	$R_o \cdot 10^{-8}$ cm	Ω [cm]³	$n_{(Islk)}$	$n_{(Islchol)}$
1. Extract solution in water		0.0243432	235.22	1.1859	0.9682	$0.9735 \cdot 10^{-23}$		
2. + ketoprofen	1.5310	0.0479356	722.28	2.1605	1.7641	$2.2903 \cdot 10^{-21}$	1.9152	2.8437
3. + cholesterol		0.0694603	1334.72	3.0001	2.4495	$6.1571 \cdot 10^{-21}$		
1. Extract solution in 0.1 mol HCl		0.0454746	661.95	2.0620	1.6836	$1.9991 \cdot 10^{-21}$		
2. + ketoprofen	1.6750	0.0484475	735.09	2.1809	1.7801	$2.3651 \cdot 10^{-21}$	0.2877	2.3686
3. + cholesterol		0.0768450	1577.75	3.2808	2.6787	$8.0519 \cdot 10^{-21}$		
1. Extract solution in phosphate buffer of $pH_{(a_{H^+})} = 6.88$		0.0486564	740.35	2.1892	1.7874	$2.3923 \cdot 10^{-21}$		
2. + ketoprofen	2.4450	0.0510619	817.58	2.3085	1.8848	$2.8051 \cdot 10^{-21}$	0.3036	1.2456
3. + cholesterol		0.0658549	1221.08	2.8619	2.3366	$5.3444 \cdot 10^{-21}$		

Table 2

Surface activity of model solutions of green tea leaf dry extracts – *Ext. Camellia sinensis* L. *folium aqu. siccum* with thermodynamic evaluation of solubilization capacity in relation to lipophilic structures of ketoprofen and cholesterol

Exposure solutions *Ext. Camellia sinensis* L. *folium aqu. siccum*	c_{exp} [g·100 cm³]	cmc [g·100 cm3]	cmc [mol/dm³]	ΔG_m^o [kJ/dm³]	γ_{cmc}^{25}; [mJ·m²]	$A_m \cdot 10^{-20}$ [m²]
1. Extract solution in water		0.720	$3.0612 \cdot 10\text{-}3$	-14.3533	68.5	118.2876
2. + ketoprofen	1.5310	0.480	$6.6456 \cdot 10^{-4}$	-18.1402	69.5	165.9842
3. + cholesterol		0.420	$3.1467 \cdot 10^{-4}$	-19.9779	68.0	103.4273
1. Extract solution in 0.1 mol HCl		0.420	$6.3451 \cdot 10^{-4}$	-18.2550	70.5	278.1358
2. + ketoprofen	1.6750	0.620	$8.4342 \cdot 10^{-4}$	-17.5499	68.5	118.2876
3. + cholesterol		0.305	$1.9965 \cdot 10^{-4}$	-21.1219	71.5	857.5824
1. Extract solution in phosphate buffer of $pH_{(a_{H^+})} = 6.88$		0.480	$6.4834 \cdot 10^{-4}$	-18.2015	70.5	278.1358
2. + ketoprofen	2.4450	0.515	$6.2991 \cdot 10^{-4}$	-18.2731	65.5	63.5248
3. + cholesterol		0.620	$5.0737 \cdot 10^{-4}$	-18.8094	66.0	68.8362

Table 3

The determined caffeine content in model solutions of green tea leaf dry extracts – *Ext. Camellia sinensis* L. *folium aqu. siccum* and equilibrium process of solubilization of ketoprofen and cholesterol

Exposure solutions of *Ext. Camellia sinensis* L. *folium aqu. siccum* - dry residue	Weight of the test portion in `g´-range	Determined content [%]	x [%] for n=6	SD [1]	RSD [2]
1. Green tea leaf dry aqueous extract – *Ext. Camellia sinensis* L. *folium aqu. siccum*	0.0127–0.0128	10.29–10.70	10.47	0.1707	1.63
2. Dry extract residue in water	0.0124–0.0128	6.48–7.16	6.82	0.3276	4.81
+ ketoprofen	0.0132–0.0128	6.86–7.05	6.97	0.1061	1.52
+ cholesterol	0.0124–0.0130	7.25–7.46	7.43	0.0943	1.27
3. Dry extract residue in 0.1 mol HCl	0.0123–0.0127	6.20–6.44	6.29	0.1445	2.30
+ ketoprofen	0.0126–0.0130	4.40–6.29	5.61	0.5052	9.01
+ cholesterol	0.0123–0.0130	5.32–5.52	5.41	0.0942	1.74
4. Dry extract residue in phosphate buffer of $pH_{(a_{H^+})} = 6.88$	0.0125–0.0125	5.47–5.52	5.44	0.0537	0.99
+ ketoprofen	0.0125–0.0128	4.20–4.32	4.29	0.1022	2.38
+ cholesterol	0.0124–0.0130	4.69–4.93	4.78	0.1769	3.70

1) - standard deviation;
2) - relative standard deviation

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It results from the analytical data demonstrated in table 3 that during the preparation of model solutions for pre-formulation tests there comes to the hydrolysis of thermodynamic and hydrotropic bonds of caffeine which is observed as a decrease in the concentration in the exposure solution and at the same time as a significant regression in the numerical value of the solubilization index of ketoprofen and cholesterol ($-n_{(Is,k)}|$ and $n_{(Is,chol)}$), (tab. 3) in model acceptor fluids in relation to the aqueous solution.

The obtained results indicate that green tea leaf infusion prepared 'ex tempore', subjected to short thermal exposure, will be characterized by – as confirmed by literature data [1-6] – significant solubilization capacity owing to the presence of glycosidic and hydrotropic caffeine bonds in the extract.

CONCLUSIONS

1. The obtained results demonstrate that in the dry aqueous extract from green tea leaves (*Ext. Camellia sinensis* L. *folium aqu. siccum*) – despite technological procedures including high temperature of drying process, there were preserved in significant content hydrotropic bonds of caffeine and other ligands, the presence of which determines solubility capacity and the order of basic viscosity ($[\eta]$, M_η) and thermodynamic values (R_o, R_{obs}, Ω). They allow calculating solubilization indices for model lipophilic structures of ketoprofen and cholesterol.

2. Quantitative course of the complex solubilization process in the environment of model exposure solutions of the extract solutions in water, 0.1 mol HCl and phosphate buffer of $pH_{(a_{H^+})}$ = 6.88 indicates a significant quantitative decrease of the process, particularly in the pharmacopoeial acceptor fluid corresponding to the duodenal contents (bile "A"). This indicates hydrolysis-induced qualitative changes in the composition of phytochemicals that are responsible for micellar and hydrotropic solubilization, as indicated by the calculated values of indices - $n_{(Is,k)}|$ and $n_{(Is,chol)}|$ presented in table 2.

3. Surface activity ($\gamma_{sol.}^{25}$) and, above all, the calculated thermodynamic potential of micelle formation – ΔG_m^o and the numerical value of Am coefficient (tab. 2) indicate a significant thermo-

dynamic stability of the adduct with cholesterol and ketoprofen, despite observed regression of its value. This in the application option translates into the appropriate pharmacological profile of the solid oral dosage form (and/or dietary supplement) with proper dose of green tea leaf titrated dry aqueous extract (*Ext. Camellia sinensis* L. *folium aqu. siccum*).

4. The caffeine content in green tea leaf dry aqueous extract determined by HPLC method indicates a significant contribution of hydrotropic bonds of caffeine in the complex (adduct caffeine from fitochemical-organic ligands) process of solubilization of ketoprofen and cholesterol (granulometric form of Φ=0.5mm in model acceptor fluids (water, 0.1 mol HCl, phosphate buffer of $pH_{(a_{H^+})}$ = 6.88). The determined caffeine content in the dry residue after the equilibrium solubilization process indicates the progressive hydrolysis of the glycosidic bonds as evidenced by a significant decrease of its content in a dry residue after exposure to 0.1 mol HCl and phosphate buffer of $pH_{(a_{H^+})}$ = 6.88. The above also indicates a significant contribution of caffeine glycosidic bonds to surface activity of dry aqueous extract in model acceptor solutions and quantitatively effective complex process of solubilization of ketoprofen and cholesterol from the surface of grain of Φ=0.5mm [22].2].

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Wybrane właściwości fizykochemiczne i solubilizacyjne farmakopealnych roztworów rzeczywistych suchego ekstraktu z liści zielonej herbaty (*Ext. Camellia sinensis* L. *folium aqu. siccum*)

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Streszczenie

Wstęp: Zielona herbata nie tylko niesie ze sobą przyjemny, delikatny smak po sporządzeniu naparu, ale również korzyści zdrowotne. Ekstrakt zawiera między innymi polifenole odpowiedzialne za właściwości antyoksydacyjne i przeciwzapalne. Zmniejszają one ryzyko wystąpienia nowotworów, a także ich obecność działa profilaktycznie w przypadku wystąpienia schorzeń układu krążenia.

Cel: Analiza wybranych właściwości fizykochemicznych i solubilizacyjnych farmakopealnych roztworów rzeczywistych suchego ekstraktu z zielone herbaty.

Metody: Oznaczono zawartość kofeiny w ekstrakcie i w suchych pozostałościach po solubilizacji metodą wysokosprawnej chromatografii cieczowej. Proces micelarnej solubilizacji granulatu cholesterolu i ketoprofenu przeprowadzono w modelowych roztworach ekstraktu z zielonej herbaty.

Wyniki: Uzyskane rezultaty wskazują, że przygotowany „ex tempore" napar z liści zielonej herbaty poddany krótkiej ekspozycji termicznej będzie charakteryzował się znaczącymi zdolnościami solubilizacyjnymi.

Wnioski: Otrzymane wyniki umożliwiają opracowanie stałej doustnej postaci leku z mianowanym suchym ekstraktem z zielonej herbaty o oczekiwanym profilu farmakoterapeutycznym.

Słowa kluczowe: *Camellia sinensis, fitozwiązki, solubilizacja, ketoprofen, kofeina, cholesterol*