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NEW FORMULA HERBAL PELLETS DEMONSTRATE A UNIFORM AND STABLE RELEASE OF THE ACTIVE INGREDIENTS *IN VITRO*

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Abstract: The aim of this study was to evaluate the effect of different capsule filling manufacturing techniques and storage conditions on the release of the active ingredients from herbal capsules during the dissolution test *in vitro*. Different techniques for the preparation of the original mixture of dry extracts were applied, and subsequently capsules with six different fillings were prepared. The stability of the capsules was evaluated in different long-term storage conditions, registering changes in the water content (loss of drying), capsule disintegration time, and phenolic compounds dissolution test *in vitro*. The baseline of phenolic compounds release in the control capsules (filled with the mixture of the powder of dry herbal extracts) was the highest, compared to other capsule groups, yet during long-term storage, these capsules accumulated too much moisture, which impeded capsule disintegration time and phenolic compounds release. The study showed that moisture and temperature changes occurring during the storage of the preparation had a negative effect on the release of phenolic compounds from herbal capsules. Capsules filled with pellets demonstrated a uniform and stable release of the active ingredients in different long-term storage conditions, which indicates that the manufacturing technology of dry herbal extracts affects the stability of the active ingredients.

Keywords: herbal pellets, ginkgo leaf, motherwort herb, hawthorn fruits

Recent studies have shown that plant secondary metabolites with antioxidant properties have a positive effect in the pathogenesis of acute and chronic diseases (1-3), including cardiovascular diseases (4). Herbal preparations attract more and more attention (5-7), because these preparations are with increasing frequency prescribed as an additional therapy along with pharmacological treatment, or as dietary supplements for disease preventions and/or rehabilitation after a disease. This tendency has also been observed in the treatment algorithms for cardiovascular diseases (1, 4).

One of the major tasks for the developers of herbal preparations is the creation of a drug form that would be acceptable to a modern consumer and would retain the therapeutic properties of plants. Herbal preparations in modern pharmaceutical industry are frequently prepared from dry herbal extracts, more commonly selecting capsules than tablets as the dosage form (8). This is due to several reasons: first of all, the manufacturing of capsules requires fewer technological operations than the manufacturing of tablets does (9), the active ingredients are released more rapidly (the tablets are pressed and thus do not dissolve that readily), and the capsules are easier to use because solid gelatin capsules, affected by saliva, are more slippery and thus easier to swallow (provided they are not too large). Filling the solid capsules with powder, granules, or pellets improves the bioavailability of the

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active ingredients due to a greater porosity of the filling mass, and has lower requirements for the powder flow of the mixture, compared to tablets; thus, the majority of dry herbal extracts are produced in the form of capsules (8).

On the basis of these trends, original capsules with the mixture of dry extracts of ginkgo leaf, motherwort herb and hawthorn fruits were developed (1 : 5 : 6). Previous studies analyzing and comparing the *in vitro* kinetics of the antioxidant effect of liquid extracts of these plants confirmed that these extracts had antioxidant properties. Antioxidant activity was found in DPPH and $ABTS^{+}$ reactions (10). Studies were also performed to evaluate and improve the technological properties of this mixture of dry herbal extracts (11, 12). On the other hand, good baseline technological characteristics do not mean that the preparation is suitable for use. In order to evaluate the quality of the herbal preparation, the dissolution test is conducted in order to test the release of the studied active ingredients (13). This test is also called *in vitro* dissolution test, and is an important criterion in the evaluation of the bioequivalence of medicinal herbal preparations – i.e., their possible behavior in biological media (14). Comparative studies for the *in vitro – in vivo* equivalence suggest that the *in vitro* test is effective, and, with the selection of appropriate conditions, correlates with *in vivo* studies (14-16). The dissolution test also allows for observing the release of the active ingredients under different storage conditions (14), as well as the change in substance release over time – i.e., the stability of the preparation (15, 17). The dissolution test is also one of the factors allowing for the evaluation of the effect of different technologies on the release of the active ingredients from the dosage form (15, 16). During this study, phenolic compounds as the active ingredients were selected because scientific literature indicates that the amount of the phenolic compounds determines the antioxidant activity of preparations (6, 18). Different techniques (granulation with different moisturizing solutions and formation of pellets) were applied to the original mixture (1 : 5 : 6) of dry extracts of ginkgo leaf, motherwort herb and hawthorn fruits and produced capsules with six different fillings; the dry extract mixture (powder) was selected as the control sample. The aim of this study was to evaluate the effect of different capsule filling manufacturing techniques and storage conditions on the release of the active ingredients from herbal capsules during the dissolution test *in vitro*.

MATERIALS AND METHODS

Materials

The dry extracts of ginkgo leaf (*Ginkgonis folium,* Eur. Ph. 6; 01/2008:1828), hawthorn fruits (*Crataegi fructus,* Eur. Ph. 6; 01/2008:1220), and motherwort herb (*Leonuri herba,* Eur. Ph. 6; 01/2008:1833) were analyzed. Detection of phenolic compounds was conducted by using chemical reagents – gallic acid (Sigma Aldrich, Germany), Folin-Ciocalteu reagent and sodium carbonate (both from Fluka Chemie, Germany).

Substances employed in the capsule dissolution test were the following: concentrated

Table 1. Composition of capsules used in the study.

Group No.	Composition, mg				Abbreviation*
	Dry ginkgo extract	Dry motherwort extract	Dry hawthorn extract	Excipients	
1	10	50	60	129	Powder
2	10	50	60	112	Granules-L
3	10	50	60	101	Granules-C
4	10	50	60	104	Granules-G
5	10	50	60	100	Granules-P
6	10	50	60	277	Pellets

*Powder – dry extract mixture (51.4%) and excipient *Prosolv HD 90* (48.6%). Granules-L – binder solution motherwort (*Leonuri*) extract; Granules-C – binder solution hawthorn (*Crataegi*) extract; Granules-G – binder solution ginkgo (*Ginkgo*) extract; Granules-P – povidone binder solution; Pellets – dry extract mixture (30%) and excipient *Avicel PH 101* (70 %).

hydrochloric acid (Fluka Chemie, Germany); sodium chloride (Merck, Germany). All other chemicals used for analysis were of analytical grade.

Hard clear colorless gelatin capsules, size 1 (Capsuline, USA) were used for filling with different plant extracts mixture formulations.

Compositions of capsules used in the study are given in Table 1. In the first experiments, six experimental groups of capsules filled with a mixture (1 : 5 : 6) of dry extracts of ginkgo leaf, motherwort herb and hawthorn fruits, prepared using different techniques (granulation with different moisturizing solutions, and formulation of pellets) were used. The dry extract mixture (powder) was used as a control sample.

METHODS

Preparation of capsules fillings

Compositions of capsules fillings are given in Table 1. Powder was prepared by simple mixing of the mixture of extracts with excipient. Granules were prepared by wet granulation. The prepared powder mass (mixture of dry herbal extracts and Prosolv HD90 as an excipient) was mixed in a granulator and wetted with binder solutions. Pellets were prepared by the extrusion/spheronization technique. All fillings were prepared under common laboratory conditions, and immediately before the stability study were dried using the ventilated oven (Type 0488, Hoffman, Germany) at 40°C for 24 h. Filled capsules were prepared using the manual capsule-filling machine (Capsuline, USA).

Dissolution conditions

Dissolution profiles of the prepared capsules were determined using the basket method (apparatus Erweka, Germany) at 100 rpm in 900 mL of artificial gastric juice without pepsin (AGJ) with pH value 1.2 or freshly bi-distilled water at 37 ± 0.5°C. AGJ contains 2.0 g of sodium chloride and 100 mL of 1 M hydrochloric acid in 898 mL of purified water [19]. Samples of about 2 mL were manually taken from dissolution vessels in 15, 30, 45, 60, 90 and 120 min time points and the released amount of total phenolic compounds was determined by a modified Folin-Ciocalteu colorimetric method. Volume adjustments of the media were made by replacement of the withdrawn sample volume with fresh buffer at the same pH or bi-distilled water stored in a reservoir at the same temperature. The mean value of six samples and a standard deviation were calculated. The evaluation of dissolution profiles was carried out in 5 times.

Determination of the capsule disintegration time

The capsule disintegration time was determined following the Eur. Ph. 5; 01/2005:20901, using the tablet and capsule disintegration test. The disintegration time was evaluated using the apparatus produced by Erweka, Germany. Six capsules were selected from each series. The disintegration time of the capsules did not exceed 15 min.

Evaluation of phenolic compounds

The total amount of phenolic compounds was determined using modified Folin-Ciocalteu colorimetry. The studied solution (0.7 mL) was placed into a 10-mL graded flask, subsequently adding the Folin-Ciocalteu reagent (400 µL), and – after 3 min – adding sodium carbonate (Na_2CO_3) solution (75 g/L). After 2 h, the suspension was centrifuged (5000 rpm for 5 min) and measured with a spectrophotometer at 760 nm wavelength. The calibration curve was made with respect to gallic acid.

Capsule stability testing

The capsules were stored at the temperature of 25 ± 2°C with 60 ± 5% relative air humidity (subsequently – environment A), and at 30 ± 2°C with 70 ± 5% relative air humidity (subsequently – environment B). Testing was performed after 6, 9, and 12 months of capsule storage in plastic containers in the environment A and the environment B. Measurements were performed on capsules from different parts of the plastic container – the superficial, the middle and the lower parts.

Evaluation of loss of drying

The loss of drying (loss of weight through drying) of powder, granules, and pellets was evaluated using the moisture analyzer (KERN MLS, Germany). Two g (with 0.001 g accuracy) of the studied sample was dried at the temperature of 100-105°C until a constant weight was reached. The result was the loss of weight through drying (%).

Statistical analysis

Data are presented as the means ± SD. Statistical analysis was performed by one-way analysis of variance (ANOVA), two-way ANOVA, and repeated measures ANOVA followed by Dunnett's and Bonferroni's *post hoc* tests. Correlation between the studied values was evaluated by calculating Spearman's correlation coefficient. The relationship between the studied values was determined by applying linear regression analysis. The level of significance was set at $p < 0.05$. Statistical analysis was conducted by using the statistical software package SPSS 19.

RESULTS

Baseline capsule dissolution test

In the first experiments, the baseline dissolution testing of the compositions of capsules presented in Table 1 were performed. The dissolution of capsule fillings was tested in two media (pH 1.2 and water), evaluating the maximal released amount of phenolic compounds.

In the next step, the dissolution medium pH 1.2 was selected in order to reach the testing conditions *in vitro* similar to those *in vivo*. To confirm the selec-

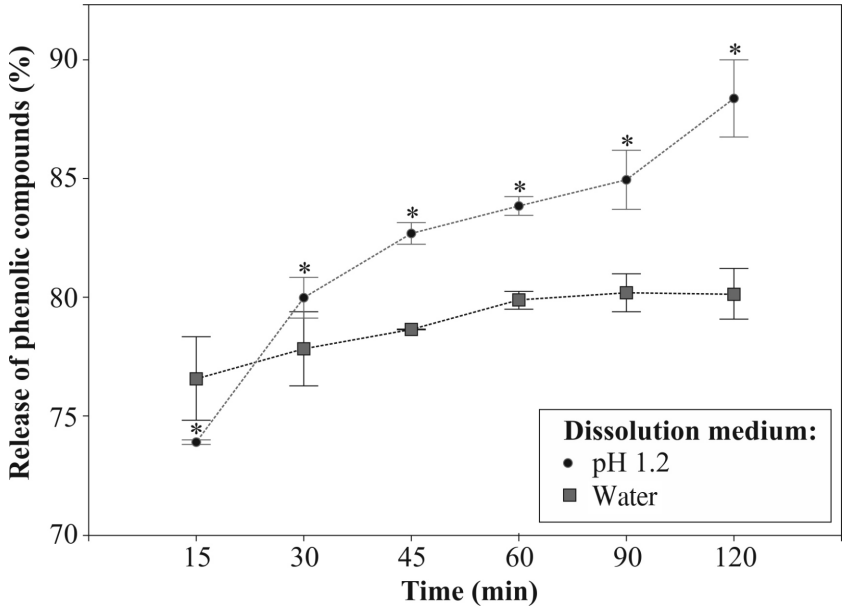

Figure 1. Pellet's dissolution test *in vitro* model, n = 5; *p < 0.05 vs. dissolution medium - water

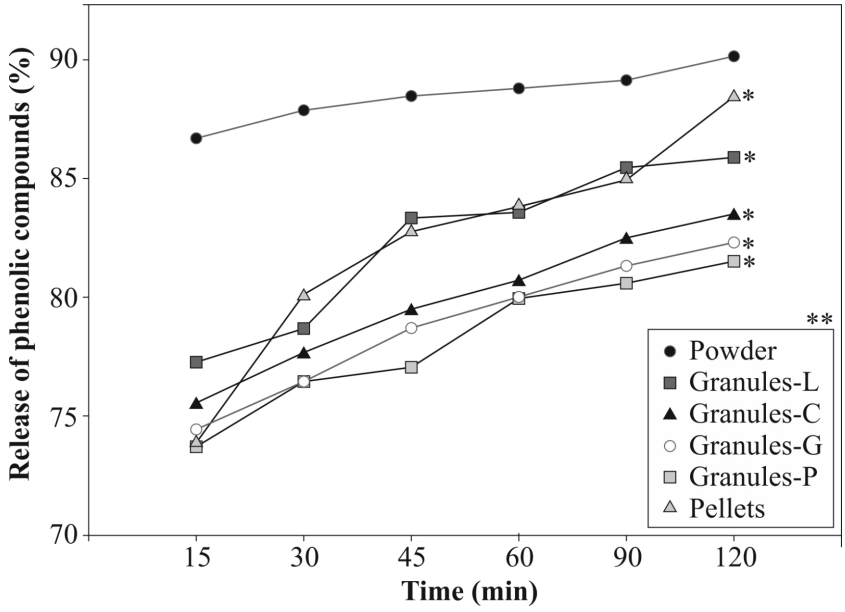

Figure 2. Baseline dissolution test *in vitro* model. Dissolution medium pH 1.2; * p < 0.05 vs. control (powder). ** The composition of capsule fillings is provided in Table 1

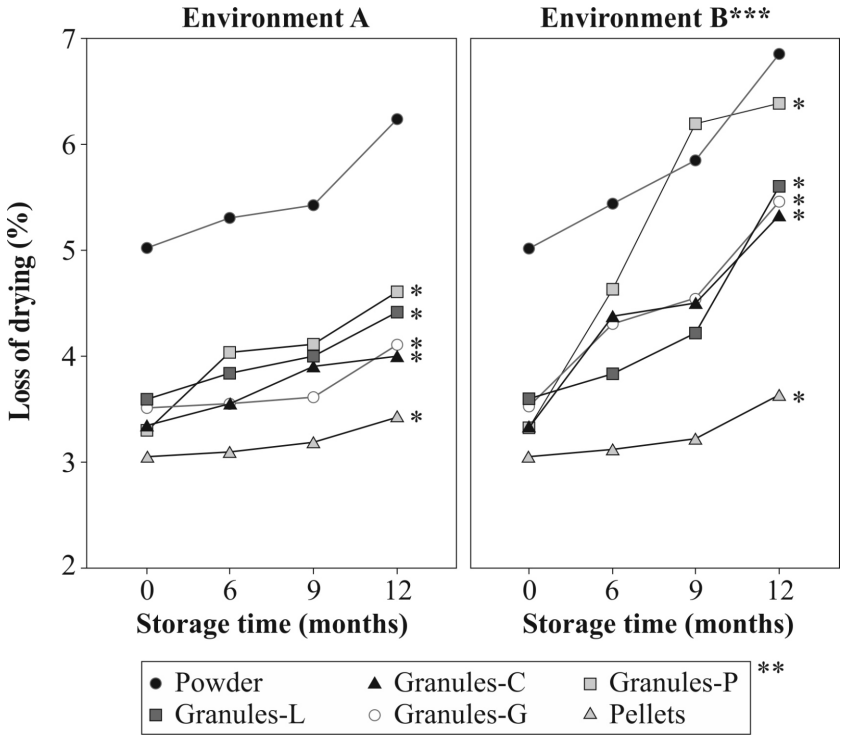

Figure 3. Changes in the loss of drying of capsule fillings in long-term storage conditions. Environment A: 25 ± 2°C, 60 ± 5% relative air humidity; environment B: 30 ± 2°C, 70 ± 5% relative air humidity. *p < 0.05 vs. baseline (0 months) and vs. control (powder). ** The composition of capsule fillings is provided in Table 1. *** p < 0.05 vs. environment A

tion of the medium, a 2-h monitoring of release of phenolic compounds from the pellet-filled capsules in different media (pH 1.2 and water) were conducted (Fig. 1). A uniform release of phenolic compounds was observed in the studied media. The dissolution test was performed for 120 min because the whole medicinal preparation usually stays in the stomach for up to 2 h. The obtained results showed that the greatest amount of the active ingredients was released in the pH 1.2 medium, compared to the water medium. Between 90 and 120 min, by 8.21% more phenolic compounds were released in the pH 1.2 medium, compared to the water medium (88.77 ± 1.01% *vs*. 80.56 ± 0.97%).

Further testing aimed at the baseline release of active substance in capsules with different fillings (Fig. 2). Powder-filled capsules (for the composition, see Table 1) were the control group. The testing showed that all groups between 90 and 120 min released lower amounts of phenolic compounds, compared to the control. The lowest difference was observed in pellet-filled capsules – the amount of the active ingredients released was by 1.75% lower than that in the control capsules (88.32 ± 0.53 *vs*. 90.07 ± 0.06), while the greatest difference was observed in capsules filled with granules-P – by 8.59% less phenolic compounds released, compared to the control capsules (81.48 ± 0.11 *vs*. 90.07 ± 0.06). The data for the baseline release of the active substances showed that after 45 min, the amount of the released phenolic compounds exceeded 75% in all the tested groups (Fig. 2).

Evaluation of capsule stability

The association between moisture content in the capsules and the time of their disintegration

The stability of capsules with different fillings was evaluated in different storage conditions: at the temperature of 25 ± 2°C with 60 ± 5% relative air humidity (subsequently – environment A), and at 30 ± 2°C with 70 ± 5% relative air humidity (subsequently – environment B).

During the study, the change in moisture content in capsules with different fillings (see Table 1) in long-term storage conditions (6, 9, and 12 months) in the environment A and the environment B (Fig. 3) were evaluated. After 12 months, all cap-

sule groups in the environments A and B demonstrated a statistically significant change in moisture content, compared to the baseline value. The greatest change in moisture content was observed in capsules filled with granules-P: in the environment A, the moisture content after 12 months increased by 1.3%, compared to baseline, and in the environment B – by – 3.08%, compared to baseline. Pellet-filled capsules demonstrated lesser changes in moisture content. In the environment A, moisture content after 12 months increased by 0.39%, compared to baseline, and in the environment B – by 0.59%. No statistically significant difference was found in moisture content change in pellet-filled capsules during measurements after 6 and 9 months in environments A and B. After 12 months, moisture content in pellet-filled capsules in the environment B was by 0.2% higher, compared to the environment A. In all groups, moisture content values statistically significantly differed from those in the control samples (powder), and moisture content in environments A and B were lower than those in the control samples (powder). Capsules filled with granules-P were an exception – the moisture content after 9 months in the environment B was higher than that in the control sample (powder).

We hypothesized that moisture content in capsules affected the capsule disintegration time due to the shell of the capsule becoming more resistant to disintegration in physiological media. Changes in disintegration time of the same capsule groups in long-term storage conditions (after 6, 9, and 12 months) (Fig. 4) were evaluated. After 12 months, the disintegration time in all capsule groups statistically significantly differed from that in the control sample (powder). The greatest difference (4 min) from the control sample (powder) was observed in pellet-filled capsules, and the lowest, yet statistically significant difference (2.67 min) – in capsules with granules-G. The greatest difference in disintegration time after 12 months, compared to the control sample (powder), was observed in pellet-filled capsules (7 min), and the smallest - in capsules filled with granules-G (2 min) and in capsules filled with granules-P (3 min). No statistically significant difference was found between capsules filled with granules-G and P concerning their disintegration time, yet the difference was significant when comparing to the disintegration time of the control sample.

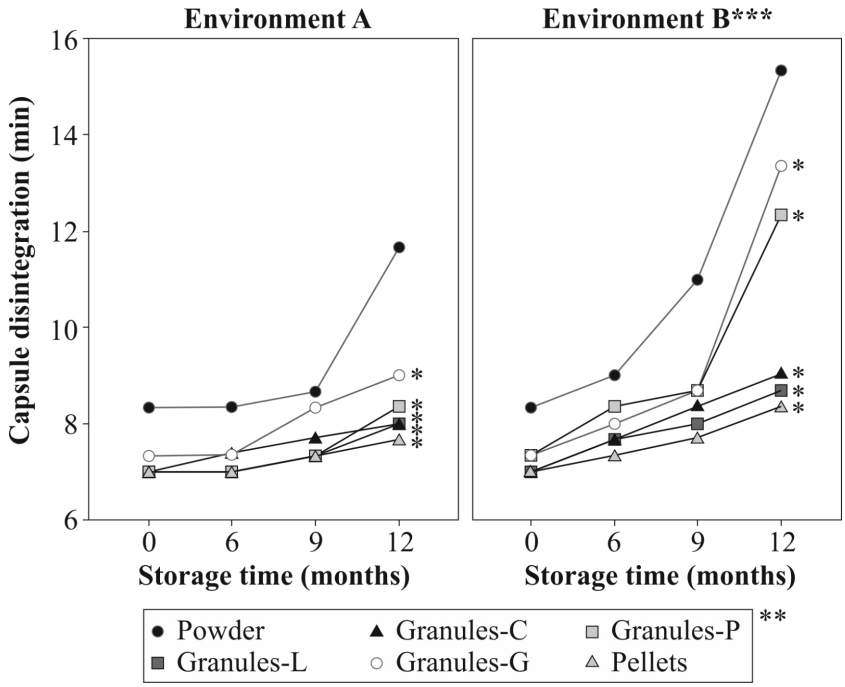

Figure 4. Changes in capsule disintegration time in long-term storage conditions. Environment A: 25 ± 2°C, 60 ± 5% relative air humidity; environment B: 30 ± 2°C, 70 ± 5% relative air humidity. *p < 0.05 vs. baseline (0 months) and vs. control (powder). ** The composition of capsule fillings is provided in Table 1

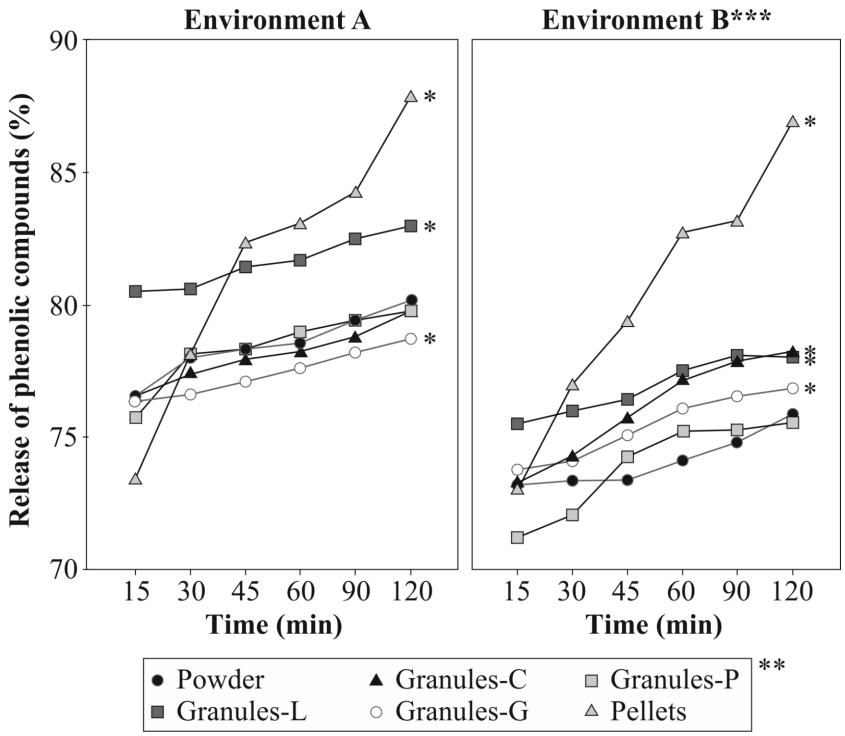

Figure 5. Release of phenolic compounds *in vitro* (after 12 months). Environment A: 25 ± 2°C, 60 ± 5% relative air humidity; environment B: 30 ± 2°C, 70 ± 5% relative air humidity. *p < 0.05 vs. baseline (0 months) and vs. control (powder). ** The composition of capsule fillings is provided in Table 1. *** p < 0.05 vs. environment A

Correlation and regression analysis was applied in order to evaluate the association between the moisture content in the capsules and the capsule disintegration time in long-term storage conditions. A statistically reliable ($p < 0.001$) very strong correlation ($r = 0.834$) was detected between the moisture content and the time of disintegration. On the basis of the regression analysis, a linear relationship was determined between the moisture content and the time of disintegration ($R^2 = 0.641$, $y = 1.3589x + 2.3536$, $p < 0.001$).

Release of phenolic compounds under long-term storage conditions

We hypothesized that the moisture content in the capsules, the capsule disintegration time, and release of phenolic compounds may be inter-related. In order to detect the associations, phenolic compounds release from the same groups of capsules during the dissolution testing performed under the same storage conditions (environments A and B), and at the same storage intervals (after 6, 9, and 12 months) as in the previously described testing were evaluated. The duration of the testing was 120 min.

After 6 months of long-term storage conditions, in the environment A, lower amounts of phenolic compounds during the period from 90 to 120 min were released from all groups of capsules, compared to the control sample (powder). In the environment B, only pellet-filled capsules released greater amounts of phenolic compounds, compared to the control sample (powder), whereas in other capsule groups, this amount was lower than that in the control sample (no graphic representation of the findings is provided).

After 9 months of long-term storage conditions, in the environment A, lower amounts of phenolic compounds during the period from 90 to 120 min were released from all groups of capsules, compared to the control sample (powder), while in the environment B, only pellet-filled capsules released greater amounts of phenolic compounds, compared to the control sample (powder). In the environment B, this difference in pellet-filled capsules that was 1.83% after 6 months, increased to 4.83% after 9 months. Compared to measurements performed

after 6 months, no statistically significant difference after 9 months in the environment A was found for the control capsules, capsules filled with granules-G, granules-P, or pellet-filled capsules, and in the environment B – for capsules filled with granules-C or pellet-filled capsules (no graphic representation of the findings is provided).

The results of the testing conducted after 12 months in different long-term storage conditions (environments A and B) are presented in Fig. 5. In the environment A, during the period from 90 to 120 min, no difference between capsules filled with granules-P, granules-C, or the control capsules was found. The release of phenolic compounds in capsules filled with granules-L and pellet-filled capsules exceeded that registered in the control (powder-filled) capsules, while phenolic compounds release from capsules filled with granules-G was lower than that in the control capsules (Fig. 5). Similarly, in the environment B, no difference was found between capsules filled with granules-P and the control (powder-filled) capsules, while the phenolic compound release from other capsule groups exceeded that registered in the control (powder-filled) capsules (Fig. 5). The greatest difference in the phenolic compound release, compared to the control (powder-filled) capsules, was observed for the pellet-filled capsules – the difference in the environment A was 7.61%, and in the environment B - 11%. A statistically significant difference in the phenolic compound release was found with respect to the storage conditions – the release was lower in the environment B than in the environment A.

DISCUSSION

Dry herbal extracts usually are highly hygroscopic powders, and moisture content in herbal extracts may determine increased microbiological pollution, development of fungi, or hydrolysis of the active ingredients (20, 21). This is the main problem identified by researchers who try to develop safe, effective, and stable solid herbal preparation forms with good consistency (tablets, pellets, capsules. etc.) (22). The powder of dry herbal extracts as the control sample was selected to evaluate the effect of technological operations on the release of the active ingredients, the moisture content in the capsules, and the capsule disintegration time.

After 12 months, the moisture content in capsules with the control sample (the powder of dry herbal extract) in environments A and B increased to, respectively, 6.20 and 6.85%. In pellet-filled capsules, the moisture remained stable – no differences between measurements after 6 and 9 months were found, and after 12 months, the moisture content was the lowest, compared to other capsule groups (between 3 and 4%). The testing proved the hypothesis that moisture content in the capsules affected capsule disintegration time due to the coating of the capsule becoming more resistant to disintegration in the physiological media. Statistically reliable ($p < 0.001$) very strong positive correlation ($r = 0.834$) between moisture content in the capsules and the capsule disintegration time was found. The regression analysis showed a statistically reliable ($p < 0.001$) linear correlation between moisture content in the capsules and the capsule disintegration time ($R^2 = 0.641$). Other researchers have indicated that the principal cause of the increase in the capsule disintegration time with increasing moisture content in the capsules is aggregation of the filling substances due to water absorption, resulting in altered homogeneity of the filling - and thus slower release of the active ingredients (8). Thus, the higher the water content in the capsules, the longer the capsule disintegration time.

The baseline release of phenolic compounds in the pH 1.2 medium demonstrated that the peak was most rapidly achieved in capsules filled with the smallest particles – i.e., the control samples (powder). Hamashita et al. found that smaller particles have a greater surface area, which improves fluid penetration into the particle, and consequently, the substances are more readily released during the dissolution test (23). On the other hand, studies with dry herbal extracts showed that these extracts are highly susceptible to moisture already during storage, which may result in the disintegration of the active substances (17, 21). In our study, after 12 months, the release of the active ingredients from the control (powder-filled) capsules dropped statistically significantly, compared to the baseline, which might be related to the increased moisture content in these capsules. Pellet-filled capsules demonstrated the most stable phenolic compound release. These capsules showed a stable and the greatest cumulative release of phenolic compounds in environments A and B after 6, 9, and 12 months, compared to other capsule groups. After 12 months, phenolic compound release from pellet-filled capsules in the environment A dropped by 0.54%, and in the environment B – by 1.45%, compared to baseline values. These changes were the lowest, compared to other capsule groups. In the environment B, phenolic compounds release was lower than that in the environment A, which means that environmental conditions (humidity and temperature) significantly affected the release of the active ingredients. Some

other authors have found that the storage of the capsules in higher-humidity conditions may result in hydrolysis in the herbal preparations; such probability increases with increasing temperature because temperature acts as the catalyst of chemical reactions (8, 21). Release of phenolic compounds statistically reliably ($p < 0.001$) correlated with moisture content in the capsules ($r = -0.484$) and the capsule disintegration time ($r = -0.449$, $p < 0.001$). Also, a negative correlation was found indicating that increasing moisture content in capsules and longer capsule disintegration time were associated with a reduced release of phenolic compounds.

According to the requirements of the European Pharmacopeia (Eur. Ph.), the capsules should release more than 75% of the active substances. During our study, the control (powder-filled) and capsules filled with granules-P failed to meet these requirements; these capsules during the testing accumulated too much moisture, which might have negatively affected capsule disintegration and release of phenolic compounds. In our previous study (11), where the fillings for these studied capsules were prepared, the results of the microscopic analysis showed that powder granulated with ethanolic povidone solution (granules-P) contained the greatest portion of fine particles (10%). Capsules of this group demonstrated the greatest increase in moisture content (humidity), which may have been due to the characteristic ability of the dry herbal extract particles to absorb moisture. The baseline release of phenolic compounds in capsules filled with granules-P was the lowest, compared to other capsule groups, and after 12 months capsules filled with granules-P did not meet the requirements of the Eur. Ph. (i.e., released less than 75% of phenolic compounds within 45 min). The finest particles – powder (the control sample) released the active substances well, yet under long-term storage conditions accumulated too much moisture, and active substance release suddenly dropped (after 12 months, less than 75% of the active substances was released after 45 min). The granules were larger, more stable, and not that susceptible to moisture, and thus their dissolution test in long-term storage conditions was good. In pellets, the release of the active substances was gradual, was uniform irrespectively of the storage conditions, and met the Eur. Ph. requirements.

CONCLUSIONS

The study showed that moisture and temperature changes arising during the storage of the preparation have a negative impact on the release of phenolic compounds from herbal capsules. Pellet-filled capsules demonstrated a uniform and stable release of the active ingredients in different long-term storage conditions, which indicates that the technology of the preparation of dry herbal extracts significantly affects the stability of the active substances.

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