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Full Length Research Paper

The investigation of phenolic compounds and technological properties of *Leonurus, Crataegus* and *Ginkgo* extracts

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The aim of this study was to prepare the formulation of herbal extract mixture in ratio - *Ginkgo*:*Leonuri*:*Crataegi* extracts (1:5:6) with excellent technological properties and identify the phenolic compounds, flavones and flavonols. The flowability study showed that excipients (Prosolv HD90, mannitol+colloidal silicon dioxide and microcrystalline cellulose+colloidal silicon dioxide) reduced powder dustiness and improved powder flow rate index, yet the evaluation of bulk density, tap density, Carr's index, Hausner ratio, and angle of repose values showed that the herbal powder mixture did not demonstrate excellent powder flow rate index. Wet granulation helped to improve the herbal powder flow rate index by 1.7 - 2.0 fold, control powder density, and control the tendency of powders to segregate. The results showed that different binder solutions had different effect on powder flow rate index. Granulation of the maidenhair tree, hawthorn, and motherwort extract powder using a natural and related binder solution - motherwort extract ethanolic solution - resulted in the lowest particle size variation. In addition, natural binder solutions had different effects on powder flow rate index and particle size, and provided the powder with better technological properties than chemical binder solutions such as ethanol or ethanolic povidone solution did. The amount of phenolic compounds, flavones and flavonols identified in the mixture of three herbal extracts determines its antioxidant activity.

Key words: Phenolic compounds, flowability, *Ginkgo biloba*, *Leonurus cardiaca*, *Crataegus monogyna*.

INTRODUCTION

Appropriate selection and optimization of the technological process requires the evaluation of the physical and technological properties of substances or their mixtures that are being encapsulated (Goutte et al., 2002). For the pharmaceutical manufacturing process, powder flowability is a very important factor (Zgoda et al., 2009). Herbal extracts are frequently poorly compressible and very hygroscopic powders with poor powder flowability. Frequent powder flowability is improved by adding excipients (Wang et al., 2009). The selection of excipients – fillers and binding solutions, not only determines the success of encapsulation but is also one of the major factors determining the stability of the capsules and their ability to disintegrate. Granulation, mostly the wet, is used to improve the technological properties of herbal extracts because this improves physical and rheologic properties of the powder (Giry et al., 2006), and helps to achieve acceptable content uniformity (Kato and Takeno, 2006). The most important physical properties of granules are: particle size and morphology, and solubility (Giry et al., 2006). The granulating fluid has been found to affect granule size (Uribarri et al., 2003). There is evidence showing that the solubility of the raw materials in the granulating fluid also affects the properties of the granules (Giry et al., 2006). Giry found that the nature of the granulating fluid modified granule distribution by size (Giry et al., 2009).

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Dry extracts of maidenhair tree (*Ginkgo biloba),* motherwort *(Leonurus cardiaca)* and hawthorn *(Crataegus monogyna)* were selected for the experimental studies. Hawthorn and motherwort preparations are widely used in treating heart disorders, and maidenhair tree preparations in treating circulatory disorders (Bernatoniene et al., 2009; Bernatoniene et al., 2008; Huerta et al., 2008; Petkeviciute et al., 2010). These plants have a positive effect on the functions of the cardiac muscle, and scavenge free radicals (Wagner and Ulrich-Merzenich, 2009; Cheng et al., 2009; Matkowski et al., 2008). Literature provides data indicating that a complex mixture of herbal extracts has a greater biological effect than individual extracts do (Wagner and Ulrich-Merzenich, 2009), and therefore we decided to design a solid dosage form, a preparation improving the functioning of the cardiovascular system. However, we failed to find any literature data about technological properties of these herbal extracts, and thus the aim of our study was: to prepare the formulation of herbal extract mixture in ratio – *Ginkgo* extract: *Leonuri* extract: *Crataegi* extract (1:5:6) with excellent technological properties and identified the phenolic compounds, flavones and flavonols.

MATERIALS AND METHODS

Chemicals

The chemicals were available commercially and were used as received: gallic acid, Folin-Ciocalteu reagent (Fluka), quercetin (Sigma), Microcrystalline cellulose (Alfa Aesar), Prosolv HD90 (JRS Pharma LP), mannitol (Bioeksma), Colloidal Silicon Dioxide (Aerosil 200, CPC Wolfgang Muhlbauer), dry *Hawthorn extract 4:1* (*Naturex*), dry G. *biloba extract 5:1 (Spain),* dry *Motherwort extract 4:1 (Spain).* All other chemicals used for analysis were of analytical grade.

Determination of phenolic compounds content

The total content of polyphenols was determined by a modified Folin-Ciocalteu colorimetric method. 0.7 ml of the test solution in dimethylsulphoxide (DMSO) (1 mg/ml) was transferred to a 10-ml volumetric flask, the Folin-Ciocalteu reagent (400 µl) was added, and after 3 min, sodium carbonate (Na_2CO_3) solution (75 g/l) was added. After 2 h, the suspension was centrifuged (5000 rpm, 5 min), and the absorbance of the supernatant was measured at 760 nm. The calibration curve was plotted versus concentrations of gallic acid. The results were expressed as a gallic acid equivalent (GAE) per 100 g of dry extract weight.

Determination of flavone and flavonol content

Flavone and flavonol contents were analyzed using the colorimetric method. 1.0 ml of the test solution in DMSO (1 mg/ml) was transferred to a 10-ml volumetric flask, 200 µl of aluminum chloride (60 g/l) in water was added, and after 3 min, methanol was added. After 30 min, the absorbance of solution was measured at 425 nm. The calibration curve was plotted versus concentrations of quercetin. The results were expressed as a quercetin equivalent (QE) per 100 g of dry extract weight.

Liquid chromatography

Liquid chromatography system HP1100 (Agilent Technologies) was equipped with autosampler, quaternary pump, and diode-array detector. The separation was carried out with a Supelcosil ABZ+Plus column (150×4.6 mm, 3 µm particle size). The mobile phase consisted of 90% 40 mM HCOOH (A) and 10% acetonitrile (B) used with gradient 0% (A) and 100% (B) within 35 min. The mobile phase flow was 1.0 $ml/Fmin^{-1}$, while column temperature was 40°C. Spectrum was scanned in the range of 200 - 600 nm, and for chromatographic analysis, wavelength of 254 nm was selected. Ten microliters of the sample in DMSO (1 mg/ml^{-1}) was injected.

Powder evaluation

Loss of weight on drying

Wastage of powder and granules was measured using moisture analyzer "KERN MLS" (Germany). 2 g (with 0.001 g accuracy) of the studied sample was dried at the temperature range of 100 - 105°C until stable mass was obtained, the result being loss of mass (%) during the drying process. A triplicate test was run for each sample.

Bulk density and tap density

They were determined on the basis of the European Pharmacopoeia 01/2005:20242.

Carr's index

The tap density apparatus (lift height 3 mm, tapping frequency 150 taps/min) was used to determine Carr's index. The tared 250-ml measuring cylinder was filled with test material to 100 ml, and the volume and weight of the material were noted. With minimal disturbance to the measuring cylinder, it was transferred to the tap density apparatus. Carr's index = (Tap density - Bulk density)/Tap density × 100 Hausner ratio = Tap density/ Bulk density

Angle of repose

Measurements were performed using the device "ERWEKA AG" (Germany). The static angle of repose, *a,* was measured using the fixed funnel and free standing cone method (Giry et al., 2009).

Flow rate index

Flow rate index was determined using the device "ERWEKA AG" (Germany), by applying 20 s vibration (Giry et al., 2006; Bernatoniene et al., 2009). The flow rate index was calculated as follows:

$$F = \frac{m}{t - 20},$$

Where F = flow rate index (g/s); m = the mass of dry extracts, dry extract mixture, or granules (g); t = total time of the experiment (s);

Table 1. Total content of polyphenols, flavones and flavonols in studied extracts*.

Sample	Total content of phenolic compounds [GAE g/100 g]	Total content of flavones and flavonols [QE g/100 g]	Quercetin [mg/g]	Rutin [mg/g]
Dry hawthorn extract (4:1)	26.4 ± 0.9	1.29 ± 0.07	< 1	< 1
Dry maidenhair tree extract (5:1)	43.2 ± 1.3	9.56 ± 0.11	67.0 ± 2.1	3.9 ± 0.2
Dry motherwort extract (4:1)	4.8 ± 0.6	0.37 ± 0.04	< 1	< 1
Dry maidenhair tree, hawthorn, and motherwort extract mixture (1:6:5)	23.3 ± 1.2	1.96 ± 0.09	3.1 ± 0.1	< 1

*The values are mean ± SD, n = 3.

and 20 = duration of vibration (s).

Formulation of herbal extract mixture and fillers

Thirty-four samples of herbal extracts with or without fillers were prepared. The first group of samples was pure extracts: dry hawthorn extract, dry maidenhair tree extract, dry motherwort extract. The second group samples were aimed towards formulation of extract mixture in ratio - *Ginkgo* extract:*Leonuri* extract:*Crataegi* extract (1:5:6). The rest of the fillers were selected Prosolv HD 90, microcrystalline cellulose: colloidal silicon dioxide (99.5:0.5), mannitol and colloidal silicon dioxide (99.5:0.5). Following this technique, the powder mixture of the drug and excipient was blended within 5 min in the mixer (Tefal Kaleo, France).

Formulation of granule from herbal extracts

The prepared powder mass (51.4% of herbal extract mixture in ratio - *Ginkgo* extract:*Leonuri* extract:*Crataegi* extract (1:5:6) and 48.6% Prosolv HD90) was mixed in a granulator (PM 220/110, Israel) and than wetted with binding solutions: 0.5 - 3% ethanolic solution of povidone in 70% ethanol; 1% ethanolic solution of maidenhair tree extract in 70% ethanol, 0.5% ethanolic solution of Hawthorn extract in 50% ethanol; 1% ethanolic solution of motherwort extract in 40% ethanol; ethanolic solution of extract mixture in equal parts. The well-moisturized mass was granulated by forcing it through a sieve with mesh diameter of 1 mm. The granules were spread and dried at the temperature of 40°C until the wastage of the granules was ca. 3 - 4%. The dried granules were forced through a sieve with 1-mm mesh, and their wastage was evaluated again.

Particle size analysis

Particle size was evaluated under an optic microscope (Germany) by measuring 500 herbal granules produced with different binding solutions. The preparations were produced by taking random granules from different sites of granulation, trying to include particles of various sizes and to ensure maximum accuracy of the ratio between the smaller and the larger measured particles. The preparations were observed under passing light and under ×40 magnification. Using the computer software, we distributed the particles into groups according to their size, and calculated their distribution and dispersion degree.

Statistical analysis

Data are presented as means ± S.E.M. Non-parametric methods were applied for making inferences about data. Differences between mean values in dependent groups were tested using Wilcoxon matched pairs test. Differences between mean values in independent groups were tested using non-parametric Kruskal-Wallis test with Dunn's post-hoc evaluation. $P < 0.05$ was taken as the level of significance. Statistical analysis was performed by using the software Statistica 1999, 5.5 StatSoft Inc., USA.

RESULTS AND DISCUSSION

In the first series of studies we analyzed technological properties of herbal extracts and their mixtures, important for the production of various pharmaceutical preparations, e.g. capsules or tablets. Flow testing of dry herbal extracts and fillers was performed using Carr's index (CI), Hausner ratio (HR), Flow Rate index (FRI), and angle of repose (AR) (Table 2). Literature indicates that Carr's index is an indirect measure of bulk density, size and shape, and is closely related to Hausner ratio. "Excellent" flow is when Carr´s index is between 1 - 10, and HR between 1.00 - 1.11; "good" flow is when CI is between 11 - 15, and HR: 1.12 - 1.18; "fair" flow is when CI: 16 - 20, HR: 1.19 - 1.25; "passable" flow when CI: 21 - 25 and HR: 1.26 - 1.34; "poor" flow when CI is between 26 - 31 and HR: 1.35 - 1.45; "very poor" flow when CI is between 32 - 37 and HR: 1.46 - 1.59, and "very very poor" flow is when HR > 38 and CI > 1.60 (Mohamed et al., 2007). Based on the obtained results, the flow of maidenhair tree, hawthorn, and motherwort

Table 2. Flow characterization of herbal extract and fillers*.

Material	Bulk density (g/ml)	Tap density (g/ml)	Carr's index	Hausner ratio	Angle of repose (°)	Flow rate Index (g/s)
Dry motherwort extract	0.46±0.01	0.62±0.02	25.27±2.35	1.34±0.04	35±0.9	4.70±0.26
Dry maidenhair tree extract	0.47±0.01	0.70±0.02	33.71±1.90	1.51±0.04	>66	0.00±0
Dry hawthorn extract	0.44±0.02	0.74±0.03	41.29±0.44	1.70±0.01	46±0.7	1.30±0.08
A mixture of herbal extracts	0.47±0.01	0.67±0	29.38±1.63	1.4±0.03	41±0.58	1.81±0.03
Extract mixture with Prosolv HD90	0.51±0.01	0.68±0.02	24.36±4.16	1.27±0.07	35±0.30	3.85±0
Extract mixture with MCC+SiO_2	0.46±0	0.61±0.03	27.3±0	1.34±0.08	38±0.04	2.50±0
Extract mixture with mannitol+SiO_2	0.56±0	0.74±0.03	25±3.21	1.32±0.06	36±0.50	3.34±0.22

*The values are mean ± SD, n = 4 - 5.

extracts and their mixture was between "passable" and "very very poor": CI was between 25.00 and 41.3, and HR between 1.34 and 1.70 (Table 2). Powder flowability is frequently improved with the following excipients: Prosolv HD90 containing microcrystalline cellulose and colloidal silicon dioxide (Marczyński et al., 2007), mannitol, colloidal silicon dioxide, and others (Javadzadeh et al., 2009) and angle of repose (AR) (Table 2). Literature indicates that Carr's index is an indirect measure of bulk density, size and shape, and is closely related to Hausner ratio. "Excellent" flow is when Carr´s index is between 1 - 10, and HR between 1.00 - 1.11; "good" flow is when CI is between 11 - 15, and HR: 1.12 - 1.18; "fair" flow is when CI: 16 - 20, HR: 1.19 - 1.25; "passable" flow when CI: 21 - 25 and HR: 1.26 - 1.34; "poor" flow when CI is between 26 - 31 and HR: 1.35 - 1.45; "very poor" flow when CI is between 32 - 37 and HR: 1.46 - 1.59, and "very very poor" flow is when HR > 38 and CI > 1.60 (Mohamed et al., 2007). Based on the obtained results, the flow of maidenhair tree, hawthorn, and motherwort extracts and their mixture was between "passable" and "very very poor": CI was between 25.00 and 41.3, and HR between 1.34 and 1.70 (Table 2). Powder flowability is frequently improved with the following excipients: Prosolv HD90 containing microcrystalline cellulose and colloidal silicon dioxide (Marczyński et al., 2007), mannitol, colloidal silicon dioxide, and others (Javadzadeh et al., 2009). Therefore, the flowability of the powder of the herbal extract mixture was improved by using different fillers: Prosolv HD90, mannitol+colloidal silicon dioxide mixture, and microcrystalline cellulose+colloidal silicon dioxide mixture. The amount of herbal extract mixture (*Ginkgo* extract:*Leonuri* extract:*Crataegi* extract (1:5:6)) was 51.4% and the amount of excipients 48.6 %. The measurements of bulk density showed that these excipients improved the flow rate index of the herbal extract mixture to "passable": CI decreased from 8% (after adding microcrystalline cellulose and silicon dioxide) to 20% (after adding Prosolv HD 90) (Table 2).

Studies of the flow rate index showed significant differences between different herbal extract powders. The flow rate index of hawthorn extract was 72% ($p < 0.05$) lower than that of motherwort extract, and maidenhair tree extract exhibited no flowability. Meanwhile, the flow rate index of the mixture (maidenhair tree, hawthorn, and motherwort extracts) was 1.81 g/s, that is, by 61% lower than that exhibited by the dry motherwort extract. After adding excipients, the flow rate index of the herbal extract mixture statistically and significantly increased by 1.38 fold (mannitol+colloidal silicon dioxide), by 1.84 fold (microcrystalline cellulose+colloidal silicon dioxide), and 2.13 fold (Prosolv HD90), compared to the initial flowability of the herbal extract mixture (Table 2).

Powder flow is characterized by the angle of repose (Aulton, 1998). Based on this, the angle of repose of the maidenhair tree extract was "very very poor", that is, over 66° (Table 2). The angle of repose of the herbal extract mixture with excipients decreased by 7 – 15%, compared to that of the initial herbal extract mixture, and may be characterized as "good". This study also showed that the powder of the mixture of the dry extracts of maidenhair tree, hawthorn, and motherwort exhibited dustiness. Excipients - Prosolv HD90, mannitol+colloidal silicon dioxide and microcrystalline cellulose+colloidal silicon dioxide – reduced dustiness and improved flowability, but the evaluation of the bulk density, tap density, Carr's index, Hausner ratio, and angle of repose values showed that the mixture did not demonstrate excellent flowability. The obtained findings showed relationships and similarities between powder flow and the Carr's index.

Literature contains data indicating that wet granulation improves physical properties of the powder (Giry et al., 2006; Giry et al., 2009). Among the studied excipients, Prosolv HD90 most significantly improved the flow rate index of the herbal extract mixture powder, and therefore we further decided to analyze the effect of wet granulation on the technological properties of this powder mixture. The binding liquids used were ethanol (70, 80, and 96%), povidone ethanolic (0.5, 1, 2, and 3%) solutions, and ethanolic solutions of herbal extract mixture (motherwort, hawthorn and maidenhair tree extracts). We evaluated the effect of the binding liquid on the flowability of the mixture, particle size, and fractional

Table 3. The effect of the granulating fluid on the technological properties of the granules*.

Granulation fluid	Bulk density (g/ml)	Tap density (g/ml)	Carr's index	Hausner ratio	Angle of repose (°)	Flow rate index (g/s)
1% ethanolic solution of motherwort extract	0.44±0.02	0.46±0.04	4.0±0.02	1.04±0.01	26±0.2	7.78±0.08
0.5% ethanolic solution of hawthorn extract	0.47±0.05	0.47±0.08	1.3±0.03	1.01±0.02	25±0.1	7.78±0.04
1% ethanolic solution of maidenhair tree extract	0.44±0.04	0.51±0.06	12.7±0.05	1.14±0.04	35±2.1	6.75±0.20
Ethanolic solution of extract mixture	0.41±0.04	0.48±0.05	14.6±0.05	1.17±0.08	32±1.4	7.41±0.12
4% ethanolic solution of povidone	0.41±0.03	0.45±0.08	7.0±0.07	1.1±0.09	27±1.3	7.45±0.11

*The values are mean ± SD, n = 3 – 4.

composition.

Literature also contains data indicating that non-aqueous binder ethanol is used in order to prevent agglomeration, while povidone aqueous solution facilitates the nucleation process in the granulation step, and the resulting granules are larger than those prepared with alcohol solution (Patel et al., 2008). For the nucleation and wetting of the studied mixture, we selected different binder solutions. The application of ethanol (70, 80, and 96%) and povidone ethanolic (0.5, 1, 2, and 3%) solutions as binders resulted in the highest granule flowability (data not provided), and the mixture did not bind as effectively as it did when using other binders – ethanolic solutions of motherwort, hawthorn, and maidenhair tree extracts and their mixture, and 4% povidone ethanolic solution (Table 3). The obtained results showed that different binder solutions had different effects on the powder flowability, yet in all the granulated powders, the flow rate index improved by 1.7 - 2.0 fold (Table 3), compared to that exhibited by the herbal extract powder mixture+Prosolv HD90 (Table 2). Granules produced using ethanolic solutions of motherwort, hawthorn, or povidone demonstrated "Excellent" flow: CI was 1.3 - 7, HR: 1.01 - 1.04 and the angle of repose <30. Powder obtained by granulating with maidenhair tree and herbal extract mixture demonstrated "fair" flow. Thus, these findings showed a statistically significant improvement in the flowability of the granulated powder. It is interesting to note that powder granulated with a related binder – ethanolic solutions of motherwort or hawthorn extract, as well as with 4% povidone solution demonstrated "excellent" flow rate index, but CI was between 1.8 and 5 fold (using, respectively, motherwort and hawthorn solutions as binders) lower than that demonstrated by powder granulated using a chemical solution, that is, povidone solution (Table 3). The quality of solvent in the binder solution statistically and significantly affected wetting and adhesive properties of the binder. The obtained results showed that wet granulation helped to improve herbal powder flow, to control powder density, and to control the tendency of powders to segregate.

There are scientific reports indicating that there is an interaction between particle size and shape, both influencing powder flow rate index (Lipsanen et al., 2008). Figure 1 presents the effect of binder solution on particle size. With respect to the recommended mesh diameters, the granules were distributed into 8 different size groups. Powders granulated using different binders demonstrated different distribution according to particle size (Figure 1). The results of microscopy showed that the greatest amount (10%) of fine particles was detected in powder granulated with povidone. According to the recommendations of the European Pharmacopoeia, the amount of particles smaller than 75 µm should not exceed 20%. When using povidone solution for granulation, the amount of particles 250.01 - 710.00 µm in size was 42%, when using maidenhair tree or hawthorn extract solutions as binders - 56%, when using motherwort extract solution - 89%, and when using extract mixture solution - 40%. When using motherwort extract solution as a binder, the particles were least scattered by their size - the amount of particles 75.01 - 250 µm in size was 5%, that is, by 5.6 fold lower, compared to that in powder granulated with povidone solution. The amount of particles whose size ranged between 710.01 and 2.800 µm was 6% (Figure 1). Teunou et al. found that the larger the particles, the smaller was the angle of repose, mainly because smaller particles tend to adhere much more strongly to each

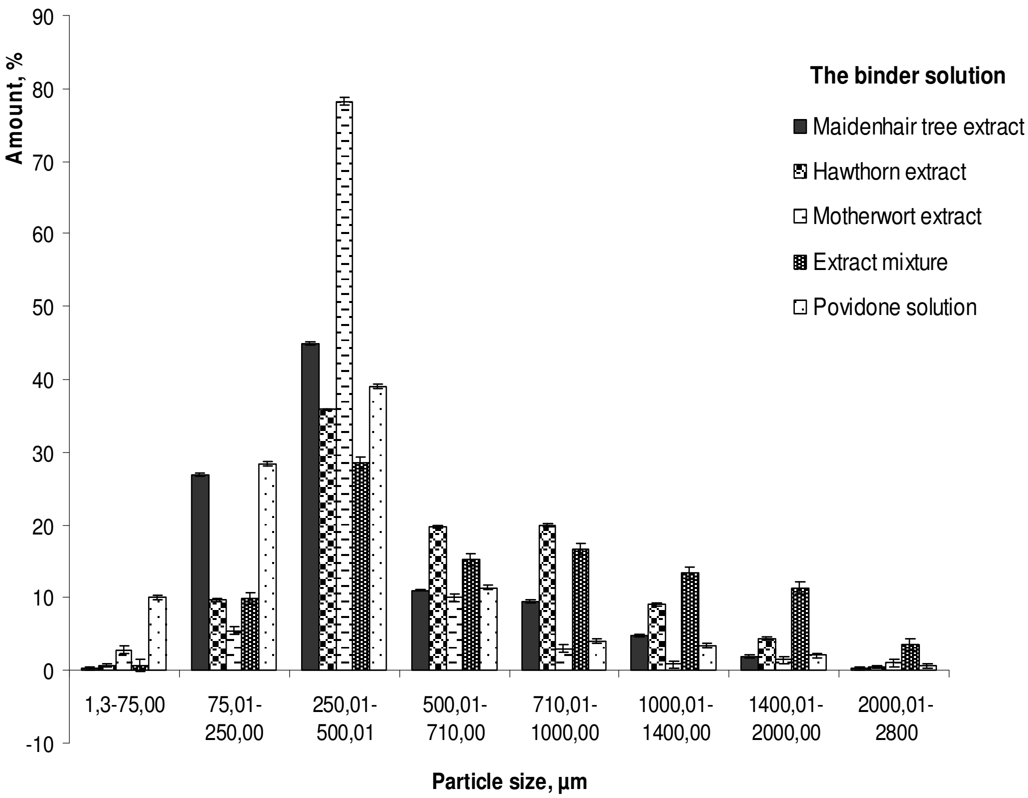

Figure 1. The influence of binder solution on the particle size of granules. The results are presented after measuring 500 granules.

other (Picker-Freyer and Brink, 2006). Our results showed that the angle of repose decreased with increasing flow rate index and decreasing Carr's index (Table 3). The greatest angle of repose was obtained by granulating the powder with maidenhair tree extract solution and extract mixture solution. The results of microscopy analysis confirmed that powder granulated with the aforementioned binder solutions was distributed in a wide range concerning particle size. Thus, our results suggest that particle size is related to the angle of repose. However, flowability of granules is determined not only by the particle size, but also by their shape, and therefore further studies should be oriented towards the effect of binder solutions on particle shape, evaluating Ferets, Martins, and projected area diameters.The determination of the total amount of phenolic, flavone and flavonol compounds showed that the extract of dry maidenhair tree (*Ginkgo*) contained the highest amount of these compounds: 43.2 ± 1.3 mg GAE g/100 g and 9.56 ±0.11 QE g/100 g, compared to other investigated extracts (Table 1). The content of phenolic compounds in motherwort extract was by 9 fold, and in hawthorn extract - by 1.6 fold statistically and significantly lower than that in the maidenhair tree extract. Flavone and flavonol content in the maidenhair tree extract was by 25 fold and 7 fold higher than in, respectively, motherwort and hawthorn extracts ($p < 0.05$). Scientific literature contains data indicating that the amount of phenolic compounds determines the antioxidant activity of preparations (Bernatoniene et al., 2009). Our previous studies in the DPPH$^{\bullet}$ and ABTS$^{\bullet+}$ reactions systems showed that fluid extracts of hawthorn, maidenhair tree and motherwort had the radical scavenging capacity (Bernatoniene et al., 2009). We also found that quercetin, rutin, and quercitrin in dose-dependent manner induced a partial uncoupling of oxidative phosphorylation by 10 - 100% (Trumbeckaite et al., 2007). Thus, the amount of phenolic compounds, flavones, and flavonols identified in the mixture of three herbal extracts determines its antioxidant activity.

Conclusion

These data suggested that wet granulation statistically significantly improved powder flow, which may be rapidly evaluated using tap powder densities. The granulation of the powder of maidenhair tree, hawthorn, and motherwort extract mixture using a related binder solution - ethanolic solution of motherwort extract, resulted in the lowest particle size variation. In addition, natural binder solution affected powder flow and particle size and provided powder with better technological properties than a chemical binder solution did.

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