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Technological Processing of Dried Powdered Rosehips to Tablets Through Wet Granulation

Original Paper

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Abstract The pseudo-fruits of Dog Rose are a rich source of L-ascorbic acid and several other active substances, which means their high supportive therapeutic potential. The study aimed to examine the impact of the chosen technological procedure for the preparation of tablets containing rosehip powder on the amount of L-ascorbic acid in the final pharmaceutical form. Drying of the plant drug was performed at room temperature to avoid possible thermal degradation of this heat-sensitive compound. Similarly, drying of the granules after wet granulation in the oven was replaced by natural drying at room temperature. The composition of two types of prepared granule formulations differed in the filler – lactose (LAC) or microcrystalline cellulose (MCC). Apart from the disintegration test, they meet the technological requirements for granules or tablets. Lactose was confirmed as a more suitable filler, which despite the unsuccessful disintegration of the granules, ensures the disintegration of tablets within 15 minutes even without the addition of a special excipient acting as a disintegrant. The content of L-ascorbic acid detected using isotachophoresis – capillary zone electrophoresis was 87.16 ± 5.06 µg in LAC tablets and 63.33 ± 2.83 µg in MCC tablets.

Keywords *L-ascorbic acid – rosehip – tablet – granule – lactose – microcrystalline cellulose*

INTRODUCTION

Ascorbic acid is a relatively low-molecular-weight vitamin (MW 176.12 g.mol^{-1}) soluble in water. It exists as two enantiomers but only the L-enantiomer is biologically active. L-ascorbic acid is more commonly known as vitamin C and is one of the most important vitamins necessary for the proper functioning of the organism. It is found in fruits, berries and vegetables. One of the important properties is its antioxidant activity acting synergistically with lipid soluble vitamin E. However, vitamin C is more than just an exogenous non-enzymatic antioxidant, it is known as an inhibitor of melanogenesis, helps in synthesis of immunoglobulins and interferon, suppresses interleukin-18, helps absorption of iron, calcium and folic acid (Caritá et al., 2020). Particularly, a lack of vitamin C can manifest in scurvy, a disease that is characterized by general weakness, bleeding into the skin caused by the decreasing elasticity of the blood vessels, bleeding gums and loosening of teeth. In infants and young children, it is manifested by anaemia, and bone ossification disorder. Supplementation is strongly recommended for inflammation, wound healing, anaemia, corticosteroid treatment, hormonal birth control, convalescence, pregnancy and breastfeeding, as well as for smokers (Buchanec et al., 2006; Kareem et al., 2020; Maxfield & Crane, 2022).

The daily recommended dose of vitamin C is 50 mg in children under 1 year of age, while with every 3 years of life this need increases by 5 mg. In the period of adolescence, the recommended intake ranges from 80 to 100 mg. In adulthood, a 70-100 mg dose of vitamin C per day is usually recommended (Buchanec et al., 2006). There is still a lively debate about the optimal daily intake of vitamin C. However, studies show that the blood is saturated with vitamin C at a dose of 100 mg/day, and any excess is excreted in the urine (Yussif, 2018) (Kareem et al., 2020). Vitamin C is unstable in presence of heat, light, air, moisture, metal ions and bases. It decomposes to biologically inactive compounds such as 2,3-diketo-L-gulonic acid, oxalic acid, L-threonic acid, L-xylonic

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acid, and L-Lyxonic acid (Deutsch, 1998). Vitamin C is more stable when its pH is lower than its pKa which is 4.2. Stability issues need to be considered in formulations for vitamin C supplementation. Ways of increasing stability include adding excipients such as chelating agents, preservatives and antioxidants. It has been demonstrated that ferulic acid and sodium metabisulfite are useful stabilizers (Sheraz et al., 2011). Stability can also be improved by using high viscosity mediums, multiple emulsion systems with polyol solvent, silicone oil and a suitable surfactant [Sherez et al., 2011], or non-aqueous mediums with reduced oxygen permeability (Caritá et al., 2020).

Rose hips are popular mainly because of their high content of vitamin C, which is found at the highest concentration in fresh fruit. Due to its inherent instability the proportion of vitamin C may considerably decline (Košťálová et al., 2012). When the high presence of vitamin C was detected in rose hips, they became a supplement which provided children with the necessary daily intake of vitamin C during the Second World War in Britain (Mancini, 2015). As a vitamin C supplement, they are widely used to this day.

Rose hips are a very popular and easily accessible source of vitamin C in the region of Central Europe. The high nutraceutical potential of the rose hips, as well as their possible use as a functional food, has been demonstrated. They can be considered not only as full-fledged ingredients in food, but also in formulations of dietary supplements (Singh et al., 2021)

The foetus of the Dog Rose is defined as a plant drug. The fruits are richly haired, hard achenes, or fruiting of achenes. Rose hips are pseudo-fruits. They serve as the "primary cover" in which the true fruits are protected. They are egg-shaped, 10-20 mm long, initially orange-yellow, and shiny red when ripe (Singh et al., 2021). Whole, ripe, hard rose hips, without signs of frost damage are collected. The wrinkled and spotted ones are removed (Mancini, 2015). The correct procedure for rose hip drying is important for the preservation of vitamins. They are dried freely in the air or with artificial heat not exceeding a temperature of 40˚C. Some techniques, e.g. ultrasonic dehydration can reduce the drying time and temperature mode (Verboloz et al., 2020). The rose hips can be dried whole (*Cynosbati fructus cum semine*) or freed from the small achenes (*Cynosbati semen*) located inside (*Cynosbati fructus sine semine*). The dried fruit of the species *Rosaceae* (*Cynosbati fructus)* is characterized by its slightly sour smell and sweet-sour taste (Ministry of Health of the Slovak Republic, 2007).

Rose hips are also beneficial in combination with analgesics/antipyretics and diaphoretics as the supportive treatment of colds or flu. Besides that, they are helpful in rheumatic and inflammatory diseases (Košťálová et al., 2012). Many studies have reported that rosehip extracts have significant antioxidant, immunomodulatory, cardio-protective, antidiabetic, neuroprotective, antineoplastic and antimicrobial properties. Their benefits have been confirmed in osteoarthritis, rheumatoid arthritis, obesity, kidney stones, non-alcoholic liver stiffness or skin problems. The mechanisms by which they interfere with various individual signalling molecule cascades, and thus mediate their therapeutic potential, differ. These are, e.g., the case of blockage of the COX-2, iNOS, NF-kappaB, PPAR-γ, p38 MAPK, caspase-3 pathways, or blockade of voltage-controlled Ca^{2+} channels. In addition to the already very favourable profile of the rose hips in terms of their use in medication (except for the allergenicity shown by *the Rosaceae* species) their use is without other side effects (Patel, 2017). In recent years, interest in the study of the antioxidant activity of rose hips, which is directly related to their phytochemical composition, has increased and could be used in treatments in which it is necessary to inhibit excessive oxidative stress and the formation of free radicals (Mármol et al., 2017).

The most important substances contained in rose hips are vitamins: vitamin C, A, B1, B2, and K. Other substances included are carotenoids, which give the rose hips their characteristic colour, triterpenes, fruit acids, pectins, galactolipids, tannins, flavonoids and anthocyanins (Košťálová et al., 2012; Winther et al., 2016). The merits of the components may have a synergistic effect (Mármol et al., 2017). Carotenoids, phenolic compounds, and vitamins C and E show anticancer and anti-mutagenic effects in addition to antioxidant activity (Popović-Djordjević et al., 2021). Due to a complexity of biologically active compounds and resulting biosynergy, rose hips are considered to be an important part of current dosage forms in pharmaceuticals or dietary supplements containing vitamin C as a main active component.

The aim of the present work was to prepare tablets with the highest possible content of rosehip powder, which can technologically process into a tablet. Subsequently, the effect of the filler (MCC versus LAC) on the physical properties and the quality of both, the granules and the final tablets, was compared. Finally, the content of L-ascorbic acid was determined in the tablets.

MATERIALS AND METHODS

Gelatine (p.a., MF: $C_{102}H_{151}O_{39}N_{31}$), Lactose (p.a., MW: 360.32, MF: $C_{12}H_{22}O_{11}$), Microcrystalline Cellulose (Avicel® PH 102, p.a., MW: 370.35, MF: $C_{14}H_{26}O_{11}$), Magnesium stearate (MW: 591.2, MF: $C_{36}H_{70}MgO_4$) were purchased from CentralChem (Bratislava, Slovakia). L-Ascorbic acid (Ph. Eur., MW: 176.12, MF: $C_6H_8O_6$) and Talc (Ph. Eur., MW: 379.27, MF: $H_2Mg_3O_{12}Si_4$) were purchased from Galvex (Banská Bystrica, Slovakia). The purified water was prepared by the distillation apparatus Kavalier (Labo SK, Bratislava, Slovakia) at the Department of Galenic Pharmacy. Demineralized water for the analytical part was prepared in Millipore Simplicity 185 (Molsheim, France). Propionic acid, oxalic acid, HCl, and β-Ala were purchased from Sigma-Aldrich – (Steinheim, Germany), VWR International (Vienna, Austria), and Merck (Darmstadt, Germany). 1% methyl-hydroxyethylcellulose (m-HEC) was prepared in Villa Labeco (Spišská Nová Ves, Slovakia).

PREPARATION OF ROSEHIP GRANULES

Rose hips were collected in Central Slovakia freely from countryside. They were left to dry at room temperature for one month. The remnants of the petal were removed and rose hips were ground with a powder grinder (Hausmeister HM 5207, Budapest, Hungary). On the laboratory shaker (Stavební strojárenství, Brno, Czech Republic), the powder pieces were allowed to shake and fall over the sieve (500 µm), separating the fine powder that was used for the preparation of granules, from tufts, which were formed by bonding sharp hairs. The granules with the content of rose hips were prepared by wet granulation. The processed rosehip powder was homogenized for 10 minutes with LAC or MCC - both were firstly sieved through sieve (250 µm) (see in Tab. 1 for the composition). As a binder, gelatine solution (5%; w/w) was used to moisten the powder mixture. The wet mass was subsequently extruded through sieve (2000 µm). To avoid vitamin C degradation, the drying of the granules was performed at room temperature for 24 hours.

Table 1. The Composition of the Rosehip Granules: Lactose Granules (LAC GRA), Microcrystalline Cellulose (MCC GRA).

	LAC GRA (g)	MCC GRA (g)
Cynosbati fructus sine semine	50.0	50.0
Lactosum monohydricum	50.0	-
Cellulosum microcrystallinum	-	50.0
Gelatinae mucilago 5 %	*q.s.* (22.37)	*q.s.* (36.97)

QUALITY ASSESSMENT OF GRANULES

Particle Size Distribution Test

Granule-size distribution was estimated by sieving on Vibratory Sieve Shaker (HAVER EML 200 digital T, Westfalen, Germany) for 5 minutes at 5th level intensity (the sieves were sorted out from top to bottom in the following order: 1250 µm, 900 µm, 710 µm, 500 µm, 375 µm and 250 µm). The granules on each sieve were weighed and expressed as the percentage proportion of the total batch (300 g). Three parallel measurements were performed for each type of granules (n=3, ± SD).

Mechanical Resistance of Granules

The granules were dusted off through sieve (250 µm). Granules (10.0 g) were weighed in a vial and left to shake for 10 minutes in a shaker (Laboratory Shaker, Stavební strojírenství, Brno, Czech Republic) at maximum intensity. The created dust was removed again through sieve (250 µm) and the percentage portion of the resistant granules was calculated (n=3, ± SD) (Tichý et al., 2015).

Disintegration of Granules

1 g of the granules was added to 50 mL of distilled water heated to 37 ± 2 °C and stirred occasionally for 10 minutes. After this time, the contents of the beaker were spilt through a sieve (800 µm). Only granules, which do not leave a residue on the sieve, pass the test (Tichý et al., 2015).

Apparent Specific Volume and Apparent Density

3 g of the granules are placed in a sealed test tube and tapped gently till constant volume. Apparent specific volume (V_s) is calculated from the average volume (V_{tap}) corresponding to the mass of the granules (m) from three measurements:

$V_S = V_{tap} / m$

Apparent density is the inverse of apparent specific volume (Tichý et al., 2015):

$\rho_A = 1 / V_s$

Flow Properties of Granules

The flowability of solid dosage forms such as powders, granules, pellets, etc. is an important characteristic of bulk material affected by the physicochemical and mechanical properties of the particles (Macho et al., 2020). The main indicators of a solid´s flow are the angle of repose, compressibility index (Carr´s index) and Hausner ratio. The compressibility of the granules was evaluated according to the pharmacopoeia procedure (Ph. Eur. 10). A quantity of the granules sufficient to complete the test was sieved through the sieve (1000 µm). Approximately 100 g (m) of the granules is gently introduced into a dry cylinder (250 mL) without compacting. The unsettled apparent volume (V_0) is read. Bulk density (ρ_B, g. mL^{-1}) is calculated by the equation:

$\rho_B = m / V_0$

Compressibility means the ability of the granules to reduce volume upon stressing. Stressing was induced by simple tapping (100-times). The volume of the granules after tapping (V_t) was read.

The compressibility index (CI) was calculated by the equation:

$CI = 100 (V_0 - V_t) / V_0$

Hausner ratio (HR) was calculated by the equation (Ph. Eur. 10, 2019a):

$HR = V_0 / V_t$

Flow Rate

20 g of the granules was poured into the hopper of the device for the measurement of the flow rate constructed in the department development workroom. The lower part of the hopper was opened for 3 seconds during which a part of the granules was poured out and then weighed. The procedure is repeated 5-times. The flow rate (g. s^{-1}) was calculated from the determined average mass (Tichý et al., 2015). However, this procedure is not a pharmacopoeia method. The methodology

is slightly modified to make possible an objective comparison of the flow properties of several formulations. The principle of the pharmacopoeia flowability test is to determine the time (s) for which 100 g of powder material flows through a funnel of the prescribed dimensions and from the prescribed material (Ph. Eur. 10, 2019c).

PREPARATION OF TABLETS

To 60 g of each type of granules (LAC or MCC) of size between 500-1000 µm, 0.6% (w/w) of magnesium stearate and 2.4% (w/w) of talc was added to improve the flow properties. The granules were gently homogenized for 10 minutes in a homogenizing cube (Turbula T2C, Basel, Switzerland). Subsequently, the granules were compressed on a rotary tablet press machine (Kilian, Cologne, Germany). The pressure and the depth of the die were set during the compression of LAC tablets so that the final hardness of the tablets was around 50 N and the weight about 300 mg. During the compression of MCC tablets the same conditions were maintained so that the tablets could be compared with each other and the influence of the filler could be evaluated. The final appearance of the tablets is shown in Fig. 2.

QUALITY ASSESSMENT OF TABLETS

Uniformity of Mass of Single Doses (Ph. Eur. 10, 2019f)

20 tablets taken at random were weighed on an analytical balance (Pioneer PA214CM/2, Ohaus Corporation, Switzerland) individually and their average mass was determined. Not more than 2 of the individual masses deviate from the average mass by more than the percentage deviation of 5% given (applies for uncoated tablets with a mass of 250 mg or more).

Resistance to crushing (Ph. Eur. 10, 2019e)

10 randomly selected tablets were tested for resistance to crushing by a hardness tester (Schleuniger-2E, Switzerland).

Friability (Ph. Eur. 10, 2019d)

10 randomly selected tablets were dusted off, weighed, and inserted into the drum of the equipment (Erweka friabilator, Heusenstamm, Germany) and left to rotate for 4 minutes (approximately 100-times). After testing the tablets are re-weighed. A loss of weight was expressed as a percentage (%).

Disintegration (Ph. Eur. 10, 2022)

The disintegration test was carried out by a disintegration tester for tablet testing (PIS SPOFA n.p. VVZ, Kroměříž, Czech Republic) described in Ph. Eur. 10 as apparatus A. 6 randomly selected tablets were inserted into the basket rack and left to move so that the basket dipped and raised repeatedly into the dissolution medium (distilled water heated to 37 °C). The time needed for the disintegration of all 6 tablets was recorded.

DETERMINATION OF L-ASCORBIC ACID IN TABLETS

Determination of L-ascorbic acid in tablets was performed by the isotachophoresis-capillary zone electrophoresis (ITP-CZE) method with simple UV detection according to Procházková et al., 1998. The electrophoretic analyzer, EA 102 (Villa Labeco, Spišská Nová Ves, Slovakia) was used in column-coupling arrangement. The first, preseparation column served for isotachophoresis and was provided by polytetrafluorethylene capillary (800 µm ID, 180 mm total length). The current in the ITP step was set at 300 µA. Analytical separation was performed in the second column (300 µm ID capillary, 160 mm total length). The current in the CZE step was set at 80 µA. Each column was equipped with contactless conductometric detector. The wavelength of UV detector was set at 254 nm. Three different electrolyte systems with optimized compositions were used. Leading electrolyte was composed of 10mM HCl + 20mM β-Ala + 0,05% m-HEC (pH 3.3), terminating electrolyte 50 mM propionic acid, and background electrolyte 50 mM propionic acid + 25 mM β-Ala (pH 3.8).

Sample preparation

Five tablets were crushed and homogenized in mortar. The exact amount of powder, corresponding to one tablet was mixed with 2.5 mL 2% oxalic acid and added with demineralized water (18.2 MΩ) to 25 mL. The mixture was homogenized for 30 min and filtered. The filtrate was 10 times diluted and injected directly into the analyser.

RESULTS

Table 2. The Quality Assessment of Lactose Granules (LAC GRA) and Microcrystalline Cellulose Granules (MCC GRA).

	LAC GRA	MCC GRA
Bulk density (g.cm^{-3})	0.470 ± 0.018	0.474 ± 0.028
Apparent specific volume (cm^3.g^{-1})	1.999 ± 0.039	1.942 ± 0.028
Apparent density (g.cm^{-3})	0.500 ± 0.010	0.515 ± 0.007
Compressibility index (%)	2.5 ± 0.0	5.0 ± 0.1
Hausner ratio	1.03 ± 0.00	1.05 ± 0.00
Mechanical resistance (%)	98.90 ± 0.60	99.59 ± 1.01
Disintegration time (min)	more than 10	more than 10
Flow rate (g. s^{-1})	4.49 ± 0.11	4.55 ± 0.10

Table 3. The Quality Assessment of Lactose Tablets (LAC TBL) and Microcrystalline Cellulose Tablets (MCC TBL).

	LAC TBL	MCC TBL
Mass (g)	0.320 ± 0.003	0.285 ± 0.003
Height (mm)	4.37 ± 0.02	4.10 ± 0.02
Diameter (mm)	9.09 ± 0.01	9.11 ± 0.01
Resistance to crushing (N)	64.80 ± 7.47	27.80 ± 2.15
Friability (%)	0.14 ± 0.07	1.15 ± 0.26
Disintegration time (min)	more than 15	14.34 ± 0.50

Table 4. The content of vitamin C in Lactose Tablets (LAC TBL) and Microcrystalline Cellulose Tablets (MCC TBL).

	LAC TBL	MCC TBL
Content of vitamin C (µg)	87.16 ± 5.06	63.33 ± 2.83
% RSD	5.80	4.47

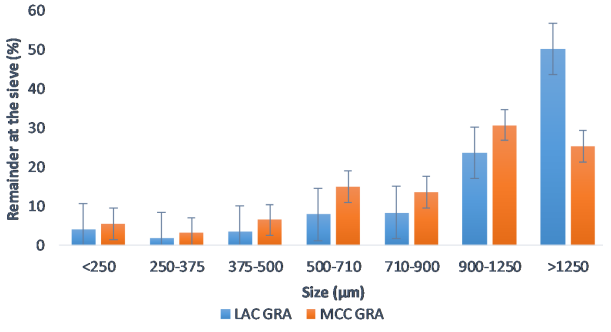

Figure 1. Particle Size Distribution: LAC versus MCC Granules.

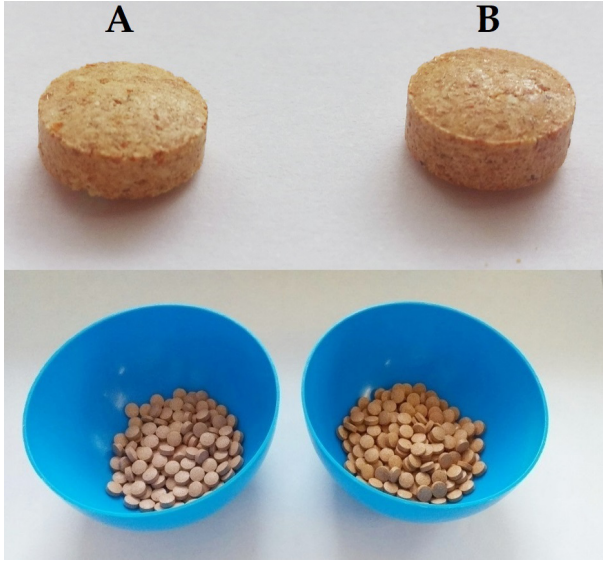

Figure 2. Tablets formulated from Rosehips powder differing in the type of filler: MCC tablet (A), LAC tablet (B).

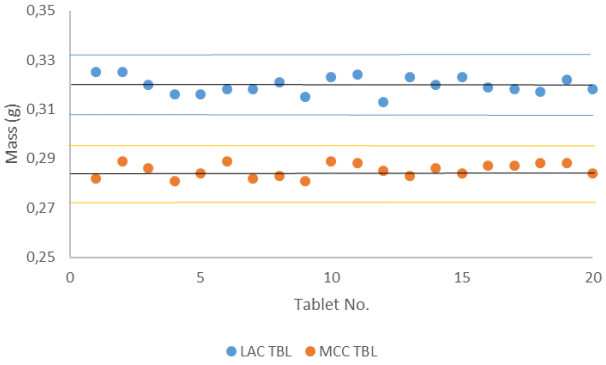

Figure 3. Uniformity of Mass: LAC versus MCC Tablets.

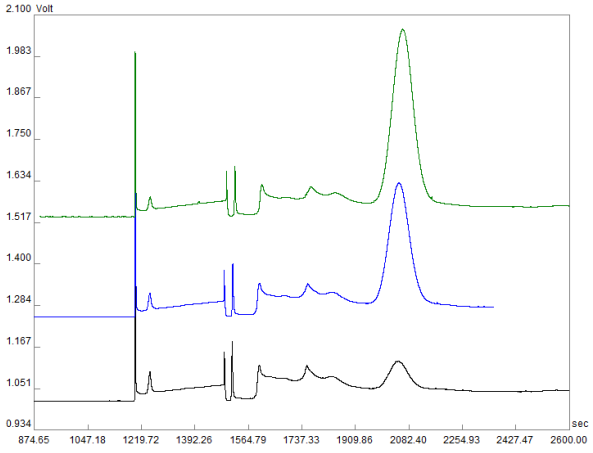

Figure 4. Electropherograms of L-ascorbic acid analysis in Microcrystalline Cellulose Tablets (MCC TBL).
A - 10 times diluted solution from MCC TBL
B - 10 times diluted solution from MCC TBL with 1 ppm addition of L-ascorbic acid
C - 10 times diluted solution from MCC TBL with 1.5 ppm addition of L-ascorbic acid

DISCUSSION

Rose hips are made up of the receptacle and the remains of the dried sepals of *Rosa canina* L., *Rosa pendulina* L., and other *Rosa* species, with the achenes removed. The dried herbal drug has to contain 0.3% of L-ascorbic acid. Before the dried drug was used to prepare formulations, its quality, i.e. L-ascorbic acid content was verified by the pharmacopoeia method (Ph. Eur. 10, 2019b). Both samples of the herbal drug - the dried one in an electric dryer at 50 °C and one freely dried at laboratory temperature, met the above-mentioned requirement for vitamin C content. Nevertheless, the herbal drug dried at laboratory temperature was used in the study.
The dried rosehips were ground, deseeded and processed into granules so that the content of the filler was the lowest possible while the content of rosehip powder was the highest. During the investigation, it was found that granules prepared by wet granulation, containing 90% of rosehip powder and

less than 10 % of the filler are not possible to compress into the tablets. Their quality was low. Further formulations contained the ratio of the rosehip powder to the filler as 1:1. The only difference in the two examined samples of granules was in the filler type (LAC or MCC). In both samples, a 5% (w/w) aqueous solution of gelatine was used as a binder during wet granulation. Binder solutions are generally considered the most effective. This is also the most common way of incorporating a binder into the granules (Aulton, 2007). The amount of binder required to wet the mixture varied depending on the type of filler. In LAC samples it was 22.37 g and in MCC samples up to 36.97 g. The moistened mixture was passed through the sieve (2000 µm) and dried at laboratory temperature. Generally, dry granulation enhances the flowability and bulk density of material but may reduce compressibility due to granule size enlargement and an increase in plastic stiffness of particles (Tofiq et al., 2022).

QUALITY ASSESSMENT OF GRANULES

The granules were compared through several tests evaluating size distribution, apparent specific volume and density, flow properties, compressibility, disintegration, and mechanical resistance. The sieve analysis revealed that the highest percentage representation has aggregates up to 1250 µm in LAC sample and up to 900 µm in MCC sample (Fig. 1). The compressibility of material is expressed through its change in volume after compression. Although compressibility is not a direct indicator of flow properties, it is related to several operations such as storage in hoppers or the behaviour of bulk materials during roller compaction (Macho et al., 2021). The compressibility index of LAC granules was 2.5% and MCC granules 5% which means excellent flow properties (Hoag, 2017) for both types of granules confirmed also due to the Hausner ratio (Table 2). The mechanical resistance of granules was higher than 95% which is an acceptable value meaning relatively low post-stress loss. None of the granules disintegrated within 10 minutes. Visible residues remained trapped on the sieve which indicated the need for the addition of special excipients acting as disintegrants to the mixture. The flow rate of both granules was similar, for MCC granules 4.55 g. s^{-1}, for LAC granules 4.49 g. s^{-1}. Bulk density includes the volume of solid particles, intra- and interparticulate volume (Buanz, 2021). Variations of the filler type did not cause a significant change. The density of solids depends not only on temperature and pressure but also on crystal structure and degree of crystallinity (Buanz, 2021).

QUALITY ASSESSMENT OF TABLETS

Both types of tablets were compacted by rotary press machine under the same conditions (set die diameter was 9.09 ± 0.02 mm, pressing pressure ensuring hardness of tablets 50 N). Stearic acid salts show a lubricating effect in low concentrations of up to 1%. Therefore, only 0.6% magnesium stearate was added extra-granularly to the granules. It can create a film on the surface of drug and/ or a filler, covering its irregularity. Many lubricants, magnesium stearate among them, have also anti-adherent properties. Talc with limited ability to reduce friction acts only as an anti-adherent. It reduces adhesion between granules and the punches and thus prevents its sticking (Aulton, 2007).

The final appearance of the tablets is shown in Fig. 2. LAC tablets are shinier; they have fewer irregularities on the surface. At first glance, they seem more compact.

The average mass of LAC tablets was about 0.320 g and of MCC tablets 0.285 g (Fig. 3). The differences in masses were manifested in the height of the tablets. LAC tablets were higher and even firmer compared to MCC tablets (Tab. 3). Lactose as a filler can therefore be considered a better option in terms of the homogeneity of prepared tablets. Ph. Eur. 10 permits, for a given category of tablets, a maximum deviation from an average weight of ± 5 % in two tablets from 20 examined and at the same time, no tablet mass shall deviate by more than twice the allowed deviation (Ph. Eur. 10, 2019f). This condition was met by both types of prepared tablets.

The hardness of the tablets was measured as the force in Newtons, which was needed to crush the tablets inserted between the moving jaws of the hardness tester. Firmer were LAC tablets, which broke under the force of 64.8 N on average, which is up to twice the average force required to break down MCC tablets. As (Tofiq et al., 2022) refers, "larger granules pack more densely than the smaller ones" during compression, resulting in higher resistance to crushing in the case of LAC tablets.

The friability test confirmed that the prepared LAC tablets were firmer than those with MCC used as the filler. Ph. Eur. 10 permits a maximum loss of 1 % of the original mass after mechanical stress in a friabilator (Ph. Eur. 10, 2019d). As Tab. 3 refers, in LAC tablets a minimal loss was determined while MCC tablets slightly exceed the permitted limit.

The disintegration of the uncoated tablets should occur under well-defined conditions within 15 minutes of insertion of the tablet into the medium. Only a sample of MCC tablets, in which complete disintegration occurred in a time of 14.34 minutes, passed the disintegration test. The LAC tablets did not disintegrate within the prescribed time limit. MCC tablets swelled in water and there was gradual disintegration of the tablets. As it was mentioned, in the composition of the granules disintegration supporting excipient was missing which could influence also the results of the disintegration test for the tablets themselves.

MCC performs several functions as an excipient. It can be used as a filler/diluent, a dry binder, a lubricant, an antiadherent, an absorbent or a disintegrant (Chaerunisaa et al., 2019). The capillary mechanism in the tablets facilitates the penetration of digestive juices into the matrix, causing it to break down quickly. It is also able to absorb some quantities of fluids in an apparent dry state therefore it is often added as an absorbing substance to tablets. The particles of MCC have

both crystalline and amorphous regions, depending on the relative position of the cellulose chain within the solid. Its compressibility depends on the cellulose source and the procedure of MCC preparation (Aulton, 2007). When MCC is used as a filler in granules production by wet granulation, the density of agglomerated particles reduces, thereby decreasing their internal surface area. In contrast, adhesion between agglomerates occurs reducing external surface area resulting in less particle interlocking and hydrogen bonding (Chaerunisaa et al., 2019) confirmed in our hardness test comparing the resistance to crushing of MCC and LAC tablets. Nevertheless, LAC is the main tablet diluent. 70% of the tablet contains LAC (Shendurse and Khedkar, 2016). It has a series of properties belonging to the perfect filler, e.g. good dissolution in water, pleasant taste, non-hygroscopicity, safety, non-reactivity, good compatibility, etc. Its main limitation is that some people have an intolerance to lactose (Aulton, 2007). In combination with MCC, they complement each other. MCC has a low bulk density (Chaerunisaa et al., 2019). Because of that, MCC as the only one diluent in the formulation might cause inconsistent die filling at higher press speed. The addition of LAC can help. Mixtures of these two main diluents in various proportions for tableting purposes are commercially available today (e.g. MicroceLac®), suitable for direct compression due to improved flowability and compactability. MCC is the first choice of replacement for lactose-free tablets (Dominici et al., 2022).

Because the prepared tablets contain about 50 % of herbal drugs - dried rosehip fruits, the taste of the tablets is specific, more or less bitter. LAC as a filler partially hides the taste. Nevertheless, a quantity of flavouring agent should be added to both tablet types, which are processed directly into the granules, most often in the form of an alcoholic solution (Aulton, 2007).

DETERMINATION OF L-ASCORBIC ACID IN TABLETS

Vitamin C was determined by on-line combination of two electrophoretic methods – isotachophoresis and capillary zone electrophoresis working in hydrodynamically closed separation system. Such orthogonal separation system is highly effective for the analysis of multicomponent mixtures, such as plant extracts, with enhanced selectivity and sensitivity. This system is characterized by the use of capillaries with wider inner diameter allowing higher sample loadability, and, by that, lower limit of detection. Moreover, additives such as methyl-hydroxyethylcellulose (m-HEC) are used to prevent hydrodynamic flow and achieve acceptable reproducibility of measurements. Oxalic acid was used as a stabilizing agent for the analyte.

A tablet with pseudo-fruits of Dog Rose represents a multicomponent matrix. The complexity of matrix was accompanied with long migration time of the investigated analyte. The migration position of the analyte was approved by addition of the vitamin C standard at known concentration to the sample. The content of vitamin C was determined by the method of standard addition. L-ascorbic acid was added into the filtrate prepared from tablets´ powder. The vitamin C content in prepared tablets was calculated with the use of different concentrations (i.e., 1.0, 1.5, and 5.0 ppm) of its standard solution added into the tablet's solutions. Illustrative records obtained from such analysis are presented in Figure 4. The content of L-ascorbic acid, determined in rosehip LAC and MCC tablets is shown in Table 4.

CONCLUSION

The content of L-ascorbic acid in the developed tablets, detected by the ITP-CZE-UV method, was lower than in the rosehip tablets available on the market. It is due to their supplementation with synthetic L-ascorbic acid for the required daily dose. Anyway, this study aimed to formulate tablets with a purely natural source of vitamin C, therefore the presented results showing the levels of L-ascorbic acid to be higher than 80 µg per MCC TBL are acceptable and have a practical value. The presence of other vitamins and compounds like pectin contained in rosehip powder is an added benefit and they may act synergistically with vitamin C. Vitamin C supplementation through tea requires a longer preparation and several hours of maceration in lukewarm water. Furthermore, many people demonstrate poor efficiency pouring hot water over the plant drug, as if it was a regular tea, degrading the contained vitamins. For these and other reasons the formulation of rosehip powder into tablet, or granules is advantageous. However, our pilot study focused on rosehip granule formulation requires the addition of other excipients, e.g., a flavour to improve the taste and an effective disintegrant to support the disintegration of a granule and a tablet. The prepared granules could be used as a promising semi-product for further processing into tablets. Other excipients such as chelating agents, preservatives, antioxidants, or other stabilizing agents (e.g., ferulic acid and sodium metabisulfite) could enhance vitamin stability and help improve the formulation with respect to longer storage times. The effect of studied fillers (LAC *versus* MCC) on the properties of granules and tablets is not particularly significant. The result of the tablet disintegration test is in favour of MCC filler. On the other hand, LAC tablets have more pleasant appearance. Hence, these results are useful for a proper selection of basic tablet components in further study.

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ABBREVIATIONS

COX-2	cyclooxygenase 2
CZE	capillary zone electrophoresis
GRA	granules
iNOS	inducible nitric oxide synthase
ITP	isotachophoresis
LAC	lactose
MCC	microcrystalline cellulose
MF	molecular formula
MW	molecular weight
NF-κB	nuclear factor kappa B cells
PPARγ	peroxisome proliferator-activated receptor gamma
p38MAPK	p38 mitogen-activated protein kinase
q.s.	*quantum satis,* the amount which is enough
TBL	tablets

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