

DRY ROSE PETAL EXTRACTS AND COMPRESSED LOZENGES: FORMULATION AND NIR – CHEMOMETRIC QUANTIFICATION OF ACTIVE PRINCIPLES

ALEXANDRU GAVAN^{1*}, ANCA MARIA TOIU², MIRCEA TAMAȘ³, IOAN TOMUȚĂ¹

“Iuliu Hațieganu” University of Medicine and Pharmacy, Faculty of Pharmacy, Cluj-Napoca, Romania

¹Department of Pharmaceutical Technology and Biopharmaceutics,

²Department of Pharmacognosy,

³Department of Pharmaceutical Botany

*corresponding author: gavan.alexandru@umfcluj.ro

Manuscript received: March 2017

Abstract

The purpose of this study was to develop a manufacturing method for dry rose petal extracts and compressed tablet lozenges and a new non-invasive near-infrared (NIR) – chemometric method for the quantification of their total polyphenolic content. Formulations with four different concentrations were obtained through pulverization of *Rosa damascena* Mill alcoholic extracts on solid isomalt support. The obtained dry extracts were further compressed into tablet lozenges. The total polyphenolic content, expressed in gallic acid, was determined in all samples using the Folin-Ciocalteu reference method and the results were used to calibrate the new developed quantification technique. The best results for the NIR – chemometric technique were obtained by calculating the first derivative of the spectral values and then applying Multiple Scatter Correction (MSC) or Standard Normal Variate (SNV) pre-processing techniques. In this way, the recovery percent of the active principle content was between 99% and 101% for both products, dry extracts and compressed tablet lozenges. In conclusion, high quality dry extracts and compressed lozenges have been developed and the active principles content could be accurately quantified from the pharmaceutical products using NIR spectroscopy and chemometrics.

Rezumat

Scopul studiului a fost obținerea extractelor uscate din petale de trandafir și a comprimatelor bucale, precum și dezvoltarea unei metode în infraroșu apropiat (NIR – *infrared spectroscopy*) – chemometrice neinvazive pentru cuantificarea conținutului polifenolic al acestora. Au fost realizate patru formulări de concentrații diferite prin pulverizarea extractului alcoolic de *Rosa damascena* Mill. pe un suport solid de isomalt. Din extractele uscate obținute au fost realizate ulterior comprimatele bucale. Conținutul total de polifenoli, exprimat în acid galic, a fost determinat în toate probele prin metoda de referință cu reactivul Folin-Ciocalteu, iar rezultatele au fost utilizate pentru calibrarea noii metode de cuantificare dezvoltate. Cele mai bune rezultate pentru metoda NIR - chemometrică au fost obținute prin calcularea derivatei de ordinul întâi a valorilor spectrale și aplicarea metodelor de preprocesare *Multiple Scatter Correction* (MSC) și *Standard Normal Variate* (SNV). Procentul de regăsire al principiilor active, atât din extractele uscate cât și din comprimate, a fost între 99% și 101%. În concluzie, au fost dezvoltate extracte uscate și comprimate bucale de înaltă calitate, ale căror principii active au putut fi cuantificate cu acuratețe, utilizând tehnici NIR – chemometrice.

Keywords: NIR spectroscopy, compressed lozenges, rose petal extract, *Rosa damascena*, gallic acid

Introduction

Successful formulation of compressed tablet lozenges involves a careful selection of excipients and manufacturing method in order to obtain a quality solid dosage form. The attributes of a good developed lozenge would be a slow dissolution, smoothness and good mouth feel. Several important aspects for the manufacturing are critical to all of the desired properties, these including the assurance of the necessary particle size and the distribution of the granulate, the maintenance of correct moisture content, the achievement of proper tablet hardness and low friability [8, 15].

Rosa damascena Mill (*Rosaceae*), one of the most important *Rosa* species, is a perennial shrub indigenous in Europe and Middle East. Due to the high content of biologically active substances of the flowers, this species has attracted considerable attention also in the pharmaceutical field [4]. Rose petal extracts are reported to have analgesic, anti-inflammatory and antimicrobial effects against a broad spectrum of bacteria and fungi, mostly due to the high polyphenolic content [3, 12].

Recently, near-infrared (NIR) methods have gained wide acceptance in the pharmaceutical industry since they have the ability to provide information with little or no sample preparation. In combination

with chemometrics, the NIR technique is offering a rapid and precise analysis, without compromising the sample during the analysis [14, 16]. To this date, there are some papers that reported the determination of the active pharmaceutical ingredient (API) content from granules or tablets by NIR methods [2, 7, 11, 17]. The aim of this study was to develop a manufacturing method for compressed tablet lozenges incorporating the active principles of the *Rosa damascena* Mill petal extract and a new NIR – chemometric quantification method for the quantification of total polyphenolic content from the dry rose petal extract and compressed tablet lozenges. The absorption of rose petal extract on isomalt provided a high quality granulate with good flow and compression properties, the tablet lozenges met all the typical properties for this kind of pharmaceutical dosage form. Also the rose petal extract conferred a sweet taste and flavour to the final product which is a very important characteristic for lozenges.

In order to standardize by quantitative means the active compounds from extracts and tablets, represented in this case by the total phenolic content, a classical Folin-Ciocalteu spectrophotometric method was used.

Materials and Methods

Materials

The active ingredients are contained in the *Rosa damascena* 1:10 ethanolic extract, which was kindly provided by Plantextrakt SRL, Romania. Isomalt (galenIQ™ 721) was purchased from Beneo GmbH, Germany. Fumed silica (Aerosil® 200) was obtained from Röhm GmbH & Co KG, Germany and magnesium stearate (Kemilub EM-F) from Undesa, Spain. All other chemicals used in this study were of analytical grade.

Dry extract preparation

Table I
Granulation conditions

Parameters	Value
Method (type)	Top spray
Duration of the dry mixing (min)	2
Nozzle diameter (mm)	0.8
Spraying rate (mL/min)	15
Atomizing pressure (atm)	0.8 - 1
Spraying time (min)	15 - 50
Inlet air temperature (°C)	50
Drying temperature (°C)	50
Bag filter shaking time (sec)	7
Duration of the final drying (min)	10

The dry rose petal extracts were obtained in a Strea 1 fluidized bed granulator (Aeromatic AG, Switzerland), through pulverization of the alcoholic rose petal extract on isomalt as a solid support. Formulations with four different amounts of ethanolic extracts were prepared using 190 mL, 380 mL, 570 mL and 760 mL of extract and 175 g of isomalt, being coded

F1, F2, F3 and F4 in increasing order of the concentration. The granulation conditions are presented in Table I. After the pulverization, the compound was dried for 10 minutes, at a drying temperature of 40°C.

Tablet preparation

The dry rose petal extract obtained using the described method presented very good flow and compressibility properties, so that it was only necessary to mix each of the four extracts with 1% magnesium stearate and 0.5% fumed silica. Tablets were compressed from the mixes using an eccentric tablet press (Korsch EK-0, Germany) fitted with a 15 mm flat-faced punch. The press was adjusted so that the manufactured tablets had an average weight of ~ 900 mg and a hardness value of ~ 250 N. This size of tablets is suitable for buccal administration of compressed lozenges.

Determination of total phenolic content

The total phenolic content of the granules was spectrophotometrically determined using the Folin-Ciocalteu method described in the European Pharmacopoeia [1] and literature [13]. For this purpose 0.5 g dry extract (granules) was dissolved in 25 mL 50% ethanolic solution. 0.5 mL extractive solution was diluted to 50 mL with the same solvent, and then 2 mL from the second solution was mixed with 1 mL Folin-Ciocalteu reagent and diluted to 25 mL with 29% Na₂CO₃ solution. After 30 minutes, the absorbance was measured at 760 nm, using distilled water as a blank, on a Jasco V-530 UV-Vis spectrophotometer (Japan). Results were presented as a mean of three determinations and were expressed in milligrams of gallic acid in 100 g of dry rose petal extract.

Dry extract characterisation

The grain size analysis of the dry extract was performed using an analyser based on a laser diffraction and scattering method, Analysette 22 (Fritsch, Germany). The results of the particle size distribution were reported through the X₁₀, X₅₀, X₉₀ values which represent the diameters of the particles at 10, 50 and 90 percentiles of the cumulative percent undersize plot respectively. The span was used to analyse the particle size distribution width, this parameter was calculated using equation 1:

$$Span = \frac{X_{90} - X_{10}}{X_{50}} \quad (1).$$

The determination of untapped density, tapped density, Carr's index (CI) and Hausner ratio of the granules was performed according to well-known methods, described in literature [10]. All analysis were performed in triplicate, reporting the average.

The humidity of the dry extract was determined using an Ohaus MB45 (USA) humidity balance. Approximately 1 g of granulate was placed onto the

sample pan and dried at 80°C until the weight change was less than 0.2% over 10 minutes and the total percent of mass loss was automatically calculated.

Tablets characterisation

For the characterisation of the compressed lozenges several parameters such as weight variation, friability percent and hardness were determined according to the European Pharmacopoeia [1]. Friability percent was determined on 10 tablets using an Erweka TA10 friabilator (Germany) for 100 rotations. Tablet hardness was tested also on 10 samples using a Dr. Schleuniger Pharmaton 6D hardness tester (Switzerland).

NIR spectroscopy

Near infrared spectra were recorded using a MPA NIR spectrometer (Bruker Optics, Germany), equipped with an indium gallium arsenide (InGaAs) detector. The granules were analysed in reflectance mode and the compressed tablet lozenges in transmittance mode, without any prior sample preparation. Each spectrum was recorded using Opus Quant software (Bruker Optics, Germany) by integrating 32 scans in the range of 10000 - 4000 cm^{-1} at a 16 cm^{-1} resolution. The development of a calibration model was based on the application of different spectral pre-treatments or combinations of pre-treatment methods, on the whole spectral domain or specific spectral ranges. The applied pre-treatment methods were: Standard

Normal Variate (SNV), Multiple Scatter Correction (MSC), Constant Offset Elimination (COE), Minimum Maximum Normalization (mMN), First Derivate (FD), and combinations of two methods, like FD followed by SNV or FD followed by MSC [9, 16]. Using the Opus Quant software, the obtained models were then applied to chemometric approaches based on the Partial Least Squares (PLS) regression. This software performs a model validation *via* full-cross-validation by applying “live-one-out” procedure. In this procedure samples are removed from the training set and predicted by the model [15]. The calibration of the developed spectral method was performed on two products with different concentrations, analysing 3 samples for each product. Further, the results obtained using the NIR – chemometric analysis were compared with the values obtained applying the classical Folin-Ciocalteu quantification method.

Results and Discussion

Dry extract evaluation

Results from the determination of the dry rose petal extracts are shown in Table II. Granule size and granulometry of the dry extracts were analysed using laser diffraction by reporting the X_{10} , X_{50} , X_{90} values based on volume distribution, then the span was calculated in order to express the distribution width.

Table II
Physical characteristics of the dry extracts

Formulation code	X_{10}	X_{50}	X_{90}	Span	Untapped density (g/mL)	Tapped density (g/mL)	Carr Index (%)	Hausner ratio	Relative humidity (%)
F1	20	103	248	2.21	0.46	0.49	6.54	1.07	5.24
F2	23	101	223	1.98	0.48	0.52	7.54	1.08	5.255
F3	23	135	262	1.77	0.44	0.47	6.89	1.07	5.595
F4	22	102	276	2.49	0.43	0.47	8.41	1.09	5.56

The differences between untapped and tapped density of the granules bed were relative low, those parameters gave Carr Indexes (CI) and Hausner ratios which display good to excellent flowability of the dry extracts [1, 5]. The volume of alcoholic rose petal extract pulverized on the solid support during the granulation process did not seem to influence the granule size or other pharmaceutical properties.

Good flow properties, compressibility and compactibility are critical attributes in order to compress the dry extracts into tablets. Materials that do not meet these criteria are difficult to compress and could lead to an improper final product.

The total phenolic content of the dry rose petal extracts was calculated given that 100 mL rose petal extractive solution had a residue of 3.53 g, which was added to the isomalt quantity in order to obtain the final dry extract. Results are presented in Table III.

Table III
Total phenolic content of the dry rose petal extracts

Formulation code	Total phenolic content (mg gallic acid/100 g dry extract)
F1	781
F2	1132
F3	1605
F4	2006

Tablets characterisation

As can be seen in Table IV, the compressed lozenge tablets had a good mass uniformity, with variations of maximum 3.8% and relatively low standard deviations. Hardness values registered for the tablets were between 230 and 300 N. The highest friability of 0.2% was obtained for the tablets with the lowest hardness, according to the specifications of the European Pharmacopoeia [1], this value being acceptable for compressed lozenges. The low weight

variations and high hardness of the tablets also reflect the high quality of the dry extracts. High hardness and low friability values are typical for buccal tablets, these properties ensuring that the

tablets do not disintegrate when maintained in the oral cavity, but slowly dissolve when maintained at this level [6].

Table IV

Weight variation, hardness and friability of tablets

Formulation code	Weight (mg) *average $\pm$ %	Hardness (N) **average $\pm$ SD	Friability (%)
F1	934 $\pm$ 2.3	250 $\pm$ 33	0.15
F2	935 $\pm$ 3.5	230 $\pm$ 18	0.20
F3	904 $\pm$ 3.8	253 $\pm$ 33	0.11
F4	912 $\pm$ 1.1	296 $\pm$ 43	0.08

*n = 20, **n = 10, SD – standard deviation

NIR analysis

The main purpose of this study was to develop a method for direct quantification of gallic acid from dry extracts and compressed lozenges, without any sample preparation, using NIR – chemometric techniques. In order to develop a good quantification method, the choice of an adequate number of principal components and spectral data pre-treatment method is critical in a PLS chemometric calibration. This is important in order to avoid the “over-fitting” phenomenon [14, 15]. The selection of the best calibration model was based on the investigation of the number of principal components and the calculation of root mean square error of cross validation (RMSECV). This kind of diagnostic test indicates both precision and accuracy of predictions and it was recalculated upon addition of each new PLS factor [15]. For each pre-processing method, the square correlation coefficient (R^2) between the known concentration value and the predicted one was determined.

As shown in Table V, in order to develop the gallic acid quantification method from the dry rose petal extract, IR spectral range was set between 10000 cm^{-1}

and 4000 cm^{-1} and the spectral values were pre-processed using different chemometric methods. The best statistical values were obtained by applying *model g* described in Table V, consisting in applying the first derivate and then the SNV pre-treatment on the spectral data. Similar results were also obtained by using *model h*, which imposes the MSC pre-treatment instead of SNV. By selecting 5 PLS factors, the R^2 value was 0.99 with a RMSECV of 42.8.

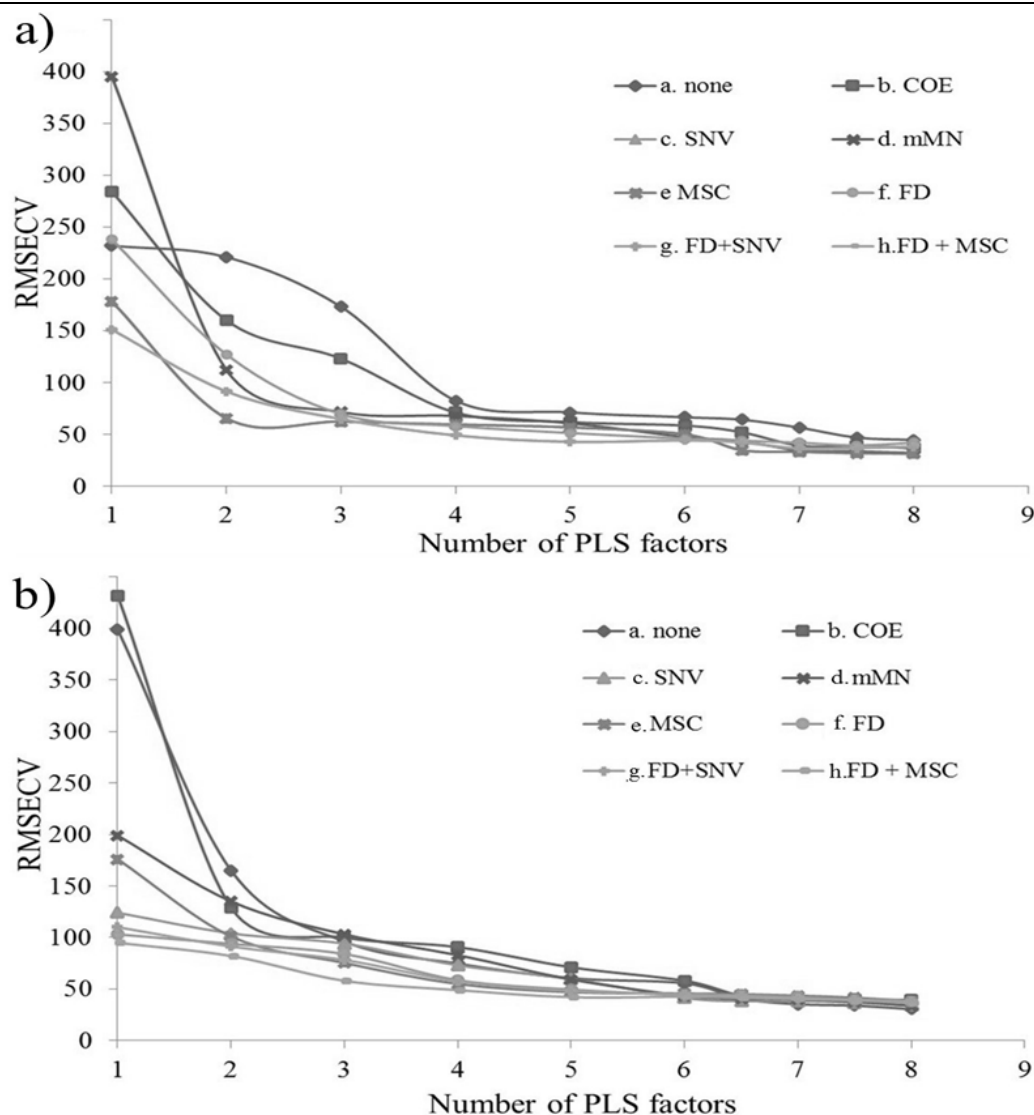
For the quantification of gallic acid content from compressed tablet lozenges, before the application of any pre-treatments, three spectral ranges were selected: 10000 - 7400, 7100 - 5600 and 5275 - 4000 cm^{-1} for further analysis. The NIR transmittance spectral regions between 7400 - 7100 cm^{-1} and 5600 - 5275 cm^{-1} presented significant differences between absorption bands and were eliminated from the analysis. By applying *model h* described in the compressed tablet lozenges section of Table V, namely the first derivate in combination with the MSC pre-treatment applied to the selected spectral range, using a number of 5 PLS factors, the registered R^2 value was 0.99, with a low RMSECV of 42.

Table V

Pre-treatment method, selected spectral range and statistical results for the quantification of gallic acid

Dry extracts								
Model	a	b	c	d	e	f	g	h
Pre-treatment	None	COE	SNV	mMN	MSC	FD	FD + SNV	FD + MSC
Selected spectral range (cm^{-1})				10000 - 4000				
PLS factors	10	8	7	8	7	8	5	5
R^2	0.9908	0.9928	0.9934	0.9944	0.9943	0.9917	0.9914	0.9913
RMSECV	44.5	39.1	34.7	34.3	34.7	42	42.8	42.8
Compressed tablet lozenges								
Model	a	b	c	d	e	f	g	h
Pre-treatment	None	COE	SNV	mMN	MSC	FD	FD + SNV	FD + MSC
Selected spectral range (cm^{-1})				10000 - 7400	7100 - 5600	5275 - 4000		
PLS factors	5	7	6	6	5	6	6	5
R^2	0.9834	0.992	0.9912	0.9913	0.9899	0.991	0.9908	0.9919
RMSECV	60.4	43.6	41.3	43.4	46.9	44.2	44.8	42

COE – constant offset elimination; SNV – standard normal variate; mMN – minim - maxim normalization; MSC – multiplicative scatter correction; FD – first derivate; FD + SNV – first derivate followed by standard normal variate; FD + MSC – first derivate followed by multiplicative scatter correction; PLS – partial least square; R^2 – correlation coefficient; RMSECV – Root-Mean-Square Error of Cross Validation.

**Figure 1.**

RMSECV variation depending on the PLS factors for quantification of gallic acid in a) dry extracts and b) compressed tablet lozenges

Legend: COE – constant offset elimination; SNV – standard normal variate; mMN – minimum - maximum normalization; MSC – multiplicative scatter correction; FD – first derivate; FD + SNV – first derivate followed by standard normal variate; FD + MSC – first derivate followed by multiplicative scatter correction; RMSECV – Root-Mean-Square Error of Cross Validation; PLS – Partial Least Square.

As Figure 1 shows, the RMSECV values improve when the number of PLS factors increases, but in the same time it is known that the increase of PLS factors causes loss of information regarding the NIR spectra. So the finding of the best balance between the RMSECV value and the number of PLS factors is a critical step in the development of prediction methods.

Applying the developed NIR – chemometric methods described above, the gallic acid content was estimated from products with intermediate concentrations (F2 and F3). 6 samples from each of the two dry extracts and 10 compressed lozenge samples from each

intermediate concentration were analysed. The results of the gallic acid content predicted by the NIR - chemometric methods and compared with the UV reference method are presented in Table VI for dry extracts and in Table VII for compressed tablet lozenges. The registered recovery of the active principles content from dry extracts, using the developed quantification method, was 100.2% for F2, respectively 99% for F3. Regarding the gallic acid content prediction from tablets, the calculated recoveries values were around 101% for the F2 and 100.6% for the F3 compressed tablet lozenges.

Table VI

Predictions of the gallic acid content from dry extracts, obtained using the NIR-chemometric method, compared with the classical method

Dry extracts										
Reference UV method		NIR - Chemometric method				Reference UV method		NIR - Chemometric method		
Pre-treatment		FD + SNV		FD + MSC		FD + SNV		FD + MSC		
Sample	Found (mg)	Found (mg)	Recovered (%)	Found (mg)	Recovered (%)	Found (mg)	Found (mg)	Recovered (%)	Found (mg)	Recovered (%)
1	1132	1094	96.63	1094	96.65	1605	1579	98.4	1579	98.4
2		1122	99.1	1122	99.1		1581	98.49	1581	98.49
3		1105	97.63	1105	97.63		1539	95.88	1539	95.88
4		1210	106.89	1210	106.91		1662	103.58	1662	103.58
5		1097	96.94	1098	96.96		1589	98.99	1589	99
6		1177	103.95	1177	103.96		1575	98.14	1575	98.14
Mean		1134	100.19	1134	100.2		1588	98.91	1588	98.91
CV		3.58		3.58			2.16		2.16	

SNV – standard normal variate; MSC – multiplicative scatter correction; FD – first derivative; FD + SNV – first derivative followed by standard normal variate; FD + MSC – first derivative followed by multiplicative scatter correction; CV – coefficient of variation.

Table VII

Predictions of the gallic acid content from compressed tablet lozenges, obtained using the NIR - chemometric method, compared with the classical method

Tablet lozenges										
Reference UV method		NIR - Chemometric method				Reference UV method		NIR - Chemometric method		
Pre-treatment		FD + SNV		FD + MSC		FD + SNV		FD + MSC		
Sample	Found (mg)	Found (mg)	Recovered (%)	Found (mg)	Recovered (%)	Found (mg)	Found (mg)	Recovered (%)	Found (mg)	Recovered (%)
1	1132	1111	98.14	1110	98.07	1605	1584	98.71	1591	99.14
2		1139	100.62	1138	100.54		1618	100.82	1618	100.82
3		1094	96.63	1098	96.96		1665	103.76	1658	103.31
4		1162	102.68	1171	103.46		1607	100.15	1605	99.98
5		1125	99.35	1118	98.79		1608	100.17	1613	100.49
6		1208	106.73	1211	106.93		1645	102.47	1644	102.44
7		1188	104.93	1182	104.41		1598	99.55	1603	99.86
8		1174	103.68	1202	106.21		1654	103.07	1641	102.24
9		1088	96.07	1075	94.99		1585	98.75	1571	97.88
10		1165	102.92	1133	100.1		1606	100.04	1593	99.25
Mean		1145	101.17	1144	101.05		1617	100.75	1614	100.54
CV		3.21		3.62			1.59		1.52	

SNV – standard normal variate; MSC – multiplicative scatter correction; FD – first derivative; FD + SNV – first derivative followed by standard normal variate; FD + MSC – first derivative followed by multiplicative scatter correction; CV – coefficient of variation.

Conclusions

In this study a new method for the manufacturing of dry rose petal extracts and compressed tablet lozenges was developed. First, a dry extract was obtained through the adsorption of alcoholic rose petal extract on isomalt. The obtained product presented excellent compressibility and flow properties which allowed it to be easily compressed into tablet lozenges with ideal size, which reached the expected quality standards regarding hardness, friability and active ingredients content.

The obtained dry extracts and tablets were characterized using a new NIR – chemometric method which was applied directly on the product, without any sample preparation. During the method development different calibration models were

evaluated for the nondestructive quantitative analysis of gallic acid and a good similarity between the results from the proposed NIR – chemometric and the UV Folin-Ciocalteu reference method was registered.

In conclusion, the developed manufacturing method permitted the manufacturing of high quality dry extracts and compressed tablet lozenges. Also the study has revealed that NIR spectrometry in association with the specified chemometric pre-processing methods can be used for the direct quantification of gallic acid from dry extracts or intact tablets, without any sample preparation or compromising the products, fact proven by the remarkably precise and accurate results obtained using this proposed method.

Acknowledgement

The authors are thankful to Plantextrakt SRL (Romania) for providing the *Rosa damascena* 1:10 ethanolic extract necessary to carry out the research work.

References

1. ***The European Pharmacopoeia, 8th ed. 2015.
2. Antonoaea P., Sylvester B., Tomuta I., Ciurba A., R  dai E., Todoran N., Muntean D.L., Direct quantification of meloxicam from transdermal therapeutic systems by NIR spectroscopy. *Farmacia*, 2017; 65(2): 230-236.
3. Basim E., Basim H., Antibacterial activity of *Rosa damascena* essential oil. *Fitoterapia*, 2003; 74(4): 394-396.
4. Bayrak A., Akg  l A., Volatile oil composition of Turkish rose (*Rosa damascena*). *J. Sci. Food. Agric.*, 1994; 64(4): 441-448.
5. Carr R.L., Evaluating Flow Properties of Solids. *Chem. Eng.*, 1965; 72(2): 163-168.
6. Gad S.C., Tablet design. In: *Pharmaceutical Manufacturing Handbook: Production and Processes*. Cary, USA: Wiley-Interscience Inc.; 2008; 977-1053.
7. Luypaert J., Massart D.L., Vander Heyden Y., Near-infrared spectroscopy applications in pharmaceutical analysis. *Talanta*, 2007; 72(3): 865-883.
8. Mendes R.W., Bhargava H., Lozenges. In: *Encyclopedia of Pharmaceutical Technology*. 3rd ed. Informa Healthcare USA, Inc.; 2007; 2231-2235.
9. Otto M., *Chemometrics: Statistics and Computer Application in Analytical Chemistry*. 3rd ed. Weinheim, Germany: Wiley-VCH Verlag; 2017.
10. Parikh D.M., *Handbook of Pharmaceutical Granulation Technology*. 2nd ed. Boca Raton, USA: Taylor & Francis Group; 2005.
11. Reich G., Near-infrared spectroscopy and imaging: Basic principles and pharmaceutical applications. *Adv. Drug. Deliv. Rev.*, 2005; 57(8): 1109-1143.
12. Shohayeb M., Abdel-Hameed E.S.S., Bazaid S.A., Maghrabi I., Antibacterial and antifungal activity of *Rosa damascena* MILL. essential oil, different extracts of rose petals. *Glob. J. Pharmacol.*, 2014; 8(1): 1-7.
13. Singleton V.L., Orthofer R., Lamuela-Raventos R.M., Analysis of total phenols and other oxidation substrates and antioxidants by means of Folin-Ciocalteu reagent. *Meth. Enzymol.*, 1999; 299: 152-178.
14. Toiu A., Vlase L., Dr  goi C.M., Vodnard D., Oniga I., Phytochemical analysis, antioxidant and antibacterial activities of *Hypericum humifusum* L. (*Hypericaceae*). *Farmacia*, 2016; 64(5): 663-667.
15. Tomuta I., Iovanov R., Bodoki E., Vonica L., Development and validation of NIR-chemometric methods for chemical and pharmaceutical characterization of meloxicam tablets. *Drug Dev. Ind. Pharm.*, 2014; 40(4): 549-559.
16. Tomuta I., Rus L., Iovanov R., Rus L.L., High-throughput NIR-chemometric methods for determination of drug content and pharmaceutical properties of indapamide tablets. *J. Pharm. Biomed. Anal.*, 2013; 8: 285-292.
17. Xiong C., Liu C., Pan W., Ma F., Xiong C., Qi L., Chen F., Lu X., Yang J., Zheng L., Non-destructive determination of total polyphenols content and classification of storage periods of Iron Buddha tea using multispectral imaging system. *Food Chem.*, 2015; 176: 130-136.