Assessing compatibility of excipients selected for a sustained release formulation of bilberry leaf extract

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The study is aimed to assess the compatibility of bilberry leaf powder extract (BLPE) with six excipients selected for sustained-release (SR) tablet formulation. The BLPE was obtained with the addition of L-arginine and Myo-inositol as the carriers. Thermogravimetric (TG–DTG) analysis and Fourier-transform infrared spectroscopy (FTIR), supported by Pearson correlation analysis, were applied to detect possible interactions in the binary mixtures (1:1) of the BLPE with each excipient. The TG–DTG showed some deviations in the thermal behavior of the BLPE / excipient mixtures. However, only the thermal behavior of magnesium stearate in the mixture significantly differed from individual samples, which suggested chemical interaction for this excipient. The FTIR analysis confirmed that the BLPE is compatible with Eudragit L100, Methocel K4M, Methocel K100LV, Avicel PH-101, and Plasdone S-630. Whereas it undergoes solid-state chemical interaction in the binary mixture with magnesium stearate. According to the FTIR-spectra, it is suggested that this interaction results in the formation of stearic acid and alkalization of the medium. These findings evidence for the possibility of using TG-DTG analysis as an independent thermal technique for compatibility studies and also confirm the earlier reported interaction of basic lubricants, e.g., stearic salts, with active ingredients containing amino groups.

Keywords: Bilberry leaves. Herbal extract. Thermogravimetric analysis. FTIR spectroscopy. Compatibility study. Pearson correlation analysis. Pearson correlation analysis.

INTRODUCTION

Nowadays herbal medicines attract a growing research interest in the field of drug development. Plant-derived drugs, due to the presence of a diversity of biologically active substances (BAS), have a unique therapeutic potential. Besides, they are much better tolerated and possess fewer adverse effects as compared to synthetic drugs. However, the efficacy of herbal drugs is often limited by their low bioavailability. To overcome this problem, several approaches to the development of herbal drug formulation are described and discussed in the literature. Among them there are novel delivery systems, including polymer- and lipid-based nanocarriers (Bilia *et al*., 2014; Conte *et al*., 2017; Mouhid *et al*., 2017), cyclodextrin inclusion complexes (Suvarna, Gujar, Murahari, 2017), phytosomes (Mancini *et al*., 2018), as well as modified-release matrix systems (Gallo *et al*., 2013; Singhal et al., 2011). The last-mentioned ones have some advantages since they are simple to formulate, inexpensive and easy to produce, and have a good in vitro–in vivo correlation (Maderuelo, Zarzuelo, Lanao, 2011). At the same time, the development of a modified-release formulation, in this case, can be challenging since herbal drugs, such as extracts, usually contain components with different physicochemical properties. Due to this, achieving synchronous release of all active extract compounds would be difficult. Therefore, a possible solution is using a hydrophilic matrix system,

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which provides drug release mainly by erosion of matrix excipients what ensures a complete drug release covering all extract compounds (Disch *et al.*, 2017).

In our work, we consider bilberry (*Vaccinium myrtillus*) leaf powder extract (BLPE) as a suitable substance for the development of herbal SR matrix tablets. Bilberry is a perennial low-growing shrub native to Europe, Northern Asia, including Japan, and also to Greenland (Nestby *et al.*, 2011). Leaves of this plant have long been used as an antidiabetic folk remedy. Recent studies revealed α-glucosidase inhibiting, antiobesity and lipid-lowering activities of their extract (Bljajić *et al.*, 2017; Cignarella *et al.*, 1996; Sidorova *et al.*, 2017; Zagayko *et al.*, 2018). The preliminary phytochemical investigation of BLPE indicated that it is rich in hydroxycinnamic acids and flavonoids. The occurrence of caffeic and p-coumaric acids, kaempferol-3-O-glucoside, and epicatechin was established, chlorogenic acid and rutin being determined as the dominant phytoconstituents of the dried water-ethanolic extract (Koshovyi *et al.*, 2016a). One of the features of BLPE is that it is obtained with the addition of L-arginine and Myo-inositol as carriers of health benefits. In previous studies, it was found that the addition of the mentioned carriers to the liquid crude extract resulted in better hypoglycemic and insulin-sensitizing activities of BLPE compared to those of the extract without carriers (the extracts were evaluated in equimolar amounts in respect to total polyphenolic content) (Koshovyi *et al.*, 2016b).

To develop SR matrix tablets containing BLPE as the active pharmaceutical ingredient (API), we have selected several pharmaceutical excipients, namely, modified release agents, diluent, binder, and lubricant (Table I). Since the API is not an individual substance but an herbal extract having a complex composition, it is hard to predict the chemical interaction and therefore incompatibility in the formulation. On the other hand, in solid dosage forms, e.g., tablets, signs of instability and incompatibility usually do not appear immediately or after a short time, as it occurs with liquids and semisolids. They often can be detected only during a real-time stability study of a final product, which is time and cost consuming. Therefore, tablet formulation development especially requires assessing drug-excipient compatibility at the pre-formulation stage to avoid possible stability problems with the designed drug formulation.

TABLE I – Pharmaceutical excipients used in the compatibility study

Brand name	Ph.Eur. / USP-NF monograph	Function in the formulation	Provider
Eudragit® L100	Methacrylic acid – methyl methacrylate copolymer (1:1) (Ph.Eur.), Methacrylic Acid and Methyl Methacrylate Copolymer (1:1) (USP-NF)	Modified release agent	Evonik, Germany
Methocel™ K4M	Hypromellose (Ph.Eur., USP-NF)	Modified release agent	Dow Chemical Company, USA
Methocel™ K100LV	Hypromellose (Ph.Eur., USP-NF)	Modified release agent	Dow Chemical Company, USA
Avicel® PH-101	Cellulose, microcrystalline (Ph.Eur.), Microcrystalline cellulose (USP-NF)	Diluent	FMC BioPolymer, USA
Plasdone™ S-630	Copovidone (Ph.Eur., USP-NF)	Binder	Ashland Inc., USA
Magnesium stearate	Magnesium stearate (Ph.Eur., USP-NF)	Lubricant	Electrogasochem Ltd., Ukraine

Note. Ph.Eur. – European Pharmacopoeia, USP-NF – the United States Pharmacopeia–National Formulary

Several techniques have been described to assess the compatibility of the API with pharmaceutical excipients at the pre-formulation stage. In general, such techniques can be divided into thermal and non-thermal ones. The former most frequently include differential scanning calorimetry (DSC), differential thermal analysis (DTA), and thermogravimetry (TG) (Lavor *et al.*, 2014). All these methods imply measuring, under programmed temperatures, certain parameters for binary mixtures "drug–excipient" and comparing them to the parameters obtained for individual samples. These parameters are the differences in heat flow (DSC), temperature (DTA), mass (TG), and mass loss rate (derivative thermogravimetry – DTG) between a sample and an inert reference.

Thermal analysis requires that along with the temperature, environmental conditions should be appropriately set and controlled during the experiment. An atmosphere of N_2, He, air, other gas, or vacuum can be applied for such purposes (Monajjemzadeh, Ghaderi, 2015). However, the use of nitrogen and air is most widely mentioned in pharmaceutical pre-formulation studies (Alves *et al.*, 2010; Lavor *et al.*, 2014; Mainardes, Gremião, Evangelista, 2006; Ziegler-Borowska, Chełminiak, Kaczmarek, 2015). If the API or excipient chemical structures suggest the possibility of oxygen degradation (which may be induced by elevated temperature, another ingredient, or impurities), the assessment, apparently, should be conducted in the presence of oxygen, i.e. air atmosphere. This route of degradation is most likely to occur in compounds with double carbon bonds (Jones, 2018), including bioactive polyphenols (Ramešová *et al.*, 2012).

One of the main drawbacks of thermal techniques is that the interactions observed under highly elevated temperatures may not correspond to those occurring under normal storage conditions (Liltorp *et al.*, 2011; Pramod *et al.*, 2015). Due to this, non-thermal techniques are used in drug-excipient compatibility screening. Fourier-transform infrared spectroscopy (FTIR) is the most popular non-thermal technique used to detect interactions in drug–excipient mixtures under common storage temperatures. However, it is suggested that the presence of overlapping bands in the FTIR spectra can complicate the interpretation of the analysis results. In this regard, mathematical tools, such as principal component analysis and Pearson correlation analysis, applied to analyze the FTIR spectra, were described as approaches to support a decision on the compatibility of ingredients (Da Silva *et al.*, 2016; De Barros Lima *et al.*, 2015; Lavor *et al.*, 2014; Wesolowski, Rojek, 2013).

It should be noted that drug–compatibility studies most commonly include FTIR, either alone or in combination with both DSC/DTA and TGA. However, there is a lack of data on the possibility of using TGA independently from DSC/DTA. Thus, the present study aims to assess the compatibility between BLPE and selected pharmaceutical excipients employing TGA and verify the obtained results by FTIR supported by Pearson correlation analysis.

MATERIAL AND METHODS

Material

L-arginine was purchased from Kyowa Hakko Co. Ltd., Tokyo, Japan. All other chemicals used for the extract preparation (i.e., Myo-inositol, Folin-Ciocalteu reagent, sodium carbonate, and standard of pyrogallol) were purchased from Sigma-Aldrich.

Extract preparation

The BLPE was obtained as described by Zagayko *et al.* (2018). The total phenolic content of the extract, expressed as pyrogallol equivalent (PE), was determined spectrophotometrically by Folin-Ciocalteu reaction, according to European Pharmacopeia's chapter 2.8.14. Determination of tannins in herbal drugs (Council of Europe, 2016). The total phenolic content of the BLPE was 99.29 ± 1.21 mg PE/g on a dry-matter basis.

The final powder extract was stored at 4°C until use.

Binary mixtures preparation

The binary mixtures were obtained by manual mixing of the BLPE with each of the excipients, in a 1:1 mass ratio, using a pestle and mortar. The proportion

was chosen on the assumption that each of the excipients will be included in the tablet formulation in an amount not exceeding the API, the equal ratio maximizing the probability of interaction detection (Talvani *et al.*, 2014).

The excipients selected for the compatibility study are listed in Table I.

Thermogravimetric analysis

TG and DTG curves of the individual samples and binary mixtures were obtained by using the measuring module TG 50 of the Mettler TA 3000 thermal analyzer under air atmosphere. The thermal scans were carried out in the temperature range from 25 to 550°C at a 5°C min^{-1} heating rate.

FTIR

The infrared (IR) spectra of the samples were obtained with KBr pellets, in the 4000–400 cm^{-1} wavelength range, using Spectrum One FTIR Spectrometer (PerkinElmer).

Pearson correlation analysis

To detect incompatibilities between the BLPE and selected excipients, Pearson correlation analysis for the obtained IR spectra was performed as described in other research works (Da Silva *et al.*, 2016; De Barros Lima *et al.*, 2015; Lavor *et al.*, 2014). The analysis was carried out by comparing the experimental spectrum of each binary mixture with the theoretical one, which was built as a linear combination of the experimental spectra of the individual samples. The spectral region from 600 to 1800 cm^{-1} (the fingerprint region) was considered in this approach. For the analysis, the following ad-hoc algorithm

(Lavor *et al.*, 2014) was applied. First, the experimental and theoretical spectra were compared as a whole, and then the comparison of each half of the spectra, each half of the halves, and so on, was carried out. Using Microsoft Excel software, the values of the correlations for each range being compared were calculated, and their averages were assigned to the corresponding regions of the IR spectrum. As reported in the literature, Pearson correlation coefficients between 0.80 and 1.00 are characteristic of a simple mixture of solids, values from 0.5 to 0.80 indicate possible interactions, and those below 0.50 are a sign of low similarity between spectra, demonstrating chemical interaction.

RESULTS AND DISCUSSION

The obtained TG–DTG curves of the BLPE showed the occurrence of five mass loss events (Figure 1). The first event occurred in the temperature range of 50 – 119°C, with the mass loss of 2.5 %, obviously corresponding to dehydration and loss of volatile compounds present in the powder extract. The second event occurred in the temperature range between 119 and 177°C and resulted in a mass loss of 4.6 %, corresponding to the first stage of BLPE decomposition. The third event, with a mass loss of 13.7 %, arose between 177 and 259°C and was followed by the fourth event in the temperature range from 259 to 348°C, which caused the most significant mass loss of 21.3 %. These two events may be attributed to thermal decomposition of the extract carriers (i.e., L-arginine and Myo-inositol) and carbohydrates, as well as other organic phytoconstituents of the plant extract (Araújo *et al.*, 2006). The fifth step of mass loss was 16.1 % and occurred between 348 and 445°C, probably corresponding to the degradation of more stable compounds and beginning of the formation of ashes.
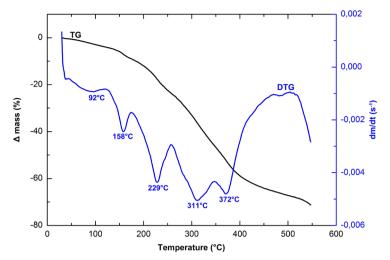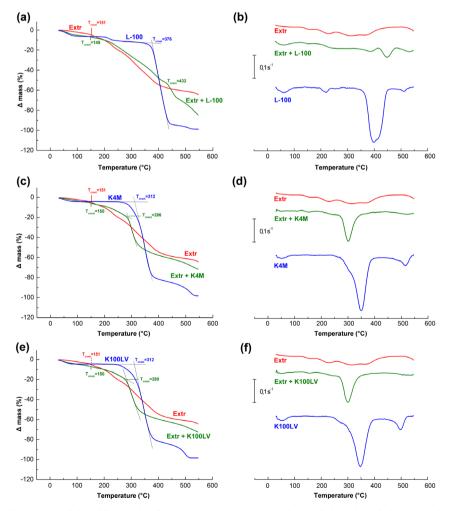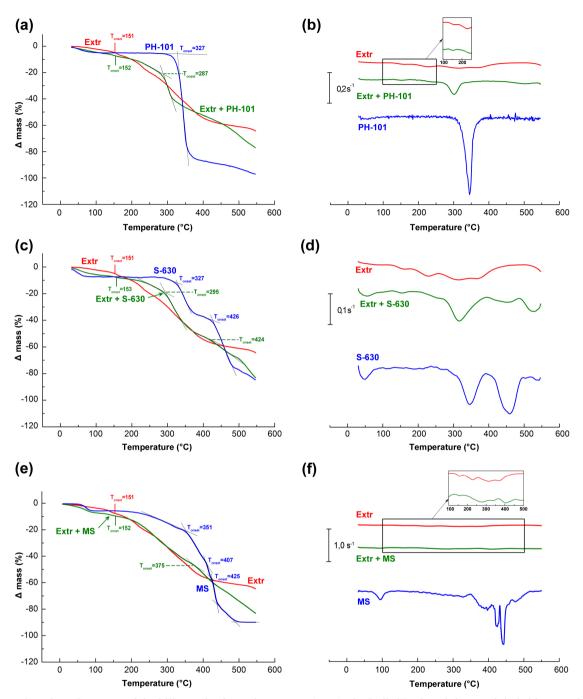
FIGURE 1 – TG and DTG curves of the bilberry leaf powder extract with the indication of peak temperatures of mass loss events.

The TG and DTG curves of the BLPE / excipient binary mixtures are shown in Figure 2 and Figure 3.

FIGURE 2 – TG and DTG curves of the bilberry leaf powder extract (Extr), the individual excipient and their binary mixture (1:1 mass ratio): Eudragit L100 (L-100) (a, b), Methocel K4M (K4M) (c, d), and Methocel K100LV (K100LV) (e, f).

FIGURE 3 – TG and DTG curves of the bilberry leaf powder extract (Extr), the individual excipient and their binary mixture (1:1 mass ratio): Avicel PH-101 (PH-101) (a, b), Plasdone S-630 (S-630) (c, d), and magnesium stearate (MS) (e, f).

According to Neto, Novák, Matos (2009), if there is no drug / excipient interaction "the T_{onset} value of the first stage of the decomposition (T_{onset} of TG–DTG curves) should remain practically unchanged, similarly when the drug is alone". However, when interpreting thermogravimetric data, we also took into consideration whether the TG–DTG curves of the binary mixtures reflected not only the thermal behavior of the powder extract but that of the excipient too.

As it can be seen from the TG–DTG curves, Eudragit L100 did not affect the first stage of thermal decomposition of the BLPE (Figures 2a and 2b).

Moreover, the T_{onset} value of the second decomposition stage was practically the same for the BLPE and the binary mixture (151 and 149°C, respectively). The third event T_{onset} values were 177 and 179°C for the API and the mixture, respectively, though the latter had a broader peak, which may be attributed to overlapping with the excipient peak that occurred in the close temperature range (T_{onset} = 189°C). The DTG curve of the binary mixture also contained a characteristic peak of Eudragit L100, which shifted to higher temperatures and was narrower compared with the excipient alone. The shift of Eudragit L100 degradation peak is also clearly seen on the TG curve (T_{onset} is 432 versus 376°C). This possibly indicates the interaction of Eudragit L100 with BLPE degradation products and the formation of more thermally stable compounds. However, these results do not suggest the incompatibility between the BLPE and Eudragit L100.

The TG–DTG curves for the binary mixtures of the BLPE with cellulose derivatives, namely, Methocel K4M (Figures 2c and 2d), Methocel K100LV (Figures 2e and 2f), and Avicel PH-101 (Figures 3a and 3b) showed a very similar thermal behavior. Each of these binary mixture DTG curves did not present any modification of the first stage of thermal decomposition of the BLPE and had a characteristic peak of the excipient degradation, which shifted to lower temperatures compared with the pure excipient (T_{peak} values were 301°C versus 350°C, 300°C versus 347°C, and 301°C versus 345°C for Methocel K4M, Methocel K100LV, and Avicel PH-101, respectively). These shifts of the peaks of the excipients indicate that the acceleration of their thermal degradation is possibly caused by the interaction with the products of the BLPE decomposition, however, it does not necessarily mean incompatibility.
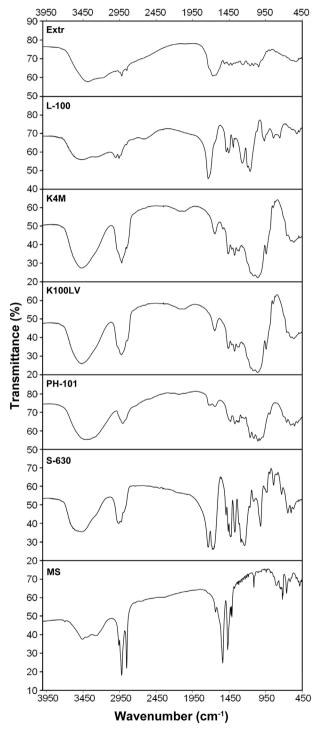
According to Figures 3c and 3d, both BLPE and Plasdone S-630 were observed in the TG–DTG curves of the binary mixture. Also, the TG–DTG curves showed that the first stage of BLPE thermal decomposition remained practically unchanged in the mixture, while the beginning of the first stage of excipient degradation shifted to lower temperatures, and the second one started at the same temperature.

The mixture of the BLPE with magnesium stearate (Figures 3e and 3f) demonstrated some distinct changes in the thermogravimetric profile as compared with the individual samples. Magnesium stearate was not observed in the TG curve of the binary mixture, and such variations in the shape of the TG curve can be indicative of incompatibility (Wesolowski, Rojek, 2013). From both TG–DTG curves of the mixture, it was identified that the first decomposition stage of the powder extract did not undergo a significant change. However, the DTG curve showed that the second decomposition stage had a much broader peak compared with that of the pure BLPE. In this case, it cannot be explained as overlapping with any of the excipient peaks. Moreover, instead of one broad and two sharp peaks for pure magnesium stearate, occurring in the temperature ranges 351–407°C, 407–425°C, and 438–489°C, respectively, there was only one broad peak in the DTG curve of the binary mixture in the temperature range of 375–530°C. Thus, these results indicate a possible interaction between BLPE and magnesium stearate.
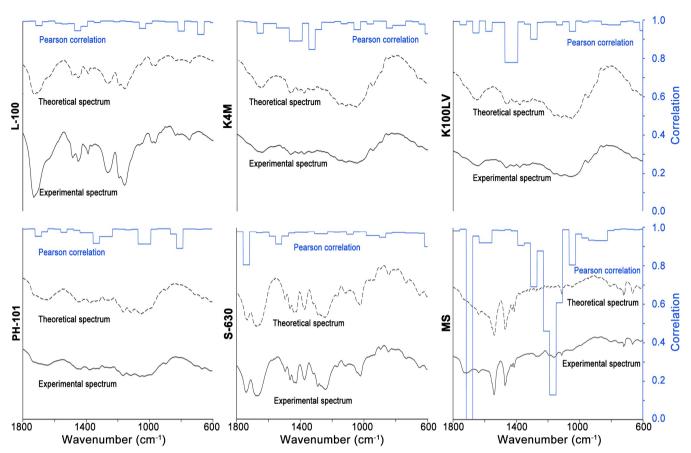
To verify the results obtained in the course of the thermogravimetric analysis, we applied FTIR spectroscopy investigation supported by Pearson correlation analysis, as described above.

The FTIR spectra of the individual samples are shown in Figure 4. In the FTIR spectrum related to the powder extract, there is broadband with peaks at 3391 and 3213 cm^{-1}, obviously resulting from superimposed O–H and NH^{3+} stretches (Silverstein, Webster, Kiemle, 2005). In this case, hydroxyl groups are attributed both to hydroxylated molecules of the extract (such as polyphenols) and to the moisture content of the extract (Santana *et al*. 2018), while NH^{3+} stretch band is attributed to L-arginine. The sharp peaks at 2920 and 2852 cm^{-1} are characteristic of carbon-hydrogen bonds (Silverstein, Webster, Kiemle, 2005). The band with peaks from 1680 to 1630 cm^{-1} is indicative of aromatic carbon-oxygen bonds (C=O) (Silverstein, Webster, Kiemle, 2005), which are present in a variety of plant secondary metabolites, in particular, tannins, flavonoids, and hydroxycinnamic acids. The peaks in the region of 1514–1491 cm^{-1} are characteristic of carbon-carbon ring bonds (Silverstein, Webster, Kiemle, 2005). The peaks that occurred from 1448 to 1360 cm^{-1} may be attributed to H–C–O groups of Myo-inositol (Mishra, Srivastava, Shukla, 2017). The

bands at 1264, 1163, 1116, and 1046 cm^{-1} are probably related to alcoholic C−O stretches (Silverstein, Webster, Kiemle, 2005).

FIGURE 4 – FTIR spectra of the individual samples: bilberry leaf powder extract (Extr), Eudragit L100 (L-100), Methocel K4M (K4M), Methocel K100LV (K100LV), Avicel PH-101 (PH-101), Plasdone S-630 (S-630), and magnesium stearate (MS).

Figure 5 shows all binary mixtures analyzed by FTIR, where the experimental spectra were compared with the theoretical ones. The Pearson correlation indicated compatibility in the binary mixtures of BLPE with Eudragit L100 and Avicel PH-101, since the correlation values were about 0.9 or higher. Most deviations of the experimental spectra from the theoretical spectra for Methocel K4M mixture were observed in the regions near 1440 and 1330 cm^{-1} and may be caused by disturbing of H−C−O groups of Myo-inositol (with the correlation values of 0.89 and 0.84, respectively). The Pearson correlation analysis of the Methocel K100LV mixture showed the same situation with the correlation values of 0.78 and 0.82 in the mentioned regions, respectively. This is, probably, an indication that these excipients may only have a physical interaction with the BLPE via hydrogen bonds. The binary mixture of Plasdone S-630 gave the lowest correlation value of 0.82 in the region near 1740 cm^{-1}, also pointing only to a possible physical interaction with the BLPE. However, The Pearson correlation for the binary mixture of magnesium stearate showed strong interactions with the BLPE. The most significant change resulting in the negative correlation value of -0.98 (not shown on a scale) was observed near 1700 cm^{-1} and appeared as the prominent peak that was not detected in the individual FTIR spectra of the BLPE and the excipient. Obviously, this peak indicates the C=O bond of aliphatic acid (Silverstein et al. 2005), which may be related to stearic acid. The other lowest correlation values were 0.13, 0.46, 0.61, and 0.69, corresponding to the regions near 1170, 1210, 1290 and 1130 cm^{-1}, respectively. Therefore, a chemical interaction of the BLPE and magnesium stearate at environment temperature can be suggested.

FIGURE 5 – Pearson correlation analysis of FTIR spectra for the binary mixtures of the bilberry leaf powder extract and the excipients: Eudragit L-100 (L-100), Methocel K4M (K4M), Methocel K100LV (K100LV), Avicel PH-101 (PH-101), Plasdone S-630 (S-630), and magnesium stearate (MS).

Such solid-state interaction of magnesium stearate with the formation of stearic acid, occurring with amino groups, was described by Castello and Mattocks (1962). Apparently, in case of BLPE, magnesium stearate interacts with L-arginine. These authors have found that magnesium stearate removes the hydrogen ion of the amino group, contributing to an alkaline medium in the adsorbed moisture. The reaction in tablets can be accelerated with elevated temperature and high humidity.

It should be noted that magnesium stearate appears to be the most mentioned excipient in terms of incompatibility with drugs. It is suggested that one of the reasons for this is associated with impurities, namely, magnesium oxide (MgO) and palmitic acid, reacting with drug molecules. For instance, the interaction of MgO with ibuprofen was reported at 40°C and 75 % RH (Kararli *et al.*, 1989). Magnesium stearate was also reported to chemically react with many drugs by itself. The mechanisms may include hydrolytic degradation at basic pH (e.g., acetylsalicylic acid and quinapril), induction of oxidative degradation (drotaverine hydrochloride), metal ion-mediated degradation (fosinopril sodium), as well as reactions with amino groups of drug molecules. The latter can also occur through stearoyl rearrangement, i.e., hydrogen ion of amino group can be removed by stearoyl moiety, forming stearamide adduct (norfloxacin after prolonged storage at 60°C) (Hotha, Roychowdhury, Subramanian, 2016; Li, Wu, 2014). Thus, although solid formulations usually contain magnesium stearate at very low concentrations (usually no more than 1 %), it is better to avoid its use with drugs whose structure suggests possible interaction; so, alternative excipients but not stearic salts should be considered as lubricants in such cases.

CONCLUSIONS

In the present study, the examination of compatibility between the bilberry leaf powder extract and the selected pharmaceutical excipients was performed utilizing thermogravimetry and FTIR techniques. The thermogravimetric analysis has provided valuable data on the compatibility between the active pharmaceutical ingredient and the excipients, which were confirmed by FTIR, involving Pearson correlation analysis as an additional tool. The obtained results showed that the bilberry leaf powder extract is compatible with Eudragit L100, Methocel K4M, Methocel K100LV, Avicel PH-101, and Plasdone S-630. Meanwhile, solid-state chemical interactions are suggested in a 1:1 mass ratio binary mixture with magnesium stearate, apparently resulting in the formation of stearic acid and alkalization of the medium. These findings indicate the possibility of using TG-DTG analysis as an independent thermal technique for compatibility studies and also confirm the earlier reported interaction of basic lubricants, namely, stearic salts, with active ingredients containing amino groups.

DISCLOSURE OF INTEREST

The authors report no conflict of interest.

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