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SHORT COMMUNICATION

Determination of diosmin in pharmaceutical formulations using Fourier transform infrared spectrophotometry

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Abstract A Fourier transform infrared (FT-IR) spectrometric method was developed for the rapid, direct measurement of diosmin in different pharmaceutical drugs. Conventional KBr-spectra were compared for best determination of active substance in commercial preparations. The Beer–Lambert law and two chemometric approaches, partial least squares (PLS) and principal component regression (PCR+) methods, were tried in data processing.

1. Introduction

Infrared spectrometry (IR) provides a useful way for the identification of drugs (USP XXII, 1990; Moffat, 1986; Ciurczak and Drennen, 2001; McClure, 1992; Garrigues et al., 1992; Miller et al., 1988) as well as for quantitative analysis, and the help of Fourier transform (FT-IR) permits continuous monitoring of the spectral baseline and simultaneous analysis of different components of the same sample.

Diosmin (5-hydroxyl-2-(3-hydroxy-4-methoxy-phenyl)-4-oxo-4H-chromen-7-yl or 3′,5,7-trihydroxy-4′-methoxyflavone-7-rutinoside) is a naturally occurring flavone glycoside, used in the treatment of venous disease, i.e., chronic venous insufficiency (CVI) and hemorrhoidal disease (HD), in acute or chronic hemorrhoids, in place of rubber-band ligation, in combination with fiber supplement, or as an adjuvant therapy to hemorrhoidectomy, in order to reduce secondary bleeding.

Diosmin is used widely in Europe for decreasing the appearance of varicose veins and spider veins, and also hemorrhoids. Diosmin and other flavonoids thought to reduce capillary

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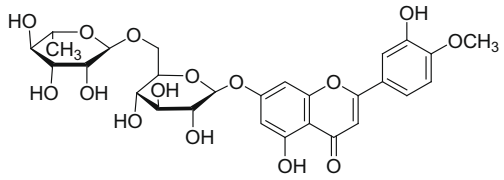
permeability and to have anti-inflammatory action, were collectively known as vitamin P, but these substances, however, are not vitamins. Hesperidin is the predominant flavonoid in lemons and oranges (Struckmann and Nicolaides, 1994). The peel and membranous parts of these fruits have the highest hesperidin concentrations. Hesperidine is classified as a citrus bioflavonoid.



Diosmin

Chemometric techniques which are known as numerical techniques are useful for the spectrophotometric resolution of complex mixtures of analytes without the need of prior separation or extraction. Although both PCR and PLS give successful results, they have several disadvantages such as using abstract mathematical theory and various softwares.

Determination of the major component in drugs with FT-IR spectrometry provides an enormous amount of spectroscopic information about a sample. Chemometric methods, such as principal component regression (PCR+, improved principal component regression) and partial least squares (PLS2, multi-component partial least squares) analysis are commonly used to extract the specific information relevant to the analyte of interest from the full spectrum (USP XXII, 1990; Haleblian and McCrone, 1969). These two techniques yields more accurate calibration models compared with multiple linear regressions (MLR) where a restricted set of absorption bands is used in the calibration (Luinge et al., 1993). The partial least squares (Projection to Latent Structures, PLS) regression method was developed by Wold (1966). There is a substantial amount of literature devoted to the theoretical elucidation of properties of PLS algorithm. A good introduction to the method is given by Geladi and Kowalski (1986).

The purpose of this study is the analysis of diosmin in pharmaceutical formulation using FT-IR spectroscopy with the application of Beer's law and/or chemometric methods (PCR+, PLS1 or PLS2), thus avoiding the sample pre-treatment steps and providing the direct FT-IR measurement.

2. Experimental

2.1. Apparatus

Data acquisition was performed using a Spectrum100 System FT-IR spectrometer equipped with Spectrum for Windows v.5.01 (Perkin–Elmer Co., Beaconsfield, Bucks, UK). This software also provided for a complete processing of the spectra measured. For quantitative determination special softwares were used, Spectrum Beer's law and Spectrum Quant+, respectively.

2.2. Reagents and materials

For fused KBr disk preparation, a potassium bromide IR spectral grade was used (Sigma–Aldrich, Taufkirchen, Germany).

The standard of diosmin was supplied by Fluka (Buchs, Switzerland).

The pharmaceutical formulation Dioven 500 (containing 500 mg per tablet products) was obtained from Amriya Pharmaceutical Industries International, Alexandria, Egypt.

2.3. Recommended procedures

Taking into consideration the heterogeneity of the specimens, major attention was paid to the sampling stage. Drug samples were ground in a coffee grinder; finer grinding and homogenization with KBr were achieved by using a 'vibrator' ball mill (WIG-L-BUG). The temperature was kept around 25 °C and the humidity was kept at a steady level in the laboratory.

Conventional fused KBr disk spectra were recorded between 4000 and 350 cm^{-1}, by averaging 64 scans for each spectrum with a resolution of 4 cm^{-1} (data point resolution/interval 1 cm^{-1}) with a deuterated triglycine sulfate (DTGS) detector. The samples were prepared by compressing 3.0 mg of sample with spectral grade KBr, while the background was spectral grade KBr. Each drug sample spectrum was collected three times for the same cup after rotation 120°. The mean of the spectra, which were collected, was then used in the following analysis steps.

For calibration, conventional fused KBr disk spectra were recorded with a DTGS detector from samples prepared by compressing a standard substance diosmin in spectral grade KBr (calibration was made using five points 1.0, 1.5, 2.0, 2.5 and 3.0 mg, respectively). The calibration procedure is based on either a modified form of principal component regression (PCR) or on a partial least squares (PLS) fit for one or more properties. The regression model for each property is refined by selecting only those factors considered to be of statistical significance in determining that property.

Experimental parameters, such as calibration methods, (PCR+, PLS1 or PLS2, respectively) were compared and recommendations on the best options for diosmin analysis were made.

3. Results and discussion

Fig. 1 presents the mean spectra for diosmin samples using the KBr disk method while the spectra of each pharmaceutical drug are presented in Fig. 2.

It is of interest to note that in the fingerprint region there are no significant differences between the spectra for KBr disk method.

In PCR and PLS2, the spectra are modeled by one set of factors and each property is modeled by relating the concentration values to those factors. In PLS1, the spectra are modeled by a different set of factors for each property and the concentration values are modeled by the respective factors. Hence PLS1 contains n separate calibrations, where n is the number of properties in the method.

The calibrations of this study were carried out with the use of the 'expert' option. The first range used was between 4000 and 400 cm^{-1} while the second range was 1570–1006 cm^{-1}. In both cases no blanks were first selected, but after calibration was performed, the computer selects itself ranges of blanks due

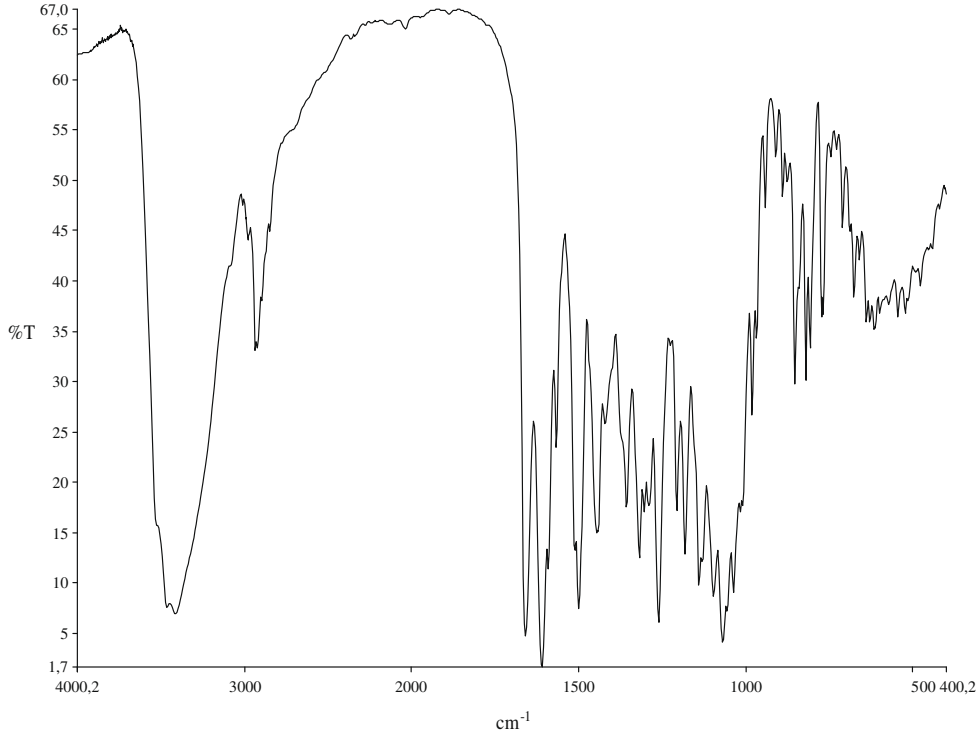


Figure 1 FT-IR spectra of diosmin – *standard substance* – in KBr-disk.

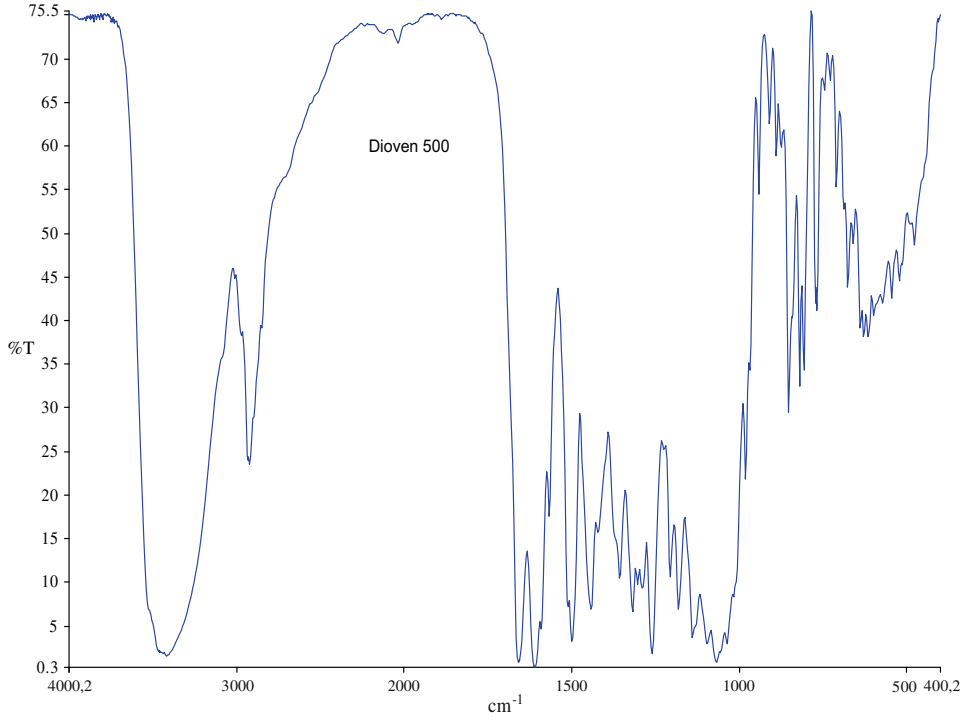


Figure 2 FT-IR spectra of pharmaceutical products – in KBr-disk.

to the thresholds. The number of data points used for analysis is 4048 and 1319, respectively. The results are similar, as shown in Table 1. We suggest the use of the PCR+ method, because the peak to peak error value must be five times bigger than root mean square (RMS) error value at the most and the smaller value of RSD ($< 3.0\%$).

We studied also the possibility to use the Beer–Lambert law for the quantitative determination of diosmin in pharmaceuti-

Table 1 Comparison of the diosmin determination in tablets using FT-IR chemometric approaches.

	Dioven	
	PCR +	PLS
Content (mg/tablet)	505.23	509.13
RSD (%) ($n = 5$)	2.25	3.06

cal formulation, but the measurements, could not be performed because we do not find a common baseline between the spectra.

4. Conclusion

FT-IR spectrometry is capable for the analytical quantification of diosmin in pharmaceutical formulation. Commercial software involving chemometric approaches, the method proposed is simple, precise and not time-consuming compared to the chromatographic methods that exist in literature. Quantification could be done in about 10–15 min, including sample preparation and spectral acquisition.

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