Quantitative determination of the ingredients of pharmaceutical tablets

Zsuzsa Bertha-Somodi and Zsofia Pap-Sziklay

Chemical Works of Gedeon Richter Ltd, H-1475 Budapest, 10, POB 27, Hungary.

Karoly Kaffka

University of Horticulture and Food Industry, H-1118 Budapest, Menesi ut 45., Hungary.

Introduction

In order to control the quality of pharmaceutical finished products it is necessary, in certain cases, not only to determine the content of the active ingredients but also of the other constituents. If test methods such as TLC, HPLC, AA, MS, IR are used, the sample preparation may be complex, often consisting of several steps for the selective measurement of the components to be tested, or the analysis may require advanced instruments which are not available in every laboratory. In the course of our work we have studied the reliability of the quantitative determination of the individual components by NIR analysis.

We first examined the pharmaceutical products in tablet form. For the most part tablets contain active substance(s) and fillers such as lactose and certain types of starch to provide the main mass of the tablets as well as talc and magnesium stearate. Other additives are not common.

We have chosen the Cavinton tablet for our study, since its composition is suited to the study of the behaviour of the general additives by NIR.

Materials and methods

Measurements were carried out with a PMC Spectralyser 10-25 type NIR instrument. Wavelength range 1000–2500 nm. Spectral data interval: 2 nm.

The composition of the Cavinton tablet is:

Vinpocetin	2 .0 w/w%
Aerosil	0.5 w/w%
Mg-stearate	1.0 w/w%
Talcum	2.0 w/w%
Amylum solani	38.5 w/w%
Lactose	56.0 w/w%

We have prepared the calibration samples by weighing the constituents on the basis of central composite design made for six factors with two repetitions in the centre. Thus we could make sure of surveying the change of composition by “several measurements” (78 calibration samples). The lower and upper levels of each factor were the equivalent of 90 and 110% of the nominal content of the components. Calibration samples were constructed by homogenisation by rubbing after their weighing together. (Measurement of tablets was also performed after careful powdering.)

Table 1. Statistical data of the calibration curves.

	PLS		MLR	
	PC = 7		$\lambda = 6$	
	Correlation	*SED*	Correlation	*SEC*
Vinpocetin	0.908	0.109	0.843	0.145
Aerosil	0.736	0.052	0.574	0.063
Mg-stearate	0.901	0.058	0.825	0.078
Talcum	0.881	0.122	0.798	0.161
Amylum	0.966	0.969	0.940	1.329
Lactose	0.964	1.020	0.933	1.430

The prediction set of 20 members in which the components derive from independent manufacturing batches was made (its basis was a 6–2 fractional factorial design with two levels and four repetitions in the centre).

In all 10 independent manufacturing batches of Cavinton tablet were examined.

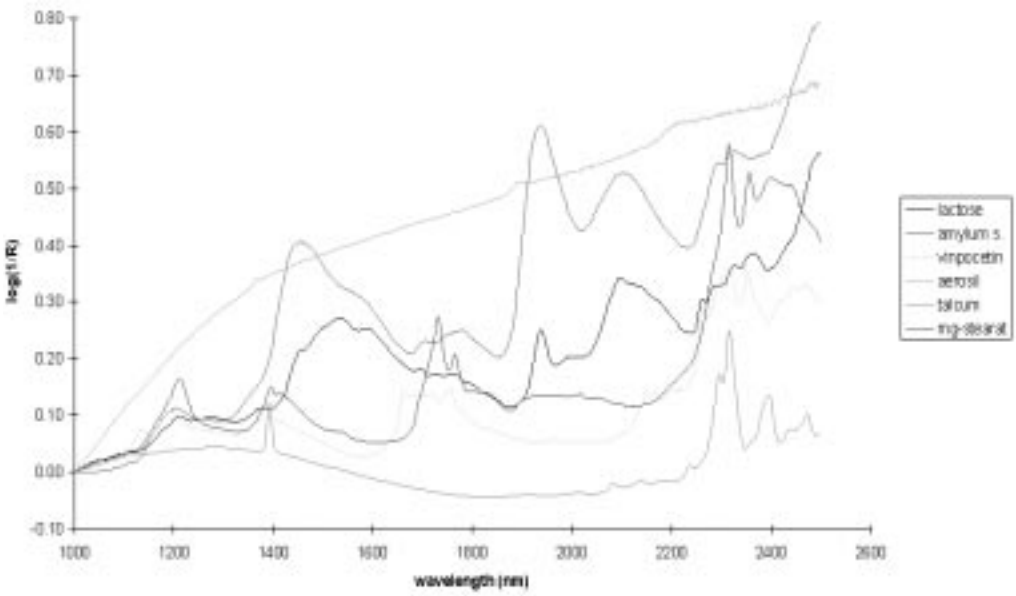

Figure 1. NIR spectra of the components of Cavinton tablets.

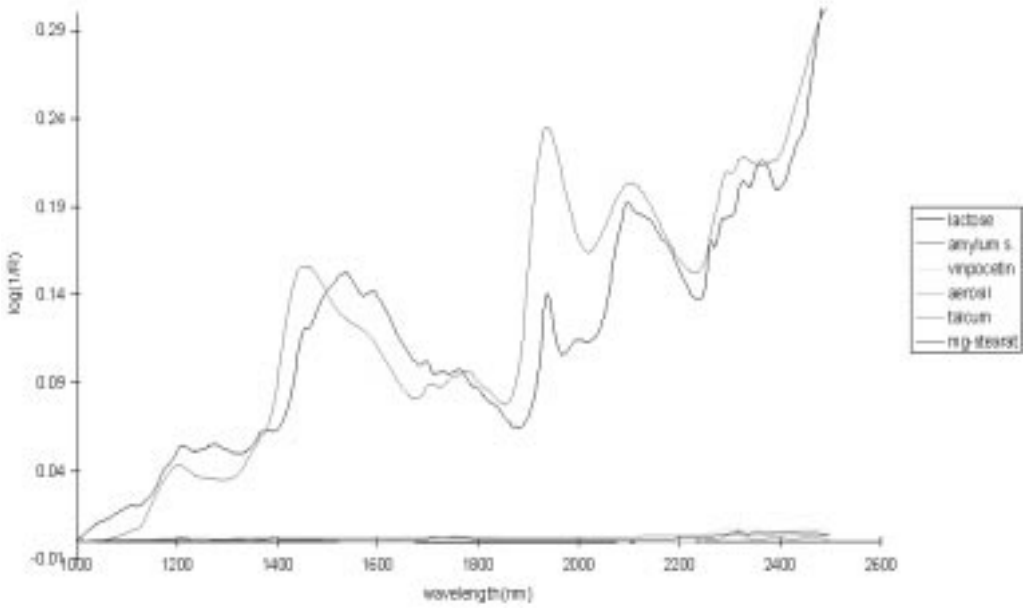

Figure 2(a). NIR spectra of the components of Cavinton tablets in their weight ratio.

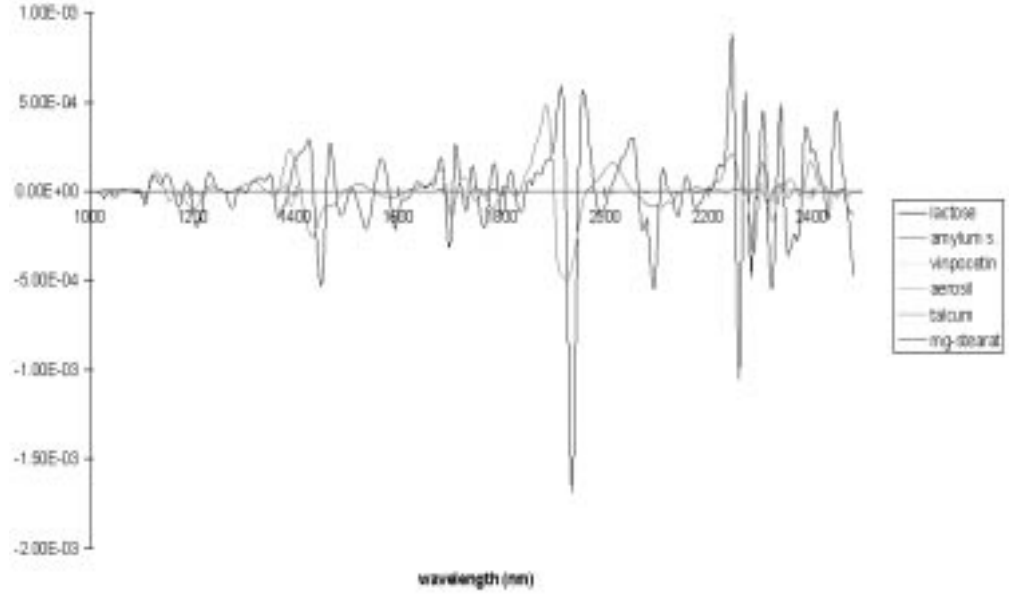

Figure 2(b). 2nd derivative of NIR spectra of the components of Cavinton tablets in their weight ratio.

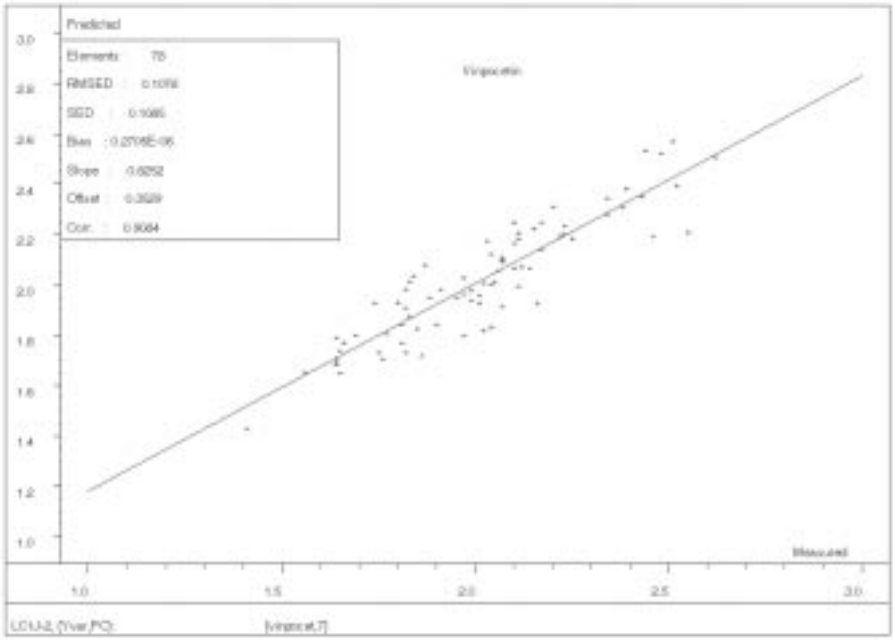

Figure 3(a). Calibration of vinpocetin with PLS (PC:7).

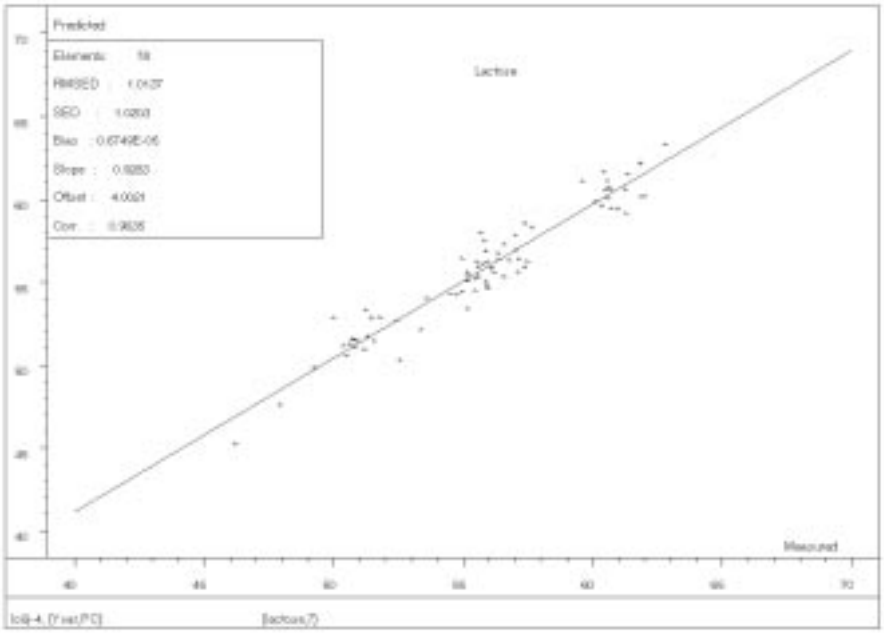

Figure 3(b). Calibration of lactose with PLS (PC:7).

Table 2. Recovery % of prediction samples.

No.	Vinpocetin	Aerosil	Mg-stearate	Talcum	Amylum	Lactose
PLS						
1	84.81	96.15	98.99	85.06	98.17	101.94
2	107.59	122.35	112.74	110.23	103.54	100.17
3	98.80	103.24	106.98	104.89	102.76	98.03
4	103.40	118.72	101.23	95.31	97.95	102.88
5	114.87	132.39	98.70	85.71	102.45	101.09
6	107.85	111.41	125.26	87.06	94.33	102.22
7	100.70	84.07	87.19	98.08	101.41	99.17
8	96.89	115.26	97.29	111.30	97.09	101.47
9	93.13	115.05	90.14	124.14	102.78	98.34
10	80.63	111.53	79.60	83.26	102.08	96.64
11	106.81	121.13	114.94	108.30	94.57	101.23
12	95.71	140.06	123.74	109.91	104.10	100.12
13	111.96	136.20	101.39	98.91	101.01	97.45
14	117.49	116.61	125.18	112.16	98.06	99.73
15	111.92	139.15	106.28	122.39	96.75	101.98
16	119.32	134.99	126.87	98.91	101.45	94.27
17	108.04	132.91	122.23	96.42	99.98	98.49
18	103.95	110.05	115.51	105.25	96.72	101.32
19	100.84	104.81	128.37	107.46	102.74	97.57
20	123.72	117.11	123.09	118.83	98.09	98.72
Mean	104.42	118.16	109.29	103.18	99.80	99.64
RSD%	10.53	12.58	13.39	11.78	3.03	2.22

Table 2 continued. Recovery % of prediction samples.

No.	Vinpocetin	Aerosil	Mg-stearate	Talcum	Amylum	Lactose
MLR						
No.	Vinpocetin	Aerosil	Mg-stearate	Talcum	Amylum	Lactose
1	90.63	128.74	112.45	94.12	100.27	98.17
2	105.20	96.52	105.60	121.03	99.34	96.51
3	106.32	115.78	102.15	87.65	104.17	101.45
4	102.28	109.65	85.23	102.74	101.36	99.12
5	105.98	118.54	123.74	113.52	96.87	102.11
6	109.42	129.40	108.45	94.16	97.51	97.89
7	89.12	102.56	97.41	87.24	102.59	100.07
8	98.73	105.28	115.82	120.79	98.64	102.18
9	97.26	107.85	95.41	116.77	102.97	97.81
10	94.26	86.50	103.27	92.78	95.73	103.09
11	109.56	128.94	121.04	88.17	102.37	100.66
12	92.14	98.21	114.61	117.55	95.17	103.47
13	104.26	118.74	84.12	94.73	103.78	98.67
14	117.20	81.23	121.09	92.36	100.92	98.05
15	100.50	117.54	97.45	117.45	97.16	102.54
16	121.40	78.21	81.24	107.39	101.24	99.12
17	98.74	114.72	108.47	99.71	97.69	96.78
18	119.45	127.41	91.43	84.16	98.53	99.32
19	106.87	108.54	100.71	103.91	104.52	103.05
20	132.56	85.24	81.29	107.38	96.11	96.11
Mean	105.09	107.98	102.55	102.18	99.85	99.81
RSD%	10.56	14.99	13.06	12.09	2.97	2.37

Table 3. Contents of 10 different Cavinton tablet batches.

PLS, $n = 5$												
	Vinpocetin		Aerosil		Mg-stearate		Talcum		Amylum		Lactose	
batch	Mean	*RSD*%	Mean	*RSD*%	Mean	*RSD*%	Mean	*RSD*%	Mean	*RSD*%	Mean	*RSD*%
1	104.2	6.7	107.9	13.7	105.2	9.7	96.4	5.7	98.7	2.7	101.1	3.4
2	106.3	12.1	108.7	6.3	99.1	6.7	102.6	6.3	101.2	3.8	98.9	2.8
3	102.7	8.3	105.1	9.5	108.1	8.6	105.4	10.4	103.4	1.5	98.7	1.4
4	99.3	5.9	107.3	8.4	112.0	11.3	101.8	9.2	100.2	3.2	101.4	2.6
5	101.7	10.7	98.6	12.7	105.4	5.4	104.3	2.4	98.4	2.9	100.9	2.9
6	104.9	9.4	111.0	14.1	107.3	11.9	100.9	10.4	99.5	4.0	101.1	1.7
7	105.8	6.8	106.2	9.2	98.7	8.2	99.5	9.5	99.9	1.5	99.5	2.0
8	103.6	12.4	103.8	15.7	106.7	12.6	106.2	12.8	102.7	3.4	97.4	1.9
9	100.4	9.7	100.6	13.1	104.9	4.9	102.8	10.3	96.9	3.7	102.5	3.3
10	102.1	11.5	104.4	10.5	103.8	7.8	101.9	9.1	99.1	2.5	100.4	2.7
MLR, $n = 5$												
	Vinpocetin		Aerosil		Mg-stearate		Talcum		Amylum		Lactose	
batch	Mean	*RSD*%	Mean	*RSD*%	Mean	*RSD*%	Mean	*RSD*%	Mean	*RSD*%	Mean	*RSD*%
1	103.7	8.7	104.2	12.7	100.6	8.8	101.1	8.7	99.4	3.1	99.9	2.3
2	104.8	10.5	110.8	10.1	102.4	11.2	100.8	10.4	102.3	2.5	97.9	2.9
3	104.2	9.2	102.7	7.4	104.3	7.9	103.4	9.3	100.8	3.7	99.4	3.1
4	101.7	10.1	111.2	9.8	106.7	12.8	102.5	11.6	97.9	1.6	102.1	1.7
5	99.9	8.6	101.3	8.9	107.2	9.4	106.1	7.2	99.4	2.2	100.3	2.1
6	102.4	11.5	105.6	12.1	103.8	10.3	102.3	9.6	98.1	1.8	101.4	1.5
7	104.7	7.4	103.7	8.3	101.6	11.2	101.2	11.4	99.1	3.4	101.2	2.4
8	105.2	6.3	108.4	12.4	105.8	9.6	103.4	5.2	101.4	2.4	98.5	1.7
9	102.4	11.4	104.9	9.4	103.5	8.4	101.8	8.3	99.2	2.9	100.7	2.1
10	100.7	8.7	106.5	13.1	102.3	10.2	103.4	7.9	102.1	2.7	98.2	3.0

The second derivative of the smoothed spectra was used for calibration, prediction and measurement of the tablets.

The program controlling the NIR spectrometer also offers Multiple Linear Regression (MLR), and we have used this to process data as well. We have chosen the wavelengths so that the *SEC* (standard error of calibration) would be smallest using the six wavelength available.

Calibration and evaluation based on principal component analysis (PLS) were also carried out using version 5.5 of UNSCRAMBLER.

Result and discussion

The NIR spectrum of each component in the Cavinton tablet can be seen on Figure 1. Spectra of components calculated on their weight ratio are shown in Figure 2(a) and their 2nd derivatives in Figure 2(b).

In both the cases when calibration was performed by MLR or PLS, it was found that correlation was only adequate for lactose and potato starch (amylum solani) when six wavelengths and seven principal components were used [see Figure 3(a), 3(b) and Table 1]. Correlation of components under 2 per cent can be only corrected by increasing the numbers of wavelengths and main components.

The results of the prediction set can be found in Table 2. This shows that the deviation of recovery percentage of components with lower concentrations is large. However, we have obtained correct results in the analysis of lactose and potato starch.

The results for 10 batches of Cavinton tablets can be found in Table 3.

On the basis of our study the “main” components of the Cavinton tablet can be measured with satisfactory accuracy and reliability within the validity limits of calibration, but in the case of components with lower concentration, both accuracy and reliability decrease considerably.

Both MLR and PLS give similar results.